Point-of-Care Troponin Testing in Patients With Symptoms Suggestive of Acute Coronary Syndrome: A Health Technology Assessment

PROSPERO Registration Number:
CRD42015023442

Product Line: Optimal Use Report
Issue Number: volume 5, no. 1b
Publication Date: March 2016
Report Length: 144 Pages
**Clinical authors:** Chuong Ho,1 Karen Cimon,1 Laura Weeks,1 Monika Mierzwinski-Urban,1 Lesley Dunfield1

**Economic authors:** Lesley Soril,2 Fiona Clement,2 Mohammed Jabr1

**Cite as:** Point-of-Care Troponin Testing in Patients With Symptoms Suggestive of Acute Coronary Syndrome: A Health Technology Assessment. Ottawa: CADTH; 2016 Mar. (CADTH optimal use report; vol.5, no.1b).

This report is prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). This report contains a comprehensive review of existing public literature, studies, materials, and other information and documentation (collectively the “source documentation”) available to CADTH at the time it was prepared, and it was guided by expert input and advice throughout its preparation.

The information in this report is intended to help health care decision-makers, patients, 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 report 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 report to ensure that its contents are accurate, complete, and up-to-date, 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 as a result of the use (or misuse) of any information contained in or implied by the information in this report.

CADTH takes sole responsibility for the final form and content of this report. The statements, conclusions, and views expressed herein do not necessarily represent the view of Health Canada or any provincial or territorial government.

Production of this report is made possible through a financial contribution from Health Canada.

Copyright © CADTH 2016. You are permitted to reproduce this document for non-commercial purposes, provided it is not modified and appropriate credit is given to CADTH.

**About CADTH:** CADTH is an independent, not-for-profit organization responsible for providing Canada’s health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

**Funding:** CADTH receives funding from Canada’s federal, provincial, and territorial governments, with the exception of Quebec.

**Views:** The views expressed herein are those of CADTH and do not necessarily reflect the views of our funders.

Contact requests@cadth.ca with inquiries about this notice or legal matters relating to CADTH services.

ISSN: 1927-0127

1 CADTH, Ottawa, Ontario
2 University of Calgary, Calgary, Alberta
External Reviewers
This document was externally reviewed by content experts and the following individuals granted permission to be cited.

Jafna L. Cox, BA, MD, FRCPC, FACC
Heart and Stroke Foundation Endowed Chair in Cardiovascular Outcomes Research, Professor of Medicine and of Community Health and Epidemiology
Dalhousie University
Halifax, Nova Scotia, Canada

Authorship

Clinical Review
Chuong Ho led the clinical project protocol development; selected studies; extracted, tabulated, and analyzed data; wrote the clinical section of the report; and revised the report based on reviewers’ comments.

Karen Cimon contributed to article selection, study quality assessment, data extraction, tabulation of data for the clinical review, and contributed to the write-up of the clinical section of the report.

Laura Weeks contributed to protocol development for the clinical review, analyzed data, and critically reviewed and revised the report based on reviewers’ comments.

Monika Mierzwinski-Urban designed and executed the literature search strategies, wrote the literature search section, and managed report referencing.

Lesley Dunfield drafted sections of the clinical review, analyzed data, and revised the report based on reviewers’ comments.

Economic Review
Lesley Soril led the economic protocol development, conducted the review of the economic literature, conducted the economic evaluation, and revised the report based on reviewers’ comments.

Fiona Clement contributed to the protocol development, contributed to the review of the economic literature, conducted economic analyses, and assisted with revisions of the report.

Mohammed Jabr contributed to the economic protocol development, contributed to the review of the economic literature, and contributed to the economic evaluation.

Acknowledgements
The authors would like to acknowledge Janice Mann, Kristen Moulton, and Tony Herd for their critical review of the project protocol and draft reports; Rhonda Boudreau for scoping and refining the topic; and Kim Ghosh for her assistance in project management support.

Conflicts of Interest
No authors declared conflicts of interest.
Table of Contents

ABBREVIATIONS .................................................................................................................. V

EXECUTIVE SUMMARY ........................................................................................................ VI

1. INTRODUCTION .................................................................................................................. 1
   1.1 Chest Pain and Acute Coronary Syndrome .................................................................. 1
   1.2 Cardiac Troponin Testing .......................................................................................... 1
   1.3 Point-of-Care Cardiac Troponin Testing .................................................................... 2
   1.4 Decision-Making About Point-of-Care Troponin Testing ........................................... 2

2. OBJECTIVES ....................................................................................................................... 3
   2.1 Research Questions ...................................................................................................... 3

3. CLINICAL REVIEW .............................................................................................................. 4
   3.1 Clinical Review Methods ............................................................................................ 4

4. CLINICAL RESULTS ........................................................................................................... 8
   4.1 Literature Search Results .......................................................................................... 8
   4.2 Study and Patient Characteristics .............................................................................. 8
   4.3 Results of Critical Appraisal ..................................................................................... 9
   4.4 Diagnostic Accuracy ................................................................................................... 10
   4.5 Clinical-Utility Results ............................................................................................. 12
   4.6 Clinical-Utility Results ............................................................................................. 13
   4.7 Guidelines ................................................................................................................ 15

5. CLINICAL DISCUSSION ...................................................................................................... 16
   5.1 Diagnostic Test Accuracy ........................................................................................ 16
   5.2 Clinical Utility in Settings With a Central Laboratory ............................................... 16
   5.3 Clinical Utility in Settings With No Central Laboratory ............................................ 17

6. ECONOMIC REVIEW ......................................................................................................... 18
   6.1 Economic Methods .................................................................................................... 18
   6.2 Strategies .................................................................................................................. 18
   6.3 Perspective ................................................................................................................ 19
   6.4 Time Horizon ............................................................................................................ 19
   6.5 Effectiveness ............................................................................................................. 19
   6.6 Decision Analytic Model .......................................................................................... 19
   6.7 Valuing Outcomes .................................................................................................... 21
   6.8 Cost Estimates and Resource Utilization .................................................................. 23
   6.9 Variability and Uncertainty ....................................................................................... 25
   6.10 Cost-Consequence Table ......................................................................................... 25

7. ECONOMIC RESULTS ....................................................................................................... 26
   7.1 Base-Case Results .................................................................................................... 26
   7.2 Variability and Uncertainty ....................................................................................... 28
   7.3 Scenario Analysis for Diagnostic Accuracy ............................................................. 30
   7.4 Cost and Consequence Tables .................................................................................. 32
8. ECONOMIC DISCUSSION ................................................................................................. 35

9. CLINICAL AND ECONOMIC REVIEW LIMITATIONS ...................................................... 36

10. CONCLUSIONS ............................................................................................................ 37

REFERENCES ................................................................................................................... 38

APPENDIX 1: POINT-OF-CARE TROPOIN Devices .............................................................. 44
APPENDIX 2: LITERATURE SEARCH STRATEGY ................................................................ 45
APPENDIX 3: FLOW CHART OF INCLUDED STUDIES .......................................................... 48
APPENDIX 4: LIST OF INCLUDED DIAGNOSTIC ACCURACY AND CLINICAL-UTILITY STUDIES ................................................................. 49
APPENDIX 5: LIST OF EXCLUDED STUDIES ................................................................... 54
APPENDIX 6: STUDY CHARACTERISTICS ....................................................................... 76
APPENDIX 7: PATIENT CHARACTERISTICS ...................................................................... 88
APPENDIX 8: CRITICAL APPRAISAL ............................................................................... 96
APPENDIX 9: DIAGNOSTIC ACCURACY ........................................................................ 122
APPENDIX 10: CLINICAL UTILITY .................................................................................. 125
APPENDIX 11: SCHEMATICS FOR THE ECONOMIC MODELS ...................................... 130
APPENDIX 12: SUMMARY RECEIVER OPERATING CHARACTERISTIC CURVE FOR THE POOLED DIAGNOSTIC ACCURACY OF POC CTN DEVICES ............................ 132

Tables
Table 1: Clinical Report Selection Criteria ........................................................................ 5
Table 2: Strategies for Context 1 and Context 2 ................................................................. 19
Table 3: Diagnostic Accuracy Inputs ................................................................................ 21
Table 4: Clinical Inputs for Contexts 1 and 2 ................................................................ 22
Table 5: Costs of Cardiac Troponin Testing Strategies ...................................................... 24
Table 6: Costs of Resource Utilization (in 2014 Canadian Dollars) ................................ 25
Table 7: Results of Base-Case Analysis for Context 1 ......................................................... 26
Table 8: Results of Base-Case Analysis for Context 2 ......................................................... 27
Table 9: Results of Select One-Way Sensitivity and Scenario Analyses for Context 1 ..... 28
Table 10: Results of Select One-Way Sensitivity and Scenario Analyses for Context 2 .... 28
Table 11: Cost and Consequence Analysis of POC cTn Testing Strategies Compared With a Central laboratory in Context 1 .............................................................. 33
Table 12: Cost and Consequence Analysis of POC cTn Testing Strategies Compared With No cTn Testing in Context 2 ................................................................. 34
Table 13: POC Troponin Devices ....................................................................................... 44
Table 14: Study Characteristics ........................................................................................ 76
Table 15: Patient Characteristics ....................................................................................... 88
Table 16: Critical Appraisal of Diagnostic-Accuracy Studies (QUADAS-2) ......................... 96
Table 17: Critical Appraisal of Clinical-Utility Studies (Downs and Black) ...................... 101
Table 18: Critical Appraisal of Evidence-Based Guidelines (AGREE II) .......................... 121
Table 19: Diagnostic Accuracy — Sensitivity and Specificity at Admission for POC Devices Measuring cTn, Considering Relevant Patient Characteristics ............................... 122
Table 20: Diagnostic Accuracy — Positive and Negative Predictive Values at Admission for POC Devices Measuring cTn, Considering Relevant Patient Characteristics and 99th Percentiles .............................................................. 123
Table 21: Diagnostic Accuracy of the POC Devices and Central Laboratory Relative to Time of Blood Sample in the Various Studies ........................................................................ 124
Table 22: Turnaround Time........................................................................................................125
Table 23: Length of Stay........................................................................................................126
Table 24: Time to Clinical Decision in the Emergency Department ..................................127
Table 25: Time to Discharge in the Emergency Department ..............................................127
Table 26: Mortality and Major Adverse Events Outcomes .................................................127
Table 27: Patients’ Quality of Life (EQ-5D) in the Emergency Department ......................128
Table 28: Staff Satisfaction in the Various Settings..........................................................129

Figures
Figure 1: Patient Population for the Economic Evaluation of Point-of-Care
            Troponin Testing...........................................................................................................18
Figure 2: Basic Schematic of the Economic Model for Cardiac Troponin Testing ............20
Figure 3: Base Case Cost-Effectiveness Analysis for Context 1........................................26
Figure 4: Base Case Cost-Effectiveness Analysis, Context 2.............................................27
Figure 5: Scenario Analyses for Diagnostic Accuracy of POC Desktop (Panel A) and
            Hand-held (Panel B) Devices Compared with a Central Laboratory (Context 1).......30
Figure 6: Scenario Analyses for Diagnostic Accuracy of POC Desktop (Panel A)
            and Hand-held (Panel B) Devices Compared With No cTn Testing (Context 2).......31
Figure 7: Schematic of the Economic Model for Context 1: POC Cardiac Troponin
            Testing Versus Central Laboratory Testing...............................................................130
Figure 8: Schematic of the Economic Model for Context 2: POC Cardiac Troponin
            Testing Versus No cTn Testing..................................................................................131
Figure 9: Desktop POC cTn Device ....................................................................................132
Figure 10: Summary Receiver Operating Characteristic Curve for the Pooled Diagnostic
            Accuracy of the Hand-held POC cTn Device ...........................................................133
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACS</td>
<td>acute coronary syndrome</td>
</tr>
<tr>
<td>AMI</td>
<td>acute myocardial infarction</td>
</tr>
<tr>
<td>CABG</td>
<td>coronary artery bypass grafting</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>cTn</td>
<td>cardiac troponin</td>
</tr>
<tr>
<td>cTnI</td>
<td>cardiac troponin I</td>
</tr>
<tr>
<td>cTnT</td>
<td>cardiac troponin T</td>
</tr>
<tr>
<td>CV</td>
<td>coefficient of variation</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>ED</td>
<td>emergency department</td>
</tr>
<tr>
<td>HTA</td>
<td>health technology assessment</td>
</tr>
<tr>
<td>LOS</td>
<td>length of stay</td>
</tr>
<tr>
<td>MI</td>
<td>myocardial infarction</td>
</tr>
<tr>
<td>NACB</td>
<td>National Academy of Clinical Biochemistry</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>non-ST segment elevation myocardial infarction</td>
</tr>
<tr>
<td>OCC</td>
<td>Ontario case costing initiative</td>
</tr>
<tr>
<td>PCI</td>
<td>percutaneous coronary intervention</td>
</tr>
<tr>
<td>POC</td>
<td>point of care</td>
</tr>
<tr>
<td>PPV</td>
<td>positive predictive value</td>
</tr>
<tr>
<td>QALY</td>
<td>quality-adjusted life-year</td>
</tr>
<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
</tr>
<tr>
<td>ROC</td>
<td>receiver operator characteristic</td>
</tr>
<tr>
<td>STEMI</td>
<td>ST segment elevation myocardial infarction</td>
</tr>
<tr>
<td>TAT</td>
<td>turnaround time</td>
</tr>
<tr>
<td>TCD</td>
<td>time to clinical decision</td>
</tr>
<tr>
<td>TTD</td>
<td>time to discharge</td>
</tr>
<tr>
<td>UA</td>
<td>unstable angina</td>
</tr>
</tbody>
</table>
Executive Summary

The Issue
Testing of cardiac biomarkers, such as cardiac troponin I or cardiac troponin T, has an important role in the diagnostic workup for acute coronary syndrome (ACS) (including acute myocardial infarction [AMI] and unstable angina), and in patients presenting with acute chest pain and a non-diagnostic electrocardiogram (ECG). Bedside testing of cardiac troponins (cTn) using point-of-care (POC) assays was developed to reduce the turnaround time of the standard tests performed in a central laboratory, and to expedite treatment. Given the introduction and increasing diffusion of POC cTn use, a review of its clinical and economic evidence is needed to inform decisions about its acquisition and use in emergency rooms and other in-hospital settings, as well as in rural health care centres and remote settings.

Objectives
The aim of this health technology assessment (HTA) is to inform decision-making about the appropriate use of POC cardiac cTn testing. The policy question of whether to adopt POC troponin testing in specific settings (rural health care centres, remote locations, in hospital, in emergency settings) has been raised in Canadian jurisdictions. This HTA will address these questions by evaluating the diagnostic accuracy, clinical utility, and cost-effectiveness of POC cTn testing in patients presenting with ACS. The economic evaluation will determine the cost per quality-adjusted life-year (QALY) gained with POC troponin compared with central laboratory troponin testing (context 1) or no POC troponin testing (context 2). This HTA will address the following research questions:

1. Using POC cTn devices approved by Health Canada, what is the diagnostic accuracy of POC cTn testing compared with central laboratory methods in patients presenting with symptoms of ACS?

2. What is the clinical utility of POC cTn testing in altering the treatment and outcomes of patients presenting with symptoms of ACS compared with:
   a. standard care in settings where a central laboratory is not available (pre-hospital settings, rural settings, or remote locations)
   b. central laboratory methods in settings where a central laboratory is available (in hospitals and emergency departments)?

3. What is the cost-effectiveness of POC cTn testing in patients presenting with symptoms of ACS compared with:
   a) standard care in settings where a central laboratory is not available (pre-hospital setting, rural setting, remote locations)
   b) central laboratory methods in settings where a central laboratory is available (in hospitals and emergency departments)?

Methods
A peer-reviewed literature search strategy was employed to identify published literature in the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid; Embase (1974–) via Ovid; The Cochrane Library (2015, Issue 1) via Wiley; and PubMed. No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication year or language. The initial search was completed on January 14, 2015 and regular alerts were conducted up to February 12, 2016. Grey literature (literature that is not commercially available)
published) was identified by searching the Grey Matters checklist ([www.cadth.ca/resources/grey-matters](http://www.cadth.ca/resources/grey-matters)). Google and other Internet search engines were used to search for additional Web-based materials.

Studies were included if they met the selection criteria detailed in the text. Data were extracted independently by one reviewer and checked for accuracy by another reviewer, and any disagreements were resolved through discussion until consensus was reached. A quality assessment of included diagnostic-accuracy studies was conducted using the QUADAS-2 tool, and studies on clinical utility were assessed using the Downs and Black checklist. Quality was appraised by one reviewer and the assessments verified by a second reviewer, with disagreements resolved through discussion.

The original search identified 1,434 citations. From these, 322 potentially relevant reports were retrieved for further scrutiny, and six reports were retrieved from search updates (alerts) and grey literature. Forty-one original publications, five companion reports, and two guidelines were selected for inclusion. Nine studies and one companion report on the diagnostic performance of POC in patients with chest pain were included. Thirty studies, three companion reports, and two guidelines on the clinical utility of POC cTn testing in patients with symptoms suggestive of ACS were included. Two additional studies and one companion report were included for both diagnostic-accuracy and clinical-utility outcomes.

The diagnostic accuracy of POC troponin testing was assessed based on the ability of POC troponin testing to predict AMI. The review on diagnostic accuracy was limited to POC cTn devices that are available in Canada and approved by Health Canada, and to studies where an elevated troponin level was based on a result above the 99th percentile cut-off threshold. Meta-analysis of diagnostic-accuracy outcomes was not possible due to heterogeneity among the included studies, such as differences in devices used. A review that includes a narrative synthesis was conducted, with results reported in tables with ranges.

The clinical utility of POC troponin testing was based on findings about the benefits and risks resulting from test use. Recommendations from evidence-based guidelines were also reported. The review on clinical utility was not limited to POC cTn devices approved for use in Canada. Meta-analysis was not possible due to clinical and methodological heterogeneity among trials, such as difference in definitions of outcomes and inconsistencies in reporting. A review that includes a narrative synthesis and summary of study findings was conducted, with results reported in tables with ranges.

For diagnostic-accuracy and clinical-utility outcomes, subgroup analyses were performed based on study design, clinical setting (e.g., emergency department, rural health care centres, or remote locations), the level of sensitivity of the central laboratory method, type of cardiac troponin test (cardiac troponin I [cTnI], cardiac troponin T [cTnT]), and study funding status (private and public).

**Diagnostic Accuracy**

Compared with central laboratory methods, POC tests tended to provide lower sensitivity, lower negative predictive value, higher specificity, and higher positive predictive value (PPV). Both positive and negative-likelihood ratios tended to be higher with POC testing compared with central laboratory testing, although only one study was available for the central laboratory comparison. This trend was maintained across different POC devices, and with blood samples taken at admission, three hours and six hours after admission, and between six to nine hours
after admission. Subgroup analyses of studies based on the study design, setting, sensitivity levels of the central laboratory methods, the types of cTn (I or T), and the funding status did not show any systematic differences in findings.

Clinical Utility

In Settings Where a Central Laboratory is Available

POC cTn testing tended to shorten turnaround time (TAT), length of hospital stay, and time to discharge. The use of POC cTn did not statistically change mortality rates or severe adverse events compared with a central laboratory in most studies, in up to one year of follow-up. There was no difference in quality of life among patients who were tested using POC or central laboratory within up to three months’ follow-up. Subgroup analyses of clinical-utility studies based on study design, setting, the level of sensitivity of the central laboratory methods, the types of cTn (I or T), and funding status did not show any differences in findings.

The majority of physicians and nurses who participated in related survey studies agreed that they were satisfied with POC testing, and that cTn testing shortened TAT, was easy to use, and led to better patient management.

The National Academy of Clinical Biochemistry (NACB) and the European Society of Cardiology (ESC) guidelines recommend that, based on sufficient and fair evidence, POC tests for cardiac troponins should be implemented when a central laboratory cannot consistently provide test results within 60 minutes.

In Settings Where No Central Laboratory is Available

In pre-hospital or ambulance settings, limited evidence points to the potential use of POC cTn tests for the diagnosis and management of patients. POC cTn testing may reduce the percentage of patients referred to the emergency department from a primary health care centre. POC cTn testing was shown to be feasible and reliable for patients transported by ambulance, and can shorten the time from first medical contact to patient disposition. The majority of physicians and nurses who participated in related surveys in rural health care centres or remote locations agreed they were satisfied with POC testing, and that cTn testing shortened TAT, was easy to use, and led to better patient management.

Economic Evaluation

An economic evaluation was conducted in which standard of care was compared with POC cardiac troponin (cTn) testing in two settings: where a central laboratory is available, either alone or in addition to POC cTn (context 1), and in settings where a central laboratory is not available (context 2). The target population was adult patients presenting with chest pain or other symptoms suggestive of ACS identified by ECG testing as having non-ST elevation. For each context, a decision-tree model was developed to simulate what could happen to patients from the chest pain presentation at the emergency department or doctor’s office until one year after their episode. The analysis assumed a payer’s perspective. A one-year time horizon was used for the economic analysis. The proportion of patients in each of the potential diagnostic categories (true-positives, false-positives, true-negatives, false-negatives) was determined by both the underlying prevalence of non-ST elevation myocardial infarction (NSTEMI) and the diagnostic accuracy of the cTn test strategy being evaluated. The primary outcome was the cost per QALY gained. Different utility estimates were included for the general population, NSTEMIs, and missed NSTEMIs. Secondary measures for context 1 include the length of stay in the emergency department and the probability of readmission due to misdiagnosis of NSTEMI, and
were accounted for and expressed as costs. No secondary measures were available for context 2. All outcomes were considered for one year. The analysis considered test costs, emergency room costs, in-patient costs, and physician fees for services that are covered in provincial fee schedules. Indirect costs, such as productivity losses, out-of-pocket patient costs, and time costs were not included in the first setting. However, in the second setting, where the patient may be transferred to the hospital from either a rural emergency room or primary care practice, limited patient-borne costs were included. A cost-effectiveness analysis was conducted in which costs were measured in dollars and the outcome was measured in QALYs.

Discussion
Our findings concur with observations from other systematic reviews that an ideal POC assay for the diagnosis of AMI does not yet exist and, despite improvement in TAT and length of hospital stay, there is no strong evidence of improvement of clinical outcomes compared with cTn testing by a central laboratory. In the absence of a central laboratory, POC cTn testing may be of additional benefit compared with standard care without troponin testing. In rural centres and remote locations, the use of POC cTn testing may lead to improved patient care, as cTn results, in addition to clinical assessment of the patient, may help prevent unnecessary transfers to hospital, thereby allowing patients to remain in their communities for follow-up and care. This may result in other benefits, such as reduced out-of-pocket costs and familial disruptions, and ensuring the transfer of only those patients who require it. The results from our clinical review must be interpreted with caution, given the limited quality of the included studies, and the outcomes analyzed are reflective of short-term follow-up times.

Generally, POC cTn testing strategies were found to be less effective and less expensive compared with standard of care, regardless of context. However, there are plausible variations in diagnostic accuracy that change the cost-effectiveness from cost-saving to cost-incurring. Generally, the weak evidence base for effectiveness and costs limited the scope of this economic evaluation.

Conclusions
Overall, given the limitations with the data and the inconsistency in diagnostic test accuracy estimates, the usefulness of POC cTn testing in settings with access to central laboratories may be limited. However, in settings with no access to a central laboratory, such as in rural health care centres or remote settings, POC cTn testing may be useful due to the potential to help reduce unnecessary transfer of patients to larger centres.
1. Introduction

1.1 Chest Pain and Acute Coronary Syndrome

Chest pain can be the result of a wide variety of causes, including acute coronary syndrome (ACS) and non-cardiac conditions, such as gastro-esophageal reflux, anxiety, and muscular pain. Individuals who present with chest pain or other symptoms suggestive of ACS undergo investigations such as clinical assessment and electrocardiogram (ECG) to rule out or rule in a potential acute myocardial infarction (AMI). However, clinical assessment and ECG findings are often inconclusive and further investigation may be required to rule out or rule in the possibility of an AMI.

ACS is a term for a group of conditions that result from a decrease of blood flow in the coronary arteries, leading to reduced blood supply to the heart muscle (myocardial ischemia) and, if severe and prolonged, to heart muscle necrosis (myocardial infarction). The most common symptom of ACS is pressure-like chest pain radiating to the left arm or jaw associated with shortness of breath, nausea, and sweating. ACS includes ST segment elevation myocardial infarction (STEMI), non-STEMI (NSTEMI), and unstable angina.

STEMI results from complete and prolonged occlusion of a coronary artery and is defined as ACS with an ST segment elevation on ECG, and an increase in cardiac biomarkers such as creatine kinase isoenzyme MB, cardiac troponin I (cTnI), or cardiac troponin T (cTnT). NSTEMI results from partial and transient occlusion of a coronary artery and is defined as ACS without an ST-segment elevation but with an elevation of cardiac biomarkers. Unstable angina results from myocardial ischemia that, unlike STEMI and NSTEMI, is not severe enough to cause myocardial damage and the release of detectable quantities of cardiac biomarkers, and is defined as ACS without an ST elevation and without an elevation of cardiac biomarkers.

A 2013 CADTH report cited that in Canada, there were an estimated 818,847 emergency visits for suspected ACS, and an estimated 109,109 hospitalizations for ACS in 2009. In Canada, AMI requiring in-patient acute care has been listed as one of the top 15 most expensive medical conditions. Given the broad range of causes of chest pain, approximately 75% to 85% of patients who present to emergency departments with chest pain are not diagnosed with ACS.

1.2 Cardiac Troponin Testing

Because of the similarity of the symptoms and the transient or non-specific ECG findings, a 2012 universal definition of AMI was published by several leading international cardiac associations using cardiac troponin (cTn) as a diagnostic determinant. For a diagnosis of AMI, there must be a “detection of a rise and/or fall of cardiac-biomarker values (preferably cardiac troponin) with at least one value above the 99th percentile upper reference limit” along with at least one other criterion, such as pathological Q waves in the electrocardiogram or symptoms of ischemia.

The conventional method of assessing cTn concentrations is via central laboratory testing. High-sensitivity cTn laboratory tests have recently emerged. Testing for cTn via a central laboratory can provide evidence of AMI with a one-hour recommended turnaround time. Due to the development of the higher-sensitivity cTn assays, the thresholds of positive cTn values have decreased approximately 40 fold since 1995. The increase in sensitivity of cardiac-biomarker tests may result in an increase in false-positive diagnoses of NSTEMI and a corresponding decrease in diagnoses of unstable angina. Blood cTn concentrations can also be increased in
non-cardiac conditions such as renal failure or neuromuscular diseases, again leading to an increased potential for false-positives.\textsuperscript{12}

A CADTH report\textsuperscript{5} generated a one-year economic model and found that, from time of presentation at the emergency department to one year later, the costs, after undergoing standard laboratory testing of cTn, ranged from $2,018 to $2,186 per patient per year, which includes the costs of false-positive hospitalizations. Multiplying the total number of emergency visits by $2,018 equals an estimated annual cost of C$1,652,433,246 to care for patients presenting with suspected ACS to emergency departments and who undergo laboratory testing for cTn. This model also assumed that each patient would receive two laboratory tests at either $3.00 (for cTnT testing) or $6.75 (for troponin I tests) per test.

1.3 Point-of-Care Cardiac Troponin Testing

Central laboratories are not always on-site, nor available for use 24 hours a day, seven days a week. Point-of-care (POC) testing is a care model that moves the assay to the patient and is now available to measure cTn levels. POC cTn tests offer a significantly shorter turnaround time for biomarker detection, typically providing results within 10 to 20 minutes.\textsuperscript{4} POC cTn testing has been used with the goal to expedite patient care both in hospital emergency departments and in various settings where central laboratory testing is not available, including use by paramedics aboard a land or air ambulance, and by health personnel in rural health care centres or remote locations. Use of POC cTn testing could potentially speed up therapeutic decisions and decisions around patient transfers, hospital admissions, and discharge for patients presenting with ACS. Theoretically, the result could be less congested emergency departments and fewer transfers of patients to larger hospitals for further assessment. Improved patient flow may result in cost reductions from fewer unnecessary hospital admissions and laboratory costs.\textsuperscript{9}

POC cTn testing is more expensive than laboratory testing, with one manufacturer citing $12.50 per test. However, a cost-per-test approach is not an informative cost comparison with laboratory testing; rather, the question is how POC testing compares with laboratory testing when examining factors beyond the costs of reagents to include the costs of running the POC program (for example, training, quality assurance and quality control, maintenance, data management) and savings from avoiding the costs of patient transfers and hospital admissions.

There are several POC troponin devices available in Canada produced by various manufacturers that test for one or both types of cTn (cTnI and cTnT). A list of POC troponin devices approved in Canada is provided in Appendix 1.

1.4 Decision-Making About Point-of-Care Troponin Testing

It is unknown whether health outcomes can be improved and if cost savings can be realized with POC cTn testing in various Canadian health care settings (such as hospitals with a central laboratory, community hospitals, remote locations, hospitals without a central laboratory, remote nursing stations, medical clinics, long-term care settings, and emergency medical services). To answer these questions, a review of the clinical and economic evidence on POC troponin testing is needed to inform decisions about its acquisition and use. As such, CADTH has undertaken a health technology assessment (HTA) on POC cTn testing. For the purpose of this HTA, we have categorized relevant health care settings as those where a central laboratory is available, such as in emergency departments and other hospital units, and those settings where central laboratory testing is not available full-time, such as in rural, remote, or other settings.
2. **Objectives**

The aim of this HTA is to inform decision-making about the appropriate use of POC cTn testing. Policy questions such as whether to adopt POC cTn testing in specific settings, including those with and without access to a central laboratory, have been raised in Canadian jurisdictions. This HTA will address these questions by evaluating the diagnostic accuracy, clinical utility, and cost-effectiveness of POC cTn testing in patients presenting with ACS. The economic evaluation will determine the cost per quality-adjusted life-year (QALY) gained with POC cTn testing compared with central laboratory testing (context 1), or no troponin testing (context 2).

2.1 **Research Questions**

1. What is the diagnostic accuracy of POC cTn testing, using POC cTn devices approved by Health Canada, compared with central laboratory methods in patients presenting with symptoms of ACS?

2. What is the clinical utility of POC cTn testing in altering the treatment and outcomes of patients presenting with symptoms of ACS compared with:
   a. standard care in settings where a central laboratory is not available (pre-hospital settings, rural settings, or remote locations)
   b. central laboratory methods in settings where a central laboratory is available (in hospitals and emergency departments)?

3. What is the cost-effectiveness of POC cTn testing in patients presenting with symptoms of ACS compared with:
   a) standard care in settings where a central laboratory is not available (pre-hospital setting; rural setting, or remote location)
   b) central laboratory methods in settings where a central laboratory is available (in hospitals and emergency departments)?
3. Clinical Review

3.1 Clinical Review Methods
A systematic review of the literature on the diagnostic accuracy and clinical utility of POC cTn testing for patients with symptoms suggestive of ACS was conducted.

3.1.1 Literature search strategy
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–) with in-process records and daily updates via Ovid; Embase (1974–) via Ovid; The Cochrane Library via Wiley; and PubMed. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine’s MeSH (Medical Subject Headings), and keywords. The main search concepts were POC and troponin.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on January 14, 2015. Regular alerts were established to update the search until the final draft was completed (February 12, 2016). 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 (www.cadth.ca/resources/grey-matters), which includes the websites of HTA agencies, clinical practice guidelines, advisories and warnings, drug and device regulatory approvals, and databases (free). Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts and industry. See Appendix 2 for more information on the grey literature search strategy.

3.1.2 Selection criteria and methods
Two reviewers (CH, KC) independently screened the titles and abstracts of all citations retrieved from the literature search and, based on the selection criteria (Table 1), ordered the full text of any articles that appeared to meet those criteria. The reviewers independently reviewed the full text of the selected articles, applied the selection criteria to the articles, and compared the independently chosen studies. Disagreements were resolved through discussion until consensus was reached. Multiple publications of the same trial were excluded, unless they provided additional information about outcomes of interest.
**Table 1: Clinical Report Selection Criteria**

<table>
<thead>
<tr>
<th>Settings</th>
<th>Diagnostic Accuracy (Question 1)</th>
<th>Clinical Utility (Question 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Medical centres where central laboratory testing is available (such as hospital emergency departments)</td>
<td>• Medical centres where central laboratory testing is available (such as hospital emergency departments)</td>
</tr>
<tr>
<td></td>
<td>• Medical centres or settings where central laboratory testing is not available (such as pre-hospital settings, rural health care centres or remote locations)</td>
<td></td>
</tr>
<tr>
<td>Population</td>
<td>Adults presenting with chest pain or other symptoms suggestive of ACS</td>
<td>Adults presenting with chest pain or other symptoms suggestive of ACS</td>
</tr>
<tr>
<td>Intervention/ Index Tests</td>
<td>POC cTn assays/tests approved for use in Canada by Health Canada that use the 99th percentile cut-off threshold&lt;sup&gt;a&lt;/sup&gt;</td>
<td>• Any POC cTn test</td>
</tr>
<tr>
<td>Comparator/ Reference Standard</td>
<td>Clinical adjudication</td>
<td>• For settings where a central laboratory is available: central laboratory methods either alone or in addition to POC cTn</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• For settings where central laboratory is not available: standard care (e.g., transfer to facility with testing capabilities)</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Clinical validity of POC cTn tests, including: sensitivity, specificity, positive predictive value, negative predictive value, positive-likelihood ratio, and negative-likelihood ratio of POC cTn testing in the detection of AMI</td>
<td>• Benefits and risks of POC cTn testing such as: turnaround time, time to clinical decision-making, time to discharge or transfer (length of hospital stay, length of emergency department stay), number of hospital admissions, adverse events rate, mortality rate, repeat emergency department visit</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Behaviour/treatment patterns of health care professionals</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Availability of the test, acceptability of and interest in the test for patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Ethical, legal, social implications of POC cTn testing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Recommendations from evidence-based guidelines</td>
</tr>
<tr>
<td>Study design</td>
<td>RCTs, cohort studies, case-control studies</td>
<td>RCTs, cohort studies, evidence-based guidelines, surveys (for outcomes related to behaviour/treatment patterns, and availability and acceptability of tests)</td>
</tr>
</tbody>
</table>

ACS = acute coronary syndrome; AMI = acute myocardial infarction; cTn = cardiac troponin; CV = coefficient of variation; POC = point of care; RCT = randomized controlled trial.

<sup>a</sup> Studies on diagnostic accuracy were included if, in addition to other inclusion criteria, they used the 99th percentile at 10% of the normal population, or the 99th percentile suggested by the manufacturer (which may be higher than 10% CV).

Studies were excluded when they did not meet the selection criteria or presented preliminary results in abstract form. Duplicate publications, narrative reviews, case studies, and editorials were excluded.
3.1.3 Data extraction
A data-extraction form for the reviews of diagnostic accuracy and clinical utility was designed a priori to document and tabulate relevant study characteristics (e.g., study design, inclusion criteria, patient characteristics, setting, and other such factors and measures of clinical utility, as outlined in Table 1) in the selected studies. Recommendations on the use of POC cTn were extracted from the included guidelines. Data were extracted independently by one reviewer and verified by another reviewer; any disagreements were resolved through discussion until consensus was reached.

3.1.4 Critical appraisal of individual studies
The quality of the included studies on diagnostic accuracy was assessed using QUADAS-2, the Downs and Black checklist was used to assess the quality of the studies on clinical utility. One reviewer appraised each study using the appropriate tool, and the assessments were then checked by a second reviewer. Disagreements were resolved through discussion. The quality of the included guidelines was assessed by one reviewer, using the AGREE II checklist, then checked by a second reviewer. Numeric scores were not calculated; instead, the strengths and limitations of the included studies were described narratively.

3.1.5 Data analysis and synthesis methods
The diagnostic accuracy of POC troponin testing was assessed based on the ability of POC troponin testing to predict AMI (clinical validity) compared with central laboratory assessments. Clinical assessment and adjudication of POC and clinical laboratory results were used to determine diagnostic accuracy of both central laboratory and POC tests. Findings were reported on: those patients who were identified as having AMI (sensitivity); those who did not have AMI (specificity); those who truly had AMI from among those who tested positive (positive predictive value), those who did not truly have AMI from among those who tested negative (negative predictive value), and the likelihood that a positive or negative test result would be expected in a patient with AMI compared with the likelihood that the same test result would be expected in a patient without AMI (positive and negative-likelihood ratio). Due to the heterogeneity of the included studies (for example, due to varying reference standards, types of central laboratory cTn test, patient characteristics, and inclusion of POC devices from different manufacturers), pooling via meta-analysis was not appropriate. Rather, study results are reported narratively in tables with ranges, with special attention paid to issues that could contribute to heterogeneity.

The clinical utility of POC troponin testing was assessed based on findings about the benefits — how testing influences management of ACS or AMI, and whether or not testing results alter clinical outcomes — and risks resulting from test use.

Meta-analysis for the clinical-utility outcomes was not possible due to clinical and methodological heterogeneity among trials, such as differences in definitions of outcomes (for example, definitions of turnaround time) and inconsistencies in reporting (such as values reported as mean or median). A review was conducted that included a narrative synthesis and summary of study findings with the goal of describing both the direction and size of any observed effects, and results were reported in tables with ranges.

For diagnostic-accuracy and clinical-utility outcomes, subgroup analyses were planned and performed based on clinical setting (emergency department, rural health care centre, or remote location), the level of sensitivity of the central laboratory method, type of cTn test (cTnI, cTnT), and study funding status. A subgroup analysis based on study design was conducted for
clinical-utility outcomes. Subgroup analyses in the absence of meta-analysis involved inspection of the results for any systematic patterns between groups.

Recommendations on the use of POC cTn testing from evidence-based guidelines were also reported. Further, relevant results within included studies regarding behaviour and treatment patterns of health care professionals for POC troponin testing, availability of testing, interest and acceptability of testing to the patient, and ethical, legal, and social implications of POC troponin testing are summarized descriptively by topic, when they were available.
4. Clinical Results

4.1 Literature Search Results

The original search identified 1,434 citations. From these, 322 potentially relevant reports were retrieved for further scrutiny, and six reports were retrieved from search updates (alerts) and grey literature. Forty-one original publications, five companion reports, and two guidelines were selected for inclusion. Nine studies and one companion report on the diagnostic performance of POC in patients with chest pain were included. Thirty studies, three companion reports, and two guidelines on the clinical utility of POC cTn testing in patients with symptoms suggestive of ACS were included. Two additional studies and one companion report were included for both diagnostic-accuracy and clinical-utility outcomes. The PRISMA flow chart is presented in Appendix 3. The lists of included and excluded studies are provided in Appendix 4 and Appendix 5, respectively.

4.2 Study and Patient Characteristics

Seven randomized controlled trials (RCTs), 26,29,39-41,50,55 22 prospective observational studies, 16-18,20-22,24-28,32-36,43-48,51,61,62 10 retrospective observational studies, 19,21,27,30,31,37,38,42,49,52 two surveys, 53,54 and two evidence-based guidelines 59,60 are included in this review. Twelve studies were from the United States, 16-20,26,27,35,36-38,42,49 five were from Australia; 28,40,41,44,52 four were from Sweden; 43,45,46,61 one from Italy; 23,24,31,33 three from Denmark; 21,48,62 three from the United Kingdom (UK); 39,50,53 two from the Netherlands; 22,34 one each from Canada, New Zealand, Germany, Finland, Slovenia, France, and China; and one study was from multiple countries (Spain, the UK, Germany, Austria, Ireland, and Sweden). The European Society of Cardiology (ESC) guidelines 59 were developed and published in 2011 by the ESC Task Force for the Management of ACS in Patients Presenting Without Persistent ST-Segment Elevation. The Laboratory Medicine Practice Guidelines 60 were developed and published in 2007 by the National Academy of Clinical Biochemistry for POC testing. In both guidelines, the level of evidence and the strength of a recommendation were graded according to pre-defined scales.

Sixteen different POC devices of interest were examined in the included studies: Stratus CS, 23,24,29,30,32,33,39,45,49,53 i-STAT, 18,20,26,27,38,40,43,46,52,53 AQT90 FLEX, 17,18,21,22,41,44 Cardiac Reader, 34,36,47,51,53 PATHFAST, 18,35 Triage, 31,53 Cobas h232, 51,62 Triage Cardiac Panel, 32 Triage Profiler SOB, 42 Triage Cardio3, 19,55 Triage Meter Pro, 28 Spectra Status, 37 GEM Immuno, 18 TropT, 46 Cardiac T, 50 and Cardio3. 16 One survey 54 did not specify what devices were used. Most study settings were hospital, medical centre, or community centre emergency department. 16-20,22-24,26-44,46,47 Additional settings utilized by some studies were: cardiology service or coronary care unit; 49-51 both emergency department and coronary care unit; 21,45 pre-hospital (ambulance); 48 both ambulance and emergency department; 55,62 primary health care; 61 remote health centre; and health trust or health care unit. 53,54

Full or partial funding by industry or author conflicts of interest were present in 22 studies, 16-18,20-22,26-29,35,36,38,43-49,55,62 16 studies did not report information on funding and/or author conflicts of interest, 19,23,24,30,34,37,40,42,45,50-54 and three studies stated they were not funded by industry and had no author conflicts of interest.
The included studies varied in size, from 31\textsuperscript{35} to 4,905\textsuperscript{48} patients. The study patients were adults with chest pain or symptoms suggestive of ACS, and there was variability in the reporting of patient comorbidities by the study authors, with many not including those characteristics in the reports.

Further details on study and patient characteristics are provided in Appendix 6 and Appendix 7, respectively.

### 4.3 Results of Critical Appraisal

The majority of the diagnostic-accuracy studies had appropriate exclusion of patients, although in some cases\textsuperscript{16,19-23,61} it was unclear whether a consecutive sample of patients was enrolled. In two studies,\textsuperscript{22,23} it was unclear whether all patients were included in the analysis and, in four studies,\textsuperscript{16,19,20,62} not all patients were included. It was unclear in many studies whether the POC cTn test results were interpreted without knowledge of the results of the central laboratory cTn test and vice versa.\textsuperscript{1,16-23,61,62} The time interval between the POC cTn test and the central laboratory cTn test was not indicated in many studies\textsuperscript{1,17,19,23,61,62} while the remaining studies reported an appropriate time interval. An additional limitation is the potential knowledge of the results of the cTn test during clinical adjudication, which may lead to confirmation bias.

Concerns about the applicability of the included studies to the research questions were generally low. In all studies, the concern that the included patients did not match the review question was low. In four studies,\textsuperscript{16,18,19,21} it was unclear whether the index test, its conduct, or its interpretation differed from the review questions.

Seven out of 32 studies on clinical utility were RCTs with an appropriate randomization process and allocation concealment,\textsuperscript{26,29,39-41,50,55} with the remaining studies being observational or pre–post studies. In all studies, the hypothesis, aim, objective, and main outcomes were clearly described. Subjects asked to participate in the study were representative of the entire population from which they were recruited in 11 studies,\textsuperscript{29,30,32,33,38,41,42,47,49,50,55} and may not be representative in the remaining, as characteristics of all patients at admission were not clearly described. About half of the studies reported having sufficient power to detect a clinically important effect for the primary outcomes,\textsuperscript{26,28-31,33-40,42,50} and the remaining studies did not report power. For six studies,\textsuperscript{29,37,39,44,55,62} it was made explicit that an attempt was made to blind patients, outcome assessors, or both, to treatment allocation. For the remaining studies, it was not possible to make an assessment of blinding. Data relevant to staff satisfaction were collected in various studies\textsuperscript{27,35,37,38,52,54,56,58} using reliable Web-based software programs designed to determine satisfaction and usage among device operators according to a 5-point scale.

The guidelines\textsuperscript{59,60} had clear scope and purpose, clear methods for searching for and selecting the evidence, and rigorous methods for formulating the recommendations based on well-conducted systematic reviews of the evidence. They provided specific and unambiguous recommendations, with health benefits, side effects, and risks stated in the recommendations, and the target users of the guidelines clearly defined. It was unclear whether patients’ views and preferences were sought, or whether the guidelines were piloted among target users. Procedures for updating the guidelines were not provided, and the potential cost implications of applying the recommendations were not considered.

Details of the critical appraisal of the included studies and guidelines are provided in Appendix 8.
4.4 Diagnostic Accuracy

4.4.1 Results

Eleven studies\textsuperscript{16-24,61,62} and two companion reports\textsuperscript{1,25} were included that assessed diagnostic-accuracy outcomes. In the following discussion of results, the article reporting the specific data (either the original study or the companion report) is referenced. Details on the diagnostic accuracy of different POC cTn tests reported at admission (Table 19 and Table 20), three hours, six hours, and six to nine hours post-admission compared with a central laboratory (Table 21) are provided in Appendix 9. The final diagnosis of myocardial infarction (MI) was based on the available biochemical laboratory data, cardiac-imaging data, electrocardiographic results, and clinical findings.

Sensitivity

POC tests tended to provide lower sensitivity compared with central laboratory methods, ranging from a low estimate of 26.0% in one study,\textsuperscript{18} to a high of 87.7% in another.\textsuperscript{16} Despite variability in the sensitivity estimates, the trend for lower sensitivity compared with a central laboratory was maintained across different POC devices, as variability was observed in sensitivity estimates for the same device in different studies. The trend was also maintained with blood samples taken at three hours, six hours, and between six to nine hours after admission (Table 21), although limited data (i.e., one study each) were available for post-admission data.

Specificity

POC tests tended to provide higher specificity compared with central laboratory methods, ranging from a low estimate of 87.0% in one study to a high of 98.0% in another. This trend was maintained across different POC devices, and with blood samples taken at admission and three hours, six hours, and between six to nine hours after admission, although limited data (i.e., one study each) were available for post-admission data.

Positive predictive value

POC tests tended to provide higher positive predictive value (PPV) compared with central laboratory methods, ranging from a low estimate of 31.0% in one study (central laboratory 31.0%), to a high of 85.0% in another (central laboratory 60.0%). In one study\textsuperscript{19} the estimated PPV was higher with central laboratory methods compared with the POC test (66% for the POC test versus 82% for central laboratory). The trend for higher PPV with POC tests was maintained across different POC devices, and with blood samples taken at admission and three hours, six hours, and between six to nine hours after admission, although limited data (i.e., one study each) were available for post-admission data.

Negative predictive value

POC tests tended to provide lower negative predictive value compared with central laboratory methods, ranging from a low estimate of 90.0% in one study (central laboratory 95%), to a high estimate of 99.0% in another (central laboratory 100%). This trend was maintained across different POC devices, and with blood samples taken at admission and three hours, six hours, and between six to nine hours after admission, although limited data (i.e., one study each) were available for post-admission measurements.

Positive-likelihood ratio

POC tests tended to provide higher positive-likelihood ratios compared with central laboratory methods, although only one study reported a positive-likelihood ratio as calculated from central
laboratory data. Positive-likelihood ratios ranged from 4.83 to 16.2 at admission with POC tests and was reported as 3.63 (95% confidence interval [CI], 2.83 to 4.65) in the one study that reported central laboratory data. One study reported positive-likelihood ratios for POC tests at three hours and six hours post-admission, and reported values of 12.9 (95% CI, 9.4 to 17.6), and 11.8 (95% CI, 8.8 to 15.9), respectively (values for central laboratory not available).

Negative-likelihood ratio
POC tests tended to provide higher negative-likelihood ratios compared with central library methods, although only one study reported a negative-likelihood ratio as calculated from central laboratory data. Negative-likelihood ratios ranged from 0.26 to 0.37 at admission with POC tests and was reported as 0.12 (0.04 to 0.35) in the one study that reported central laboratory data. One study reported negative-likelihood ratios at three hours and six hours post-admission and reported values of 0.16 (95% CI, 0.09 to 0.28) and 0.14 (95% CI, 0.07 to 0.25), respectively (values for central laboratory not available).

4.4.2 Subgroup analyses for diagnostic accuracy
Settings
Except for one study that included patients at primary health care centres and one study in the pre-hospital or paramedic setting, all studies included patients who presented to the emergency department.

Subgroup analyses based on settings did not reveal any differences by setting, with diagnostic accuracy similar in both settings. Findings from the one study at primary health care centres and the study in the pre-hospital or paramedic setting agreed with those in emergency departments for the reported diagnostic-accuracy outcomes.

High-sensitivity assays
Three studies had central laboratory assays that were high-sensitivity assays. Subgroup analyses based on high-sensitivity assays did not reveal any systematic pattern for the reported outcomes. Similar results were reported in studies using high-sensitivity central laboratory assays compared with other assays.

Types of cardiac troponin test
Eight studies measured cTnI, and three studies measured cTnT. Subgroup analyses based on types of cTn found no difference in the outcomes with cTnI or cTnT.

Study funding status
Eight of the 11 included studies reported funding by industry (total or in part), or the author(s) received lecture fees from industry. One study was not funded by industry, and two studies did not report the funding status. Subgroup analyses based on study funding status did not reveal any systematic pattern for the reported outcomes.

Diagnostic accuracy results summary
In general, compared with central laboratory methods, POC tests tended to provide lower sensitivity, lower negative predictive value, higher specificity, and higher PPV. Both positive and negative-likelihood ratios tended to be higher with POC testing compared with a central laboratory, although only one study was available for the central laboratory comparison. This trend was maintained across different POC devices and with blood samples taken at admission.
and three hours, six hours, and between six and nine hours after admission. Subgroup analyses of studies based on the study setting, sensitivity levels of the central laboratory methods (high sensitivity or not), the type of cTn (I or T), and the funding status did not show any systematic patterns.

4.5 Clinical-Utility Results

4.5.1 Settings where a central laboratory is available

Thirty-two studies reported on clinical-utility outcomes, and 25 were in a setting with a central laboratory. Clinical utility outcomes of POC testing such as turnaround time (TAT), length of hospital stay (LOS), time to clinical decision (TCD), time to discharge (TTD), mortality rates, adverse event rates, staff satisfaction, and patient quality of life were reported in studies where central labs exist, such as emergency departments and coronary care units. Clinical-utility outcomes are provided in Appendix 10.

Turnaround time

Fifteen studies reported TAT with various definitions, with the majority defining TAT as time from blood draw to result. Thirteen studies measured TAT in the emergency department (ED) and two studies in cardiology services or coronary care units. Data suggest that POC cTn testing consistently reduced TAT compared with central library methods. Using a definition of turnaround time as from blood draw to result, the reported time saved in the ED ranges from 18 minutes to 93 minutes and, in cardiology services or coronary care units, two studies reported time saved as 56.5 minutes and 59 minutes. Based on other varied definitions of turnaround time, reported time saved ranged from a low of 54 minutes based on “door to result,” to a high of 147 minutes saved when defined as “time from presentation to anti-ischemic therapy.” Results are summarized in Table 22.

Length of stay

Eight studies reported LOS. Five studies determined LOS in the (length of ED stay), and three studies in cardiology services or coronary care units (length of hospital stay). Data suggest that POC cTn testing consistently reduced LOS compared with central library methods. In all but one study, length of ED stay was reduced, with a range between 0.2 hours to 2.7 hours. In the one study where length of ED stay was increased, it was lengthened by six minutes. LOS in hospital was reduced with POC cTn testing compared with central laboratory testing, with hospital stays being reduced between 2.2 hours and 15.7 hours in the studies (Table 23).

Time to clinical decision (time to disposition)

Two studies reported TCD (defined as the conclusion of disposition decision-making) in an ED setting. Data suggest that POC cTn testing reduced TCD compared with central library methods, with nine minutes saved in one study, and 26 minutes saved in the other (Table 24).

Time to discharge

Three studies reported TTD from an ED. Data suggest that POC cTn testing reduced TTD compared with central library methods, with time saved ranging from five minutes to 26 minutes (Table 25).
Mortality and major adverse events

Seven studies reported mortality or major adverse events such as non-fatal AMI, life-threatening arrhythmia, and emergency revascularization.39,41,43,44,46,47,50 Six studies39,41,44,46,47,63 reported mortality and major adverse events in the ED, and one study reported such events in a cardiology services or coronary care unit.50 Data from the majority of studies suggest the use of POC cTn did not statistically change mortality rates or severe adverse events compared with a central laboratory in up to a one-year follow-up. Similar adverse events occurred in both groups, except for one study that reported significantly fewer deaths with POC testing than with central laboratory methods (Table 26).46

Patients’ quality of life

One study reported patients’ quality of life in an ED setting, using the EuroQoL 5-Dimensions Questionnaire.39 During three months of follow-up, there was no statistically significant difference in quality of life for patients who had been tested for troponin by POC or central laboratory (Table 27).

Staff satisfaction

Four studies reported staff satisfaction in the ED; the majority of physicians and nurses agreed they were satisfied with POC testing, that cTn testing shortened TAT, was easy to use, and led to better management.27,33,37,38 In one study,37 participating staff rated the perceived accuracy of central laboratory testing as higher than POC testing (4.33 versus 3.68 on a five-point scale), although they reported higher overall satisfaction with POC testing compared with a central laboratory (4.00 versus 2.06 on a five-point scale) (Table 28).

4.6 Clinical-Utility Results

4.6.1 Settings where a central laboratory is not available

Thirty-two studies reported on clinical-utility outcomes, and seven included results from a setting with no central laboratory.48,52-65,61,62

Percentage of patients referred to emergency department

One study, from Sweden, reported the percentage of patients referred to an ED from three primary health care centres using POC cTnT, and four primary health care centres not using POC cTnT.61 Data suggest that primary health care centres using POC cTn tests reduced the number of patients referred to an ED by 18% compared with centres that did not use POC cTn tests (32 of 128 patients [25%] from primary health care centres with POC cTnT, and 29 of 68 patients [43%] from centres without POC cTnT).

Staff satisfaction

One study reported staff satisfaction with the use of POC testing in a remote setting, with 33 remote health centres from the Northern Territory in Australia participating.52 A questionnaire was implemented using an online survey provider, and results were analyzed descriptively. Questionnaire feedback showed the implementation of POC testing increased staff satisfaction with cTn testing. Ninety-five per cent of 39 respondents stated that POC testing was more convenient than transporting patients to central laboratory services. A separate survey of 100 health professionals in an unspecified setting found that 47% of staff strongly agreed that POC usage increased patient convenience, while 13% disagreed.53 A further survey from 406 health care units found the primary reason for staff using POC was shortening of TAT or lack of availability of clinical laboratory testing.54
In pre-hospital or ambulance settings
Limited evidence\(^{48,55}\) reported the use of POC cTn tests for the diagnosis and management of patients in pre-hospital or ambulance settings. In one study, a pre-hospital POC cTnT test was performed by paramedics in 928 patients with suspected AMI. The median time from symptom onset to blood sampling was 83 minutes (46 minutes to 167 minutes).\(^{48}\) In another study, 601 patients with chest pain were randomized to usual care or pre-hospital POC cTnI testing in ambulance.\(^{55}\) The time from first medical contact to discharge from ED or admission to hospital was shorter in patients in the POC testing group (median 8.8 hours [range 6.2 hours to 10.8 hours]) compared with usual care (median 9.1 hours [range 6.7 hours to 11.2 hours]; \(P = 0.05\)). There was no difference among the groups in repeat ED visits, hospitalizations, or death in the next 30 days.

4.6.2 Subgroup analyses for clinical-utility studies

Study design
Seven studies were RCTs,\(^{26,29-41,50,55}\) and 25 studies were observational. Subgroup analyses based on study design did not show a difference between data from RCTs and observational studies for any of the reported clinical-utility outcomes, acknowledging that, for most outcomes, few studies were available to assess meaningful differences.

Study setting
Settings were the ED in 21 studies,\(^{26-44,46,47}\) primary health care centres in one study,\(^{61}\) pre-hospital or ambulance in three studies,\(^{48,55,62}\) cardiac or coronary care units in four studies,\(^{45,49-51}\) remote centres in one study,\(^{52}\) and not specified in two surveys on staff satisfaction and patients’ quality of life.\(^{54,56}\) Subgroup analyses based on settings did not show a systematic difference between studies conducted in different settings, acknowledging that for most outcomes, few studies were available to assess meaningful differences.

High-sensitivity central laboratory method
One study used high-sensitivity central laboratory methods as a comparator.\(^{41}\) The results of this study for the reported clinical-utility outcomes were not meaningfully different from studies using other central laboratory assays.

Type of cardiac troponin
Twenty studies measured cTnI,\(^{26,28-33,35,37-40,43-46,49,55,56,64}\) 10 studies measured cTnT,\(^{27,34,36,41,47,48,50,51,61,62}\) one measured both cTnI and cTnT,\(^{54}\) and one did not specify the type of cTn.\(^{53}\) Subgroup analyses based on the type of cTn measured did not show a difference in the clinical-utility outcomes in studies that used cTnI or cTnT for the reported outcomes, acknowledging that, for most outcomes, few studies were available to assess meaningful differences.

Funding status
Fourteen of the included studies reported being funded by industry either totally or in part, or the author(s) received lecture fees from industry.\(^{26-29,35,36,43-47,49,55,62}\) Ten studies were not funded by industry.\(^{30,39-41,48,50-52,58,61}\) and eight studies did not report the funding.\(^{31-34,37,38,42,54}\) Subgroup analyses based on the funding status did not show a systematic difference between data from the studies funded by industry and the studies not funded by industry for the reported outcomes, acknowledging that, for most outcomes, few studies were available to assess meaningful differences.
4.7 Guidelines
The European Society of Cardiology guidelines (page 3,006) for the management of ACS in patients presenting without persistent ST segment elevation,\(^5\) recommend that “point-of-care tests for troponins should be implemented when a central laboratory cannot consistently provide test results within 60 min.”

The National Academy of Clinical Biochemistry (NACB) Laboratory Medicine Practice Guideline on POC testing\(^6\) states that:

- Institutions that cannot consistently deliver cardiac marker TATs of approximately 1 h should implement POCT devices. (Strength B, Level II)

- While it is recognized that qualitative systems do provide useful information, it is recommended that point-of-care systems provide quantitative results. (Strength C, Level II) (page 17)

Strength B: The NACB recommends adoption; there is at least fair evidence that it improves important health outcomes and concludes that benefits outweigh harms.

Strength C: The NACB recommends against adoption; there is evidence that it is ineffective or that it harms outweigh benefits.

Level II: Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence.
5. Clinical Discussion

5.1 Diagnostic Test Accuracy

This systematic review on the diagnostic accuracy of POC cTn tests in patients with symptoms suggestive of ACS shows that currently available POC tests have lower sensitivity and negative predictive value, and higher specificity and PPV than central laboratory methods. Both positive- and negative-likelihood ratios tended to be higher with POC testing compared with central laboratory testing, although only one study was available for the central laboratory comparison. This trend was maintained across different POC devices and with blood samples taken at admission, and at three hours, six hours, and between six and nine hours after admission.

Subgroup analyses of the results of diagnostic-accuracy studies based on the study setting, sensitivity levels of the central laboratory methods (high sensitivity or not), the types of cTn (I or T), and the funding status did not show any systematic patterns for any of the reported diagnostic outcomes.

A reason for the wide variability of the reported data on the diagnostic performance for the POC devices is unclear, although several factors likely contribute. It is possible that some of the variability can be attributed to different methodological aspects of POC assays performed from studies that used different generations of POC assays, using fresh blood or frozen plasma, different clinical staff or technicians, and different reference-standard tests. Patient selection, including the proportion of participants included with prior AMI, or the exclusion of participants with STEMI, may also be factors that could contribute to variability. Given the limited amount of reported information on these variables, we were unable to explore these issues systematically. The time of the patients’ presentation to the health care centre was variable across the studies included in this review and, likewise, also could have contributed to the observed variation in results. It is expected that test sensitivity would increase with later presentation time. In addition, the different troponin cut-offs used in different studies would affect the diagnostic test accuracy results, although we controlled for this possibility by including only studies that used the 99th percentile cut-off threshold. Due to the observed variability and the many factors that may have attributed to the heterogeneity in diagnostic-accuracy outcomes across studies, only some studies were used to develop the economic model. Specifically, studies with a high detection rate of AMI were excluded\(^{16,21}\) as the patient selection may have been biased, and studies that appeared to be an outlier or lacked sufficient details to determine the reason for the possibly skewed results were also excluded.\(^{18}\)

5.2 Clinical Utility in Settings With a Central Laboratory

The clinical utility of POC cTn testing in patients with symptoms suggestive of ACS was assessed within two settings for this review: settings where central laboratory tests are available (hospital EDs and other hospital units), and settings where central laboratory tests are not available (primary health care centres, remote stations, rural hospitals or clinics, and ambulance settings). In general, in settings where central laboratories are available, POC cTn testing tends to shorten TAT, LOS, and TTD compared with central laboratory settings. Given the studies that reported adverse event outcomes were not sufficiently powered to detect a difference in adverse events, including mortality, clinical significance of potential differences is likely a more relevant assessment than statistical significance. Overall, reported differences in mortality rates and severe adverse events were not statistically significant between POC testing and central laboratory testing in up to one year of follow-up, although observed numerical differences might be clinically significant. It could be argued that saving time in the ED and shortening TCD is an
important effect to balance the potential differences in adverse events. Patient quality of life was assessed in one study, and was found to be similar in those who were tested using POC and those who were tested using central laboratory testing.

In those studies that assessed staff satisfaction, the majority of physicians and nurses in settings with a central laboratory were satisfied with POC testing and agreed that POC cTn testing shortened TAT, was easy to use, and led to better patient management.

Our findings concur with observations from other systematic reviews on POC testing in suspected AMI in EDs\textsuperscript{65-67} that POC cTn assays are accurate and improve TAT and LOS, although there was no reported statistical change in clinical outcomes, such as mortality. Subgroup analyses of clinical-utility studies in our review based on study setting, the level of sensitivity of the central laboratory methods (high sensitivity or not), the types of cTn (I or T), and funding status did not show any systematic patterns.

The NACB\textsuperscript{60} and the European Society of Cardiology guidelines\textsuperscript{59} recommend that, based on sufficient and fair evidence, POC tests for cTn should be implemented when a central laboratory cannot consistently provide test results within 60 minutes. This recommendation was not adopted by the Centers for Medicare & Medicaid Services due to a recall of the POC cTn device.\textsuperscript{58}

### 5.3 Clinical Utility in Settings With No Central Laboratory

Although the evidence identified from primary studies on the clinical utility of POC cTn testing in settings without a central laboratory was limited, the data suggest that referrals to an ED can be reduced by use of POC cTn testing, and that use in ambulance settings may be beneficial. In one study, primary health care centres using POC cTn tests reduced by 18\% the number of patients referred to an ED compared with centres that did not use of POC cTn tests.\textsuperscript{51} This reduction of emergency referrals may come at the cost of an increased risk of missing patients with AMI, although no such data were available for this review.

In pre-hospital or ambulance settings, a limited quantity of evidence points to the potential of implementation of POC cTn tests for the diagnosis and management of patients with symptoms suggestive of ACS.\textsuperscript{46,62} In one study, quantitative POC cTn testing was shown to be feasible and reliable for patients transported by ambulance.\textsuperscript{48} Further, POC devices may shorten the time from first medical contact to clinical disposition.\textsuperscript{55} Additional equipment and training of staff are required for the implementation of POC testing in pre-hospital setting. The distance and time to a hospital may also be a consideration.

Other published information about the use of POC testing in rural areas indicates that POC troponin devices are being implemented to facilitate AMI diagnosis in areas with challenging geographic settings.\textsuperscript{69} An opinion paper suggested that implementation of POC cTn in rural hospitals in Australia reduced the 30-day readmission rate.\textsuperscript{70} In our review for remote health care centres where central labs were not available, the implementation of POC testing increased the volume of patients tested for cTn and increased staff satisfaction. In one study, 95\% of staff believed POC testing was more convenient than transporting patients to settings with a central laboratory.\textsuperscript{52,56} Therefore, use of POC troponin testing in rural Canadian settings may be a feasible option. The information on the use of POC testing in remote areas would be most valuable from a Canadian perspective, but the evidence is limited to one Australian study.\textsuperscript{52}
6. Economic Review

6.1 Economic Methods

6.1.1 Type of economic evaluation
A cost-utility analysis was conducted. A cost-utility analysis incorporates both mortality and quality-of-life impacts of disease and treatment. The primary outcome was a cost per QALY gained. A cost per QALY allows for comparison across a wide spectrum of interventions and populations with a standardized measure of benefit (i.e., QALY).

6.1.2 Target population
The target population for the economic evaluation is adult patients presenting with chest pain or other symptoms suggestive of ACS identified as having non-ST elevation from ECG testing. These include patients suspected of having NSTEMI or unstable angina (Figure 1).

Figure 1: Patient Population for the Economic Evaluation of Point-of-Care Troponin Testing

ACS = acute coronary syndrome; ECG = electrocardiogram; MI = myocardial infarction; NSTEMI = non-ST segment elevation myocardial infarction; STEMI = ST segment elevation myocardial infarction.

6.2 Strategies
a) Comparators: The comparators are dependent on the contexts reported in Table 2.
b) Intervention: POC cTn testing devices approved by Health Canada.
Table 2: Strategies for Context 1 and Context 2

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Context 1</th>
<th>Context 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central laboratory testing of cTn</td>
<td>E.g., emergency department settings of large, urban (academic or non-academic) hospitals</td>
<td>Standard care (no cTn testing available via a central laboratory)</td>
</tr>
<tr>
<td>Comparator</td>
<td>E.g., non-hospital settings, small or rural hospitals or remote settings without a central laboratory</td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>POC cTn testing</td>
<td>POC cTn testing</td>
</tr>
</tbody>
</table>

cTn = cardiac troponin; POC = point of care.

6.3 Perspective
The perspective of a publicly funded health care system was adopted. The costs in the analysis included test costs, emergency room costs, in-patient costs, and physician fees for services that are covered in provincial fee schedules. Indirect costs, such as productivity losses, out-of-pocket patient costs, and time costs were not included in context 1. These costs are not expected to vary significantly between treatment strategies, as both POC and central laboratory troponin are completed while the patient remains in the emergency room. However, in context 2, where the patient may be transferred to the hospital from either a rural emergency room or primary care practice, limited patient-borne costs were included as availability in reported literature allowed.

6.4 Time Horizon
A one-year time horizon was used in the model. Although best-practice guidelines suggest a lifetime horizon, it is unlikely that the decision to use a POC device or central laboratory for cTn testing would have an impact on a patient over a lifetime. As such, extrapolating the analysis over the course of a patient’s lifetime was deemed to increase the uncertainty in the model and could lead to inappropriate attribution of the strategies to the resulting clinical outcomes. Given that the longest time of reported follow-up in the clinical literature was one year, a one-year time horizon was deemed to be the most appropriate selection.

6.5 Effectiveness
The primary outcome was the cost per QALY gained. The measure of effectiveness was the QALY measured using the Health Utilities Index Mark 3. Different utility estimates were included for the general population, NSTEMIs and missed NSTEMIs (see section on utility values for more details). Secondary measures for context 1 include the LOS in the ED and the probability of readmission due to misdiagnosis of NSTEMI and were accounted for and expressed as costs. No secondary measures were available for context 2. All outcomes were considered for one year.

6.6 Decision Analytic Model
For each context, a decision-tree model was developed to simulate what could happen to patients from chest pain presentation at the ED or doctor’s office to one year after their episode. A basic graphical representation of the economic model is provided in Figure 2. For the detailed depictions of the decision-tree models in contexts 1 and 2, please see Appendix 11.
As shown in Figure 2, candidate patients can undergo one of two strategies in each context and the basic pathway and decisions for each patient are assumed to be the same following either strategy. Among those who test positive, there will be a proportion who have NSTEMI (true-positive) and a proportion who do not have NSTEMI (false-positive). Among those who test negative, there will be a proportion who have NSTEMI (false-negative) and those who do not have NSTEMI (true-negative). The proportion of patients in each of the potential diagnostic categories (true-positives, false-positives, true-negatives, false-negatives) was determined by both the underlying prevalence of NSTEMI and the diagnostic accuracy of the cTn test strategy being evaluated.

Four kinds of outcomes were incorporated into the model: true-positives, false-positives, true-negatives, and false-negatives. For all strategies, patients with a positive cTn test at presentation were assumed to be admitted to hospital (context 1) or transferred (context 2) and received treatment. This included both true- and false-positives. Patients with a negative cTn test at presentation could be either discharged and not receive treatment, or held in the ED and retested (serial test) after four to six hours. Patients with a positive serial cTn test were assumed to have been admitted to hospital and to have received treatment, whereas those with a negative serial cTn test were assumed to have been discharged and to have not received treatment. For true-negatives (patients without NSTEMI who test negative), no additional health or cost consequences are accrued. For false-negatives (patients with NSTEMI who test negative), patients are likely to continue to experience chest pain and re-present at the emergency room. The costs of a subsequent emergency room visit and hospitalization, as well as the decrement to their quality of life from continued chest pain, are incorporated.
All patients are followed for up to one year following their presentation of chest pain with an ongoing risk of death. The proportions of NSTEMI patients who died differed, depending on whether or not NSTEMI was diagnosed and treated. For example, patients who have a positive cTn test and are treated are assumed to have a lower mortality rate than NSTEMI patients who are not diagnosed and, thus, untreated. Patients who do not have NSTEMI have one-year mortality rates similar to the general population. Finally, patients who are alive after one year are assigned utility values for their health state; these values are dependent on whether they had NSTEMI or not.

6.7 Valuing Outcomes

A number of clinical variables were used to populate the model and estimate the number of expected QALYs for each cTn test strategy. Studies identified from the clinical systematic review were used as the primary source for the clinical inputs. Additionally, targeted literature searches were used to identify sources for parameters that were not available from the clinical systematic review. Details of the value and sources of the clinical variables used in the economic model are provided in Table 3 and Table 4.

6.7.1 Diagnostic accuracy

Given the observed heterogeneity in study quality and designs, POC cTn devices, and reported outcome measures, the clinical review team did not pool across studies. Diagnostic accuracy was drawn from three high-quality studies, that were selected based on quality, perceived validity, and reporting by the clinical review team. Three devices were assessed (i-STAT (Abbott), Stratus CS (Siemens), and Cardio3 Panel (Alere). The sensitivity and specificity for the POC cTn, by device, were provided by the clinical systematic review team. The diagnostic accuracy for central laboratory cTn testing was derived from a meta-analysis of conventional cTn tests (Lipinski et al., 2015). The diagnostic accuracy for the no–cTn testing strategy (context 2) was derived from a study reporting the diagnostic accuracy of primary care practitioners to identify heart-related chest pain at presentation. The values for sensitivity and specificity for each cTn testing strategy, stratified by context, are provided in Table 3.

### Table 3: Diagnostic Accuracy Inputs

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Sensitivity, Presentation (95% CI)</th>
<th>Specificity, Presentation (95% CI)</th>
<th>Sensitivity, Serial Test (4 to 6 hours) (95% CI)</th>
<th>Specificity, Serial Test (4 to 6 hours) (95% CI)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Context 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conventional cTn Central Laboratory</td>
<td>74.9 (72.8 to 76.9)</td>
<td>93.8 (93.2 to 94.3)</td>
<td>89.5 (86.7 to 91.9)</td>
<td>95.2 (94.4 to 95.9)</td>
<td>Lipinski (2015)</td>
</tr>
<tr>
<td>Desktop POC (Stratus CS), % (95% CI)</td>
<td>63.6 (53.9 to 72.6)</td>
<td>93.1 (90.2 to 95.4)</td>
<td>87.5a (77.9 to 93.3)</td>
<td>92.6a (90.2 to 94.4)</td>
<td>Amodio (2007)</td>
</tr>
<tr>
<td>Hand-held POC (Cardio3 Panel), % (95% CI)</td>
<td>66.7 (55.2 to 76.5)</td>
<td>95.9 (94.0 to 97.2)</td>
<td>87.5a (77.9 to 93.3)</td>
<td>92.6a (90.2 to 94.4)</td>
<td>Diercks (2012)</td>
</tr>
<tr>
<td>Desktop POC (i-STAT)</td>
<td>63.0</td>
<td>94.0</td>
<td>87.5a (77.9 to 93.3)</td>
<td>92.6a (90.2 to 94.4)</td>
<td>Lee-Lewandrowski (2011)</td>
</tr>
<tr>
<td>Context 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No cTn testing, % (95% CI)</td>
<td>93.3</td>
<td>22.7</td>
<td>93.3b</td>
<td>22.7a</td>
<td>Bruins Slot (2011)</td>
</tr>
</tbody>
</table>

CI = confidence interval; cTn = cardiac troponin; POC = point of care.

a Serial values assumed to be the same as Diercks (2012).
b Serial values assumed to be the same as presentation values.
6.7.2 Prevalence of non-ST segment elevation myocardial infarction
Based on a high-quality meta-analysis, the estimate of the underlying prevalence of NSTEMI among those who present with chest pain was 16.0% (95% CI, 9.0 to 24.0%). This was used as the base-case prevalence of NSTEMI in both context 1 and 2.

6.7.3 Mortality
The one-year mortality rate after NSTEMI was assumed to be 16.26% and was applied to patients with NSTEMI and who were assumed to receive treatment. This was a pooled estimate of one-year mortality among included studies in a previous meta-analysis conducted by CADTH (2013). The estimated relative risk of one-year mortality of patients with NSTEMI and who were discharged, relative to those who received treatment, was obtained from an RCT that compared central laboratory testing with a panel of POC troponin tests and followed the patients for three months to ascertain diagnostic accuracy and mortality (Goodacre et al., 2011). Thus, the ratio of one-year mortality of untreated MI (21%) to treated MI (11%) patients is equivalent to a relative risk. Lastly, for patients without NSTEMI, the annual mortality risk was based on unadjusted mortality data reported for Canada by Statistics Canada (2014).

6.7.4 Emergency department length of stay
Estimates of the ED LOS for patients that underwent POC cTn testing and central laboratory cTn testing were obtained from a study identified from the clinical systematic review. These estimates were applied to all patients in their respective testing strategies and expressed as costs.

6.7.5 Utility values
To calculate QALYs for each strategy, utility values were applied to patients who were alive one year after presenting to the ED. The general population utility value, based on data published by Mittmann (1999), was applied to patients who did not have NSTEMI (utility estimate = 0.93). For patients who had NSTEMI, a utility decrement was applied to general population utility values if the patient received treatment (admitted or transferred, utility decrement = 0.0627) or did not (discharged, utility decrement = 0.08). The decrement for those who were admitted was based on an RCT of 18,624 patients with AMI who received treatment and who had survived an MI after one year (Nikolic et al., 2013). The decrement for those who did not receive treatment was based on annual utility decrements for those with AMI in the community (Ward et al., 2007).

Table 4: Clinical Inputs for Contexts 1 and 2

<table>
<thead>
<tr>
<th>Source</th>
<th>Prevalence of NSTEMI, % (95% CI)</th>
<th>Probability of discharge if cTn test negative, %</th>
<th>ED LOS, mean hours</th>
<th>1-year mortality, NSTEMI, admitted, %</th>
<th>Relative risk of one-year mortality, NSTEMI, discharged</th>
<th>One-year mortality no NSTEMI, %</th>
<th>One-year utility decrement, NSTEMI, admitted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooled estimate, CADTH Optimal Use Report (2013)</td>
<td>16.0 (9.0 to 24.0)</td>
<td>12.0</td>
<td>4.52</td>
<td>16.26</td>
<td>1.91</td>
<td>0.489</td>
<td>0.0627</td>
</tr>
</tbody>
</table>
6.8 Cost Estimates and Resource Utilization

Various costs were used to populate the model and estimate the expected cost per cTn test strategy. Details of the value and sources of the included costing data for the testing strategies and resource utilization are provided in Table 4 and Table 5, respectively. Whenever possible, the most current cost estimates were used. All cost estimates were adjusted to 2014 Canadian dollars using the Bank of Canada’s Consumer Price Index inflation calculator.

6.8.1 Point-of-care cardiac troponin test and program

Manufacturers were contacted regarding the costs of POC cTn devices, the average lifetime of the device, and the cost of materials (e.g., testing strips). Specifically, the costs of the three POC cTn testing strategies (i.e., Stratus CS, Cardio3 Panel, i-STAT) were applied to the POC cost per test in the respective device-specific analyses. All remaining costs, including the cost for staffing the POC program and quality control, were obtained from laboratory experts in the provinces of Ontario and Alberta. It was assumed that the average annual number of POC cTn tests performed was 1,000 based on expert opinion and, based on this information, a cost of $23.21, $31.31, $26.20 per test was assigned to the Stratus CS, Cardio3 Panel, and i-STAT POC testing strategies, respectively.

6.8.2 Standard practice

In context 1, the cost of central laboratory cTn testing, including the capital costs of the equipment, costs of the reagents and materials, and staffing costs, as well as specimen-procurement costs, were obtained from laboratory experts in the provinces of Ontario and Alberta. A cost of $22 per test was assigned for the central laboratory cTn testing strategy. In context 2, it was assumed that no additional assay or device costs would apply in the no-cTn testing strategy.
Table 5: Costs of Cardiac Troponin Testing Strategies

<table>
<thead>
<tr>
<th>POCT cTn testing strategies</th>
<th>Device</th>
<th>Testing Materials (e.g., Strips), per Test</th>
<th>Average Lifetime of Device</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stratus CS (Siemens)</td>
<td>$35,000</td>
<td>$8.50</td>
<td>8.5 years</td>
<td>Siemens</td>
</tr>
<tr>
<td>Cardio3 Panel (Alere)</td>
<td>$5,000</td>
<td>$20</td>
<td>7 years</td>
<td>Alere</td>
</tr>
<tr>
<td>i-STAT (Abbott)</td>
<td>$8,000</td>
<td>$14</td>
<td>5 years</td>
<td>Expert input (Ontario laboratory estimate)</td>
</tr>
<tr>
<td>Cost of staff for POCT program (per annum)</td>
<td>$10,000</td>
<td></td>
<td></td>
<td>Expert Input (Ontario laboratory estimates)</td>
</tr>
<tr>
<td>Cost of calibration and quality control of POCT cTn testing (per annum)</td>
<td>$600</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of annual POCT tests</td>
<td>1,000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard care</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conventional cTn central laboratory testing, e.g., device, materials, staff (per test)</td>
<td>$10</td>
<td></td>
<td>Expert input (Alberta laboratory estimates)</td>
<td></td>
</tr>
<tr>
<td>Specimen procurement by central laboratory</td>
<td>$12</td>
<td></td>
<td>Expert input (Alberta laboratory estimates)</td>
<td></td>
</tr>
</tbody>
</table>

POC = point of care; cTn = cardiac troponin.

6.8.3 In-hospital costs

Table 5 outlines all of the costs related to resource utilization. The cost of true-positive NSTEMI and false-positive NSTEMI hospital admissions was obtained from estimates derived in previous work and adjusted to 2014 Canadian dollars. These previous estimates were derived using data from the Ontario Case Costing Initiative (OCCI) database, the Ontario Schedule of Benefits for Physician Services, and the literature.

In this previous work, a multi-step process was used to estimate the cost of a true-positive NSTEMI hospitalization. Briefly, the average hospital costs for the following case mix groups were obtained: MI with coronary artery bypass grafting (CABG), MI with percutaneous coronary intervention (PCI), and MI without CABG or PCI. Physician fees for treating each of the case mix groups were added to the respective hospital costs. The average cost of treating all MI was then derived by weighting each of the in-patient costs by assumed proportions of NSTEMI patients who would receive a CABG, PCI, or neither procedure.

The estimate for the daily hospital cost for false-positive hospitalization was based on the average in-patient cost and a 3.9-day stay in hospital for unstable angina, one initial consultation, and one subsequent visit by an internal medicine physician. The total cost of a false-positive hospitalization was then based on a two-day in-patient LOS, which was an assumption provided from expert opinion received in the previous work.

6.8.4 Emergency department costs

For patients who have a negative cTn test at presentation and are held and retested, additional ED costs were applied to account for a repeat ECG and an additional six hours of wait time in the ED. These estimates were adjusted to 2014 Canadian dollars and derived from previous
work\textsuperscript{5} that drew upon Ontario costing data from the published literature\textsuperscript{82,83} and the Ontario Schedule of Benefits.\textsuperscript{80} For patients who were initially discharged following a negative cTn test and readmitted, an additional cost — accounting for the cost of an ED visit and the cost of a true-positive NSTEMI hospitalization — was applied; this estimate was also drawn from previous work.\textsuperscript{5}

Table 6: Costs of Resource Utilization (in 2014 Canadian Dollars)

<table>
<thead>
<tr>
<th>Description</th>
<th>Estimate</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost of true-positive hospitalization for NSTEMI</td>
<td>$11,741</td>
<td>CADTH 2013 Optimal Use Report\textsuperscript{5}</td>
</tr>
<tr>
<td>Cost of false-positive hospitalizations</td>
<td>$2,203</td>
<td>CADTH 2013 Optimal Use Report\textsuperscript{5}</td>
</tr>
<tr>
<td>Cost of death</td>
<td>$14,368</td>
<td>Shrive (2005)\textsuperscript{84}</td>
</tr>
<tr>
<td>Cost of ground ambulance transfer with patient</td>
<td>$928</td>
<td>CADTH expert input</td>
</tr>
<tr>
<td>Cost of holding and retesting in ED (i.e., serial testing)</td>
<td>$149.20</td>
<td>CADTH 2013 Optimal Use Report\textsuperscript{5}</td>
</tr>
<tr>
<td>Cost of false-negatives (readmission for missed diagnosis of NSTEMI)</td>
<td>$11,894</td>
<td>Derived from costs estimates provided in the CADTH 2013 Optimal Use Report\textsuperscript{5}</td>
</tr>
</tbody>
</table>

ED = emergency department; NSTEMI = Non-ST elevation myocardial infarction.

6.9 Variability and Uncertainty

The variability in the model was assessed primarily through deterministic sensitivity analysis. Specifically, all model parameters were varied in one-way sensitivity analysis. Probabilities such as the prevalence of NSTEMI, discharge following a negative cTn test and one-year mortality, as well as the relative risk of mortality and utility values, were varied within their respective 95% CIs. Costs of testing strategies and resource utilization were varied within $\pm 50\%$ of the average calculated estimate. Key scenario analysis — excluding POC cTn device costs, varying the staff costs, varying the quality-control costs, and excluding the costs of POC testing all together — were also performed to inform contexts where the device might already have been purchased or might operate with variable workflow. A similar analysis was completed with the capital cost for central laboratory testing excluded, as the infrastructure to complete cTn tests may already be acquired. In addition, recognizing that high-sensitivity cTn assays are commonly used, a scenario analysis was completed using the diagnostic-accuracy assays and cost of high-sensitivity assays for the central laboratory (sensitivity: 88.4\%; specificity: 81.6\%; cost: $15 total per test [$3/test, $12/specimen]).\textsuperscript{5,71} Lastly, for context 2, a scenario analysis was completed that included the indirect costs. Specifically, the costs of lost productivity for NSTEMI patients transferred (170 hours)\textsuperscript{85} and for false-positives transferred (i.e., misdiagnosed as NSTEMI [6.5 hours]).\textsuperscript{86}

To assess the impact of uncertainty in the diagnostic accuracy of all POC devices and central laboratory testing, various scenario analyses were completed. Using a pooled receiver operator characteristic (ROC) curve using all studies identified, a range of sensitivity and specificity estimates were applied in the models (Appendix 12). Threshold analyses were completed to document the POC diagnostic accuracy when the costs were equal between central laboratory and POC, and when the effectiveness was equal between central laboratory and POC. The diagnostic accuracy of the central laboratory was similarly varied to establish the same thresholds.

6.10 Cost-Consequence Table

Based on the diagnostic accuracy and target population size, the number of people with each testing outcome was calculated. The total cost per first test was included. The costs associated with each test outcome were also included. In context 2, the costs of serial testing were also included. The same diagnostic accuracy was assumed for the serial test and the same cost as in context 1 was assumed for true positives.
7. Economic Results

7.1 Base-Case Results

The base-case results of the cost-utility analysis for context 1 are summarized in Table 7 and the total costs and QALYs of each strategy are plotted in Figure 3. The base-case analysis compared central laboratory cTn testing to each of the i-STAT, Stratus CS, and Cardio3 Panel POC cTn testing strategies. Central laboratory cTn testing was associated with an average total cost of $2,632 and 0.8953 QALYs per patient. The Stratus CS, Cardio3 Panel and i-STAT POC cTn testing strategies were found to cost less and result in fewer QALYs per patient compared with a central laboratory, resulting in an incremental cost-utility ratio of $62,322, $86,123, and $68,782 saved per QALY lost, respectively.

Table 7: Results of Base-Case Analysis for Context 1

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cost ($)</th>
<th>Incremental Cost Compared With a Central Laboratory ($)</th>
<th>Effectiveness (QALY)</th>
<th>Incremental Effectiveness Compared with a Central Laboratory (QALY)</th>
<th>Cost per QALY ($/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central laboratory</td>
<td>2,632</td>
<td>0.8953</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Status CS</td>
<td>2,518</td>
<td>–114</td>
<td>0.8935</td>
<td>–0.0018</td>
<td>62,322 for central laboratory</td>
</tr>
<tr>
<td>Cardio3 Panel</td>
<td>2,497</td>
<td>–135</td>
<td>0.8937</td>
<td>–0.0016</td>
<td>86,123 for central laboratory</td>
</tr>
<tr>
<td>i-STAT</td>
<td>2,503</td>
<td>–129</td>
<td>0.8934</td>
<td>–0.0019</td>
<td>68,782 for central laboratory</td>
</tr>
</tbody>
</table>

QALY = quality-adjusted life-year.

Figure 3: Base Case Cost-Effectiveness Analysis for Context 1

cTn = cardiac troponin; POC = point of care.
The base-case results of the cost-utility analysis for context 2 are presented in Table 8 and the total costs and QALYs of each strategy are plotted in Figure 4. Standard practice or no cTn testing was associated with an estimated total cost of $4,905 and 0.896 QALYs per patient. All three cTn POC devices were found to be less costly and less effective than no cTn testing.

Table 8: Results of Base-Case Analysis for Context 2

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cost ($)</th>
<th>Incremental Cost Compared With No cTn Testing ($)</th>
<th>Effectiveness (QALY)</th>
<th>Incremental Effectiveness Compared with No cTn Testing (QALY)</th>
<th>Cost per QALY ($/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cTn testing</td>
<td>4,905</td>
<td>0.8962</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Status CS</td>
<td>2,658</td>
<td>–2.247</td>
<td>0.8935</td>
<td>–0.00276</td>
<td>812,945 for no cTn testing</td>
</tr>
<tr>
<td>Cardio3 Panel</td>
<td>2,618</td>
<td>–2.287</td>
<td>0.8937</td>
<td>–0.00251</td>
<td>912,802 for no cTn testing</td>
</tr>
<tr>
<td>i-STAT</td>
<td>2,636</td>
<td>–2.269</td>
<td>0.8934</td>
<td>–0.00282</td>
<td>806,414 for no cTn testing</td>
</tr>
</tbody>
</table>

cTn = cardiac troponin; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Figure 4: Base Case Cost-Effectiveness Analysis, Context 2

cTn = cardiac troponin; POC = point of care.
7.2 Variability and Uncertainty

7.2.1 One-way sensitivity and scenario analyses

Overall, the model results were robust to variations in all parameters varied, with the exception of the utility value for those with NSTEMI assumed to receive treatment (i.e., admitted) in context 1. The results of this and other select one-way sensitivity and scenario analyses for context 1 and 2 are presented in Table 9 and Table 10, respectively.

Table 9: Results of Select One-Way Sensitivity and Scenario Analyses for Context 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value ($)</th>
<th>Stratus CS ICUR ($/QALY)</th>
<th>Cardio3 Panel ICUR ($/QALY)</th>
<th>i-STAT ICUR ($/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base-case results</td>
<td></td>
<td>62,322 for CL</td>
<td>86,123 for CL</td>
<td>68,782 for CL</td>
</tr>
<tr>
<td>One-Way Sensitivity Analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annual number of POC cTn tests</td>
<td>500</td>
<td>62,299 for CL</td>
<td>78,932 for CL</td>
<td>62,299 for CL</td>
</tr>
<tr>
<td></td>
<td>50,000</td>
<td>75,136 for CL</td>
<td>93,169 for CL</td>
<td>75,135 for CL</td>
</tr>
<tr>
<td>One-year utility NSTEMI, admitted</td>
<td>0.70</td>
<td>Dominates CL</td>
<td>Dominates CL</td>
<td>Dominates CL</td>
</tr>
<tr>
<td></td>
<td>0.75</td>
<td>219,425 for CL</td>
<td>303,224 for CL</td>
<td>242,170 for CL</td>
</tr>
<tr>
<td>POC quality-control cost</td>
<td>600</td>
<td>62,322 for CL</td>
<td>86,123 for CL</td>
<td>68,782 for CL</td>
</tr>
<tr>
<td></td>
<td>5,000</td>
<td>59,920 for CL</td>
<td>83,327 for CL</td>
<td>66,444 for CL</td>
</tr>
<tr>
<td>POC staff cost</td>
<td>10,000</td>
<td>62,322 for CL</td>
<td>86,123 for CL</td>
<td>68,782 for CL</td>
</tr>
<tr>
<td></td>
<td>75,000</td>
<td>26,837 for CL</td>
<td>44,815 for CL</td>
<td>34,240 for CL</td>
</tr>
<tr>
<td>No capital cost of the POC device</td>
<td></td>
<td>64,570 for CL</td>
<td>86,577 for CL</td>
<td>69,633 for CL</td>
</tr>
<tr>
<td>No capital cost for CL</td>
<td></td>
<td>56,863 for CL</td>
<td>79,768 for CL</td>
<td>63,468 for CL</td>
</tr>
<tr>
<td>No cost for cTn testing in POC or CL</td>
<td></td>
<td>62,986 for CL</td>
<td>92,042 for CL</td>
<td>71,014 for CL</td>
</tr>
<tr>
<td>Cost of false negatives (readmission for missed diagnosis of NSTEMI)</td>
<td>50% decrease ($5,947)</td>
<td>62,476 for CL</td>
<td>86,286 for CL</td>
<td>68,935 for CL</td>
</tr>
<tr>
<td></td>
<td>50% increase ($17,841)</td>
<td>62,168 for CL</td>
<td>85,960 for CL</td>
<td>68,629 for CL</td>
</tr>
<tr>
<td>hs cTn CL as comparator</td>
<td></td>
<td>215,010 for CL</td>
<td>248,509 for CL</td>
<td>216,749 for CL</td>
</tr>
</tbody>
</table>

CL = central laboratory; cTn = cardiac troponin; hs cTn = high-sensitivity cardiac troponin; ICUR = incremental cost-utility ratio; NSTEMI = non-ST elevation myocardial infarction; POC = point of care; QALY = quality-adjusted life-year.

Table 10: Results of Select One-Way Sensitivity and Scenario Analyses for Context 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value ($)</th>
<th>Stratus CS ICUR ($/QALY)</th>
<th>Cardio3 Panel ICUR ($/QALY)</th>
<th>i-STAT ICUR ($/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base-case results</td>
<td></td>
<td>812,945 for no cTn testing</td>
<td>912,802 for no cTn testing</td>
<td>806,414 for no cTn testing</td>
</tr>
<tr>
<td>One-Way Sensitivity Analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annual number of POC cTn tests</td>
<td>500</td>
<td>807,620 for no cTn testing</td>
<td>908,286 for no cTn testing</td>
<td>802,078 for no cTn testing</td>
</tr>
<tr>
<td></td>
<td>50,000</td>
<td>818,164 for no cTn testing</td>
<td>917,227 for no cTn testing</td>
<td>810,663 for no cTn testing</td>
</tr>
<tr>
<td>1-year utility NSTEMI, admitted</td>
<td>0.70</td>
<td>Dominates central laboratory</td>
<td>Dominates central laboratory</td>
<td>Dominates central laboratory</td>
</tr>
<tr>
<td></td>
<td>0.75</td>
<td>2,862,238 for no cTn testing</td>
<td>3,213,816 for no cTn testing</td>
<td>2,839,244 for no cTn testing</td>
</tr>
<tr>
<td>POC quality-control cost</td>
<td>600</td>
<td>812,945 for no cTn testing</td>
<td>912,802 for no cTn testing</td>
<td>806,414 for no cTn testing</td>
</tr>
<tr>
<td></td>
<td>5,000</td>
<td>811,353 for no cTn testing</td>
<td>911,045 for no cTn testing</td>
<td>804,850 for no cTn testing</td>
</tr>
</tbody>
</table>
The per-patient cost of the POC cTn testing strategies varied by make and portability of the device (i.e., desktop or hand-held) and were based on the annual number of POC cTn tests. In the base case, the annual number of POC cTn tests was assumed to be 1,000. Anticipating potential variability in annual POC cTn tests among clinical settings of different sizes, the annual number of POC cTn tests was varied within expert-reported ranges plausible for each context (between 500 and 50,000). Within these range, the model results were robust: the Stratus CS, i-STAT, and Cardio3 Panel POC cTn testing strategies remained less expensive but also effective compared with a central laboratory. Similarly, in context 2, all cTn testing strategies remained less expensive and less effective compared with the no-cTn testing strategy within the range of annual POC cTn tests.

There was considerable uncertainty surrounding the estimated one-year utility value for patients who had NSTEMI and were assumed to receive treatment; therefore, a threshold analysis was conducted for this parameter. The range used in the threshold analysis was within ± 50% of the base-case estimate (based on applying a utility decrement of 0.0627 to the general population utility value of 0.933 (Mittmann 1999; Nikolic 2013)). In contexts 1 and 2, at a utility value of 0.75 or above, POC remains less expensive and less effective than central laboratory or no cTn testing. However, at a utility value below approximately 0.70, POC is less expensive and more effective than central laboratory or no cTn testing (POC becomes the dominant strategy). It is unknown if these are within a plausible range for the NSTEMI utility estimates.

Lastly, for the base-case analysis it was assumed that the capital costs of the testing equipment (i.e., immunoanalyzer for the central laboratory and desktop or hand-held device for the POC strategy) would need to be accounted for in the cost per patient. However, given potential variability in the clinical settings’ existing resources and capacity, purchasing decisions may be made with or without consideration of the capital cost of the device. For example, within context 1, the incremental investment into a given testing strategy would vary for a central laboratory already equipped with the appropriate immunoanalyzer equipment for cTn testing compared with a central laboratory with neither an immunoanalyzer nor POC cTn testing device. Therefore, to inform purchasing decisions made independent of capital costs, a scenario analysis that excluded POC cTn device costs was performed. In both context 1 and 2, the results of the model from the base case remained unchanged. This is due to the cost of the POC devices being relatively small. The major cost driver is the diagnostic accuracy and the costs of hospitalizations due to either true-positives, false-positives, or false-negatives (which are subsequently admitted to hospital).
### 7.3 Scenario Analysis for Diagnostic Accuracy

To assess the uncertainty due to the diagnostic accuracy of POC, central laboratory, and no cTn testing, Figure 5 presents the results of a range of sensitivity and specificity variations. A pooled ROC was calculated using all available studies identified by the clinical review. There was significant heterogeneity across studies; however, a pooled ROC was required, despite the heterogeneity to relate sensitivity and specificity. The results are presented on a cost-effectiveness plane with the y-axis presenting incremental cost compared with a central laboratory, and the x-axis representing incremental effectiveness compared with a central laboratory. There are large variations in the incremental cost and effectiveness within plausible ranges of the diagnostic accuracy. For example, at a sensitivity of 0.2 and a specificity of 0.97, a desktop POC device is associated with a cost savings of approximately $1,100 and a lower effectiveness of 0.015 QALYs compared with a central laboratory (Figure 5, Panel A). However, at a sensitivity of 0.95 and a specificity of 0.81, a desktop POC device is more expensive (an increase of roughly $400) and more effective (0.001 QALYs) than central laboratory testing. POC and central laboratory testing are equal in cost at a sensitivity of 0.699 and specificity of 0.88 for a POC desktop device or a sensitivity of 0.685 and specificity of 0.955 for central laboratory testing (Figure 5, Panel A). POC and central laboratory testing are equally effective at a POC sensitivity of 0.85, specificity of 0.855, or a central laboratory sensitivity of 0.675 and specificity of 0.96. Panel B demonstrates similar findings for hand-held POC devices. Figure 6 (panels A and B) presents similar analyses for context 2.

**Figure 5: Scenario Analyses for Diagnostic Accuracy of POC Desktop (Panel A) and Hand-held (Panel B) Devices Compared with a Central Laboratory (Context 1)**

**Panel A: Desktop POC - Context 1**
Figure 6: Scenario Analyses for Diagnostic Accuracy of POC Desktop (Panel A) and Hand-held (Panel B) Devices Compared With No cTn Testing (Context 2)

Panel B: POC Handheld - Context 1

Panel A: Desktop POC - Context 2

CL = central laboratory; ICER = incremental cost-effectiveness ratio; POC = point of care; QALY = quality-adjusted life-year; sens = sensitivity; spec = specificity.
7.4 Cost and Consequence Tables

Given the multiple health-system outcomes likely to be affected by the POC cTn testing strategies, a cost-consequence analysis was performed for both context 1 (Table 11) and context 2 (Table 12). The cost-consequence analysis draws directly from the decision analysis model. The clinical and cost inputs are the same as outlined earlier. The number of first tests (excluding serial tests) was assumed based on the estimated utilization within a typical urban ED (context 1) and a typical primary care practice (context 2).

In context 1, all three POC strategies (Stratus CS, i-STAT and Cardio3 Panel) resulted in cost savings compared with a central laboratory. Of note, there are trade-offs with each POC device resulting in more false-positives and false-negatives than central laboratory testing. In context 2, all POC strategies resulted in cost savings compared with no cTn testing. However, each POC strategy results in more missed NSTEMI compared with no cTn testing.
Table 11: Cost and Consequence Analysis of POC cTn Testing Strategies Compared With a Central Laboratory in Context 1

<table>
<thead>
<tr>
<th># Events</th>
<th>Central Laboratory</th>
<th>Stratus CS</th>
<th>Cardio3 Panel</th>
<th>i-STAT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Consequence</td>
<td>Cost</td>
<td>Consequence</td>
<td>Cost</td>
</tr>
<tr>
<td>Annual number of first tests</td>
<td>50,000</td>
<td>$1,100,000</td>
<td>50,000</td>
<td>$1,160,500</td>
</tr>
<tr>
<td>True-positives (NSTEMI cases)</td>
<td>5,992</td>
<td>$70,356,147</td>
<td>5,088</td>
<td>$59,741,668</td>
</tr>
<tr>
<td>True-negatives (not NSTEMI cases)</td>
<td>39,396</td>
<td>–</td>
<td>3,9102</td>
<td>–</td>
</tr>
<tr>
<td>False-negatives (missed NSTEMI cases)</td>
<td>2,008</td>
<td>$21,362&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2,912</td>
<td>$123,148&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>False-positives (misdiagnosed as NSTEMI)</td>
<td>2,604</td>
<td>$5,735,388</td>
<td>2898</td>
<td>$14,801,001</td>
</tr>
<tr>
<td><strong>TOTAL cost ($)</strong></td>
<td><strong>77,212,897</strong></td>
<td><strong>$67,408,248</strong></td>
<td><strong>$68,124,521</strong></td>
<td><strong>$66,163,620</strong></td>
</tr>
<tr>
<td>Difference compared with a central laboratory ($)</td>
<td>–$9,804,649</td>
<td>–$9,088,375</td>
<td>–$11,049,276</td>
<td></td>
</tr>
</tbody>
</table>

cTn = cardiac troponin; NSTEMI = non-ST elevated myocardial infarction; POC = point of care; RCT = randomized controlled trial.

<sup>a</sup> After presentation cTn test.
<sup>b</sup> Based on RCT data, only 0.08% of those patients with a false-negative re-present at the hospital with an associated total hospitalization cost of $11,894.
<sup>c</sup> Based on RCT data, only 0.3% of those patients with a false-negative re-present at the hospital with an associated total hospitalization cost of $11,894.
Table 12: Cost and Consequence Analysis of POC cTn Testing Strategies Compared With No cTn Testing in Context 2

<table>
<thead>
<tr>
<th># Events</th>
<th>No cTn Testing</th>
<th>Stratus CS</th>
<th>Cardio3 Panel</th>
<th>i-STAT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Consequence</td>
<td>Cost</td>
<td>Consequence</td>
<td>Cost</td>
</tr>
<tr>
<td>Annual number of first tests</td>
<td>2,500</td>
<td>0</td>
<td>2,500</td>
<td>$58,025</td>
</tr>
<tr>
<td>True-positives (NSTEMI cases) †</td>
<td>373</td>
<td>$4,729,844</td>
<td>254</td>
<td>$3,223,167</td>
</tr>
<tr>
<td>True-negatives (not NSTEMI cases) †</td>
<td>477</td>
<td>--</td>
<td>1,955</td>
<td>--</td>
</tr>
<tr>
<td>False-negatives (missed NSTEMI cases) †</td>
<td>27</td>
<td>--</td>
<td>146</td>
<td>--</td>
</tr>
<tr>
<td>True-positives identified with serial test within 4 to 6 hours (NSTEMI cases)</td>
<td>25</td>
<td>$292,373</td>
<td>93</td>
<td>$1,090,678</td>
</tr>
<tr>
<td>False-positives (misdiagnosed as NSTEMI) †</td>
<td>1623</td>
<td>$5,080,474</td>
<td>145</td>
<td>$453,614</td>
</tr>
<tr>
<td>TOTAL Cost ($)</td>
<td>$10,102,692</td>
<td>$4,825,483</td>
<td>$4,406,564</td>
<td>$4,588,638</td>
</tr>
<tr>
<td>Difference compared with no cTn testing ($)</td>
<td>$–$5,277,209</td>
<td>$–$5,669,128</td>
<td></td>
<td>$–$5,514,054</td>
</tr>
</tbody>
</table>

cTn = cardiac troponin; NSTEMI = non-ST elevated myocardial infarction; POC = point of care.
† After presentation cTn test.
8. Economic Discussion

All three of the POC cTn testing strategies examined were less effective than central laboratory cTn testing for patients presenting to the ED with symptoms suggestive of ACS. The Stratus CS, Cardio3 Panel and i-STAT POC cTn testing strategies cost less per patient compared with a central laboratory. When POC cTn testing was compared with no cTn testing, the POC cTn testing strategy was less effective and cost less per test.

In both contexts, the model was sensitive to the variability in the utility value for those with NSTEMI who were admitted and assumed to receive treatment. When this parameter was lowered below the identified threshold values, all of the POC cTn testing strategies became the dominant strategy. However, it is unknown if the threshold values evaluated were within the plausible range for the NSTEMI utility estimates. The cost for each cTn testing strategy was based on information provided by the manufacturers, with the exception of the i-STAT POC cTn test and central laboratory costs, which were provided by experts in Alberta and Ontario. It was unclear whether these provided costs were the manufacturers' wholesale or list prices. Despite the uncertainty in the cTn testing costs, sensitivity analyses varying the cost per assay and removing the POC device costs found the model findings were not sensitive to variability in these costs.

The model results varied significantly with the estimates of diagnostic accuracy for both central laboratory and POC devices. Within plausible ranges of sensitivity and specificity, POC devices (both hand-held and desktop) varied from less costly to more costly and less effective to more effective. There is significant uncertainty associated with the point estimates of cost-effectiveness due to the uncertainty in the diagnostic accuracy.
9. Clinical And Economic Review Limitations

The results from our clinical review must be interpreted with caution, given the heterogeneity of the included studies and the small number of RCTs. The analysis of clinical utility is based on mostly observational studies, which have a level of evidence that is not as robust as RCT data. In many of the diagnostic-accuracy studies, it was unclear whether the POC cTn test results were interpreted without knowledge of the central laboratory test results, and vice versa. Furthermore, if final clinical adjudication was done with knowledge of the troponin results, this could introduce additional potential bias. The diagnostic-accuracy results may have been affected by the prior MI rate among included participants, the use of the manufacturer’s 99th percentile (as opposed to the 99th percentile at a 10% coefficient of variation), the exclusion of patients with STEMI, and time to presentation to the ED. In addition, there were some inconsistencies between studies and the reported 99th percentile for the same device.

Many studies on clinical utility did not have sufficient power to detect a clinically important effect for the primary outcomes. The mortality and adverse events outcomes analyzed are reflective of the short-term follow-up times that have been reported to date. The included studies were conducted in different settings, using different POC tests and different reference-standard tests, leading to a large variability in findings. Further, the majority of included studies include data collected in EDs or other settings with access to central laboratory testing, but include limited available data from settings without access to a central laboratory. More data on the utility of POC cTn testing in rural health care centres or remote settings would have been informative. For this HTA, the data analyzed on the clinical utility of POC testing is not from Canadian centres and, as such, might limit generalizability to the Canadian setting. A pooled estimate of the clinical outcomes is not provided, since a meta-analysis was not possible due to clinical heterogeneity among trials, such as differences in definitions of outcomes and inconsistencies in reporting.

There are significant limitations to the economic evaluation. The limited availability of accurate cost data influenced the costs that were included in the model. The exact cost per POC test, the cost of central laboratory testing and the cost of missed diagnoses were imprecise. However, the model was robust to multiple variations in these estimates. The time horizon was limited to one year. However, given that the testing with POC or a central laboratory is unlikely to affect the long-term survival of patients, this is a realistic assumption. The largest limitations are with the observed changes in cost-effectiveness, with plausible changes in the utility estimate for the NSTEMI patients, and the diagnostic accuracy of the both POC and central laboratory testing. More robust estimates for these variables would allow for more certainty in the cost-effectiveness of all strategies.

The indirect costs (patient-borne costs) that were included were limited. In the literature, we were able to identify only the costs of lost productivity. The lack of published estimates limited the findings, particularly in context 2 where the costs of travel and accommodation for the family may be significant.
10. Conclusions

cTn testing has an important role in the diagnostic workup of patients presenting to EDs with acute chest pain and non-diagnostic ECG. Our findings concur with observations from other systematic reviews that a preferred POC assay for the diagnosis of AMI does not yet exist and, despite improvement in TAT and LOS, there is no strong evidence of improvement in clinical outcomes compared with cTn testing by a central laboratory. In the absence of a central laboratory, POC cTn testing may be of benefit.

In rural health care centres or remote settings where a central laboratory is not available, POC cTn testing increased staff satisfaction and may reduce the transfer rate of patients to emergency rooms. In rural centres or remote settings, the use of POC troponin testing may lead to improved patient care, as the assessment of the patient along with cTn results may prevent unnecessary transfer to hospital, thereby allowing patients to remain in their community for follow-up and care. This may result in other benefits, such as reduced out-of-pocket costs and familial disruption and ensuring the transfer of only those patients who require it.

The results from our clinical review must be interpreted with caution, given the limited quality of the included studies, and because the outcomes analyzed are reflective of short-term follow-up times.

Generally, POC cTn testing strategies were found to be less effective and less expensive than standard of care, regardless of context. However, there are plausible variations in diagnostic accuracy that change the cost-effectiveness from cost-saving to cost-incurring. Generally, the weak evidence base for effectiveness and costs limited the scope of this economic evaluation.

Overall, given the limitations with the data and the inconsistency in diagnostic test accuracy, the usefulness of POC in settings with access to central laboratories may be limited. However, in settings with no access to a central laboratory, such as in rural health care centres or remote settings, POC troponin testing may be useful, as it could help reduce unnecessary transfers to larger centres.
References


## Appendix 1: Point-of-Care Troponin Devices

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Device Name</th>
<th>99th Percentile, mcg/L (% CV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott</td>
<td>i-STAT (cTnI)</td>
<td>80 (16.5)</td>
</tr>
<tr>
<td>Alere</td>
<td>Cardio3 (cTnI)</td>
<td>Cardio3: 0.022 (17)</td>
</tr>
<tr>
<td></td>
<td>Cardio2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Triage Troponin I</td>
<td>To be used with Triage MeterPro testing platform</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LifeSign/</td>
<td>LifeSign MI Troponin I</td>
<td>NR</td>
</tr>
<tr>
<td>Princeton BioMedtech Corp.</td>
<td>LifeSign MI Myoglobin/Troponin I</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LifeSign MI CK-MB/Myoglobin/Troponin I</td>
<td></td>
</tr>
<tr>
<td>Radiometer</td>
<td>AQT90 Flex</td>
<td>cTnI: 0.023 (12.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cTnT: 0.017 (15.2)</td>
</tr>
<tr>
<td>Response Biomedical</td>
<td>RAMP</td>
<td>0.0100 (20)</td>
</tr>
<tr>
<td>Roche/Cobas</td>
<td>Cobas h 232 (cTnT)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>CARDIAC Trop T Sensitive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cardiac Reader</td>
<td></td>
</tr>
<tr>
<td>Siemens</td>
<td>Stratus CS (cTnI)</td>
<td>0.070 (10)</td>
</tr>
<tr>
<td>ZBx Corporation/Innova</td>
<td>ZAP Troponin I</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>ZAP Troponin I/Myoglobin</td>
<td></td>
</tr>
</tbody>
</table>

cTnI = cardiac troponin I; CTnT = cardiac troponin T; CV = coefficient of variation; NR = not reported; POC = point-of-care.
# Appendix 2: Literature Search Strategy

## Overview

<table>
<thead>
<tr>
<th>Interface:</th>
<th>Ovid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Databases:</td>
<td>Embase 1974 to 2015 (with daily update)</td>
</tr>
<tr>
<td></td>
<td>MEDLINE(R) In-Process &amp; Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present</td>
</tr>
<tr>
<td>Note:</td>
<td>Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.</td>
</tr>
<tr>
<td>Date of search:</td>
<td>January 14, 2015</td>
</tr>
<tr>
<td>Alerts:</td>
<td>Monthly search updates began January 14, 2015 and ran until the final draft was completed (February 12, 2016)</td>
</tr>
<tr>
<td>Study types:</td>
<td>No filters were applied to limit the retrieval by study type</td>
</tr>
<tr>
<td></td>
<td>Conference abstracts were removed</td>
</tr>
<tr>
<td>Limits:</td>
<td>Humans</td>
</tr>
<tr>
<td></td>
<td>No date limits were applied</td>
</tr>
</tbody>
</table>

## Syntax Guide

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>/</td>
<td>At the end of a phrase, searches the phrase as a subject heading</td>
</tr>
<tr>
<td>MeSH</td>
<td>Medical Subject Heading</td>
</tr>
<tr>
<td>exp</td>
<td>Explode a subject heading</td>
</tr>
<tr>
<td>*</td>
<td>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</td>
</tr>
<tr>
<td>adj</td>
<td>Requires words are adjacent to each other (in any order)</td>
</tr>
<tr>
<td>adj#</td>
<td>Adjacency within # number of words (in any order)</td>
</tr>
<tr>
<td>.ti</td>
<td>Title</td>
</tr>
<tr>
<td>.ab</td>
<td>Abstract</td>
</tr>
<tr>
<td>.pt</td>
<td>Publication type</td>
</tr>
<tr>
<td>.po</td>
<td>Population group [PsycInfo only]</td>
</tr>
<tr>
<td>.dm</td>
<td>Device manufacturer (in Embase)</td>
</tr>
<tr>
<td>.dv</td>
<td>Device trade name (in Embase)</td>
</tr>
<tr>
<td>use pmez</td>
<td>Limit search line to MEDLINE database only</td>
</tr>
<tr>
<td>use oemezd</td>
<td>Limit search line to Embase database only</td>
</tr>
</tbody>
</table>

## Multi-database Strategy

<table>
<thead>
<tr>
<th>#</th>
<th>Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>exp Troponin/</td>
</tr>
<tr>
<td>2</td>
<td>(troponin* or cTn* or TnI* or TnT*).ti,ab.</td>
</tr>
<tr>
<td>3</td>
<td>or/1-2</td>
</tr>
<tr>
<td>4</td>
<td>Point-of-Care Systems/</td>
</tr>
<tr>
<td>5</td>
<td>(&quot;point of care&quot; or POC or POCT or near patient or bedside* or bed-side* or portable or hand-held or handheld or ambulatory or rapid screen* OR rapid diagnos* or test kit* or transportable).ti,ab.</td>
</tr>
<tr>
<td>6</td>
<td>(test* or assay) adj10 (rapid* or quick or remot* or immediate* or mobile)).ti,ab.</td>
</tr>
<tr>
<td>7</td>
<td>or/4-6</td>
</tr>
<tr>
<td>8</td>
<td>3 and 7</td>
</tr>
<tr>
<td>9</td>
<td>(&quot;i-STAT&quot; or iSTAT or triage cardiac or cardio2 or cardio3 or Alfa Scientific or Instant View or (Vidas adj5 ultra) or miniVidas or LifeSign or Meritas or PathFast or Cardiac STATus or AQT90 or AQT90flex or (Response and RAMP) or Cobas h232 or &quot;Cobas h 232&quot; or Cardiac Reader or &quot;Stratus CS&quot; or (ZAP and troponin) or GEM Immuno).ti,ab.</td>
</tr>
<tr>
<td>10</td>
<td>(triage and Alere).ti,ab.</td>
</tr>
<tr>
<td>11</td>
<td>(bioMerieux and Vidas).ti,ab.</td>
</tr>
<tr>
<td>12</td>
<td>(Roche and (&quot;Trop T&quot; or &quot;Troponin T&quot; or TropT) and cardiac).ti,ab.</td>
</tr>
<tr>
<td>13</td>
<td>or/9-12</td>
</tr>
<tr>
<td>#</td>
<td>Strategy</td>
</tr>
<tr>
<td>-----</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>14</td>
<td>(3 or 7) and 13</td>
</tr>
<tr>
<td>15</td>
<td>8 or 14</td>
</tr>
<tr>
<td>16</td>
<td>15 use pmez</td>
</tr>
<tr>
<td>17</td>
<td>exp Troponin/</td>
</tr>
<tr>
<td>18</td>
<td>(troponin* or cTn* or TnI* or TnT*).ti,ab,dv,dm.</td>
</tr>
<tr>
<td>19</td>
<td>or/17-18</td>
</tr>
<tr>
<td>20</td>
<td>Point of care testing/</td>
</tr>
<tr>
<td>21</td>
<td>(&quot;point of care* or POC or POCT or near patient or bedside* or bed-side* or portable or hand-held or handheld or ambulatory or rapid screen* OR rapid diagnos* or test kit* or transportable).ti,ab.</td>
</tr>
<tr>
<td>22</td>
<td>((test* or assay) adj10 (rapid* or quick or remot* or immediate* or mobile)).ti,ab.</td>
</tr>
<tr>
<td>23</td>
<td>or/20-22</td>
</tr>
<tr>
<td>24</td>
<td>19 and 23</td>
</tr>
<tr>
<td>25</td>
<td>(&quot;i-STAT&quot; or iSTAT or triage cardiac or cardio2 or cardio3 or Alfa Scientific or Instant View or (Vidas adj5 ultra) or miniVidas or LifeSign or Meritas or PathFast or Cardiac STATus or AQT90 or AQT90flex or (Response and RAMP) or Cobas h232 or &quot;Cobas h232&quot; or Cardiac Reader or &quot;Stratus CS&quot; or (ZAP and troponin) or GEM Immuno).ti,ab,dv,dm.</td>
</tr>
<tr>
<td>26</td>
<td>(triage and Alere).ti,ab,dv,dm.</td>
</tr>
<tr>
<td>27</td>
<td>(bioMerieux and Vidas).ti,ab,dv,dm.</td>
</tr>
<tr>
<td>28</td>
<td>(Roche and (&quot;Trop T&quot; or &quot;Troponin T&quot; or TropT) and cardiac).ti,ab,dv,dm.</td>
</tr>
<tr>
<td>29</td>
<td>or/25-28</td>
</tr>
<tr>
<td>30</td>
<td>(19 or 23) and 29</td>
</tr>
<tr>
<td>31</td>
<td>24 or 30</td>
</tr>
<tr>
<td>32</td>
<td>31 use oemezd</td>
</tr>
<tr>
<td>33</td>
<td>16 or 32</td>
</tr>
<tr>
<td>34</td>
<td>exp animals/</td>
</tr>
<tr>
<td>35</td>
<td>exp animal experimentation/ or exp animal experiment/</td>
</tr>
<tr>
<td>36</td>
<td>exp models animal/</td>
</tr>
<tr>
<td>37</td>
<td>nonhuman/</td>
</tr>
<tr>
<td>38</td>
<td>exp vertebrate/ or exp vertebrates/</td>
</tr>
<tr>
<td>39</td>
<td>animal.po.</td>
</tr>
<tr>
<td>40</td>
<td>or/34-39</td>
</tr>
<tr>
<td>41</td>
<td>exp humans/</td>
</tr>
<tr>
<td>42</td>
<td>exp human experimentation/ or exp human experiment/</td>
</tr>
<tr>
<td>43</td>
<td>human.po.</td>
</tr>
<tr>
<td>44</td>
<td>or/41-43</td>
</tr>
<tr>
<td>45</td>
<td>40 not 44</td>
</tr>
<tr>
<td>46</td>
<td>33 not 45</td>
</tr>
<tr>
<td>47</td>
<td>conference abstract.pt.</td>
</tr>
<tr>
<td>48</td>
<td>46 not 47</td>
</tr>
<tr>
<td>49</td>
<td>remove duplicates from 48</td>
</tr>
</tbody>
</table>
Other Databases

<table>
<thead>
<tr>
<th>Database</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>PubMed</td>
<td>Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.</td>
</tr>
<tr>
<td>Cochrane Library</td>
<td>Same MeSH, keywords, and date limits used as per MEDLINE search, excluding study types and Human restrictions. Syntax adjusted for Cochrane Library databases.</td>
</tr>
</tbody>
</table>

Grey Literature

- Dates for Search: January 2015
- Keywords: Included terms for point of care (POC) and troponin
- Limits: No date limits

Relevant websites from the following sections of the CADTH grey literature checklist, “Grey matters: a practical tool for searching health-related grey literature” (http://www.cadth.ca/resources/grey-matters), were searched:

- Health Technology Assessment Agencies
- Clinical Practice Guidelines
- Health Economics
- Advisories & Warnings
- Drug and Device Regulatory Approvals
- Databases (free) Internet Search.
Appendix 3: Flow Chart of Included Studies

1,434 citations identified from electronic literature search and screened

1,112 citations excluded

322 potentially relevant articles retrieved for scrutiny (full text, if available)

328 potentially relevant reports

6 potentially relevant reports retrieved from other sources (grey literature, supplemental search, alerts)

280 reports excluded:
- inappropriate population (7)
- inappropriate intervention (82)
- inappropriate comparator (20)
- inappropriate outcomes (35)
- inappropriate study design (15)
- review (72)
- other (e.g., abstract, duplicate, letter) (49)

41 studies plus 5 companion reports and 2 evidence-based guidelines
Appendix 4: List of Included Diagnostic Accuracy and Clinical-Utility Studies


Lee-Lewandrowski E, Benzer T, Corboy D, Lewandrowski K. Cardiac marker testing as part of an emergency department point-of-care satellite laboratory in a large academic medical center: practical issues concerning implementation. Point Care. 2002 Sep;1(3):145-54.


**Included Guidelines**


Appendix 5: List of Excluded Studies

Inappropriate Population


Inappropriate Intervention


Stratface AL, Myers JH, Kirchick HJ, Blick KE. A rapid point-of-care cardiac marker testing strategy facilitates the rapid diagnosis and management of chest pain patients in the emergency department. Am J Clin Pathol. 2008 May;129(5):788-95.


Inappropriate Comparator


Inappropriate Outcomes


Collinson P, Gaze D, Goodacre S. Comparison of contemporary troponin assays with the novel biomarkers, heart fatty acid binding protein and copeptin, for the early confirmation or exclusion of myocardial infarction in patients presenting to the emergency department with chest pain. Heart.2014 Jan;100(2):140-5.


Makam AN, Nguyen OK. Use of cardiac biomarker testing in the emergency department. JAMA Intern Med.2015 Jan 1;175(1):67-75.


**Inappropriate Study Design**


**Review**


Other (E.g., Abstract, Letter, Duplicate)


Buescher JJ, Kane KY. Can a bedside blood test predict death or myocardial infarction (MI) in patients with chest pain? J Fam Pract. 2001 Sep;50(9):800.


Juárez Herrera U, Ojeda LA, Rosas Peralta M, Luna Guerra J, Lopez Rodriguez MC, Chuquiure Valenzuela E, et al. [The utility of rapid qualitative determination of troponin T, the MB fraction of


Liu YC, Chen CH, Ding PY. Usefulness of a rapid cardiac troponin I test kit in patients with non-diagnostic chest pain or elevated CK enzyme in a Coronary Care Unit. Int J Cardiol.2000 Jan 15;72(2):193-4.


## Table 14: Study Characteristics

<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Country of Origin</th>
<th>Study Design</th>
<th>Funding Source</th>
<th>Study Setting</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>AMI Definition</th>
<th>POC Device/Manufacturer</th>
<th>Test Protocol</th>
<th>Central Laboratory Instrument/Manufacturer</th>
<th>Test Protocol</th>
<th>Health Personnel Conducting POC Test</th>
<th>Clinical Adjudication for Final MI Diagnosis (Diagnostic-Accuracy Studies Only)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnostic-Accuracy Studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amodio, 2007</td>
<td>Italy</td>
<td>Prospective observational study</td>
<td>Research group plus industry funding Some authors had received funding from industry</td>
<td>Hospital ED 29 months (Nov. 2007 to Apr. 2010)</td>
<td>Symptoms suggestive of cardiac ischemia (acute chest, epigastric, neck, jaw, or arm pain, or discomfort or pressure without an apparent non-cardiac source)</td>
<td>&lt; 18 years of age, not able to provide consent, not willing to participate, not available for follow-up</td>
<td>Universal definition: rise and/or fall of cTnI with at least one value about the 99th percentile, with symptoms of ischemia</td>
<td>Cardiac3/Alere cTnI At presentation (0 h), and 2 h</td>
<td>NR</td>
<td>Architect Troponin I/Abbott cTnI At presentation (0 h) and at least 6 h later. Additional sample taken at 2 h post-presentation for study laboratory cTnI measurement, at 0 h and 2 h for freezing for later analysis using other cTnI assays</td>
<td>Diagnoses on admission and at follow-up were determined independently by a cardiologist and a cardiology research clinician who were blinded to the results of the test assays. A second cardiologist was involved in cases of discrepancy.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Di Serio, 2005</td>
<td>Italy</td>
<td>Prospective observational study</td>
<td>Funding NR Conflicts of interest NR</td>
<td>Hospital ED Duration NR</td>
<td>Patients presenting to ED with chest pain</td>
<td>STEMI</td>
<td>ESC/ACC criteria</td>
<td>Status CS/ Dade Behring cTnI On admission, 6 h, 12 h, 24 h</td>
<td>ED/ cardiology department staff</td>
<td>Dimension RxL/ Dade Behring cTnI On admission, 6 h, 12 h, 24 h</td>
<td>Final diagnosis of AMI in the ICU was made according to ESC/ACC diagnostic criteria by ICU cardiologists.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Di Serio, 2007</td>
<td>Italy</td>
<td>Prospective observational with retrospective data analysis</td>
<td>Funding NR Conflicts of interest NR</td>
<td>Hospital ED 7 months (Feb. to Sept. 2005)</td>
<td>Patients presenting to ED with chest pain and suspected clinical angina or AMI</td>
<td>STEMI or left bundle-brunch block of recent onset</td>
<td>ESC/ACC diagnostic criteria</td>
<td>Status CS/ Dade Behring cTnI Within 15 min of admission, then patients with cTnI &gt; 0.07 mcg/L followed up every 6 h; and patients with cTnI ≤ 0.07 mcg/L followed up every 3 h</td>
<td>NR</td>
<td>Dimension RxL/ Dade Behring cTnI Within 15 min of admission, then patients with cTnI &gt; 0.07 mcg/L followed up every 6 h; patients with cTnI ≤ 0.07 mcg/L followed up every 3 h</td>
<td>Final diagnosis of AMI was assessed according to ESC/ACC diagnostic criteria; cardiac marker follow-up after hospital admission was performed in a CL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First Author, Year of Publication</td>
<td>Country of Origin</td>
<td>Study Design</td>
<td>Funding Source</td>
<td>Conflicts of interest</td>
<td>Study Setting/Study Duration</td>
<td>Inclusion Criteria</td>
<td>Exclusion Criteria</td>
<td>AML Definition</td>
<td>POC Device/Manufacturer</td>
<td>Test</td>
<td>Test Protocol</td>
<td>Central Laboratory Instrument/Manufacturer</td>
<td>Test</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>------------------</td>
<td>--------------</td>
<td>----------------</td>
<td>----------------------</td>
<td>-----------------------------</td>
<td>-------------------</td>
<td>------------------</td>
<td>---------------</td>
<td>------------------------</td>
<td>------</td>
<td>----------------</td>
<td>---------------------------------------------</td>
<td>-----</td>
</tr>
<tr>
<td>Diercks, 2012**</td>
<td>US</td>
<td>Secondary analysis of a multi-centre blinded observational study</td>
<td>Industry funding</td>
<td>Conflicts of interest NR</td>
<td>18 hospital EDs 13 months (May 2006 to Jun. 2007)</td>
<td>Adults &gt; 18 years, presenting to the ED with chest pain or ischemic symptoms that had been occurring for at least 30 min but not more than 8 h before blood sampling</td>
<td>NR</td>
<td>Standard ACC/AHA definition</td>
<td>Triage Cardio 3/ Biosite cTnI</td>
<td>At presentation, 90 min, 3 h, and 6 h</td>
<td>NR</td>
<td>DxI AccuTnl/Beckman Coulter cTnI</td>
<td>At presentation, 90 min, 3 h, and 6 h</td>
</tr>
<tr>
<td>Hjortshoj, 2011**</td>
<td>Denmark</td>
<td>Retrospective, observational study</td>
<td>Assays provided by industry</td>
<td>Conflicts of interest NR</td>
<td>Hospital ED and CCUs 20 months (Feb. 2003 to Oct. 2004)</td>
<td>Chest pain and suspected ACS</td>
<td>Documented MI within the week before admission, or admitted with STEMI</td>
<td>New universal definition; detection of rise and/or fall of cTnl &gt; 0.03 mcg/L together with signs indicative of ischemia (clinical symptoms, ECG)</td>
<td>AQT90 FLEX/ Radiometer cTnl</td>
<td>At arrival, 6 h to 9 h, and 12 h to 24 h; samples were taken at these points, then frozen for later analysis</td>
<td>Trained laboratory staff</td>
<td>Access AccuTnl/Beckman Coulter AxSYM ADV assay/ Abbott At arrival, 6 h to 9 h, and 12 h to 24 h; samples were taken at these points, then frozen for later analysis</td>
<td>Patients were diagnosed with AMI according to the new universal definition of AMI.</td>
</tr>
<tr>
<td>Ivandic, 2014**</td>
<td>Germany</td>
<td>Prospective, observational study</td>
<td>Funding from industry</td>
<td>2 authors employed by a group that consulted for industry</td>
<td>Hospital ED 16 months (Mar. 2009 to Jun. 2010)</td>
<td>New-onset chest pain and NSTEMI</td>
<td>Patients with chest pain of non-cardiac origin, or patients with STEMI</td>
<td>Chest pain with cTnl ≥ 30 nm/L in at least 1 sample during the first 6 h after admission</td>
<td>AQT90 FLEX/ Radiometer GmbH cTnl</td>
<td>At admission, 3 h and 6 h</td>
<td>NR</td>
<td>Elecsys 2010 Cobas e 411/ Roche cTnl</td>
<td>At admission, 3 h and 6 h</td>
</tr>
<tr>
<td>Lee-Lewandrowski, 2011**</td>
<td>US</td>
<td>Prospective, observational study</td>
<td>Partially funded by industry</td>
<td>2 authors had received funding from industry</td>
<td>Hospital ED 18 days</td>
<td>Symptoms of ACS</td>
<td>NR</td>
<td>Universal criteria</td>
<td>i-STAT/Abbott and Triage Cardiac Reader/Inverness Biosite cTnl Protocol NR</td>
<td>1 or 2 experienced clinicians using all available medical records per ACC/AHA criteria using local biomarker results. Reviewers were blinded to the POC cTnl findings.</td>
<td>Medical technologists</td>
<td>Elecsys E170/Roche Protocol NR</td>
<td>Using the available laboratory data, ECG results and clinical findings, ED physicians (or in-patient, hospital-based physicians) determined the final diagnosis</td>
</tr>
<tr>
<td>First Author, Year</td>
<td>Country of Origin</td>
<td>Study Setting</td>
<td>Study Duration</td>
<td>Inclusion Criteria</td>
<td>Exclusion Criteria</td>
<td>AMI Definition</td>
<td>POC Device/ Manufacturer Troponin Test Test Protocol</td>
<td>Health Personnel Conducting POC Test</td>
<td>Central Laboratory Instrument/Manufacturer Troponin Test Test Protocol</td>
<td>Clinical Adjudication for Final MI Diagnosis (Diagnostic-Accuracy Studies Only)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------------</td>
<td>---------------</td>
<td>----------------</td>
<td>-------------------</td>
<td>-------------------</td>
<td>----------------</td>
<td>-----------------------------------------------</td>
<td>----------------------------------</td>
<td>--------------------------------------</td>
<td>-----------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nilsson, 2013</td>
<td>Sweden</td>
<td>Prospective, observational, cross-sectional study</td>
<td>Government funding No conflicts of interest declared</td>
<td>7 primary health care settings 20 months (May 2009 to Jan. 2011)</td>
<td>Chest pain, dyspnea on exertion unexplained weakness, and/or fatigue; symptoms commenced or worsened during the last 7 days; age ≥ 35 years</td>
<td>NR</td>
<td>NR</td>
<td>Cobas h232/ Roche cTnT Protocol NR</td>
<td>NR</td>
<td>No CL testing</td>
<td>The cases of AMI and UA in the study were diagnosed in conjunction with the first GP visit. The diagnoses of AMI and UA were based on the current definitions.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palamalai, 2013</td>
<td>US</td>
<td>Prospective, observational study</td>
<td>Partially funded by industry Conflicts of interest NR</td>
<td>Hospital ED Duration NR</td>
<td>Symptoms suggestive of ACS</td>
<td>NR</td>
<td>Clinical symptoms of ischemia with increasing cTnI, with at least one cTn value above the 99th percentile</td>
<td>GEM Immuno/ Instrumentation Laboratory; AQT90 FLEX/ Radiometer Medical; i-STAT/ Abbott; PATHFAST/ Mitsubishi Chemical Medience cTnI At presentation, 3 h and at 6 h (samples were frozen and later thawed for evaluations)</td>
<td>Research laboratory technologists</td>
<td>Vitros ECI ES/Ortho-Clinical Diagnostics cTnI At presentation, 3 h and at 6 h (samples were frozen and later thawed for evaluations)</td>
<td>Diagnosis of MI was determined by attending clinicians (internal medicine or emergency medicine) caring for each patient according to the Universal Definition of Myocardial Infarction recommendations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stengaard, 2013</td>
<td>Denmark</td>
<td>Prospective, observational study</td>
<td>University, foundation, and industry funding 2 authors had received fees or grants from industry</td>
<td>Ambulance and EDs 12 months (May 2010 to May 2011)</td>
<td>Ongoing or prolonged periods of chest discomfort within the past 12 h, acute dyspnea in the absence of known pulmonary disease, or a clinical suspicion of AMI</td>
<td>Subjects were only included once in survival analysis at first admission if they had first admission if they had pre-hospital POC cTnT analysis performed on more occasions</td>
<td>Universal Definition of Myocardial Infarction using the 99th percentile URL as diagnostic cut point</td>
<td>Cobas h232/Roche cTnT Heparinized blood taken in ambulance</td>
<td>Paramedics in ambulance</td>
<td>Roche (Instrument NR) Protocol NR</td>
<td>All admissions were evaluated by any 2 of 3 primary adjudicators who were blinded to the decision of the other and the pre-hospital cTnT levels. The definitive diagnosis of AMI was established in accordance with the Universal Definition Of Myocardial Infarction.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First Author, Year</td>
<td>Country of Origin</td>
<td>Study Design</td>
<td>Study Setting</td>
<td>Inclusion Criteria</td>
<td>Exclusion Criteria</td>
<td>AMI Definition</td>
<td>POC Device/ Manufacturer</td>
<td>Health Personnel Conducting POC Test</td>
<td>Central Laboratory Instrument/Manufacturer</td>
<td>Clinical Adjudication for Final MI Diagnosis (Diagnostic-Accuracy Studies Only)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td>------------------</td>
<td>--------------</td>
<td>---------------</td>
<td>-------------------</td>
<td>-------------------</td>
<td>----------------</td>
<td>--------------------------</td>
<td>--------------------------------------</td>
<td>--------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ter Avest, 2014*</td>
<td>The Netherlands</td>
<td>Prospective, observational study</td>
<td>Medical centre ED</td>
<td>Patients ≥ 18 years presenting to ED with at least 5 min of chest pain related to ACS</td>
<td>Patients presenting with only dyspnea, palpitations, fatigue, nausea, or dizziness; inter-hospital referrals; previously included patients; STEMI</td>
<td>Third universal definition of AMI: rise and/or fall of cardiac-biomarker values, with at least 1 value above the 99th percentile, with symptoms of ischemia, new significant ST-segment T-wave depression, new left bundle-branch block, or pathological Q waves on the ECG</td>
<td>AQT90 FLEX/ Radiometer cTnT</td>
<td>NR</td>
<td>Modular E170/Roche cTnT On presentation in ED; 6 h later if patients presented to ED within 6 h of symptoms</td>
<td>The diagnosis of AMI was made during hospitalization by the treating cardiologist using Roche Modular E170 hs-cTnT results (URL 14 ng/L), and adjudicated through coronary angiography in the majority of patients diagnosed with AMI. The treating cardiologist was blinded to the POC test results, as these were provided only to the investigators.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Altinier, 2001**</td>
<td>Italy</td>
<td>Prospective, observational study</td>
<td>Hospital ED</td>
<td>Patients presenting to ED with chest pain and clinical findings suggesting ACS</td>
<td>NR</td>
<td>Stratus CS/Dade Behring; and Triage Cardiac Panel/Biosite cTnI Protocol</td>
<td>NR</td>
<td>Stratus CS/Dade Behring; and Triage Cardiac Panel/Biosite cTnI Protocol</td>
<td>NR</td>
<td>Dimension RxL/Dade Behring cTnI Protocol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apple, 2006†</td>
<td>US</td>
<td>Retrospective, observational, before/after study</td>
<td>Hospital cardiology service</td>
<td>Symptoms of ACS</td>
<td>Patients for whom less than 2 blood samples were obtained and patients without at least one sample ≥ 8 h post-baseline</td>
<td>ESC, ACC, and AHA guidelines</td>
<td>Stratus CS/Dade Behring cTnI Baseline, 4 h, 8 h, and 12 h</td>
<td>Nurses</td>
<td>Dimension RxL/Dade Behring cTnI Baseline, 4 h, 8 h, and 12 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Clinical-Utility Studies**
<table>
<thead>
<tr>
<th>First Author, Year Country of Origin Study Design</th>
<th>Funding Source Conflicts of interest</th>
<th>Study Setting Study Duration</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>AMI Definition</th>
<th>POC Device/ Manufacturer Troponin Test Protocol</th>
<th>Health Personnel Conducting POC Test</th>
<th>Central Laboratory Instrument/Manufacturer Troponin Test Protocol</th>
<th>Clinical Adjudication for Final MI Diagnosis (Diagnostic-Accuracy Studies Only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asha, 2014 Australia RCT</td>
<td>Government funding No conflicts of interest declared</td>
<td>Hospital ED 6 months (Dec. 2011 to May 2012)</td>
<td>Patients ≥ 18 years presenting to ED with suspected ACS</td>
<td>STEMI</td>
<td>NR</td>
<td>AO190 FLEX/ Radiometer cTnT At initial assessment, then every 6 h if abnormal; at 6 h if normal. If pain onset at presentation &gt; 6 h, only taken at presentation</td>
<td>NR</td>
<td>Cobas/Roche cTnT At initial assessment, then every 6 h if abnormal; at 6 h if normal. If pain onset at presentation &gt; 6 h, only taken at presentation</td>
<td></td>
</tr>
<tr>
<td>Caragher, 2002 US Prospective, observational study</td>
<td>Funding NR Conflicts of interest NR</td>
<td>Hospital ED 16 days</td>
<td>Patients presenting to ED with chest pain</td>
<td>NR</td>
<td>NR</td>
<td>Status CS/ Dade Behring cTnl Within 10 min of admission, then at 2 h, 6 h, and 9 h</td>
<td>Nurses</td>
<td>Stratus II/Dade Behring cTnl Within 10 min of admission, then at 2 h, 6 h, and 9 h</td>
<td></td>
</tr>
<tr>
<td>Collinson, 2004 England RCT</td>
<td>Partly funded by government Conflicts of interest NR</td>
<td>Hospital CCU 8 months</td>
<td>Patients assessed in ED at high risk of ACS on clinical grounds</td>
<td>None</td>
<td>1. STEMI 2. NSTEMI with significant changes in serial cardiac biomarkers and symptoms suggestive of cardiac disease</td>
<td>CARDIAC T/ Roche cTnT 12 h after CCU admission</td>
<td>NR</td>
<td>Elecsys 1010/Roche Diagnostics cTnT 12 h after CCU admission</td>
<td></td>
</tr>
<tr>
<td>Cramer, 2007 the Netherlands Prospective, observational study</td>
<td>Funding NR Conflicts of interest NR</td>
<td>Hospital ED 9 months (Jun. 2001 to Mar. 2002)</td>
<td>Patients presenting to ED with suspected ACS</td>
<td>STEMI</td>
<td>NR</td>
<td>Cardiac Reader/ Roche cTnT At presentation</td>
<td>Nurses</td>
<td>Immulite 2000/Diagnostic Products cTnl At presentation</td>
<td></td>
</tr>
<tr>
<td>Cullen, 2012 Australia Prospective, observational study</td>
<td>Medical research foundation Reagents and AQ90 Flex instrument supplied by industry Authors had received fees and support from industry</td>
<td>Hospital ED Duration NR; 30-day follow-up</td>
<td>All adult patients (&gt; 18 years) presenting to the ED with at least 5 min of chest pain suggestive of ACS</td>
<td>Pregnant, inter-hospital transfers Defined under current guidelines. Along with symptoms suggestive of ACS, if there was a rise and/or fall of the CL cTn with one or more values above the 99th percentile (&gt; 0.04 mg/L)</td>
<td>AQ90 FLEX/ Radiometer cTnT At presentation and 2 h</td>
<td>NR</td>
<td>Access AccuTnI/Beckman Coulter cTnl At presentation, and then at least 6 h afterwards</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First Author, Year Country of Origin Study Design</td>
<td>Funding Source Conflicts of interest</td>
<td>Study Setting Study Duration</td>
<td>Inclusion Criteria</td>
<td>Exclusion Criteria</td>
<td>AMI Definition</td>
<td>POC Device/ Manufacturer Troponin Test Test Protocol</td>
<td>Health Personnel Conducting POC Test</td>
<td>Central Laboratory Instrument/Manufacturer Troponin Test Test Protocol</td>
<td>Clinical Adjudication for Final MI Diagnosis (Diagnostic-Accuracy Studies Only)</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Deleda, 2011** US Retrospective, observational, before/after study</td>
<td>Funding NR Conflicts of interest NR</td>
<td>1 academic and 1 community centre ED 8 months (4 months before and 4 months after) (Nov. 2004 to Feb. 2005, and Nov. 2005 to Feb. 2006)</td>
<td>Patients presenting to ED with chief symptom of chest pain or other ACS symptoms, or who had hospital discharge diagnosis of ACS and had cTnl testing in the ED</td>
<td>NR</td>
<td>NR</td>
<td>Triage Profiler SOB/ Biosite cTnl Testing at 0 min, 90 min, 180 min</td>
<td>Trained ED paramedics and patient care assistants</td>
<td>Device NR cTnl Testing at 0 min, 90 min, 180 min</td>
<td></td>
</tr>
<tr>
<td>Di Serio, 2003** Italy Retrospective, observational study</td>
<td>Funding NR Conflicts of interest NR</td>
<td>Hospital ED 4 years</td>
<td>Patients presenting to ED with chest pain</td>
<td>NR</td>
<td>NR</td>
<td>Triage/ Biosite cTnl On admission to ED; no other details provided</td>
<td>Nurses</td>
<td>Dimension RxL/Dade Behring cTnl On admission to ED; no other details provided</td>
<td></td>
</tr>
<tr>
<td>Eggers, 2011* Sweden pooled analysis of two RCTs (FAST II and FASTER-I)</td>
<td>Some funding from industry All authors have affiliation with industry</td>
<td>Coronary care units of 4 hospitals FAST II was 10 months (May 2000 to Mar. 2001); FASTER-I was 10 months (Oct. 2002 to Aug. 2003)</td>
<td>Chest pain with ≥ 15 min duration within the last 8 h; patients were enrolled after being admitted to coronary care unit from the ED</td>
<td>Pathological STEMI leading to reperfusion therapy or consideration of reperfusion therapy</td>
<td>Troponin-based standard applying cTnl ≥ 0.1 mcg/L (Stratus CS; 10% CV level) within 24 h from admission for least 2 samples</td>
<td>Stratus CS/Siemens cTnl At admission to CCU, at 30 or 40 min, 90 or 80 min, then 2 h, 3 h, 6 h, 12 h, and 24 h</td>
<td>NR</td>
<td>AxSYM/ Abbott for the FAST II trial cTnl At admission to CCU, at 30 min or 40 min, 90 min or 80 min, then 2 h, 3 h, 6 h, 12 h, and 24 h</td>
<td></td>
</tr>
<tr>
<td>Ezekowitz, 2015* Canada RCT</td>
<td>Government and industry funding One author has affiliation with industry</td>
<td>Ambulance; 19 months</td>
<td>Patients with chest pain activating pre-hospital emergency medical services ST elevation or a previous diagnosis compatible with a non-cardiovascular cause</td>
<td>NR</td>
<td></td>
<td>Radio2/Alere cTnl In ambulance</td>
<td>Emergency medical service personnel in ambulance</td>
<td>AccuTnl/ Beckman cTnl; At admission</td>
<td></td>
</tr>
<tr>
<td>Fitzgibbon, 2010* Fitzgibbon, 2007* UK (Northern Ireland) Survey</td>
<td>Government funding Conflicts of interest NR</td>
<td>5 health trusts Duration NR</td>
<td>POC device users in 10 major hospitals in Northern Ireland</td>
<td>NR</td>
<td></td>
<td>i-STAT Abbott; Triage/Biosite; Stratus/Dade Behring; Cardiac Reader/Roche Troponin test NR Protocol NR</td>
<td>Clinicians, nurses, laboratory scientists</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>First Author, Year</td>
<td>Country of Origin</td>
<td>Study Design</td>
<td>Funding Source</td>
<td>Conflicts of interest</td>
<td>Study Setting</td>
<td>Study Duration</td>
<td>Inclusion Criteria</td>
<td>Exclusion Criteria</td>
<td>AMI Definition</td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------------</td>
<td>--------------</td>
<td>----------------</td>
<td>----------------------</td>
<td>---------------</td>
<td>----------------</td>
<td>-------------------</td>
<td>-------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Goodacre, 2011</td>
<td>UK</td>
<td>Multi-centre RCT</td>
<td>Government funding</td>
<td>No conflicts of interest declared</td>
<td>6 hospital EDs</td>
<td>2,658 days</td>
<td>Adults with chest pain due to suspected but not proven MI, and no other potentially serious alternative pathology or comorbidity</td>
<td>An obvious non-cardiac morbidity; known CHD; prolonged or recurrent episodes of typical cardiac-type pain; serious non-coronary pathology requiring diagnostic ECG changes for AMI or high-risk ACS comorbidity or social problems; presentation more than 12 h after the most significant episode of pain; previous participation in the RATPAC trial</td>
<td>Universal definition for acute, evolving or recent AMI, troponin level above the 99th percentile of the values for a reference control group; or STEMI on ECG</td>
</tr>
<tr>
<td>First Author, Year, Country of Origin, Study Design</td>
<td>Funding Source</td>
<td>Conflicts of interest</td>
<td>Study Setting</td>
<td>Study Duration</td>
<td>Inclusion Criteria</td>
<td>Exclusion Criteria</td>
<td>AMI Definition</td>
<td>POC Device/Manufacturer</td>
<td>Troponin Test</td>
</tr>
<tr>
<td>---------------------------------------------------</td>
<td>----------------</td>
<td>-----------------------</td>
<td>---------------</td>
<td>---------------</td>
<td>-------------------</td>
<td>------------------</td>
<td>----------------</td>
<td>------------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Guo, 2006 China Prospective, observational study</td>
<td>Hospital funding Conflicts of interest NR</td>
<td>Hospital CCU or cardiac department; 37 months (May 2001 to Jun. 2004)</td>
<td>Chest pain</td>
<td>NR</td>
<td>Either of the following two criteria: 1. a typical rise and gradual fall of troponin or more rapid rise and fall of CK-MB, with at least one of the following: ischemic symptoms, pathological Q waves on the ECG, STEMI, or coronary artery intervention 2. pathological findings of an AMI (cTnI, CK, and CK-MB)</td>
<td>Cardiac Reader/ Roche cTnT At admission, then after 6 and 12 h</td>
<td>Doctors or nurses of the cardiac department or coronary care unit</td>
<td>AccuTnI 33340/Beckman Coulter cTnI At admission, then every 6 h on day 1, and every 24 h for next 6 days</td>
<td></td>
</tr>
<tr>
<td>Koehler, 2013 US Retrospective, observational, before/after study</td>
<td>Partially funded by industry 2 authors are speakers for industry</td>
<td>Hospital ED Pre-POC testing 4 days (Mar. 2010) post-POC testing 3 months (Apr. to May, Jul., and Sept. 2010)</td>
<td>Chest, abdominal, or shoulder pain with a cTn test ordered as part of the clinical workup</td>
<td>NR</td>
<td>NR</td>
<td>i-STAT/Abbott cTnI At admission and 2 h (at discretion of clinician)</td>
<td>Physicians, nurses, and ED technicians</td>
<td>ADVIA Centaur XP Immunoassay System, TnI Ultra Assay/Siemens cTnI At admission and 2 h (at discretion of clinician)</td>
<td></td>
</tr>
<tr>
<td>Lee-Lewandrowski, 2002 US Retrospective, observational, before/after study</td>
<td>Funding NR Conflicts of interest NR</td>
<td>Hospital ED 12 month implementation of POC</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Spectral Status cTnl Protocol NR</td>
<td>NR</td>
<td>Elecsys 1010/ Roche cTnT Protocol NR</td>
<td></td>
</tr>
<tr>
<td>Liikanen, 2005 Finland Survey</td>
<td>Funding NR Conflicts of interest NR</td>
<td>Health care units Duration NR</td>
<td>Health care units using POC testing</td>
<td>NA</td>
<td>NA</td>
<td>Devices NR cTnI and cTnT Protocol NR</td>
<td>Nurses, porters, secretaries, MLTs, physicians, home aids</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>First Author, Year Country of Origin Study Design</td>
<td>Funding Source Conflicts of interest</td>
<td>Study Setting Study Duration</td>
<td>Inclusion Criteria</td>
<td>Exclusion Criteria</td>
<td>AMI Definition</td>
<td>POC Device/ Manufacturer Troponin Test Protocol</td>
<td>Health Personnel Conducting POC Test</td>
<td>Central Laboratory Instrument/Manufacturer Troponin Test Protocol</td>
<td>Clinical Adjudication for Final MI Diagnosis (Diagnostic-Accuracy Studies Only)</td>
</tr>
<tr>
<td>--------------------------------------------------</td>
<td>--------------------------------------</td>
<td>-----------------------------</td>
<td>-------------------</td>
<td>------------------</td>
<td>----------------</td>
<td>-----------------------------------------------</td>
<td>-----------------------------------</td>
<td>----------------------------------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>Loten, 2010&lt;sup&gt;10&lt;/sup&gt; Australia RCT (cluster randomized)</td>
<td>Government funding Conflicts of interest NR</td>
<td>2 hospital EDs 12 weeks (Nov 2007 to Jan 2008)</td>
<td>Adults &gt; 25 years, admitted to ED with possible ACS, with troponin measurement taken</td>
<td>Transfer from another hospital with known ACS or known elevated troponin, ST elevation upon arrival, departure against medical advice</td>
<td>NR</td>
<td>i-STAT/Abbott cTnI At admission and at least 8 h after onset of symptoms</td>
<td>Medical and nursing staff</td>
<td>AccuTnI/Beckman Coulter At admission and at least 8 h after onset of symptoms</td>
<td></td>
</tr>
<tr>
<td>Meek, 2012&lt;sup&gt;28&lt;/sup&gt; Australia Prospective, observational, before/after study</td>
<td>Industry provided the POC device and testing materials No conflicts of interest declared</td>
<td>Hospital ED 81 days before POC 66 days after POC</td>
<td>Chest pain for which the physician ordered serial cardiac enzyme testing</td>
<td>Cardiac enzyme testing once only; diagnosed early with a STEMI (or other); ACS based on a diagnostic ECG and/or initial cardiac enzyme results; early transfer to either a critical care ward or another hospital or had an alternative non-cardiac diagnosis</td>
<td>NR</td>
<td>Triage MeterPro second generation/ Alere cTnI On arrival and at 2 h; high-risk patients had a third assay at 6 h</td>
<td>NR</td>
<td>Beckman Coulter (second generation)/Beckman Coulter On arrival and at 6 h; high-risk patients had a third cTnI assay at 10 h</td>
<td></td>
</tr>
<tr>
<td>Mozina, 2010&lt;sup&gt;30&lt;/sup&gt; Slovenia Prospective, observational study</td>
<td>Hospital funding tests donated by industry Conflicts of interest NR</td>
<td>Hospital ED Duration NR</td>
<td>Chest pain</td>
<td>NR</td>
<td>NR</td>
<td>PATHFAST/ Mitsubishi, Kagaku Iatron cTnI At admission</td>
<td>NR</td>
<td>LIAISON/DiaSorin cTnI At admission</td>
<td></td>
</tr>
<tr>
<td>Nilsson, 2013&lt;sup&gt;14&lt;/sup&gt; Andersson, 2015&lt;sup&gt;1&lt;/sup&gt; Sweden Prospective, observational, cross-sectional study</td>
<td>Government funding No conflicts of interest declared</td>
<td>7 primary health care settings 20 months (May 2009 to Jan 2011)</td>
<td>Chest pain, dyspnea on exertion; unexplained weakness and/or fatigue; symptoms commenced or worsened during the last 7 days; and age ≥ 35 years</td>
<td>NR</td>
<td>NR</td>
<td>Cobas h232/Roche cTnT Protocol NR</td>
<td>NR</td>
<td>No CL testing</td>
<td></td>
</tr>
<tr>
<td>First Author, Year, Country of Origin</td>
<td>Study Design</td>
<td>Study Setting</td>
<td>Inclusion Criteria</td>
<td>Exclusion Criteria</td>
<td>AMI Definition</td>
<td>POC Device/Manufacturer</td>
<td>Health Personnel Conducting</td>
<td>Central Laboratory Instrument/Manufacturer</td>
<td>Clinical Adjudication for Final MI Diagnosis (Diagnostic-Accuracy Studies Only)</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>--------------</td>
<td>---------------</td>
<td>--------------------</td>
<td>-------------------</td>
<td>----------------</td>
<td>------------------------</td>
<td>--------------------------</td>
<td>------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Ordonez-Llanos, 2006&lt;sup&gt;7&lt;/sup&gt; Spain, Great Britain, Germany, Austria, Ireland, Sweden Prospective, observational study</td>
<td>Funded by industry, One author employed by industry</td>
<td>5 hospital EDs 17 months (Aug. 1998 to Jan. 2000)</td>
<td>Chest pain and suspected ACS</td>
<td>NR</td>
<td>cTnT ≥ 0.05 mcg/L or CK-MB ≥ 10 mcg/L within 24 h of admission; or new abnormal Q-wave on ECG or STEMI</td>
<td>Cardiac Reader/ Roche cTnT On admission, 1, 2, 4, 24, and 48 h</td>
<td>ED personnel</td>
<td>ELECSYS 1010 or 2010/ Roche cTnT On admission, 1, 2, 4, 24, and 48 h</td>
<td></td>
</tr>
<tr>
<td>Renaud, 2008&lt;sup&gt;8&lt;/sup&gt; France RCT</td>
<td>Reagents provided by industry, One author has been supported by industry</td>
<td>Hospital ED 17 months (Nov. 2002 to Apr. 2004)</td>
<td>1. Adults ≥ 18 years in ED with symptoms suspicious of ACS 2. One of the above symptoms and either cTnI ≥ 0.1 mcg/L, or at least 2 of: ≥ 60 years, at least 3 cardiovascular risk factors, history of CAD, chest pain, or NSTEMI ECG changes indicating ischemia</td>
<td>Previous enrollment in study; STEMI</td>
<td>ESC/ACC guidelines</td>
<td>Status CS/Dade Behring cTnI Protocol NR</td>
<td>Nurses</td>
<td>Dimension RoL-HM/Dade Behring cTnI Protocol NR</td>
<td></td>
</tr>
<tr>
<td>Ryan, 2009&lt;sup&gt;9&lt;/sup&gt; US RCT</td>
<td>Funded in part by industry, 2 authors had received research grants from industry</td>
<td>4 medical centre EDs 2 years</td>
<td>Patients ≥ 21 years, presenting to ED with symptoms suggestive of ACS</td>
<td>Tachydysrhythmia (ventricular tachycardia, supraventricular tachycardia, rapid atrial fibrillation), or 12-lead ECG diagnostic of AMI</td>
<td>NR</td>
<td>i-STAT/Abbott cTnI Baseline, 90 min, 180 min, 360 min</td>
<td>NR</td>
<td>Device NR cTnI 3 sites used baseline, 90 min, 180 min, 360 min; 1 site used baseline, 8 h, 12 h</td>
<td></td>
</tr>
<tr>
<td>First Author, Year of Publication</td>
<td>Country of Origin</td>
<td>Study Design</td>
<td>Conflicts of interest</td>
<td>Study Setting</td>
<td>Study Duration</td>
<td>Inclusion Criteria</td>
<td>Exclusion Criteria</td>
<td>AMI Definition</td>
<td>POC Device/Manufacturer</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>-------------------</td>
<td>-------------</td>
<td>-----------------------</td>
<td>--------------</td>
<td>----------------</td>
<td>------------------</td>
<td>-------------------</td>
<td>-----------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Shephard, 2014 &amp; Shephard, 2012</td>
<td>Australia</td>
<td>Implementation review</td>
<td>No funding received, Conflicts of interest NR</td>
<td>Remote health centres</td>
<td>First 4 years of program</td>
<td>Remote health centres</td>
<td>NR</td>
<td>NR</td>
<td>i-STAT/Abbott cTnI Protocol NR</td>
</tr>
<tr>
<td>Singer, 2015</td>
<td>US</td>
<td>Retrospective, observational, before/after study</td>
<td>Funding NR, One author was a speaker for industry</td>
<td>Hospital ED</td>
<td>Approx. 1 month</td>
<td>All ED patients triaged to critical care</td>
<td>NR</td>
<td>NR</td>
<td>i-STAT/Abbott cTnI Protocol NR</td>
</tr>
<tr>
<td>Singer, 2005</td>
<td>US</td>
<td>Retrospective, observational, before/after study</td>
<td>No funding received, Conflicts of interest NR</td>
<td>Hospital ED</td>
<td>4 weeks (2 weeks each before and after)</td>
<td>Chest pain</td>
<td>STEMI: patients not being admitted to hospital</td>
<td>NR</td>
<td>Stratus/ Dade Behring cTnI Protocol NR</td>
</tr>
<tr>
<td>Sorensen, 2011</td>
<td>Denmark</td>
<td>Prospective, observational study</td>
<td>Foundation and service company funding, 2 authors are affiliated with one of the service companies providing funding</td>
<td>Pre-hospital setting (ambulance)</td>
<td>15 months (Jun. 2008 to Sept. 2009)</td>
<td>Patients transported by an ambulance equipped with POC troponin testing</td>
<td>NR</td>
<td>Universal definition of MI using a rise or fall of cTnT above the 99th percentile, together with symptoms of ischemia, or ECG changes indicative of new ischemia</td>
<td>TROPT/Roche cTnT Heparinized blood taken in ambulance</td>
</tr>
<tr>
<td>Stengaard, 2013</td>
<td>Denmark</td>
<td>Prospective, observational study</td>
<td>University, foundation and industry funding, 2 authors have received fees or grants from industry</td>
<td>Ambulance and EDs</td>
<td>12 months (May 2010 to May 2011)</td>
<td>Ongoing or prolonged periods of chest discomfort within the past 12 h, acute dyspnea in the absence of known pulmonary disease, or a clinical suspicion of AMI</td>
<td>Subjects were only included once in survival analysis at first admission if they had pre-hospital POC cTnT analysis performed on more occasions</td>
<td>Universal Definition of Myocardial Infarction using the 99th percentile URL as diagnostic cut point</td>
<td>Cobas h232/Roche cTnT Heparinized blood taken in ambulance</td>
</tr>
<tr>
<td>First Author, Year</td>
<td>Country of Origin</td>
<td>Study Design</td>
<td>Funding Source</td>
<td>Conflicts of interest</td>
<td>Study Setting</td>
<td>Study Duration</td>
<td>Inclusion Criteria</td>
<td>Exclusion Criteria</td>
<td>AML Definition</td>
</tr>
<tr>
<td>--------------------</td>
<td>-------------------</td>
<td>-------------</td>
<td>----------------</td>
<td>----------------------</td>
<td>--------------</td>
<td>----------------</td>
<td>-------------------</td>
<td>-------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Storrow, 2006&lt;sup&gt;13&lt;/sup&gt;</td>
<td>US</td>
<td>Prospective, observational study</td>
<td>Industry</td>
<td>Conflicts of interest</td>
<td>NR</td>
<td>1 teaching hospital ED + 1 community-based ED</td>
<td>Duration NR; 30-day follow-up of patients</td>
<td>ED patients ≥ 21 years presenting with ACS symptoms; NSTEMI; enrolled within 1 h of ECG</td>
<td>Need for emergent catheterization or reperfusion therapy; hospitalized for ACS within past 4 weeks; trauma; presentation with a new left bundle-branch block or STEMI</td>
</tr>
<tr>
<td>Venge, 2013&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Sweden</td>
<td>Prospective, observational study</td>
<td>Partially funded by industry</td>
<td>Authors had consultant or advisory roles with industry</td>
<td>Hospital ED 13 months (Nov 2004 to May 2005 and Oct 2006 to May 2007); deaths recorded over a 31-month period</td>
<td>Suspected MI plus troponin analysis requested by clinician</td>
<td>NR</td>
<td>NR</td>
<td>i-STAT/Abbott cTnI Whole blood by Stratus CS at the ED and/or in heparinized plasma by architect in the clinical chemistry laboratory</td>
</tr>
<tr>
<td>Venge, 2010&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Sweden</td>
<td>Prospective, observational study</td>
<td>Assays provided by industry</td>
<td>2 authors affiliated with industry</td>
<td>Hospital ED 13 months (Nov 2004 to May 2005 and Oct 2006 to May 2007)</td>
<td>Admission to ED with a troponin analysis requested as part of the clinical workup</td>
<td>NR</td>
<td>NR</td>
<td>i-STAT/Abbott and Stratus CS/ Siemens cTnl Protocol NR</td>
</tr>
</tbody>
</table>

ACC = American College of Cardiology; ACS = acute coronary syndrome; AHA = American Heart Association; AMI = acute myocardial infarction; CAD = coronary artery disease; CCU = coronary care unit; CHD = coronary heart disease; CL = clinical laboratory; cTn = cardiac troponin; cTnI = cardiac troponin I; cTnT = cardiac troponin T; ECG = electrocardiogram; ED = emergency department; ESC = European Society of Cardiology; GP = general practitioner; h = hours; hs-cTnT = high-sensitivity cardiac troponin T; ICU = intensive care unit; MI = myocardial infarction; min = minutes; MLT = medical laboratory technologist; NA = not applicable; NR = not reported; NSTEMI = non-ST segment elevation myocardial infarction; POC = point of care; RCT = randomized controlled trial; STEMI = ST segment elevation myocardial infarction; UA = unstable angina; UK = United Kingdom; URL = upper reference limit; US = United States.
## Appendix 7: Patient Characteristics

### Table 15: Patient Characteristics

<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Number of Patients Enrolled (N)</th>
<th>Number Completed</th>
<th>Reasons for Withdrawal</th>
<th>Age (Years)</th>
<th>Sex</th>
<th>Symptoms</th>
<th>Comorbidities</th>
<th>Time From Symptom Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnostic-Accuracy Studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Aldous, 2014<sup>16</sup> | N = 1,184 962 (81%) completed | NR | Median 66 (IQR 56 to 76) | 59% male (n = 568) | Cardiac ischemia | • Diabetes, 153 (15.9%)  
• Prior ischemic heart disease, 474 (49.3%)  
• Hypertension, 583 (60.6%)  
• Dyslipidemia, 539 (56.0%)  
• Current smoker, 141 (14.7%)  
• Previous smoker, 437 (45.4%) | NR | |
| Di Serio, 2005<sup>17</sup> | N = 41 All completed | NR | Mean 61 ± SD 11.6 | 80% male (n = 33) | Chest pain | NR | Mean 6 h ± SD 4 h | |
| Di Serio, 2007<sup>18</sup> Amodio, 2007<sup>19</sup> | N = 516 All completed | NA | Mean 61 | 60% male (n = 308) | Chest pain | • Hypertension, 209 (40%);  
• Diabetes, 110 (21%);  
• Smoking, 109 (21%);  
• Previous smoker, 200 (38%);  
• Previous MI, 120 (23%);  
• Congestive heart failure, 101 (19%) | Mean 5.0 h | |
| Diercks, 2012<sup>20</sup> | N = 1,107 858 (78%) completed | 48 with symptom onset > 8 hours before blood work  
201 did not have all 3 samples drawn | Median 57.0 (IQR 48.0 to 67.0) | 55.5% male (n = 476) | Chest pain or ischemic symptoms  
• Diabetes mellitus, 224 (26.1%);  
• Hypertension, 575 (67%);  
• Hyperlipidemia, 482 (56.2%);  
• Renal insufficiency, 173 (20.2%);  
• Prior cardiac surgery, 328 (38.2%);  
• Prior MI, 230 (26.8%);  
• Smoker, 253 (29.5%) | Median 5.9 h (IQR 2.7 to 5.2 h) | |
| Hjortshoj, 2011<sup>21</sup> | N = 458 Completed NR | NR | Median 63 (range 27 to 96) | 64% male (n = 293) | Chest pain  
• Angina pectoris, 167 (35%);  
• Previous MI, 48 (11%);  
• CABG, 20 (4%);  
• PCI, 27 (6%);  
• Diabetes, 55 (12%);  
• Hypertension, 188 (41%);  
• CHF, 33 (7%) | Median 2.20 h (range 0.75 to 6.00 h) | |
<p>| Ivandic, 2014&lt;sup&gt;22&lt;/sup&gt; | N = 151 Completed NR | NR | Median 69 (range 37 to 90) | 72% male (n = 109) | Chest pain | NR | NR | |</p>
<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Number of Patients Enrolled (N)</th>
<th>Number Completed</th>
<th>Reasons for Withdrawal</th>
<th>Age (Years)</th>
<th>Sex</th>
<th>Symptoms</th>
<th>Comorbidities</th>
<th>Time From Symptom Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee-Lewandrowski, 2011</td>
<td>N = 201</td>
<td>All completed</td>
<td>NA</td>
<td>Mean 61.7</td>
<td>53.9% male (n = 110)</td>
<td>Resting or exertional chest pain; arm, shoulder, or jaw pain; exertional dyspnea; palpitations; syncope; nausea and/or diaphoresis and new ECG abnormalities</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Nilsson, 2013</td>
<td>N = 196</td>
<td>All completed</td>
<td>NA</td>
<td>POC: mean 66 ± SD 14</td>
<td>POC: 56% male (n = 71)</td>
<td>POC: chest pain 110 (86%) weakness and/or dyspnea on exertion, no chest pain, 16 (14%)</td>
<td>POC: angina pectoris, 22 (17%) previous AMI, 20 (16%) coronary revascularization, 16 (13%) stroke, 5 (3.9%) heart failure, 12 (9.4%) aortic valve disease, 6 (4.7%) potential causes of increase in troponin T in the absence of overt ischemic heart disease, 3 (2.3%)</td>
<td>NR</td>
</tr>
<tr>
<td>Palamalai, 2013</td>
<td>N = 169</td>
<td>All completed</td>
<td>NA</td>
<td>Mean 58 ± SD16</td>
<td>60% male (n = 101)</td>
<td>Symptoms suggestive of ACS</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Stengaard, 2013</td>
<td>N = 985</td>
<td>924 completed</td>
<td>NR</td>
<td>985 cases were 936 individual patients; 9 foreign citizens and 1 emigrant lost to follow-up; 2 patients had no status data</td>
<td>NR</td>
<td>Chest pain within past 12 hours, acute dyspnea in absence of known pulmonary disease</td>
<td>Hypercholesterolemia, diabetes, hypertension, smoking (current and previous)</td>
<td>Median 70 min (range 35–180 min)</td>
</tr>
<tr>
<td>ter Avest, 2014</td>
<td>N = 281</td>
<td>Completed NR</td>
<td>NR</td>
<td>Mean 62 (range 16 to 93)</td>
<td>61% male (n = 159)</td>
<td>Chest pain</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Clinical-Utility Studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Altinier, 2001</td>
<td>N = 100</td>
<td>Completed NR</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NR</td>
</tr>
<tr>
<td>Apple, 2006</td>
<td>N = 555</td>
<td>551 (99%) completed POC: N = 274 CL: N = 271</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NR</td>
</tr>
<tr>
<td>Asha, 2014</td>
<td>N = 487</td>
<td>452 (93%) completed POC: N = 235 229 (97%) completed CL: N = 233 223 (96%) completed</td>
<td>19 enrolment forms not returned; 10 enrolled twice; 1 enrolled 3 times; 1 enrolled 5 times</td>
<td>POC: median 61.9 ± SD16.6 CL: median 61.7 ± SD 16.6</td>
<td>POC: 53% male (n = 122) CL: 52% male (n = 117)</td>
<td>Chest pain</td>
<td>Diabetes, renal disease, coronary artery disease (POC, 29%; CL, 48%) Previous MI (POC, 23%; CL, 33%)</td>
<td>NR</td>
</tr>
<tr>
<td>Caragher, 2002</td>
<td>N = 205</td>
<td>Completed NR</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NR</td>
</tr>
<tr>
<td>First Author, Year</td>
<td>Number of Patients Enrolled (N)</td>
<td>Number Completed</td>
<td>Reasons for Withdrawal</td>
<td>Age (Years)</td>
<td>Sex</td>
<td>Symptoms</td>
<td>Comorbidities</td>
<td>Time From Symptom Onset</td>
</tr>
<tr>
<td>-------------------</td>
<td>---------------------------------</td>
<td>------------------</td>
<td>------------------------</td>
<td>-------------</td>
<td>-----</td>
<td>----------</td>
<td>---------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Collinson, 2004† ‡</td>
<td>N = 263</td>
<td>All completed</td>
<td>NA</td>
<td>All: median 65.3 (IQR 27 to 88)</td>
<td>All: 67% male (n = 177)</td>
<td>NR</td>
<td>POC: smoker, 23 (18%)</td>
<td>POC: median 6.5 h</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PO: median 64.9 (IQR 39 to 88)</td>
<td></td>
<td>POC: 70% male (n = 92)</td>
<td>NR</td>
<td>previous smoker, 46 (35%)</td>
<td>CL: median 5.0 h</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CL: median 65.8 (IQR 25 to 87)</td>
<td></td>
<td>CL: 64% male (n = 85)</td>
<td>NR</td>
<td>diabetes, 23 (18%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>previous history of ischemic heart disease, 66 (50%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>hypertension, 54 (41%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>hypercholesterolemia, 26 (20%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>dysrhythmia, 10</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>unstable angina pain, 24</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>non-ischemic chest pain, 9</td>
<td></td>
</tr>
<tr>
<td>Cramer, 2007‡ ‡</td>
<td>N = 358</td>
<td>Completed NR</td>
<td>NR</td>
<td>Mean 64 ± SD 14</td>
<td>58% male (n = 208)</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Cullen, 2012**</td>
<td>N = 976</td>
<td>704 (72%) completed</td>
<td>272 patients did not have index blood drawn at appropriate time</td>
<td>Median 53 (IQR: 44 to 65)</td>
<td>62.1% male (n = 606)</td>
<td>Chest pain</td>
<td>Hypertension, diabetes, dyslipidemia, smoking or prior angina, coronary artery disease, chronic heart failure, stroke, coronary artery bypass graft, or percutaneous cardiac intervention</td>
<td></td>
</tr>
<tr>
<td>Deledda, 2011†</td>
<td>All: N = 4,888</td>
<td>All completed</td>
<td>PO: N = 2,446</td>
<td>CL: N = 2,440</td>
<td>NA</td>
<td>PO: median 56.3 ± SD 15.7</td>
<td>CL: median 57.4 ± SD 16.0</td>
<td>Chest pain or other symptoms of ACS</td>
</tr>
<tr>
<td>Di Serio, 2003†</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Chest pain</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

NR = Not reported
<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Number of Patients Enrolled (N)</th>
<th>Number Completed</th>
<th>Reasons for Withdrawal</th>
<th>Age (Years)</th>
<th>Sex</th>
<th>Symptoms</th>
<th>Comorbidities</th>
<th>Time From Symptom Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eggers, 2011&lt;sup&gt;11&lt;/sup&gt;</td>
<td>N = 454 Completed NR</td>
<td>NR</td>
<td></td>
<td>Median 65 (IQR 57 to 76)</td>
<td>69.5% male (n = 299)</td>
<td>Acute chest pain</td>
<td>• Hypertension, 187 (41.2%) • Diabetes, 78 (17.2%) • Hyperlipidemia, 165 (36.3%) • Previous AMI, 155 (34.1%) • Congestive heart failure, 76 (16.7%) • Previous revascularization, 132 (29.1%) • Smoker: 80 (17.6%) • Previous smoker, 195 (43.0%)</td>
<td>NR</td>
</tr>
<tr>
<td>Ezekowitz, 2015&lt;sup&gt;15&lt;/sup&gt;</td>
<td>N = 601 544 (91%) completed per protocol analysis</td>
<td>2 patients allocated to usual care received POC; 55 patients allocated to POC did not receive POC testing</td>
<td></td>
<td>All: median 66 (IQR 53 to 79) Usual care: median 68 (IQR 53 to 79) POC: median 64 (IQR 53 to 76)</td>
<td>All: 56.6% (n = 340) Usual care: 54% male (n = 160) POC: 59% male (n = 180)</td>
<td>Acute chest pain POC: • previous MI, 96 (31.5%) • heart failure, 21 (6.9%) • diabetes, 80 (26.2%) Usual care: • previous MI, 82 (27.7%) • heart failure, 29 (9.8%) • diabetes, 72 (24.3%) • hypertension, 181 (61.1%)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Fitzgibbon, 2010&lt;sup&gt;8&lt;/sup&gt; Fitzgibbon, 2007&lt;sup&gt;38&lt;/sup&gt;</td>
<td>100 health care personnel at 10 major hospitals responded to survey</td>
<td>NA</td>
<td></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Goodacre, 2011&lt;sup&gt;11&lt;/sup&gt;</td>
<td>N = 2,263 2,243 (99%) completed</td>
<td>12 not adequate consent 2 consent withdrawn; 6 recruited in error and not followed up</td>
<td></td>
<td>Mean 54.5 ± SD 14.1</td>
<td>58% male (n = 1,307)</td>
<td>• Indigestion/ burning, 154 (7%) • Stabbing/sharp chest pain, 459 (21%) • Aching/dull chest pain, 567 (26%) • Gripping/crushing/ heavy chest pain, 794 (36%) • Non-specific/other chest pain, 239 (11%) • Known coronary artery disease, 269 (12%) • Diabetes, 178 (8%) • Hypertension, 737 (33%) • Hyperlipidemia, 553 (27%) • Smoker, 626 (28%) • Previous smoker, 273 (13%) • Cocaine use, 16 (1%)</td>
<td>All: mean 230 min ± SD 425 POC: 241 min ± SD 504 CL: 219 min ± 325 SD</td>
<td></td>
</tr>
<tr>
<td>Guo, 2006&lt;sup&gt;7&lt;/sup&gt;</td>
<td>N = 551 502 (91%) completed</td>
<td>NR</td>
<td></td>
<td>NR</td>
<td>Chest pain</td>
<td>Hypertension, diabetes, renal failure, tumour, stroke, or previous MI</td>
<td>Onset of chest pain ranged from 0.5 h to 24 h before hospital admission</td>
<td></td>
</tr>
<tr>
<td>Koehler, 2013&lt;sup&gt;3&lt;/sup&gt;</td>
<td>N = 201 Completed NR</td>
<td>NR</td>
<td></td>
<td>NR</td>
<td>Chest, abdominal, or shoulder pain</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>First Author, Year</td>
<td>Number of Patients Enrolled (N)</td>
<td>Number Completed</td>
<td>Reasons for Withdrawal</td>
<td>Age (Years)</td>
<td>Sex</td>
<td>Symptoms</td>
<td>Comorbidities</td>
<td>Time From Symptom Onset</td>
</tr>
<tr>
<td>---------------------</td>
<td>---------------------------------</td>
<td>------------------</td>
<td>------------------------</td>
<td>-------------</td>
<td>-----</td>
<td>----------</td>
<td>---------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Lee-Lewandrowski, 2002&lt;sup&gt;2&lt;/sup&gt;</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Liikanen, 2005&lt;sup&gt;5&lt;/sup&gt;</td>
<td>401 surveys sent 301 (75%) responses</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NR</td>
</tr>
<tr>
<td>Loten, 2010&lt;sup&gt;10&lt;/sup&gt;</td>
<td>N = 912 All completed</td>
<td>NA</td>
<td>POC: median 60 (range 25 to 101)</td>
<td>POC: 52.2% male (n = 244)</td>
<td>CL: median 62 (range 25 to 99)</td>
<td>CL: 49.7% male (n = 221)</td>
<td>Symptoms suggestive of ACS</td>
<td>NR</td>
</tr>
<tr>
<td>Meek, 2012&lt;sup&gt;12&lt;/sup&gt;</td>
<td>N = 671 All completed</td>
<td>NR</td>
<td>POC: median 62 (IQR 50 to 73)</td>
<td>POC: 52.7% male (n = 136)</td>
<td>CL: median 63 (IQR 52 to 77)</td>
<td>CL: 56.7% male (n = 234)</td>
<td>Chest pain</td>
<td>NR</td>
</tr>
<tr>
<td>Mozina, 2010&lt;sup&gt;3&lt;/sup&gt;</td>
<td>N = 31 All completed</td>
<td>NA</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Chest pain</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Nilsson, 2013&lt;sup&gt;11&lt;/sup&gt;, Andersson, 2015&lt;sup&gt;1&lt;/sup&gt;</td>
<td>N = 196 POC: 128 All completed</td>
<td>NA</td>
<td>POC: mean 66 ± SD 14</td>
<td>POC: 56% male (n = 71)</td>
<td>POC: chest pain, 110 (86%) weakness and/or dyspnea on exertion, no chest pain, 18 (14%)</td>
<td>POC: angina pectoris, 22 (17%) previous AMI, 20 (16%) coronary revascularization, 16 (13%) stroke, 5 (3.9%) heart failure, 12 (9.4%) aortic valve disease, 6 (4.7%) potential causes of increase in troponin T in the absence of overt ischemic heart disease, 3 (2.3%)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Ordonez-Llanos, 2006&lt;sup&gt;17&lt;/sup&gt;</td>
<td>N = 1,410 Completed NR</td>
<td>NR</td>
<td>Mean 63 ± SD 14.6</td>
<td>64% male (n = 906)</td>
<td>Chest pain</td>
<td>NR</td>
<td>Median 285 min</td>
<td></td>
</tr>
<tr>
<td>First Author, Year</td>
<td>Number of Patients Enrolled (N)</td>
<td>Number Completed</td>
<td>Reasons for Withdrawal</td>
<td>Age (Years)</td>
<td>Sex</td>
<td>Symptoms</td>
<td>Comorbidities</td>
<td>Time From Symptom Onset</td>
</tr>
<tr>
<td>--------------------</td>
<td>---------------------------------</td>
<td>------------------</td>
<td>------------------------</td>
<td>-------------</td>
<td>-----</td>
<td>----------</td>
<td>---------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Renaud, 2008&lt;sup&gt;10&lt;/sup&gt;</td>
<td>N = 833</td>
<td>Completed NR</td>
<td>NR</td>
<td>POC: median 62 (IQR 49 to 75)</td>
<td>POC: 62% male (n = 260)</td>
<td>POC: • chest pain (58%) • left arm pain (13%) • general malaise (19%) • dyspnea (32%) • epigastric pain (8%)</td>
<td>CL: • high BMI, 59% • hypertension, 49% • diabetes, 21% • hyperlipidemia, 33% • history of smoking, 52% history of atherosclerosis, 47%</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>N = 2,134</td>
<td>2,000 (94%) completed</td>
<td>62 met exclusion criteria, 24 unable to obtain blood, 14 process or assay error, 15 withdrew consent, 10 left ED prior to data collection, 6 unable to consent, 2 no patient data available, 1 physician refused further participation</td>
<td>POC: mean 60 ± SD 16</td>
<td>POC: dyspnea, 524 (52%) • diaphoresis, 216, (22%) • nausea, 255 (26%) • weakness, 310 (31%) • dizziness, 236 (24%) • palpitations, 166 (17%)</td>
<td>CL: dyspnea, 481 (48%) • diaphoresis, 213 (21%) • nausea, 260 (26%) • weakness, 320 (32%) • dizziness, 243 (24%) • palpitations, 147 (15%)</td>
<td>CL: • current smoker, 253 (25%) • current cocaine user, 14 (1%) • hypertension, 625 (62%) • diabetes, 209 (21%) • previous MI, 181 (18%) • previous arrhythmia, 198 (20%) • hyperlipidemia, 436 (44%) • previous PCI, 273 (27%) • previous CABG, 115 (12%)</td>
<td>POC: • &lt; 1 h, 148 (15%) • ≥ 1 h to &lt; 3 h, 217 (22%) • ≥ 3 h to &lt; 6 h, 125 (12%) • ≥ 6 h, 509 (51%)</td>
</tr>
<tr>
<td>First Author, Year</td>
<td>Number of Patients Enrolled (N)</td>
<td>Number Completed</td>
<td>Reasons for Withdrawal</td>
<td>Age (Years)</td>
<td>Sex</td>
<td>Symptoms</td>
<td>Comorbidities</td>
<td>Time From Symptom Onset</td>
</tr>
<tr>
<td>-------------------</td>
<td>---------------------------------</td>
<td>-----------------</td>
<td>------------------------</td>
<td>-------------</td>
<td>-----</td>
<td>----------</td>
<td>---------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Shephard, 2014&lt;sup&gt;12&lt;/sup&gt;</td>
<td>33 remote health centres; 3 aboriginal community health centres; 506 trained staff</td>
<td>N = 2,386</td>
<td>All completed</td>
<td>POC: 190 cTn tests</td>
<td>63 ± SD 16</td>
<td>58% male (n = 205)</td>
<td>Chest pain</td>
<td>POC: hypertension, 41 (32%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CL: 845 cTn tests</td>
<td>POC: 60.8 ± SD 16.9</td>
<td>All: 56% male (n = 205)</td>
<td>64.2 ± SD 15.5</td>
<td>CL: 54% male (n = 128)</td>
<td>POC: history of smoking, 34 (31%)</td>
<td>NR</td>
</tr>
<tr>
<td>Singer, 2015&lt;sup&gt;13&lt;/sup&gt;</td>
<td>N = 366</td>
<td>All completed</td>
<td>NA</td>
<td>All: mean 63 ± SD 16</td>
<td>PO: 5% male (n = 565)</td>
<td>Chest pain</td>
<td>PO: diabetes, 22 (20%)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NR</td>
<td>POC: median 66 (IQR 55 to 78)</td>
<td>CL: median 67 (IQR 55 to 78)</td>
<td>POC: hypercholesterolemia, 29 (26%)</td>
<td>CL: hypertension, 77 (35%)</td>
<td>NR</td>
</tr>
<tr>
<td>Singer, 2005&lt;sup&gt;13&lt;/sup&gt;</td>
<td>N = 4,905.</td>
<td>Completed NR</td>
<td>5 failure of test kit</td>
<td>PO: median 66 (IQR 55 to 78)</td>
<td>59% male (n = 2,386)</td>
<td>Chest pain</td>
<td>PO: previous MI, 276 (25%)</td>
<td>PO: median 83 min (IQR 46 to 167 min)</td>
</tr>
<tr>
<td></td>
<td>Completed NR</td>
<td>Completed NR</td>
<td>18 inability to draw blood</td>
<td>CL: 60% male (n = 2,386)</td>
<td></td>
<td></td>
<td>PO: previous PCI or CABG, 218 (24%)</td>
<td>CL: 165 min (110 to 276 min)</td>
</tr>
<tr>
<td>Sorensen, 2011&lt;sup&gt;13&lt;/sup&gt;</td>
<td>N = 4,985; 928 (97%) completed</td>
<td>N = 985</td>
<td>Completed NR</td>
<td>PO: median 66 (IQR 55 to 78)</td>
<td>59% male (n = 2,386)</td>
<td>Chest pain</td>
<td>PO: previous PCI or CABG, 831 (23%)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Completed NR</td>
<td>Completed NR</td>
<td>CL: N = 3,947</td>
<td>CL: median 67 (IQR 55 to 78)</td>
<td></td>
<td></td>
<td>PO: diabetes, 111 (12%)</td>
<td>Median 70 min (range 35 to 180 min)</td>
</tr>
<tr>
<td>Stenggaard, 2013&lt;sup&gt;9&lt;/sup&gt;</td>
<td>N = 985</td>
<td>924 completed</td>
<td>985 cases were 936 individual patients; 9 foreign citizens and 1 emigrant lost to follow-up; 2 patients had no status data</td>
<td>57.1 ± SD 14.6</td>
<td>52.5% male (n = 117)</td>
<td>Symptoms suggestive of ACS</td>
<td>Hypercholesterolemia, diabetes, hypertension, smoking (current and previous)</td>
<td>NR</td>
</tr>
<tr>
<td>Storrow, 2006&lt;sup&gt;10&lt;/sup&gt;</td>
<td>N = 253 223 (88%) completed</td>
<td>24 chose to withdraw after baseline blood work; 2 left ED; 2 were excluded by treating physician; 17 were lost to follow-up; 1 had laboratory markers drawn pre-ED; 5 lacked documented ED arrival time</td>
<td>Mean 57.1 ± SD 14.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NR</td>
</tr>
<tr>
<td>First Author, Year</td>
<td>Number of Patients Enrolled (N)</td>
<td>Number Completed</td>
<td>Reasons for Withdrawal</td>
<td>Age (Years)</td>
<td>Sex</td>
<td>Symptoms</td>
<td>Comorbidities</td>
<td>Time From Symptom Onset</td>
</tr>
<tr>
<td>--------------------</td>
<td>--------------------------------</td>
<td>------------------</td>
<td>------------------------</td>
<td>-------------</td>
<td>-----</td>
<td>----------</td>
<td>--------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Venge, 2013^2</td>
<td>N = 508</td>
<td>All completed</td>
<td>NA</td>
<td>Male: mean 68.8 ± 17.8 SD Female: mean 70.2 ± SD17.8</td>
<td>51% male (n = 259)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Venge, 2010^-2</td>
<td>N = 1,069</td>
<td>851 (80%) completed (outcome available for this number)</td>
<td>NR</td>
<td>Male: mean 70.1 ± SD18.1 Female: mean 72.8 ± SD 17.7</td>
<td>53% male (n = 567)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

ACS = acute coronary syndrome; AMI = acute myocardial infarction; BMI = body mass index; CABG = coronary artery bypass graft; CHF = congestive heart failure; CL = clinical laboratory; ECG = electrocardiogram; ED = emergency department; h = hours; IQR = interquartile ratio; MI = myocardial infarction; min = minutes; N = number; NA = not applicable; NR = not reported; PCI = percutaneous coronary intervention; POC = point of care; SD = standard deviation.
## Appendix 8: Critical Appraisal

### Table 16: Critical Appraisal of Diagnostic-Accuracy Studies (QUADAS-2)

<table>
<thead>
<tr>
<th>First Author, Publication Date</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| **Aldous, 2014**<sup>16</sup> | Patient selection:  
- case-control design avoided  
- the study avoided inappropriate exclusions  
- the selection of patients could have introduced bias (risk: low)  
- concern that the included patients did not match the review question (concern: low)  
Reference standard:  
- the reference standard was likely to correctly classify the target condition  
- the reference-standard results were interpreted without knowledge of the results of the index test  
- the reference standard, its conduct, or its interpretation could have introduced bias (risk: low)  
- concern that the reference-standard test, its conduct, or interpretation differs from the review question (concern: low)  
Flow and timing:  
- there was an appropriate interval between index test and reference standard  
- all patients received a reference standard  
- all patients received the same reference standard  
- the patient flow could have introduced bias (risk: low) | Patient selection:  
- unclear if consecutive sample of patients were enrolled  
Index tests:  
- unsure if the index test results were interpreted without knowledge of the results of the reference standard  
- the conduct or interpretation of the index test could have introduced bias (risk: unclear)  
- concern that the index test, its conduct, or interpretation differs from the review question (concern: unclear)  
Flow and timing:  
- not all patients were included in the analysis |
| **Di Serio, 2005**<sup>23</sup> | Patient selection:  
- case-control design avoided  
- concern that the included patients did not match the review question (concern: low)  
Index tests:  
- concern that the index test, its conduct, or interpretation differs from the review question (concern: low)  
Reference standard:  
- the reference standard was likely to correctly classify the target condition  
- concern that the reference standard test, its conduct, or interpretation differs from the review question (concern: low)  
Flow and timing:  
- all patients received a reference standard  
- all patients received the same reference standard | Patient selection:  
- unclear if consecutive sample of patients were enrolled  
Index tests:  
- unsure if the index test results were interpreted without knowledge of the results of the reference standard  
- the selection of patients could have introduced bias (risk: uncertain)  
Reference standard:  
- unsure if the reference-standard results were interpreted without knowledge of the results of the index test  
- the reference standard, its conduct, or its interpretation could have introduced bias (risk: unclear) |
<table>
<thead>
<tr>
<th>First Author, Publication Date</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Di Serio, 2007; Amodio, 2007 | Patient selection:  
- consecutive sample of patients enrolled  
- case-control design avoided  
- the study avoided inappropriate exclusions  
- the selection of patients could have introduced bias (risk: low)  
- concern that the included patients did not match the review question (concern: low)  
 Index tests:  
- concern that the index test, its conduct, or interpretation differs from the review question (concern: low)  
 Flow and timing:  
- all patients were included in the analysis  
- the patient flow could have introduced bias (risk: low) | Reference standard:  
- there was no reference standard done  
 Flow and timing:  
- unclear if there was an appropriate interval between index test and reference standard  
- unsure if all patients were included in the analysis  
- the patient flow could have introduced bias (risk: uncertain) |
| Diercks, 2012 | Patient selection:  
- case-control design avoided  
- the study avoided inappropriate exclusions  
- concern that the included patients did not match the review question (concern: low)  
 Reference standard:  
- the reference standard was likely to correctly classify the target condition  
- concern that the reference-standard test, its conduct, or interpretation differs from the review question (concern: low)  
 Flow and timing:  
- all patients received a reference standard  
- all patients received the same reference standard | Patient selection:  
- unclear if consecutive sample of patients were enrolled  
- the selection of patients could have introduced bias (risk: unclear)  
 Index tests:  
- unsure if the index test results were interpreted without knowledge of the results of the reference standard  
- concern that the index test, its conduct, or interpretation differs from the review question (concern: uncertain)  
- the conduct or interpretation of the index test could have introduced bias (risk: unclear)  
 Reference standard:  
- unclear if the reference-standard results were interpreted without knowledge of the results of the index test  
- the reference standard, its conduct, or its interpretation could have introduced bias (risk: unclear)  
 Flow and timing:  
- unclear if there was an appropriate interval between index test and reference standard  
- not all patients were included in the analysis  
- the patient flow could have introduced bias (risk: uncertain) |
<table>
<thead>
<tr>
<th>First Author, Publication Date</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Hjortshoj, 2011²¹ | Patient selection:  - case-control design avoided  - concern that the included patients did not match the review question (concern: low)  
Reference standard:  - the reference standard was likely to correctly classify the target condition  - concern that the reference-standard test, its conduct, or interpretation differs from the review question (concern: low)  
Flow and timing:  - there was an appropriate interval between index test and reference standard  - all patients received a reference standard  - all patients received the same reference standard  - all patients were included in the analysis  - the patient flow could have introduced bias (risk: low) | Patient selection:  - unclear if consecutive sample of patients were enrolled  - unclear if the study avoided inappropriate exclusions  - the selection of patients could have introduced bias (risk: unclear)  
Index tests:  - unsure if the index test results were interpreted without knowledge of the results of the reference standard  - concern that the index test, its conduct, or interpretation differs from the review question (concern: uncertain)  - the conduct or interpretation of the index test could have introduced bias (risk: unclear)  
Reference standard:  - unsure if the reference-standard results were interpreted without knowledge of the results of the index test  - the reference standard, its conduct, or its interpretation could have introduced bias (risk: low) |}

| Ivandic, 2014¹⁷ | Patient selection:  - consecutive sample of patients enrolled  - case-control design avoided  - the study avoided inappropriate exclusions  - the selection of patients could have introduced bias (risk: low)  - concern that the included patients did not match the review question (concern: low)  
Index tests:  - concern that the index test, its conduct, or interpretation differs from the review question (concern: low)  
Reference standard:  - the reference standard was likely to correctly classify the target condition  - concern that the reference-standard test, its conduct, or interpretation differs from the review question (concern: low)  
Flow and timing:  - all patients were included in the analysis | Index tests:  - unsure if the index test results were interpreted without knowledge of the results of the reference standard  - the conduct or interpretation of the index test could have introduced bias (risk: unclear)  
Reference standard:  - unsure if the reference-standard results were interpreted without knowledge of the results of the index test  - the reference standard, its conduct, or its interpretation could have introduced bias (risk: unclear)  
Flow and timing:  - unclear if there was an appropriate interval between index test and reference standard  - unclear if all patients received a reference standard  - the patient flow could have introduced bias (risk: unclear) |
<table>
<thead>
<tr>
<th>First Author, Publication Date</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Lee-Lewandrowski, 2011 | Patient selection:  
- case-control design avoided  
- concern that the included patients did not match the review question (concern: low)  
Index tests:  
- the index test results were interpreted without knowledge of the results of the reference standard  
- the conduct or interpretation of the index test could have introduced bias (risk: low)  
- concern that the index test, its conduct, or interpretation differs from the review question (concern: low)  
Reference standard:  
- the reference standard was likely to correctly classify the target condition  
- the reference standard, its conduct, or its interpretation could have introduced bias (risk: low)  
- concern that the reference-standard test, its conduct, or interpretation differs from the review question (concern: low)  
Flow and timing:  
- there was an appropriate interval between index test and reference standard  
- all patients received a reference standard  
- all patients received the same reference standard  
- the patient flow could have introduced bias (risk: low) | Patient selection:  
- unclear if consecutive sample of patients were enrolled  
- unclear if the study avoided inappropriate exclusions  
- the selection of patients could have introduced bias (risk: unclear)  
Reference standard:  
- unclear if the reference standard results were interpreted without knowledge of the results of the index test  
Flow and timing:  
- not all patients were included in the analysis |
| Nilsson, 2013; Andersson, 2015 | Patient selection:  
- case-control design avoided  
- the study avoided inappropriate exclusions  
- concern that the included patients did not match the review question (concern: low)  
Index tests:  
- concern that the index test, its conduct, or interpretation differs from the review question (concern: low)  
Flow and timing:  
- all patients were included in the analysis | Patient selection:  
- unclear if consecutive sample of patients were enrolled  
- the selection of patients could have introduced bias (risk: unclear)  
Index tests:  
- unsure if the index test results were interpreted without knowledge of the results of the reference standard  
- the conduct or interpretation of the index test could have introduced bias (risk: unclear)  
Flow and timing:  
- unclear if there was an appropriate interval between index test and reference standard  
- not all patients received a reference standard  
- the patient flow could have introduced bias (risk: unclear) |
<table>
<thead>
<tr>
<th>First Author, Publication Date</th>
<th>Patient selection:</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Palaimalai, 2013<sup>1</sup> | • consecutive sample of patients enrolled  
• case-control design avoided  
• concern that the included patients did not match the review question (concern: low) | Patient selection: | • unclear if the study avoided inappropriate exclusions  
• the selection of patients could have introduced bias (risk: unclear) |
|                               | Reference standard: | Index tests: | • unsure if the index test results were interpreted without knowledge of the results of the reference standard  
• concern that the index test, its conduct, or interpretation differs from the review question (concern: uncertain)  
• the conduct or interpretation of the index test could have introduced bias (risk: unclear) |
|                               | • the reference standard was likely to correctly classify the target condition  
• concern that the reference-standard test, its conduct, or interpretation differs from the review question (concern: low) | Reference standard: | • unsure if the reference-standard results were interpreted without knowledge of the results of the index test  
• the reference standard, its conduct, or its interpretation could have introduced bias (risk: unclear) |
|                               | Flow and timing:  | Flow and timing: | • unclear if there was an appropriate interval between index test and reference standard  
• not all patients were included in the analysis  
• the patient flow could have introduced bias (risk: uncertain) |
|                               | • there was an appropriate interval between index test and reference standard  
• all patients received a reference standard  
• all patients received the same reference standard  
• all patients were included in the analysis  
• the patient flow could have introduced bias (risk: low) | |
| Stengaard, 2013<sup>2</sup>  | Patient selection: | Index tests: | • the conduct or interpretation of the index test could have introduced bias (risk: unclear) |
|                               | • consecutive sample of patients enrolled  
• case-control design avoided  
• the study avoided inappropriate exclusions  
• the selection of patients could have introduced bias (risk: low)  
• concern that the included patients did not match the review question (concern: low) | Reference standard: | • unsure if the reference-standard results were interpreted without knowledge of the results of the index test  
• the reference standard, its conduct, or its interpretation could have introduced bias (risk: unclear) |
|                               | Index tests: | Flow and timing: | • unclear if there was an appropriate interval between index test and reference standard  
• not all patients were included in the analysis  
• the patient flow could have introduced bias (risk: uncertain) |
|                               | • the index test results were interpreted without knowledge of the results of the reference standard  
• concern that the index test, its conduct, or interpretation differs from the review question (concern: low) | |
|                               | Reference standard: | |
|                               | • the reference standard was likely to correctly classify the target condition  
• concern that the reference-standard test, its conduct, or interpretation differs from the review question (concern: low) | |
|                               | Flow and timing: | |
|                               | • all patients received a reference standard  
• all patients received the same reference standard | |
<table>
<thead>
<tr>
<th>First Author, Publication Date</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| ter Avest, 2014<sup>22</sup> | Patient selection:  
- case-control design avoided  
- the study avoided inappropriate exclusions  
- the selection of patients could have introduced bias (risk: low)  
- concern that the included patients did not match the review question (concern: low)  

Index tests:  
- concern that the index test, its conduct, or interpretation differs from the review question (concern: low)  

Reference standard:  
- the reference-standard results were interpreted without knowledge of the results of the index test  
- the reference standard was likely to correctly classify the target condition  
- concern that the reference-standard test, its conduct, or interpretation differs from the review question (concern: low)  

Flow and timing:  
- there was an appropriate interval between index test and reference standard  
- all patients received a reference standard  
- all patients received the same reference standard  
- the patient flow could have introduced bias (risk: low) | Patient selection:  
- unclear if consecutive sample of patients were enrolled  

Index tests:  
- the index test results were interpreted with knowledge of the results of the reference standard  
- the conduct or interpretation of the index test could have introduced bias (risk: uncertain)  

Reference standard:  
- the reference standard, its conduct, or its interpretation could have introduced bias (risk: low)  

Flow and timing:  
- unclear if all patients were included in the analysis |

<table>
<thead>
<tr>
<th>First Author, Publication Date</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Asha, 2014<sup>41,57</sup> | The hypothesis/aim/objective of the study was clearly described.  
- The main outcomes to be measured were clearly described.  
- The characteristics of the patients included in the study were clearly described.  
- The interventions of interest were clearly described.  
- The distribution of principal confounders in each group of subjects to be compared was clearly described.  
- The main findings of the study were clearly described.  
- The study provided estimates of the random variability in the data for the main outcomes.  
- All important adverse events that may have been a consequence of the intervention were reported.  
- The characteristics of patients lost to follow-up were described. | No attempt was made to blind study subjects to the intervention they received.  
- No attempt was made to blind those measuring the main outcomes of the intervention.  
- Compliance with the intervention (regarding patient enrolment) was not reliable.  
- The study may not have had sufficient power to detect a clinically important effect when the probability value for a difference being due to chance was < 5%. |
<table>
<thead>
<tr>
<th>First Author, Publication Date</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Actual probability values were reported (except where ( P ) is less than 0.001).</td>
<td>• No attempt was made to blind study subjects to the intervention they received.</td>
</tr>
<tr>
<td></td>
<td>• The subjects asked to participate in the study were representative of the entire population from which they were recruited.</td>
<td>• No attempt was made to blind those measuring the main outcomes of the intervention.</td>
</tr>
<tr>
<td></td>
<td>• The staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients receive.</td>
<td>• It is unclear if the time period between the intervention and outcome was the same for cases and controls.</td>
</tr>
<tr>
<td></td>
<td>• It was made clear if any of the results of the study were based on data dredging.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The time period between the intervention and outcome was the same for cases and controls.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Statistical tests used to assess the main outcomes were appropriate.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The main outcome measures used were accurate (valid and reliable).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The cases and controls were recruited from the same population.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The cases and controls were recruited over the same time.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Study subjects were randomized to intervention groups.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The randomized intervention assignment was concealed from both patients and health care staff until recruitment was complete and irrevocable.</td>
<td></td>
</tr>
<tr>
<td>Collinson, 2004(^{50})</td>
<td>• There was adequate adjustment for confounding in the analyses from which the main findings were drawn.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Losses of patients to follow-up were taken into account.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The hypothesis/aim/objective of the study was clearly described.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The main outcomes to be measured were clearly described.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The characteristics of the patients included in the study were clearly described.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The interventions of interest were clearly described.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The distributions of principal confounders in each group of subjects to be compared was clearly described.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The main findings of the study were clearly described.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The study provided estimates of the random variability in the data for the main outcomes.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• All important adverse events that may have been a consequence of the intervention were reported.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The characteristics of patients lost to follow-up were described.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Actual probability values were reported (except where ( P &lt; 0.001 )).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The subjects asked to participate in the study were representative of the entire population from which they were recruited.</td>
<td></td>
</tr>
<tr>
<td>First Author, Publication Date</td>
<td>Strengths</td>
<td>Limitations</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
|                                | • The staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients receive.  
  • It was made clear if any of the results of the study were based on data dredging.  
  • Compliance with the intervention was reliable.  
  • The main outcome measures used were accurate (valid and reliable).  
  • Statistical tests used to assess the main outcomes were appropriate.  
  • The cases and controls were recruited from the same population.  
  • The cases and controls were recruited over the same time.  
  • Study subjects were randomized to intervention groups.  
  • The randomized intervention assignment was concealed from both patients and health care staff until recruitment was complete and irrevocable.  
  • There was adequate adjustment for confounding in the analyses from which the main findings were drawn.  
  • Losses of patients to follow-up were taken into account.  
  • The study had sufficient power to detect a clinically important effect when the probability value for a difference being due to chance was < 5%.  
  • The hypothesis/aim/objective of the study was clearly described.  
  • The main outcomes to be measured were clearly described.  
  • Study subjects were randomized to intervention group.  
  • The characteristics of the patients included in the study were clearly described.  
  • The interventions of interest were clearly described.  
  • Those measuring the main outcomes of the intervention were blinded to the allocation.  
  • The distributions of principal confounders in each group of subjects to be compared were clearly described.  
  • The main findings of the study were clearly described.  
  • The study provided estimates of the random variability in the data for the main outcomes.  
  • All important adverse events that may have been a consequence of the intervention were reported.  
  • The subjects asked to participate in the study were representative of the entire population from which they were recruited.  
  • Actual probability values were reported.  
  • The staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients receive.  
  • It could not be determined whether the study had sufficient power to detect a clinically important effect when the probability value for a difference being due to chance was < 5%.) |
<table>
<thead>
<tr>
<th>First Author, Publication Date</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Goodacre, 2011<sup>3</sup>     | - The hypothesis/aim/objective of the study was clearly described.  
- The main outcomes to be measured were clearly described.  
- The characteristics of the patients included in the study were clearly described.  
- The interventions of interest were clearly described.  
- The distributions of principal confounders in each group of subjects to be compared were clearly described.  
- The main findings of the study were clearly described.  
- The study provided estimates of the random variability in the data for the main outcomes.  
- An attempt was made to blind those measuring the main outcomes of the intervention.  
- All important adverse events that may have been a consequence of the intervention were reported.  
- The characteristics of patients lost to follow-up were described.  
- Actual probability values were reported.  
- The staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients receive.  
- It was made clear if any of the results of the study were based on data dredging.  
- The time period between the intervention and outcome was the same for cases and controls.  
- Statistical tests used to assess the main outcomes were appropriate.  
- The main outcome measures used were accurate (valid and reliable).  
- The cases and controls were recruited from the same population.  
- There was adequate adjustment for confounding in the analyses from which the main findings were drawn. | - No attempt was made to blind study subjects to the intervention they received.  
- It is unclear if compliance with the intervention was reliable.  
- It could not be determined whether the randomized intervention assignment was concealed from both patients and health care staff until recruitment was complete and irrevocable.  
- It could not be determined whether the subjects asked to participate in the study were representative of the entire population from which they were recruited. |
<table>
<thead>
<tr>
<th>First Author, Publication Date</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
|                               | • Losses of patients to follow-up were taken into account.  
  • The study had sufficient power to detect a clinically important effect when the probability value for a difference being due to chance was < 5%. | • The characteristics of the patients included in the study were not clearly described.  
  • The distributions of principal confounders in each group of subjects to be compared were not described.  
  • Adverse events that may have been a consequence of the intervention were not reported.  
  • Compliance with the intervention was not reliable.  
  • It could not be determined whether an attempt was made to blind study subjects to the intervention they received.  
  • It could not be determined whether an attempt was made to blind those measuring the main outcomes of the intervention.  
  • It could not be determined whether randomized intervention assignment was concealed from both patients and health care staff until recruitment was complete and irrevocable.  
  • It could not be determined if there was adequate adjustment for confounding in the analyses from which the main findings were drawn.  
  • It could not be determined whether the subjects asked to participate in the study were representative of the entire population from which they were recruited. | |
| Loten, 2010^a | • The hypothesis/aim/objective of the study was clearly described.  
  • The main outcomes to be measured were clearly described.  
  • The interventions of interest were clearly described.  
  • The main findings of the study were clearly described.  
  • The study provided estimates of the random variability in the data for the main outcomes.  
  • The characteristics of patients lost to follow-up were described.  
  • Actual probability values were reported.  
  • The staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients receive.  
  • It was made clear if any of the results of the study were based on data dredging.  
  • The time period between the intervention and outcome was the same for cases and controls.  
  • Statistical tests used to assess the main outcomes were appropriate.  
  • The main outcome measures used were accurate (valid and reliable).  
  • The cases and controls were recruited from the same population.  
  • Study subjects were randomized to intervention group.  
  • Losses of patients to follow-up were taken into account.  
  • The study had sufficient power to detect a clinically important effect when the probability value for a difference being due to chance was < 5%. | |
| Renaud, 2008^b | • The hypothesis/aim/objective of the study was clearly described.  
  • The main outcomes to be measured were clearly described.  
  • The characteristics of the patients included in the study were clearly described.  
  • The interventions of interest were clearly described.  
  • The distribution of principal confounders in each group of subjects to be compared was clearly described.  
  • The main findings of the study were clearly described.  
  • The study provided estimates of the random variability in the data for the main outcomes.  
  • All important adverse events that may have happened were reported.  
  • The number and characteristics of patients lost to follow-up were not described.  
  • The staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients receive, except that the study only occurred on weekdays, which may differ from weekend processes and procedures.  
  • No attempt was made to blind study subjects to the intervention they received.  
  • Some attempt was made to blind those measuring the main outcomes of the intervention, but those performing the testing and treating patients directly were not blinded.  
  • It is unclear if losses of patients to follow-up were taken into account. | |
<table>
<thead>
<tr>
<th>First Author, Publication Date</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
|                               | - been a consequence of the intervention were reported.  
|                               | - Actual probability values were reported (except where \( P < 0.001 \)).  
|                               | - The subjects asked to participate in the study were representative of the entire population from which they were recruited.  
|                               | - It was made clear if any of the results of the study were based on data dredging.  
|                               | - The time period between the intervention and outcome was the same for cases and controls.  
|                               | - Statistical tests used to assess the main outcomes were appropriate.  
|                               | - Compliance with the intervention was reliable.  
|                               | - The main outcome measures used were accurate (valid and reliable).  
|                               | - The cases and controls were recruited from the same population.  
|                               | - The cases and controls were recruited over the same time.  
|                               | - Study subjects were randomized to intervention groups.  
|                               | - The randomized intervention assignment was concealed from both patients and health care staff until recruitment was complete and irrevocable.  
|                               | - There was adequate adjustment for confounding in the analyses from which the main findings were drawn.  
|                               | - The study had sufficient power to detect a clinically important effect (except for mortality) when the probability value for a difference being due to chance was < 5%.  
| Ryan, 2009<sup>6</sup>         | - The hypothesis/aim/objective of the study was clearly described.  
|                               | - The main outcomes to be measured were clearly described.  
|                               | - The characteristics of the patients included in the study were clearly described.  
|                               | - The interventions of interest were clearly described.  
|                               | - The distributions of principal confounders in each group of subjects to be compared were clearly described.  
|                               | - The main findings of the study were clearly described.  
|                               | - The study provided estimates of the random variability in the data for the main outcomes.  
|                               | - The characteristics of patients lost to follow-up were described.  
|                               | - The staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients receive.  
|                               | - It was made clear if any of the results of the study were based on data dredging.  
|                               | - The time period between the intervention and outcome was the same for cases and controls.  
|                               | - The subjects asked to participate in the study were not completely representative of the entire population from which they were recruited, as this was a convenience sample.  
|                               | - It could not be determined whether an attempt was made to blind study subjects to the intervention they received.  
|                               | - It could not be determined whether randomized intervention assignment was concealed from both patients and health care staff until recruitment was complete and irrevocable.  
|                               | - It is unclear if an attempt was made to blind those measuring the main outcomes of the intervention.  
|                               | - Compliance with the intervention was not reliable.  
|                               | - Actual probability values were not reported.  
|                               | - Adverse events that may have been a consequence of the intervention were not reported.  
|                               | - The subjects asked to participate in the study were not completely representative of the entire population from which they were recruited, as this was a convenience sample.  
|                               | - It could not be determined whether an attempt was made to blind study subjects to the intervention they received.  
|                               | - It could not be determined whether randomized intervention assignment was concealed from both patients and health care staff until recruitment was complete and irrevocable.  
|                               | - It is unclear if an attempt was made to blind those measuring the main outcomes of the intervention.  
|                               | - Compliance with the intervention was not reliable.
<table>
<thead>
<tr>
<th>First Author, Publication Date</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
|                               | - Outcome was the same for cases and controls.  
|                               |   - Statistical tests used to assess the main outcomes were appropriate.  
|                               |   - The main outcome measures used were accurate (valid and reliable).  
|                               |   - The cases and controls were recruited from the same population.  
|                               |   - The cases and controls were recruited over the same time.  
|                               |   - Study subjects were randomized to intervention group.  
|                               |   - There was adequate adjustment for confounding in the analyses from which the main findings were drawn.  
|                               |   - Losses of patients to follow-up were taken into account.  
|                               |   - The study had sufficient power to detect a clinically important effect when the probability value for a difference being due to chance was < 5%.  |   - The characteristics of the patients included in the study were not described.  
|                               |   - Adverse events that may have been a consequence of the intervention were not reported.  
|                               |   - The characteristics of patients lost to follow-up were not described.  
|                               |   - No attempt was made to blind those measuring the main outcomes of the intervention.  
|                               |   - It was not made clear if any of the results of the study were based on data dredging.  
|                               |   - It is unclear if compliance with the intervention was reliable.  
|                               |   - Study subjects were not randomized to intervention groups.  
<p>|                               |   - Losses of patients to follow-up were not reported.  |</p>
<table>
<thead>
<tr>
<th>First Author, Publication Date</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Apple, 2006<sup>3</sup> | • The hypothesis/aim/objective of the study was clearly described.  
• The main outcomes to be measured were clearly described.  
• The characteristics of the patients included in the study were clearly described.  
• The interventions of interest were clearly described.  
• The distribution of principal confounders in each group of subjects to be compared was clearly described.  
• The main findings of the study were clearly described.  
• The study provided estimates of the random variability in the data for the main outcomes.  
• All important adverse events that may have been a consequence of the intervention were reported.  
• Actual probability values were reported (except where $P < 0.001$).  
• The subjects asked to participate in the study were representative of the entire population from which they were recruited.  
• It was made clear if any of the results of the study were based on data dredging.  
• The time period between the intervention and outcome was the same for cases and controls.  
• Statistical tests used to assess the main outcomes were appropriate.  
• Compliance with the intervention was reliable.  
• The main outcome measures used were accurate (valid and reliable).  
• The cases and controls were recruited from the same population. | • The characteristics of patients lost to follow-up were not described.  
• The staff, places, and facilities where the patients were treated were not completely representative of the treatment the majority of patients receive (patients were selected from a cardiology service, not a hospital ED).  
• No attempt was made to blind study subjects to the intervention they received.  
• No attempt was made to blind those measuring the main outcomes of the intervention.  
• The cases and controls were not recruited over the same time, as this was a pre/post study.  
• Study subjects were not randomized to intervention groups.  
• There was not adequate adjustment for confounding in the analyses from which the main findings were drawn.  
• Losses of patients to follow-up were taken into account.  
• It is unclear if losses of patients to follow-up were taken into account.  
• The study did not have sufficient power to detect a clinically important effect when the probability value for a difference being due to chance was $< 0.05$. |
| Caragher, 2002<sup>3</sup> | • The hypothesis/aim/objective of the study was clearly described.  
• The main outcomes to be measured were clearly described.  
• The interventions of interest were clearly described.  
• The main findings of the study were clearly described.  
• All important adverse events that may have been a consequence of the intervention were reported.  
• The subjects asked to participate in the study were representative of the entire population from which they were recruited.  
• The staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients receive.  
• It was made clear if any of the results of the study were based on data dredging.  
• The time period between the intervention and outcome was the same for cases and controls. | • The characteristics of the patients included in the study were not described.  
• The study did not provide estimates of the random variability in the data for the main outcomes.  
• The characteristics of patients lost to follow-up were not described.  
• Actual probability values were not reported.  
• No attempt was made to blind those measuring the main outcomes of the intervention.  
• It is unclear if statistical tests used to assess the main outcomes were appropriate.  
• Study subjects were not randomized to intervention groups.  
• There was no adjustment for confounding in the analyses from which the main findings were drawn.  
• Losses of patients to follow-up were not reported.  
• It is unclear if the study had sufficient power to detect a clinically important effect when the probability value for a difference being due to chance was $< 0.05$. |
<table>
<thead>
<tr>
<th>First Author, Publication Date</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
|                               | - Compliance with the intervention was reliable.  
  - The main outcome measures used were accurate (valid and reliable).  
  - The cases and controls were recruited from the same population.  
  - The cases and controls were recruited over the same time. | - detect a clinically important effect when the probability value for a difference being due to chance was < 5%. |
| Cramer, 2007<sup>24</sup>     | - The hypothesis/aim/objective of the study was clearly described.  
  - The main outcomes to be measured were clearly described.  
  - The interventions of interest were clearly described.  
  - The main findings of the study were clearly described.  
  - All important adverse events that may have been a consequence of the intervention were reported.  
  - The characteristics of patients lost to follow-up were described.  
  - Actual probability values were reported (except where $P < 0.001$).  
  - It was made clear if any of the results of the study were based on data dredging.  
  - The time period between the intervention and outcome was the same for cases and controls.  
  - Statistical tests used to assess the main outcomes were appropriate.  
  - The main outcome measures used were accurate (valid and reliable).  
  - The cases and controls were recruited from the same population.  
  - The cases and controls were recruited over the same time.  
  - The study had sufficient power to detect a clinically important effect when the probability value for a difference being due to chance was < 5%. | - The characteristics of the patients included in the study were not clearly described.  
  - The study did not provide estimates of the random variability in the data for the main outcomes.  
  - It is unclear if the subjects asked to participate in the study were representative of the entire population from which they were recruited.  
  - It is unclear if the staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients receive.  
  - No attempt was made to blind those measuring the main outcomes of the intervention.  
  - It is unclear if compliance with the intervention (regarding patient enrolment) was reliable.  
  - Study subjects were not randomized to intervention groups.  
  - There was no adjustment for confounding in the analyses from which the main findings were drawn.  
  - It is unclear if losses of patients to follow-up were taken into account. |
<table>
<thead>
<tr>
<th>First Author, Publication Date</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Cullen, 2012⁴⁴ | - The hypothesis/aim/objective of the study was clearly described.  
- The main outcomes to be measured were clearly described.  
- The interventions of interest were clearly described.  
- The main findings of the study were clearly described.  
- The study provided estimates of the random variability in the data for the main outcomes.  
- All important adverse events that may have been a consequence of the intervention were reported.  
- Actual probability values were reported.  
- The staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients receive.  
- The characteristics of the patients included in the study were clearly described.  
- The distributions of principal confounders in each group of subjects to be compared were clearly described.  
- It was made clear if any of the results of the study were based on data dredging.  
- An attempt was made to blind those measuring the main outcomes of the intervention.  
- Statistical tests used to assess the main outcomes were appropriate.  
- The main outcome measures used were accurate (valid and reliable).  
- The time period between the intervention and outcome was the same for cases and controls.  
- The cases and controls were recruited from the same population. | - The characteristics of patients lost to follow-up were not described.  
- It could not be determined if compliance with the intervention was reliable.  
- Study subjects were not randomized to intervention group.  
- It could not be determined if there was adequate adjustment for confounding in the analyses from which the main findings were drawn.  
- It is unclear whether losses of patients to follow-up were not taken into account.  
- It could not be determined whether the subjects asked to participate in the study were representative of the entire population from which they were recruited.  
- It could not be determined whether the study had sufficient power to detect a clinically important effect where the probability value for a difference being due to chance < 5%. |
| Deledda, 2011⁴⁵ | - The hypothesis/aim/objective of the study was clearly described.  
- The main outcomes to be measured were clearly described.  
- The characteristics of the patients included in the study were clearly described.  
- The interventions of interest were clearly described.  
- The distribution of principal confounders in each group of subjects to be compared was clearly described.  
- The main findings of the study were clearly described.  
- The study provided estimates of the random variability in the data for the main outcomes.  
- The subjects asked to participate in the study were representative of the entire population from which they were recruited.  
- The staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients receive. | - Adverse events that may have been a consequence of the intervention were not reported.  
- The characteristics of patients lost to follow-up were not described.  
- Probability values were not reported.  
- No attempt was made to blind study subjects to the intervention they received.  
- No attempt was made to blind those measuring the main outcomes of the intervention.  
- It is unclear if compliance with the intervention was reliable.  
- The cases and controls were not recruited from the same population.  
- The cases and controls were not recruited over the same time.  
- Study subjects were not randomized to intervention groups.  
- There was no adjustment for confounding in the analyses from which the main findings were drawn. |
| First Author, Publication Date | Strengths                                                                                                                                                                                                 | Limitations                                                                                                                                                                                                 
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Di Serio, 2003⁴¹</td>
<td>- The hypothesis/aim/objective of the study was clearly described.</td>
<td>- The characteristics of the patients included in the study were not described.</td>
</tr>
<tr>
<td></td>
<td>- The main outcomes to be measured were clearly described.</td>
<td>- No adverse events that may have been a consequence of the intervention were reported.</td>
</tr>
<tr>
<td></td>
<td>- The interventions of interest were clearly described.</td>
<td>- It is unclear if subjects asked to participate in the study were representative of the entire population from which they were recruited.</td>
</tr>
<tr>
<td></td>
<td>- The main findings of the study were clearly described.</td>
<td>- It is unclear if the staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients receive.</td>
</tr>
<tr>
<td></td>
<td>- The study provided estimates of the random variability in the data for the main outcomes.</td>
<td>- No attempt was made to blind those measuring the main outcomes of the intervention.</td>
</tr>
<tr>
<td></td>
<td>- One probability value was reported.</td>
<td>- It was not clear if any of the results of the study were based on data dredging.</td>
</tr>
<tr>
<td></td>
<td>- The time period between the intervention and outcome was the same for cases and controls.</td>
<td>- It is not clear if compliance with the intervention was reliable.</td>
</tr>
<tr>
<td></td>
<td>- Statistical tests used to assess the main outcomes were appropriate.</td>
<td>- It is not clear if the cases and controls were recruited from the same population.</td>
</tr>
<tr>
<td></td>
<td>- The study had sufficient power to detect a clinically important effect where the probability value for a difference being due to chance &lt; 5%.</td>
<td>- It is not clear if the cases and controls were recruited over the same time.</td>
</tr>
<tr>
<td></td>
<td>- The authors indicated the main outcome measures used were a limitation.</td>
<td>- Study subjects were not randomized to intervention groups.</td>
</tr>
<tr>
<td></td>
<td>- Losses of patients to follow-up were not taken into account.</td>
<td>- There was no adjustment for confounding in the analyses from which the main findings were drawn.</td>
</tr>
<tr>
<td></td>
<td><strong>Limitations</strong></td>
<td>- Losses of patients to follow-up were not taken into account.</td>
</tr>
</tbody>
</table>

| Eggers, 2011⁴²                | - The hypothesis/aim/objective of the study was clearly described.                                                                                                                                      | - The characteristics of patients lost to follow-up were not described.                                                                                                                                    |
|                               | - The main outcomes to be measured were clearly described.                                                                                                                                               | - No adverse events that may have been a consequence of the intervention were reported.                                                                                                                    |
|                               | - The characteristics of the patients included in the study were clearly described.                                                                                                                      | - It is unclear if subjects asked to participate in the study were representative of the entire population from which they were recruited.                                                                 |
|                               | - The interventions of interest were clearly described.                                                                                                                                                   | - It is unclear if the staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients receive. |
|                               | - The distributions of principal confounders in each group of subjects to be compared were clearly described.                                                                                              | - No attempt was made to blind those measuring the main outcomes of the intervention.                                                                                                                     |
|                               | - The main findings of the study were clearly described.                                                                                                                                                   | - It was not clear if any of the results of the study were based on data dredging.                                                                                                                          |
|                               | - The study provided estimates of the random variability in the data for the main outcomes.                                                                                                                | - It is not clear if compliance with the intervention was reliable.                                                                                                                                         |
|                               | - The characteristics of patients lost to follow-up were not described.                                                                                                                                    | - It is not clear if the cases and controls were recruited from the same population.                                                                                                                        |
|                               | - Study subjects were not randomized to intervention groups.                                                                                                                                              | - It is not clear if the cases and controls were recruited over the same time.                                                                                                                               |
|                               | - There was no adjustment for confounding in the analyses from which the main findings were drawn.                                                                                                           | - Study subjects were not randomized to intervention groups.                                                                                                                                              |
|                               | - Losses of patients to follow-up were not taken into account.                                                                                                                                           | - There was no adjustment for confounding in the analyses from which the main findings were drawn.                                                                                                           |

**First Author, Publication Date:**  
**Strengths:**  
- It was made clear if any of the results of the study were based on data dredging.  
- The time period between the intervention and outcome was the same for cases and controls.  
- Statistical tests used to assess the main outcomes were appropriate.  
- The study had sufficient power to detect a clinically important effect where the probability value for a difference being due to chance < 5%.  

**Limitations:**  
- The authors indicated the main outcome measures used were a limitation.  
- Losses of patients to follow-up were not taken into account.
<table>
<thead>
<tr>
<th>First Author, Publication Date</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
|                               | variability in the data for the main outcomes.  
• All important adverse events that may have been a consequence of the intervention were reported.  
• Actual probability values were reported.  
• The staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients receive.  
• It was made clear if any of the results of the study were based on data dredging.  
• The time period between the intervention and outcome was the same for cases and controls.  
• Statistical tests used to assess the main outcomes were appropriate.  
• The main outcome measures used were accurate (valid and reliable).  
• The cases and controls were recruited from the same population.  
• There was adequate adjustment for confounding in the analyses from which the main findings were drawn. | It could not be determined whether the study had sufficient power to detect a clinically important effect where the probability value for a difference being due to chance < 5%. |
| Guo, 2006²¹ | The hypothesis/aim/objective of the study was clearly described.  
• The main outcomes to be measured were clearly described.  
• The interventions of interest were clearly described.  
• The distributions of principal confounders in each group of subjects to be compared were clearly described.  
• The main findings of the study were clearly described.  
• The study provided estimates of the random variability in the data for the main outcomes.  
• All important adverse events that may have been a consequence of the intervention were reported.  
• The characteristics of patients lost to follow-up were described.  
• Actual probability values were reported.  
• The staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients receive.  
• It was made clear if any of the results of the study were based on data dredging.  
• The time period between the intervention and outcome was the same for cases and controls.  
• Statistical tests used to assess the main outcomes were appropriate.  
• Compliance with the intervention was reliable.  
• The main outcome measures used were accurate (valid and reliable).  
• The cases and controls were recruited from the same population. | The characteristics of all patients included in the study were not clearly described.  
• It could not be determined whether an attempt was made to blind those measuring the main outcomes of the intervention.  
• Study subjects were not randomized to intervention group.  
• It could not be determined whether the subjects asked to participate in the study were representative of the entire population from which they were recruited.  
• It could not be determined whether the study had sufficient power to detect a clinically important effect where the probability value for a difference being due to chance < 5%. |
<table>
<thead>
<tr>
<th>First Author, Publication Date</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Koehler, 2013\(^3\)           | • The hypothesis/aim/objective of the study was clearly described.  
• The main outcomes to be measured were clearly described.  
• The interventions of interest were clearly described.  
• The main findings of the study were clearly described.  
• The study provided estimates of the random variability in the data for the main outcomes.  
• Actual probability values were reported.  
• The staff, places, and facilities where the patients were treated were representative of the treatment majority of patients receive.  
• It was made clear if any of the results of the study were based on data dredging.  
• Statistical tests used to assess the main outcomes were appropriate.  
• The main outcome measures used were accurate (valid and reliable). | • The characteristics of the patients included in the study were not clearly described.  
• The distributions of principal confounders in each group of subjects to be compared were not clearly described.  
• No attempt was made to blind study subjects to the intervention they received.  
• It could not be determined whether an attempt was made to blind those measuring the main outcomes of the intervention.  
• The time period between the intervention and outcome was not the same for cases and controls.  
• Adverse events that may have been a consequence of the intervention were reported.  
• It is unclear if compliance with the intervention was reliable.  
• The cases and controls were not recruited from the same population.  
• It could not be determined if there was adequate adjustment for confounding in the analyses from which the main findings were drawn.  
• Study subjects were not randomized to intervention group.  
• It could not be determined whether the subjects asked to participate in the study were representative of the entire population from which they were recruited.  
• It could not be determined whether the study had sufficient power to detect a clinically important effect where the probability value for a difference being due to chance < 5%. |
| Lee-Lewandowski, 2002\(^3\)    | • The hypothesis/aim/objective of the study was clearly described.  
• The main outcomes to be measured were clearly described.  
• The interventions of interest were clearly described.  
• The main findings of the study were clearly described.  
• Actual probability values were reported (except where \(P\) is less than 0.001).  
• The staff, places, and facilities where the patients were treated were representative of the treatment majority of patients receive.  
• An attempt was made to blind those measuring the main outcomes of the intervention.  
• It was made clear if any of the results of the study were based on data dredging. | • The characteristics of the patients included in the study were not described.  
• The distributions of principal confounders in each group of subjects to be compared were not described.  
• The study did not provide estimates of the random variability in the data for the main outcomes.  
• Adverse events that may have been a consequence of the intervention were not reported.  
• It is unclear if the subjects measured in the study were representative of the entire population from which they were recruited because there was no patient information.  
• The characteristics of patients lost to follow-up were not described.  
• It is unclear if statistical tests used to assess |
<table>
<thead>
<tr>
<th>First Author, Publication Date</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meek, 2012&lt;sup&gt;28&lt;/sup&gt;</td>
<td>• The hypothesis/aim/objective of the study was clearly described.</td>
<td>• The characteristics of the patients included in the study were not clearly described.</td>
</tr>
<tr>
<td></td>
<td>• The main outcomes to be measured were clearly described.</td>
<td>• The distributions of principal confounders in each group of subjects to be compared were not clearly described.</td>
</tr>
<tr>
<td></td>
<td>• The interventions of interest were clearly described.</td>
<td>• The time period between the intervention and outcome was not the same for cases and controls.</td>
</tr>
<tr>
<td></td>
<td>• The main findings of the study were clearly described.</td>
<td>• The cases and controls were not recruited from the same population.</td>
</tr>
<tr>
<td></td>
<td>• The study provided estimates of the random variability in the data for the main outcomes.</td>
<td>• The characteristics of patients lost to follow-up were not described.</td>
</tr>
<tr>
<td></td>
<td>• All important adverse events that may have been a consequence of the intervention were reported.</td>
<td>• It could not be determined if compliance with the intervention was reliable.</td>
</tr>
<tr>
<td></td>
<td>• Actual probability values were reported.</td>
<td>• It could not be determined whether an attempt was made to blind those measuring the main outcomes of the intervention.</td>
</tr>
<tr>
<td></td>
<td>• The staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients receive.</td>
<td>• Study subjects were not randomized to intervention group.</td>
</tr>
<tr>
<td></td>
<td>• It was made clear if any of the results of the study were based on data dredging.</td>
<td>• It could not be determined if there was adequate adjustment for confounding in the analyses from which the main findings were drawn.</td>
</tr>
<tr>
<td></td>
<td>• Statistical tests used to assess the main outcomes were appropriate.</td>
<td>• Losses of patients to follow-up were not taken into account.</td>
</tr>
<tr>
<td></td>
<td>• The main outcome measures used were accurate (valid and reliable).</td>
<td>• It could not be determined whether the subjects asked to participate in the study were representative of the entire population from which they were recruited.</td>
</tr>
<tr>
<td></td>
<td>• The study had sufficient power to detect a clinically important effect where the probability value for a difference being due to chance &lt; 5%.</td>
<td>• No attempt was made to blind those</td>
</tr>
<tr>
<td>Mozina, 2010&lt;sup&gt;35&lt;/sup&gt;</td>
<td>• The hypothesis/aim/objective of the study was clearly described.</td>
<td>• The characteristics of the patients included in the study were not described.</td>
</tr>
<tr>
<td></td>
<td>• The main outcomes to be measured were clearly described.</td>
<td>• No adverse events that may have been a consequence of the intervention were reported.</td>
</tr>
<tr>
<td></td>
<td>• The interventions of interest were clearly described.</td>
<td>• The characteristics of patients lost to follow-up were not described.</td>
</tr>
<tr>
<td></td>
<td>• The main findings of the study were clearly described.</td>
<td>• It is not clear if the subjects asked to participate in the study were representative of the entire population from which they were recruited.</td>
</tr>
<tr>
<td></td>
<td>• The study provided estimates of the random variability in the data for the main outcomes.</td>
<td>• It is not clear if the staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients receive.</td>
</tr>
<tr>
<td></td>
<td>• Actual probability values were reported (except where ( P &lt; 0.001 )).</td>
<td>• No attempt was made to blind those</td>
</tr>
<tr>
<td></td>
<td>• The staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients receive.</td>
<td></td>
</tr>
<tr>
<td>First Author, Publication Date</td>
<td>Strengths</td>
<td>Limitations</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>• It was made clear if any of the results of the study were based on data dredging.</td>
<td>measuring the main outcomes of the intervention.</td>
</tr>
<tr>
<td></td>
<td>• The time period between the intervention and outcome was the same for cases and controls.</td>
<td>• Study subjects were not randomized to intervention groups.</td>
</tr>
<tr>
<td></td>
<td>• Statistical tests used to assess the main outcomes were appropriate.</td>
<td>• There was no adjustment for confounding in the analyses from which the main findings were drawn.</td>
</tr>
<tr>
<td></td>
<td>• Compliance with the intervention was reliable.</td>
<td>• Losses of patients to follow-up were not reported.</td>
</tr>
<tr>
<td></td>
<td>• The main outcome measures used were accurate (valid and reliable).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The cases and controls were recruited from the same population.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The cases and controls were recruited over the same time.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The study had sufficient power to detect a clinically important effect where the probability value for a difference being due to chance &lt; 5%.</td>
<td></td>
</tr>
<tr>
<td>Nilsson, 2013&lt;sup&gt;61&lt;/sup&gt;</td>
<td>• The hypothesis/aim/objective of the study was clearly described.</td>
<td>• It could not be determined whether an attempt was made to blind those measuring the main outcomes of the intervention.</td>
</tr>
<tr>
<td></td>
<td>• The main outcomes to be measured were clearly described.</td>
<td>• Study subjects were not randomized to intervention group.</td>
</tr>
<tr>
<td></td>
<td>• The characteristics of the patients included in the study were clearly described.</td>
<td>• It could not be determined whether the subjects asked to participate in the study were representative of the entire population from which they were recruited.</td>
</tr>
<tr>
<td></td>
<td>• The interventions of interest were clearly described.</td>
<td>• It could not be determined whether the study had sufficient power to detect a clinically important effect where the probability value for a difference being due to chance &lt; 5%.</td>
</tr>
<tr>
<td></td>
<td>• The distributions of principal confounders in each group of subjects to be compared were clearly described.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The main findings of the study were clearly described.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The study provided estimates of the random variability in the data for 2 main outcomes.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• All important adverse events that may have been a consequence of the intervention were reported.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The characteristics of patients lost to follow-up were described.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Actual probability values were reported.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients receive.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• It was made clear if any of the results of the study were based on data dredging.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Statistical tests used to assess the main outcomes were appropriate.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The main outcome measures used were accurate (valid and reliable).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The cases and controls were recruited over the same time.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• There was adequate adjustment for confounding in the analyses from which the main findings were drawn.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Losses of patients to follow-up were taken into account.</td>
<td></td>
</tr>
<tr>
<td>First Author, Publication Date</td>
<td>Strengths</td>
<td>Limitations</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-----------</td>
<td>-------------</td>
</tr>
</tbody>
</table>
| Ordonez, Llanos, 2006<sup>47</sup> | • The hypothesis/aim/objective of the study was clearly described.  
• The main outcomes to be measured were clearly described.  
• The interventions of interest were clearly described.  
• The main findings of the study were clearly described.  
• All important adverse events that may have been a consequence of the intervention were reported.  
• The subjects asked to participate in the study were representative of the entire population from which they were recruited.  
• The staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients receive.  
• It was made clear if any of the results of the study were based on data dredging.  
• The time period between the intervention and outcome was the same for cases and controls.  
• Statistical tests used to assess the main outcomes were appropriate.  
• Compliance with the intervention was reliable.  
• The main outcome measures used were accurate (valid and reliable).  
• The cases and controls were recruited from the same population.  
• The cases and controls were recruited over the same time. | • The characteristics of the patients included in the study were not clearly described.  
• The distribution of principal confounders in each group of subjects to be compared was not clearly described.  
• The study did not provide estimates of the random variability in the data for the clinical-utility outcomes.  
• The characteristics of patients lost to follow-up were not described.  
• Actual probability values were not reported.  
• No attempt was made to blind study subjects to the intervention they received.  
• No attempt was made to blind those measuring the main outcomes of the intervention.  
• Study subjects were not randomized to intervention groups.  
• There was no adjustment for confounding in the analyses from which the main findings were drawn.  
• Losses of patients to follow-up were not taken into account.  
• It was not stated if the study had sufficient power to detect a clinically important effect where the probability value for a difference being due to chance < 5%. |
| Singer, 2015<sup>91</sup> | • The hypothesis/aim/objective of the study was clearly described.  
• The main outcomes to be measured were clearly described.  
• The characteristics of the patients included in the study were clearly described.  
• The interventions of interest were clearly described.  
• The distribution of principal confounders in each group of subjects to be compared was clearly described.  
• The main findings of the study were clearly described.  
• The study provided estimates of the random variability in the data for the main outcomes.  
• Actual probability values were reported (except where \( P < 0.001 \)).  
• The subjects asked to participate in the study were representative of the entire population from which they were recruited.  
• It was made clear if any of the results of the study were based on data dredging.  
• Statistical tests used to assess the main outcomes were appropriate.  
• The study had sufficient power to detect a | • Adverse events that may have been a consequence of the intervention were not reported.  
• The characteristics of patients lost to follow-up were not described.  
• No attempt was made to blind study subjects to the intervention they received.  
• No attempt was made to blind those measuring the main outcomes of the intervention.  
• The time period between the intervention and outcome was not the same for cases and controls.  
• The authors indicated the main outcome measures used were not accurate (valid and reliable).  
• Compliance with the intervention was not reliable.  
• The cases and controls were not recruited from the same population.  
• The cases and controls were not recruited over the same time.  
• Study subjects were not randomized to intervention groups.  
• There was no adjustment for confounding in |
<table>
<thead>
<tr>
<th>First Author, Publication Date</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Singer, 2005<sup>50</sup>     | • The hypothesis/aim/objective of the study was clearly described.  
• The main outcomes to be measured were clearly described.  
• The characteristics of the patients included in the study were clearly described.  
• The interventions of interest were clearly described.  
• The distribution of principal confounders in each group of subjects to be compared was clearly described.  
• The main findings of the study were clearly described.  
• The study provided estimates of the random variability in the data for the main outcomes.  
• The subjects asked to participate in the study were representative of the entire population from which they were recruited.  
• The staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients receive.  
• It was made clear if any of the results of the study were based on data dredging.  
• The time period between the intervention and outcome was the same for cases and controls. Statistical tests used to assess the main outcomes were appropriate.  
• Compliance with the intervention was reliable.  
• The main outcome measures used were accurate (valid and reliable).  
• The cases and controls were recruited from the same population.  
• There was adequate adjustment for confounding in the analyses from which the main findings were drawn.  
• The study had sufficient power to detect a clinically important effect where the probability value for a difference being due to chance < 5%. | • No adverse events that may have been a consequence of the intervention were reported.  
• Patients lost to follow-up were not reported.  
• Actual probability values were not reported.  
• No attempt was made to blind study subjects to the intervention they received.  
• No attempt was made to blind those measuring the main outcomes of the intervention.  
• The cases and controls were not recruited over the same time, as this was a pre/post study.  
• Study subjects were not randomized to intervention groups.  
• Losses of patients to follow-up were not reported. |
| Sorensen, 2011<sup>48</sup>     | • The hypothesis/aim/objective of the study was clearly described.  
• The main outcomes to be measured were clearly described.  
• The characteristics of the patients included in the study were clearly described.  
• The interventions of interest were clearly described.  
• The distributions of principal confounders in each group of subjects to be compared were clearly described.  
• The main findings of the study were clearly described. | • The time period between the intervention and outcome was not the same for cases and controls.  
• It could not be determined if compliance with the intervention was reliable.  
• The cases and controls were not recruited from the same population.  
• It could not be determined if losses of patients to follow-up were taken into account.  
• It could not be determined whether an attempt was made to blind those measuring the main outcomes of the intervention.  
• Study subjects were not randomized to intervention group. |
<table>
<thead>
<tr>
<th>First Author, Publication Date</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
|                               | - The study provided estimates of the random variability in the data for the main outcomes.  
- All important adverse events that may have been a consequence of the intervention were reported.  
- The characteristics of patients lost to follow-up were described.  
- Actual probability values were reported.  
- The staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients receive.  
- It was made clear if any of the results of the study were based on data dredging.  
- Statistical tests used to assess the main outcomes were appropriate.  
- The main outcome measures used were accurate (valid and reliable).  
- There was adequate adjustment for confounding in the analyses from which the main findings were drawn. | - It could not be determined whether the subjects asked to participate in the study were representative of the entire population from which they were recruited.  
- It could not be determined whether the study had sufficient power to detect a clinically important effect where the probability value for a difference being due to chance < 5%. |
| Stengaard, 2013[13] | - The hypothesis/aim/objective of the study was clearly described.  
- The main outcomes to be measured were clearly described.  
- The characteristics of the patients included in the study were clearly described.  
- The interventions of interest were clearly described.  
- The distributions of principal confounders in each group of subjects to be compared were clearly described.  
- The main findings of the study were clearly described.  
- The study provided estimates of the random variability in the data for the main outcomes.  
- All important adverse events that may have been a consequence of the intervention were reported.  
- The characteristics of patients lost to follow-up were described.  
- Actual probability values were reported.  
- The staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients receive.  
- It was made clear if any of the results of the study were based on data dredging.  
- An attempt was made to blind those measuring the main outcomes of the intervention.  
- Statistical tests used to assess the main outcomes were appropriate.  
- Compliance with the intervention was reliable.  
- The main outcome measures used were accurate (valid and reliable).  
- The cases and controls were recruited from the same population. | - No attempt was made to blind study subjects to the intervention they received.  
- It is unclear if the time period between the intervention and outcome was the same for cases and controls.  
- Study subjects were not randomized to intervention group.  
- It could not be determined whether the subjects asked to participate in the study were representative of the entire population from which they were recruited.  
- It could not be determined whether the study had sufficient power to detect a clinically important effect where the probability value for a difference being due to chance < 5%. |
<table>
<thead>
<tr>
<th>First Author, Publication Date</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• The cases and controls were recruited over the same time.</td>
<td>• Adverse events that may have been a consequence of the intervention were not reported.</td>
<td></td>
</tr>
<tr>
<td>• There was adequate adjustment for confounding in the analyses from which the main findings were drawn.</td>
<td>• The characteristics of patients lost to follow-up were described.</td>
<td></td>
</tr>
<tr>
<td>• Losses of patients to follow-up were taken into account.</td>
<td>• The characteristics of patients lost to follow-up were not described.</td>
<td></td>
</tr>
<tr>
<td>Storrow, 2006&lt;sup&gt;36&lt;/sup&gt;</td>
<td>• The hypothesis/aim/objective of the study was clearly described.</td>
<td>• It is unclear if the subjects asked to participate in the study were representative of the entire population from which they were recruited.</td>
</tr>
<tr>
<td>• The main outcomes to be measured were clearly described.</td>
<td>• No attempt was made to blind those measuring the main outcomes of the intervention.</td>
<td></td>
</tr>
<tr>
<td>• The characteristics of the patients included in the study were clearly described.</td>
<td>• It is unclear if compliance with the intervention was reliable.</td>
<td></td>
</tr>
<tr>
<td>• The interventions of interest were clearly described.</td>
<td>• Study subjects were not randomized to intervention groups.</td>
<td></td>
</tr>
<tr>
<td>• The main findings of the study were clearly described.</td>
<td>• There was no adjustment for confounding in the analyses from which the main findings were drawn.</td>
<td></td>
</tr>
<tr>
<td>• The study provided estimates of the random variability in the data for the main outcomes.</td>
<td>• The characteristics of patients lost to follow-up were not described.</td>
<td></td>
</tr>
<tr>
<td>• Actual probability values were reported (except where ( P &lt; 0.001 )).</td>
<td>• It could not be determined if compliance with the intervention was reliable.</td>
<td></td>
</tr>
<tr>
<td>• The staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients receive.</td>
<td>• It could not be determined whether an attempt was made to blind those measuring the main outcomes of the intervention.</td>
<td></td>
</tr>
<tr>
<td>• It was made clear if any of the results of the study were based on data dredging.</td>
<td>• Study subjects were not randomized to intervention groups.</td>
<td></td>
</tr>
<tr>
<td>• The time period between the intervention and outcome was the same for cases and controls.</td>
<td>• No attempt was made to blind those measuring the main outcomes of the intervention.</td>
<td></td>
</tr>
<tr>
<td>• Statistical tests used to assess the main outcomes were appropriate.</td>
<td>• It is unclear if compliance with the intervention was reliable.</td>
<td></td>
</tr>
<tr>
<td>• The main outcome measures used were accurate (valid and reliable).</td>
<td>• Study subjects were not randomized to intervention groups.</td>
<td></td>
</tr>
<tr>
<td>• The cases and controls were recruited from the same population.</td>
<td>• There was no adjustment for confounding in the analyses from which the main findings were drawn.</td>
<td></td>
</tr>
<tr>
<td>• The cases and controls were recruited over the same time.</td>
<td>• The characteristics of patients included in the study were not clearly described.</td>
<td></td>
</tr>
<tr>
<td>• Losses of patients to follow-up were taken into account.</td>
<td>• The distributions of principal confounders in each group of subjects to be compared were not clearly described.</td>
<td></td>
</tr>
<tr>
<td>• The study had sufficient power to detect a clinically important effect where the probability value for a difference being due to chance &lt; 5%.</td>
<td>• The characteristics of patients lost to follow-up were not described.</td>
<td></td>
</tr>
<tr>
<td>Venge, 2013&lt;sup&gt;35&lt;/sup&gt;</td>
<td>• The hypothesis/aim/objective of the study was clearly described.</td>
<td>• It could not be determined if compliance with the intervention was reliable.</td>
</tr>
<tr>
<td>• The main outcomes to be measured were clearly described.</td>
<td>• It could not be determined whether an attempt was made to blind those measuring the main outcomes of the intervention.</td>
<td></td>
</tr>
<tr>
<td>• The interventions of interest were clearly described.</td>
<td>• Study subjects were not randomized to intervention group.</td>
<td></td>
</tr>
<tr>
<td>• The main findings of the study were clearly described.</td>
<td>• The characteristics of patients included in the study were not clearly described.</td>
<td></td>
</tr>
<tr>
<td>• The study provided estimates of the random variability in the data for the main outcomes.</td>
<td>• The distributions of principal confounders in each group of subjects to be compared were not clearly described.</td>
<td></td>
</tr>
<tr>
<td>• All important adverse events that may have been a consequence of the intervention were reported.</td>
<td>• The characteristics of patients lost to follow-up were not described.</td>
<td></td>
</tr>
<tr>
<td>• Actual probability values were reported.</td>
<td>• It could not be determined if compliance with the intervention was reliable.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First Author, Publication Date</td>
<td>Strengths</td>
<td>Limitations</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------</td>
<td>-------------</td>
</tr>
</tbody>
</table>
|                               | - The staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients receive.  
- It was made clear if any of the results of the study were based on data dredging.  
- Statistical tests used to assess the main outcomes were appropriate.  
- The main outcome measures used were accurate (valid and reliable).  
- The time period between the intervention and outcome was the same for cases and controls.  
- The cases and controls were recruited from the same population. | - It could not be determined if there was adequate adjustment for confounding in the analyses from which the main findings were drawn.  
- Losses of patients to follow-up were not taken into account.  
- It could not be determined whether the subjects asked to participate in the study were representative of the entire population from which they were recruited.  
- It could not be determined whether the study had sufficient power to detect a clinically important effect where the probability value for a difference being due to chance < 5%. |
| Venge, 2010** | - The hypothesis/aim/objective of the study was clearly described.  
- The main outcomes to be measured were clearly described.  
- The interventions of interest were clearly described.  
- The main findings of the study were clearly described.  
- The study provided estimates of the random variability in the data for the main outcomes.  
- All important adverse events that may have been a consequence of the intervention were reported.  
- Actual probability values were reported.  
- The staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients receive.  
- It was made clear if any of the results of the study were based on data dredging.  
- The time period between the intervention and outcome was the same for cases and controls.  
- Statistical tests used to assess the main outcomes were appropriate.  
- The main outcome measures used were accurate (valid and reliable).  
- The cases and controls were recruited from the same population. | - The characteristics of the patients included in the study were not described.  
- The distributions of principal confounders in each group of subjects to be compared were not described.  
- The characteristics of patients lost to follow-up were not described.  
- It could not be determined if compliance with the intervention was reliable.  
- It is unclear if there was adequate adjustment for confounding in the analyses from which the main findings were drawn.  
- It is unclear if losses of patients to follow-up were taken into account.  
- It could not be determined whether an attempt was made to blind those measuring the main outcomes of the intervention.  
- Study subjects were not randomized to intervention group.  
- It could not be determined whether the subjects asked to participate in the study were representative of the entire population from which they were recruited.  
- It could not be determined whether the study had sufficient power to detect a clinically important effect where the probability value for a difference being due to chance < 5%. |
### Table 18: Critical Appraisal of Evidence-Based Guidelines (AGREE II)\(^{15}\)

<table>
<thead>
<tr>
<th>Guideline Producer, Publication Year</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| European Society of Cardiology guidelines, 2011\(^{53}\) | • Scope and purpose of the guidelines are clear  
• Recommendations are specific and unambiguous  
• The method for searching for and selecting the evidence are clear  
• Methods used for formulating the recommendations are clearly described  
• Health benefits, side effects, and risks were stated in the recommendations  
• Target users of the guideline are clearly defined  
• Level of evidence was graded | • Unclear whether patients’ views and preferences were sought  
• Unclear whether the guidelines were piloted among target users  
• Procedure for updating the guidelines not provided  
• Potential cost implications of applying the recommendations was not considered |
| National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines, 2007\(^{60}\) | • Scope and purpose of the guidelines are clear  
• Recommendations are specific and unambiguous  
• The method for searching for and selecting the evidence are clear  
• Methods used for formulating the recommendations are clearly described  
• Health benefits, side effects, and risks were stated in the recommendations  
• Target users of the guideline are clearly defined  
• Level of evidence was graded | • Unclear whether patients’ views and preferences were sought  
• Unclear whether the guidelines were piloted among target users  
• Procedure for updating the guidelines not provided  
• Potential cost implications of applying the recommendations was not considered |
### Appendix 9: Diagnostic Accuracy

#### Table 19: Diagnostic Accuracy — Sensitivity and Specificity at Admission for POC Devices Measuring cTn, Considering Relevant Patient Characteristics

<table>
<thead>
<tr>
<th>Study and Sample Size</th>
<th>% Diagnosed with MI</th>
<th>99th Percentile(^a) mcg/L (% CV)</th>
<th>Patient Characteristics</th>
<th>Sensitivity % (95% CI)</th>
<th>Specificity % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>cTn Device</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee- Lewandrowski(^b)</td>
<td>N = 204</td>
<td>10.8</td>
<td>0.080 (16.5) NR</td>
<td>63.0</td>
<td>94.0</td>
</tr>
<tr>
<td>Palamalai(^c)</td>
<td>N = 169</td>
<td>11.2</td>
<td>0.080 (16.5) NR</td>
<td>32.0 (13.0 to 57.0)</td>
<td>26.0 (9.0 to 51.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>92.0 (86.0 to 96.0)</td>
<td>93.0 (87.0 to 96.0)</td>
</tr>
<tr>
<td>Ivandic(^d)</td>
<td>N = 119</td>
<td>NR</td>
<td>0.020 (12.3) Excluded STEMI</td>
<td>76.1 (64.1 to 85.7)</td>
<td>95.0 (87.7 to 98.6)</td>
</tr>
<tr>
<td>Hjortshøj(^e)</td>
<td>N = 458</td>
<td>23.0</td>
<td>0.039 (10)</td>
<td>58.0 (47.0 to 69.0)</td>
<td>94.0 (91.0 to 96.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amodio(^f); (Di Serio(^g))</td>
<td>N = 516</td>
<td>21.3</td>
<td>0.070 (10) 23% prior MI</td>
<td>83.8 (53.9 to 72.6)</td>
<td>93.1 (90.2 to 95.4)</td>
</tr>
<tr>
<td>Diercks(^h)</td>
<td>N = 858</td>
<td>9.6</td>
<td>0.050 (10)(^a)</td>
<td>66.7 (55.2 to 76.5)</td>
<td>95.9 (94.0 to 97.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>83.8 (53.9 to 72.6)</td>
<td>93.1 (90.2 to 95.4)</td>
</tr>
<tr>
<td><strong>cTnT Device</strong></td>
<td></td>
<td>AQT90 cTnT</td>
<td>Cobas</td>
<td>AQT90 cTnT</td>
<td>Cobas</td>
</tr>
<tr>
<td>Ter Avest(^i)</td>
<td>N = 41</td>
<td>NR</td>
<td>0.070 (10) NR</td>
<td>68.0 (49.0 to 82.0)</td>
<td>87.0 (82.0 to 91.0)</td>
</tr>
<tr>
<td>Andersson; Nilsson(^j)</td>
<td></td>
<td></td>
<td></td>
<td>67.0</td>
<td>98.0</td>
</tr>
<tr>
<td>Stengaard(^k)</td>
<td>NR</td>
<td>0.014 (NR) Patients in ambulance</td>
<td>39.0 (32.0 to 46.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval; cTn = cardiac troponin; cTnI = cardiac troponin I; cTnT = cardiac troponin T; CV = coefficient of variation; h = hours; MI = myocardial infarction; NR = not reported; POC = point of care; STEMI = ST segment elevation myocardial infarction.

\(^a\) Manufacturer 99th percentile and corresponding CV, or the 99th percentile at 10% CV.

\(^b\) Study used 0.050 mcg/L threshold, as researchers developed their own reference.

---

**CADTH OPTIMAL USE REPORT**

122
## Table 20: Diagnostic Accuracy — Positive and Negative Predictive Values at Admission for POC Devices Measuring cTnI, Considering Relevant Patient Characteristics and 99th Percentiles

<table>
<thead>
<tr>
<th>Study and Sample Size</th>
<th>% Diagnosed With MI</th>
<th>99th Percentile&lt;sup&gt;a&lt;/sup&gt; mcg/L (% CV)</th>
<th>Patient Characteristics</th>
<th>Positive Predictive Value % (95% CI)</th>
<th>Negative Predictive Value % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>I-STAT</td>
<td>ATQ90</td>
</tr>
<tr>
<td>Lee-Lewandrowski&lt;sup&gt;20&lt;/sup&gt; N = 204</td>
<td>10.8</td>
<td>0.080 (16.5)</td>
<td>NR</td>
<td>58.0</td>
<td>95.0</td>
</tr>
<tr>
<td>Palmalai&lt;sup&gt;18&lt;/sup&gt; N = 169</td>
<td>11.2</td>
<td>0.080 (16.5)</td>
<td>ATQ90: 0.023 (12.3)</td>
<td>NR</td>
<td>33.0 (13.0 to 59.0)</td>
</tr>
<tr>
<td>Ivanic&lt;sup&gt;17&lt;/sup&gt; N = 119</td>
<td>NR</td>
<td>0.020 (12.3)</td>
<td>Excluded STEMI</td>
<td>84.9</td>
<td>91.5</td>
</tr>
<tr>
<td>Hjortshoj&lt;sup&gt;21&lt;/sup&gt; N = 458</td>
<td>23.0</td>
<td>0.039 (10)</td>
<td>• Excluded STEMI</td>
<td>71.0 (58.0 to 81.0)</td>
<td>90.0 (86.0 to 93.0)</td>
</tr>
<tr>
<td>Aldous&lt;sup&gt;16&lt;/sup&gt; N = 962</td>
<td>22.9</td>
<td>0.050 (17)</td>
<td>29% prior MI</td>
<td>79.1 (75.3 to 82.1)</td>
<td>96.2 (95.0 to 97.3)</td>
</tr>
<tr>
<td>Diercks&lt;sup&gt;19&lt;/sup&gt; N = 858</td>
<td>9.6</td>
<td>0.050 (10)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>• Excluded low pre-test probability of cardiac disease</td>
<td>85.8 (54.3 to 75.6)</td>
<td>96.0 (94.2 to 97.3)</td>
</tr>
<tr>
<td>Amodio&lt;sup&gt;25&lt;/sup&gt; N = 516</td>
<td>21.3</td>
<td>0.070 (10)</td>
<td>23% prior MI</td>
<td>56.7</td>
<td>93.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>cTnI Device</th>
<th>cTnT Device</th>
<th>AQT90 cTnT</th>
<th>Cobas</th>
<th>AQT90 cTnT</th>
<th>Cobas</th>
</tr>
</thead>
<tbody>
<tr>
<td>i-STAT</td>
<td>AQT90 cTnT</td>
<td>Cobas</td>
<td></td>
<td>AQT90 cTnT</td>
<td>Cobas</td>
</tr>
<tr>
<td>Ter Avest&lt;sup&gt;**&lt;/sup&gt;</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andersson&lt;sup&gt;14&lt;/sup&gt;; Nilsson&lt;sup&gt;15&lt;/sup&gt;</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stengaard&lt;sup&gt;**&lt;/sup&gt;</td>
<td>NR</td>
<td>0.014 (NR)</td>
<td>Patients in ambulance</td>
<td>68.0 (59.0 to 71.0)</td>
<td>86.0 (84.0 to 88.0)</td>
</tr>
</tbody>
</table>

CI = confidence interval; cTnI = cardiac troponin I; cTnT = cardiac troponin T; CV = coefficient of variation; h = hours; MI = myocardial infarction; NR = not reported; POC = point of care; STEMI = ST segment elevation myocardial infarction.

<sup>a</sup>Manufacturer 99th percentile and corresponding CV, or the 99th percentile at 10% CV.

<sup>b</sup>Study used 0.050 mcg/L threshold (although literature states the threshold is 0.020 mcg/L) and stated the 10% CV was used.
### Table 21: Diagnostic Accuracy of the POC Devices and Central Laboratory Relative to Time of Blood Sample in the Various Studies

<table>
<thead>
<tr>
<th>Time of Blood Draw</th>
<th>i-STAT</th>
<th>AQ T90 FLEX</th>
<th>Cardio3 Panel</th>
<th>Cobas h232</th>
<th>Stratus</th>
<th>Central Laboratory</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission</td>
<td>32%(^{18}) 63%(^{20})</td>
<td>26%(^{18}) 76%(^{17})</td>
<td>67%(^{19}) 88%(^{16})</td>
<td>67%(^{1})</td>
<td>77%(^{25})</td>
<td>68%(^{18}) 88%(^{20}) 90%(^{16}) 91%(^{1}) 100%(^{1})</td>
</tr>
<tr>
<td>3 h</td>
<td>68%(^{18})</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>95%(^{18})</td>
</tr>
<tr>
<td>6 h</td>
<td>68%(^{18})</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>100%(^{18})</td>
</tr>
<tr>
<td>6 to 9 h</td>
<td>NR</td>
<td>85%(^{1})</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>98%(^{1})</td>
</tr>
<tr>
<td></td>
<td>Specificity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission</td>
<td>92%(^{18}) 94%(^{20})</td>
<td>87%(^{22}) 95%(^{17})</td>
<td>93%(^{16}) 96%(^{19})</td>
<td>98%(^{1})</td>
<td>84%(^{25})</td>
<td>75%(^{18}) 81%(^{17}) 84%(^{20}) 87%(^{16}) 94%(^{18})</td>
</tr>
<tr>
<td>3 h</td>
<td>90%(^{18})</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>81%(^{18})</td>
</tr>
<tr>
<td>6 h</td>
<td>91%(^{18})</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>84%(^{18})</td>
</tr>
<tr>
<td>6 to 9 h</td>
<td>NR</td>
<td>91%(^{1})</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>78%(^{1})</td>
</tr>
<tr>
<td></td>
<td>Positive Predictive Value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission</td>
<td>33%(^{18}) 58%(^{20})</td>
<td>31%(^{18}) 85%(^{17})</td>
<td>66%(^{19}) 79%(^{16})</td>
<td>50%(^{1})</td>
<td>57%(^{25})</td>
<td>10%(^{1}) 31%(^{18}) 48%(^{17}) 60%(^{20}) 82%(^{18})</td>
</tr>
<tr>
<td>3 h</td>
<td>46%(^{18})</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>38%(^{18})</td>
</tr>
<tr>
<td>6 h</td>
<td>50%(^{18})</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>44%(^{18})</td>
</tr>
<tr>
<td>6 to 9 h</td>
<td>NR</td>
<td>71%(^{1})</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>53%(^{1})</td>
</tr>
<tr>
<td></td>
<td>Negative Predictive Value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission</td>
<td>91%(^{18}) 95%(^{20})</td>
<td>90%(^{21}) 95%(^{22})</td>
<td>94% to 97%(^{19}) (range from 1 study)</td>
<td>99%(^{1})</td>
<td>93%(^{25})</td>
<td>95%(^{18}) 97%(^{19}) 98%(^{20}) 100%(^{1})</td>
</tr>
<tr>
<td>3 h</td>
<td>96%(^{18})</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>99%(^{18})</td>
</tr>
<tr>
<td>6 h</td>
<td>96%(^{18})</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>100%(^{18})</td>
</tr>
<tr>
<td>6 to 9 h</td>
<td>NR</td>
<td>96%(^{1})</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>99%(^{1})</td>
</tr>
<tr>
<td></td>
<td>Positive-Likelihood Ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission</td>
<td>5.37(^{22})</td>
<td>16.2(^{19})</td>
<td>NR</td>
<td>4.83(^{25})</td>
<td>3.63(^{22})</td>
<td></td>
</tr>
<tr>
<td>3 h</td>
<td>12.9(^{19})</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>6 h</td>
<td>11.8(^{19})</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Negative-Likelihood Ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission</td>
<td>0.26(^{18}) 0.37(^{22})</td>
<td>0.35(^{19})</td>
<td>NR</td>
<td>0.27(^{25})</td>
<td>0.12(^{22})</td>
<td></td>
</tr>
<tr>
<td>3 h</td>
<td>0.12(^{18}) 0.16(^{19})</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>6 h</td>
<td>0.08(^{18}) 0.14(^{19})</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

h = hours; NR = not reported; POC = point of care.
### Appendix 10: Clinical Utility

**Table 22: Turnaround Time**

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Design</th>
<th>Number of Patients (N)</th>
<th>Type of cTn</th>
<th>Point of Care</th>
<th>Central Laboratory</th>
<th>Time Saved (Minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Setting: Emergency Department</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Definition of Turnaround Time: Time From Blood Draw to Result</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ryan&lt;sup&gt;26&lt;/sup&gt;</td>
<td>RCT</td>
<td>N = 2,134</td>
<td>cTnI</td>
<td>Median 15 min (range 11 to 23 min)</td>
<td>Median 58 min (range 44 to 81 min)</td>
<td>43 min</td>
</tr>
<tr>
<td>Altiner&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Prospective</td>
<td>N = 100</td>
<td>cTnI</td>
<td>Median 17 min</td>
<td>Median 83 min</td>
<td>66 min (P = 0.0001)</td>
</tr>
<tr>
<td>Cramer&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Prospective</td>
<td>N = 358</td>
<td>cTnT</td>
<td>Median, 20 min (range 15 to 25 min)</td>
<td>Median 92 min (range 75 to 124 min)</td>
<td>72 min</td>
</tr>
<tr>
<td>Mozina&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Prospective</td>
<td>N = 31</td>
<td>cTnI</td>
<td>Mean, 20 min ± 5 min (SD)</td>
<td>(Core laboratory): Mean 104 min ± 33 min (SD)</td>
<td>84 min (P &lt; 0.001)</td>
</tr>
<tr>
<td>Storrow&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Prospective</td>
<td>N = 253</td>
<td>cTnT</td>
<td>Mean 126 min ± 84 (SD) or 126 min</td>
<td>Mean 144 min ± 108 (SD)</td>
<td>18 min (P = 0.001)</td>
</tr>
<tr>
<td>Caraghe;&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Prospective</td>
<td>N = 205</td>
<td>cTnI</td>
<td>Mean 39 min ± 12.1 min (SD)</td>
<td>Mean 87 min ± 27.5 min (SD)</td>
<td>48 min</td>
</tr>
<tr>
<td>Lee-Lewandrowski&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Pre/post</td>
<td>N = NR</td>
<td>cTnI</td>
<td>Mean 17 min</td>
<td>Mean 110 min</td>
<td>93 min</td>
</tr>
<tr>
<td>Singer&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Pre/post</td>
<td>N = 2,386</td>
<td>cTnI</td>
<td>Median 45 min (range 34 to 69 min)</td>
<td>Median 70 min (range 55 to 101 min)</td>
<td>25 min</td>
</tr>
<tr>
<td><strong>Other Definitions of Turnaround Time</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Singer&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Pre/post</td>
<td>N = 366</td>
<td>cTnI</td>
<td>Mean 15 min (95% CI, 14 to 15)</td>
<td>Mean 83 min (95% CI, 77–89)</td>
<td>From blood in analyzer to result: • time saved: 68 min</td>
</tr>
<tr>
<td>Koehler&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Pre/post</td>
<td>N = 201</td>
<td>cTnT</td>
<td>Mean 51 min</td>
<td>Mean 105 min</td>
<td>From door to result: • time saved: 54 min (P &lt; 0.000)</td>
</tr>
<tr>
<td>Meek&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Pre/post</td>
<td>N = 671</td>
<td>cTnI</td>
<td>Median 18 min (range 16 to 20 min)</td>
<td>Median 77 min (range 60 to 108 min)</td>
<td>Time from loading to printed results: • time saved: 59 min</td>
</tr>
<tr>
<td>Renaud&lt;sup&gt;29&lt;/sup&gt;</td>
<td>RCT</td>
<td>N = 833</td>
<td>cTnI</td>
<td>Time from collection to physician notification: • Median 38 min (range 35 to 42 min); Time from presentation to anti-ischemic therapy: • Median 151 min (range 139 to 162 min)</td>
<td>Time from collection to physician notification: • Median 109 min (range 104 to 115 min)</td>
<td>Time from collection to physician notification: • Time saved: 71 min (P &lt; 0.001)</td>
</tr>
<tr>
<td>Di Serio&lt;sup&gt;31&lt;/sup&gt;</td>
<td>Retrospective</td>
<td>N = NR</td>
<td>cTnI</td>
<td>Median 26 min</td>
<td>Median 83 min</td>
<td>&quot;Arm to report&quot; time: • Time saved: 57 min (P = 0.0001)</td>
</tr>
</tbody>
</table>

*CADTH OPTIMAL USE REPORT* 125
### Setting: Cardiology Services and Coronary Care Units

#### Definition of Turnaround Time: Time From Blood Draw to Result

<table>
<thead>
<tr>
<th>First Author</th>
<th>Type of cTn, Study Design</th>
<th>Point of Care</th>
<th>Central Laboratory</th>
<th>Time Saved (Minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apple</td>
<td>Pre/post</td>
<td>cTnI</td>
<td>Mean, 19 min (95% CI, 17 to 20)</td>
<td>Mean 76 min (95% CI, 68 to 84)</td>
</tr>
<tr>
<td>Collinson</td>
<td>RCT</td>
<td>cTnT</td>
<td>Median, 20 min (range, 20 to 38 min)</td>
<td>Median 79 min (range 25 to 1,018 min)</td>
</tr>
</tbody>
</table>

CI = confidence interval; cTn = cardiac troponin; cTnI = cardiac troponin I; cTnT = cardiac troponin T; min = minutes; NR = not reported; POC = point of care; RCT = randomized controlled trial; SD = standard deviation.

Note: $P$ values are not available when not indicated.

### Table 23: Length of Stay

#### Length of Emergency Room Stay

<table>
<thead>
<tr>
<th>First Author</th>
<th>Type of cTn, Study Design</th>
<th>Point of Care</th>
<th>Central Laboratory</th>
<th>Time Saved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meek</td>
<td>cTnI, Pre/post</td>
<td></td>
<td>For discharged patients: median 4.9 h (range 3.8 to 7.3 h)</td>
<td>For discharged patients: median 9.1 h (range 7.6 to 11.3 h) ($P &lt; 0.0001$)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>For admitted patients: median 10.2 h (range 7.7 to 14.3 h)</td>
<td>For admitted patients: median 12.2 h 733.5 (range 8.9 to 17.8 h) ($P = 0.007$)</td>
</tr>
<tr>
<td>Loten</td>
<td>cTnI, RCT</td>
<td>Median 6.4 h</td>
<td>Median 7.2 h ($P = 0.063$)</td>
<td>0.8 h (48 min)</td>
</tr>
<tr>
<td>Renaud</td>
<td>cTnI, RCT</td>
<td>Median 5.2 h</td>
<td>Median 5.1 h (range 3.8 to 6.7 h) ($P = 0.99$)</td>
<td>-0.1 h (~6 min)</td>
</tr>
<tr>
<td>Singer</td>
<td>cTnI, Pre/post</td>
<td>Mean 5.2 h (95% CI, 4.6 to 5.8)</td>
<td>Mean 7.1 h (95% CI, 6.6 to 7.7)</td>
<td>1.9 h (114 min)</td>
</tr>
<tr>
<td>Asha</td>
<td>cTnT, RCT</td>
<td>Mean 4.3 h</td>
<td>Mean 4.5 h ($P = 0.21$)</td>
<td>0.2 h (12 min)</td>
</tr>
</tbody>
</table>

#### Length of Hospital Stay

<table>
<thead>
<tr>
<th>First Author</th>
<th>Setting</th>
<th>Type of cTn, Study Design</th>
<th>Point of Care</th>
<th>Central Laboratory</th>
<th>Time Saved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apple</td>
<td>Cardiology services</td>
<td>cTnI, pre/post</td>
<td>Mean 52.6 h</td>
<td>Mean 56.6 h ($P = 0.05$)</td>
<td>4.0 h (240 min)</td>
</tr>
<tr>
<td>Collinson</td>
<td>CCU</td>
<td>cTnT, RCT</td>
<td>Median, 202.3 h (95% CI, 166.9 to 240.8)</td>
<td>Median 218.0 h (95% CI, 192.6 to 258.8) ($P$ not statistically significant)</td>
<td>15.7 h (942 min)</td>
</tr>
<tr>
<td>Goodacre</td>
<td>ED</td>
<td>cTnI, RCT</td>
<td>Mean 29.6 h</td>
<td>Mean 31.8 h (95% CI, 3.7 to 8.0 hours) ($P = 0.462$)</td>
<td>2.2 h (132 min)</td>
</tr>
</tbody>
</table>

CI = confidence interval; CCU = coronary care unit; cTn = cardiac troponin; cTnI = cardiac troponin I; cTnT = cardiac troponin T; ED = emergency department; h = hours; RCT = randomized controlled trial.

Note: $P$ values are not available when not indicated.
Table 24: Time to Clinical Decision in the Emergency Department

<table>
<thead>
<tr>
<th>First Author</th>
<th>Type of cTn</th>
<th>Study Design (Number of Patients)</th>
<th>Point of Care</th>
<th>Central Laboratory</th>
<th>Time Saved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ryan</td>
<td>cTnI</td>
<td>RCT (n = 2,134)</td>
<td>Median: 321 min (range 245 to 440 min)</td>
<td>Median: 330 min (range 250 to 451 min)</td>
<td>9 min</td>
</tr>
<tr>
<td>Deledda</td>
<td>Multiple markers</td>
<td>Pre/post (n = 4,886)</td>
<td>Mean: 195 min (SD 129)</td>
<td>Mean: 221 min (SD 149)</td>
<td>26 min</td>
</tr>
</tbody>
</table>

cTn = cardiac troponin; cTnI = cardiac troponin I; min = minutes; RCT = randomized controlled trial; SD = standard deviation.
Note: P values are not available when not indicated.

Table 25: Time to Discharge in the Emergency Department

<table>
<thead>
<tr>
<th>Study Setting, Type of cTn</th>
<th>Study Design</th>
<th>Number of Patients</th>
<th>Point of Care</th>
<th>Central Laboratory</th>
<th>Time Saved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ryan</td>
<td>ED, cTnI</td>
<td>RCT (n = 2,134)</td>
<td>Median: 270 min (range 208 to 364 min)</td>
<td>Median: 277 min (range 209 to 365 min)</td>
<td>7 min</td>
</tr>
<tr>
<td>Asha</td>
<td>ED, cTnT</td>
<td>RCT (n = 487)</td>
<td>Mean: 205 min</td>
<td>Mean: 210 min</td>
<td>5 min (P = 0.04)</td>
</tr>
<tr>
<td>Deledda</td>
<td>ED, multiple markers</td>
<td>Pre/post (n = 4,886)</td>
<td>Mean: 195 min (SD 129)</td>
<td>Mean: 221 min (SD 149)</td>
<td>26 min</td>
</tr>
</tbody>
</table>

cTn = cardiac troponin; cTnI = cardiac troponin I; cTnT = cardiac troponin T; ED = emergency department; min = minutes; RCT = randomized controlled trial; SD = standard deviation.
Note: P values are not available when not indicated.

Table 26: Mortality and Major Adverse Events Outcomes

<table>
<thead>
<tr>
<th>First Author; Setting Type of cTn; Study Design Number of Patients</th>
<th>Outcome</th>
<th>Point of Care</th>
<th>Central Laboratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asha;† ‡ † ‡ ‡ ‡ ED cTnT; RCT n = 487</td>
<td>Death</td>
<td>0.5%</td>
<td>0%</td>
</tr>
<tr>
<td>Collinson;§ § CCU cTnT; RCT n = 263</td>
<td>6 month mortality</td>
<td>12.2% (16/131)</td>
<td>9.8% (13/132) P = NS</td>
</tr>
<tr>
<td>Goodacre;† ‡ ‡ ‡ ED cTnT; RCT n = 2,243</td>
<td>Death</td>
<td>1% (6/1, 125)</td>
<td>0.2% (2/1, 118) (P = 0.142)</td>
</tr>
<tr>
<td>Ordonez-Llanos;† ‡ ‡ ED cTnT; prospective n = 1,410</td>
<td>Non-cardiac death after 1 year follow-up (OR)</td>
<td>1.4% (95% CI, 0.4 to 5.7)</td>
<td>2.4% (95% CI, 0.6 to 9.0)</td>
</tr>
<tr>
<td>First Author; Setting</td>
<td>Type of cTn; Study Design</td>
<td>Number of Patients</td>
<td>Outcome</td>
</tr>
<tr>
<td>-----------------------</td>
<td>---------------------------</td>
<td>--------------------</td>
<td>---------</td>
</tr>
</tbody>
</table>
| Venge;<sup>43</sup> ED cTnI; prospective n = 508 | | | Prediction of death during 31-month follow-up period | i-STAT:  
- sensitivity: 36%  
(95% CI, 24 to 49)  
- specificity: 89%  
(95% CI, 96 to 92)  
- PPV: 33%  
(95% CI, 22 to 46)  
- NPV: 91%  
(95% CI, 87 to 93)  
- Stratus CS:  
- sensitivity: 40%  
(95% CI, 28 to 54)  
- specificity: 84%  
(95% CI, 81 to 88)  
- PPV: 27%  
(95% CI, 18 to 37)  
- NPV: 91%  
(95% CI, 87 to 93) | Access (CL):  
- sensitivity: 77%  
(95% CI, 65 to 87)  
- specificity: 68%  
(95% CI, 72 to 80)  
- PPV: 32%  
(95% CI, 25 to 40)  
- NPV: 87%  
(95% CI, 93 to 98) |
| Venge;<sup>40</sup> ED cTnI; prospective n = 1,069 | | | Prediction of death (median follow-up: 3.3 months) | i-STAT: 50% Stratus: 54% | Access: 88% Architect: 81% |

### Cardiac Events

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of cTn; Study Design</th>
<th>Setting</th>
<th>Number of Patients</th>
<th>Outcome</th>
<th>Point of Care</th>
<th>Central Laboratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cullen;&lt;sup&gt;44&lt;/sup&gt; ED cTnI; RCT n = 2,243</td>
<td>30-day cardiac event rate in low-risk patients</td>
<td></td>
<td></td>
<td>0% (95% CI, 0 to 25.9)</td>
<td>0% (95% CI, 0 to 21.5)</td>
<td></td>
</tr>
<tr>
<td>Cullen;&lt;sup&gt;44&lt;/sup&gt; ED cTnI; RCT n = 2,243</td>
<td>30-day cardiac event rate in high-risk patients</td>
<td></td>
<td></td>
<td>24.8% (95% CI, 20.2 to 30.1)</td>
<td>28.6% (95% CI, 23.4 to 34.4)</td>
<td></td>
</tr>
<tr>
<td>Ordonez-Llanos;&lt;sup&gt;47&lt;/sup&gt; ED cTnI; prospective n = 1,410</td>
<td>Cardiac events after 1 year follow-up (OR)</td>
<td></td>
<td></td>
<td>2.1 (95% CI, 1.5 to 3.0)</td>
<td>2.2 (95% CI, 1.6 to 3.1)</td>
<td></td>
</tr>
</tbody>
</table>

### Other Adverse Events and Composite End Points

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of cTn; Study Design</th>
<th>Setting</th>
<th>Number of Patients</th>
<th>Outcome</th>
<th>Point of Care</th>
<th>Central Laboratory</th>
</tr>
</thead>
</table>
| Goodacre;<sup>39</sup> ED cTnI; RCT n = 2,243 | Major AE after 3 month follow-up | | | 3% (36/1,125) | 2% (26/1,118)  
\(P = 0.313\) |
| Collinson;<sup>50</sup> CCU cTnI; RCT n = 263 | CEP (death, MI, unstable angina, readmission with UA or need for urgent revascularization) at 6 months | | | 67% (88/131) | 66% (87/132)  
\(P = \text{NS}\) |
| Asha;<sup>41,57</sup> ED cTnI; RCT n = 487 | CEP events (AMI, coronary revascularization, cardiac arrest, or mortality) in patient with a negative first cTn test at 3 months follow-up | | | 10.4% | 5.4% |

AE = adverse event; AMI = acute myocardial infarction; CCU = coronary care unit; CEP = composite end points; CI = confidence interval; CL = central laboratory; cTn = cardiac troponin; cTnI = cardiac troponin I; cTnT = cardiac troponin T; CVD = cardiovascular disease; ED = emergency department; h = hours; MI = myocardial infarction; NPV = negative predictive value; NR = not reported; NS = not significant; OR = odds ratio; PPV = positive predictive value; RCT = randomized controlled trial; UA = unstable angina. Note: \(P\) values are not available when not indicated.

### Table 27: Patients’ Quality of Life (EQ-5D) in the Emergency Department

<table>
<thead>
<tr>
<th>Author, cTn Type, Study Design, Number of Patients</th>
<th>Time Point</th>
<th>Point of Care</th>
<th>Central Laboratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goodacre;&lt;sup&gt;9&lt;/sup&gt; ED; cTnI; RCT n = 2,243</td>
<td>1 month</td>
<td>0.742</td>
<td>0.759, (P = 0.614)</td>
</tr>
<tr>
<td></td>
<td>3 months</td>
<td>0.752</td>
<td>0.759, (P = 0.638)</td>
</tr>
</tbody>
</table>

cTn = cardiac troponin; cTnI = cardiac troponin I; ED = emergency department; EQ-5D = EuroQol 5-Dimensions Questionnaire; RCT = randomized controlled trial.
Table 28: Staff Satisfaction in the Various Settings

<table>
<thead>
<tr>
<th>Author; cTn Type</th>
<th>Study Design; Number of Patients</th>
<th>Setting</th>
<th>Staff Satisfaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koehler; cTnT</td>
<td>Pre/post; n = 201</td>
<td>ED</td>
<td>82% of staff rated satisfaction as excellent with POC testing</td>
</tr>
</tbody>
</table>
| Altinier; cTnI   | Prospective; n = 100             | ED      | • POC easy to use: 100%  
• Safety for operator 91%  
• Essential in the ED: 64%  
• Better management: 82% |
| Lee-Lewandrowski; cTnI | Pre/post; n = NR | ED      | Staff satisfaction with accuracy:  
• POC: 3.68/5  
• CL: 4.33/5 |
| Singer; cTnI     | Pre/post; n = 2,386              | ED      | • 92% of staff found POC testing had great overall value  
• 88% of physicians agreed that POC testing improved patient flow |
| Shephard; remote centres | Survey; n = 33 health centres | Remote Health Care Centres (No Central Laboratory) | 95% of device-operator respondents stated that POC testing was more convenient than transporting patients for CL services.  
• Staff satisfaction with cTn testing: 96% with POC; 31% with no POC ($P < 0.001$) |
| FitzGibbon; unspecified setting and type of cTn | Survey; n = 100 health professionals | Unspecified Health Care Setting (Unclear if Central Laboratory Available) | • cTnI is the most commonly used cardiac marker (75%)  
• 47% of staff strongly agree POC usage increased patient convenience (13% disagree)  
• 40% strongly agree POC reduced TAT (0% disagree)  
• 33% strongly agree POC enables earlier treatment (0% disagree)  
• 0% strongly agree POC reduced reoperation and readmission (13% disagree) |
| Liikanen; unspecified setting or type of cTn | Survey; n = 406 health care units | Reasons for staff using POC:  
• shortening of TAT: 96%  
• laboratory test not available: 71% |

CL = central laboratory; cTn = cardiac troponin; cTnI = cardiac troponin I; cTnT = cardiac troponin T; ED = emergency department; NR = not reported; POC = point of care; TAT = turnaround time.

Note: $P$ values are not available when not indicated.
Appendix 11: Schematics for the Economic Models

Figure 7: Schematic of the Economic Model for Context 1: POC Cardiac Troponin Testing Versus Central Laboratory Testing

cTn = cardiac troponin; hrs = hours; NSTEMI = non-ST segment elevation myocardial infarction; POC = point of care.
Figure 8: Schematic of the Economic Model for Context 2: POC Cardiac Troponin Testing Versus No cTn Testing

Candidate Patients for POC Cardiac Troponin Testing

- No cTn Testing available
- POC cTn testing on site

NSTEMI

- cTn Positive (sensitivity)
  - Transfer (early treatment)
  - cTn Positive
    - Transfer (late treatment)
  - cTn Negative
    - Discharge (untreated)

- cTn Negative
  - Discharge (untreated)
  - Hold/Re-test (6 hrs)

No NSTEMI

- cTn Positive
  - Transfer (early treatment)
  - cTn Positive
    - Transfer (late treatment)
  - cTn Negative
    - Discharge (untreated)

- cTn Negative
  - Discharge (untreated)
  - Hold/Re-test (6 hrs)

Alive OR Dead

cTn = cardiac troponin; hrs = hours; NSTEMI = non-ST segment elevation myocardial infarction; POC = point of care.
Appendix 12: Summary Receiver Operating Characteristic Curve for the Pooled Diagnostic Accuracy of POC cTn Devices

Figure 9: Desktop POC cTn Device

cTn = cardiac troponin; hierarchical summary receiver operating characteristic; POC = point of care.
Figure 10: Summary Receiver Operating Characteristic Curve for the Pooled Diagnostic Accuracy of the Hand-held POC cTn Device

cTn = cardiac troponin; hierarchical summary receiver operating characteristic; POC = point of care.