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Health Technology Assessment

Volume 25 • Issue 33 • May 2021

ISSN 1366-5278

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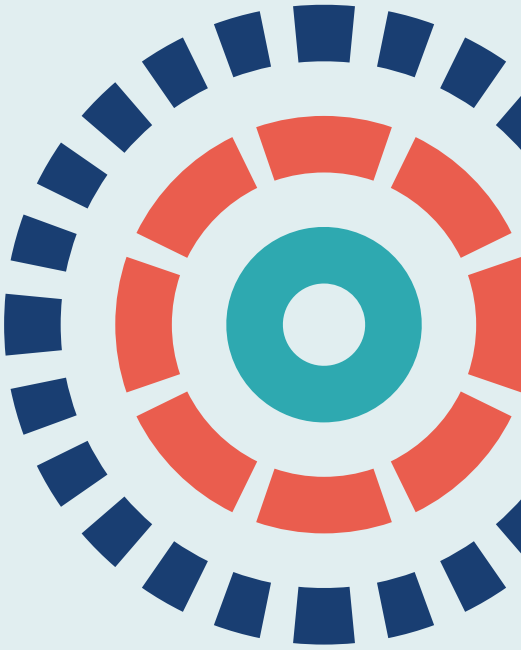

DOI 10.3310/hta25330

High-sensitivity troponin assays for early rule-out of acute myocardial infarction in people with acute chest pain: a systematic review and economic evaluation

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Declared competing interests of authors: none

Published May 2021
DOI: 10.3310/hta25330

This report should be referenced as follows:

Westwood M, Ramaekers B, Grimm S, Worthy G, Fayter D, Armstrong N, *et al.* High-sensitivity troponin assays for early rule-out of acute myocardial infarction in people with acute chest pain: a systematic review and economic evaluation. *Health Technol Assess* 2021;**25**(33).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE, *Science Citation Index Expanded* (SciSearch®) and *Current Contents®*/ Clinical Medicine.

Health Technology Assessment

NICE TAR and DAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 3.370

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, the Cochrane Library and Clarivate Analytics Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

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This report

The research reported in this issue of the journal was commissioned and funded by the Evidence Synthesis Programme on behalf of NICE as project number NIHR130462. The protocol was agreed in September 2019. The assessment report began editorial review in March 2020 and was accepted for publication in August 2020. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

High-sensitivity troponin assays for early rule-out of acute myocardial infarction in people with acute chest pain: a systematic review and economic evaluation

Marie Westwood,[1*] Bram Ramaekers,[2] Sabine Grimm,[2] Gill Worthy,[1] Debra Fayter,[1] Nigel Armstrong,[1] Titas Buksnys,[1] Janine Ross,[1] Manuela Joore[2] and Jos Kleijnen[1,3]

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Background: Early diagnosis of acute myocardial infarction is important, but only 20% of emergency admissions for chest pain will actually have an acute myocardial infarction. High-sensitivity cardiac troponin assays may allow rapid rule out of myocardial infarction and avoid unnecessary hospital admissions.

Objectives: To assess the clinical effectiveness and cost-effectiveness of high-sensitivity cardiac troponin assays for the management of adults presenting with acute chest pain, in particular for the early rule-out of acute myocardial infarction.

Methods: Sixteen databases were searched up to September 2019. Review methods followed published guidelines. Studies were assessed for quality using appropriate risk-of-bias tools. The bivariate model was used to estimate summary sensitivity and specificity for meta-analyses involving four or more studies; otherwise, random-effects logistic regression was used. The health economic analysis considered the long-term costs and quality-adjusted life-years associated with different troponin testing methods. The de novo model consisted of a decision tree and a state–transition cohort model. A lifetime time horizon (of 60 years) was used.

Results: Thirty-seven studies (123 publications) were included in the review. The high-sensitivity cardiac troponin test strategies evaluated are defined by the combination of four factors (i.e. assay, number and timing of tests, and threshold concentration), resulting in a large number of possible combinations. Clinical opinion indicated a minimum clinically acceptable sensitivity of 97%. When considering single test strategies, only those using a threshold at or near to the limit of detection for the assay, in a sample taken at presentation, met the minimum clinically acceptable sensitivity criterion. The majority of the multiple test strategies that met this criterion comprised an initial rule-out step, based on high-sensitivity cardiac troponin levels in a sample taken on presentation and a minimum symptom duration, and a second stage for patients not meeting the initial rule-out criteria, based on presentation levels of high-sensitivity cardiac troponin and absolute change after 1, 2 or 3 hours. Two large cluster randomised controlled trials found that implementation of an early rule-out pathway for myocardial infarction reduced length of stay and rate of hospital admission without increasing cardiac events. In the base-case analysis, standard troponin testing was both the most effective

and the most costly. Other testing strategies with a sensitivity of 100% (subject to uncertainty) were almost equally effective, resulting in the same life-year and quality-adjusted life-year gain at up to four decimal places. Comparisons based on the next best alternative showed that for willingness-to-pay values below £8455 per quality-adjusted life-year, the Access High Sensitivity Troponin I (Beckman Coulter, Brea, CA, USA) [(symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 5 ng/l at 0 to 2 hours)] would be cost-effective. For thresholds between £8455 and £20,190 per quality-adjusted life-year, the Elecsys® Troponin-T high sensitive (Roche, Basel, Switzerland) (< 12 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours) would be cost-effective. For a threshold > £20,190 per quality-adjusted life-year, the Dimension Vista® High-Sensitivity Troponin I (Siemens Healthcare, Erlangen, Germany) (< 5 ng/l at 0 hours AND Δ < 2 ng/l at 0 to 1 hours) would be cost-effective.

Conclusions: High-sensitivity cardiac troponin testing may be cost-effective compared with standard troponin testing.

Study registration: This study is registered as PROSPERO CRD42019154716.

Funding: This project was funded by the National Institute for Health Research (NIHR) Evidence Synthesis programme and will be published in full in *Health Technology Assessment*; Vol. 25, No. 33. See the NIHR Journals Library website for further project information.

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Glossary

Cost-effectiveness analysis An economic analysis that converts effects into health terms and describes the costs for additional health gain.

Decision modelling A mathematical construct that allows the comparison of the relationship between costs and outcomes of alternative health-care interventions.

False negative An incorrect negative test result (i.e. the number of diseased persons with a negative test result).

False positive An incorrect positive test result (i.e. the number of non-diseased persons with a positive test result).

Incremental cost-effectiveness ratio The difference in the mean costs of two interventions in the population of interest divided by the difference in the mean outcomes in the population of interest.

Index test The test that is being evaluated.

Likelihood ratio The likelihood ratio describes how many times more likely it is that a person with the target condition will receive a particular test result than a person without the target condition.

Meta-analysis Statistical techniques used to combine the results of two or more studies and obtain a combined estimate of effect.

Meta-regression Statistical technique used to explore the relationship between study characteristics and study results.

Opportunity costs The cost of forgone outcomes that could have been achieved through alternative investments.

Publication bias Bias arising from the preferential publication of studies with statistically significant results.

Quality-adjusted life-year A measure of health gain used in economic evaluations, in which survival duration is weighted or adjusted by the patient's quality of life during the survival period.

Quality of life An individual's emotional, social and physical well-being and their ability to perform the ordinary tasks of living.

Receiver operating characteristic curve A graph that illustrates the trade-offs between sensitivity and specificity that result from varying the diagnostic threshold.

Reference standard The best, currently available, method for diagnosing the target condition. The index test is compared against this to allow calculation of estimates of accuracy.

Sensitivity The proportion of people with the target disorder who have a positive test result.

Specificity The proportion of people without the target disorder who have a negative test result.

State–transition model A model in which individuals move (transition) between disease states as their condition changes over time. Time spent in each disease state for a single model cycle (and transitions between states) is associated with a cost and a health outcome.

True negative A correct negative test result (i.e. the number of non-diseased persons with a negative test result).

True positive A correct positive test result (i.e. the number of diseased persons with a positive test result).

List of abbreviations

ACC	American College of Cardiology
ACS	acute coronary syndrome
ADAPT	2-Hour Accelerated Diagnostic Protocol to Assess Patients With Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarker
AHA	American Heart Association
AiC	academic in confidence
AMI	acute myocardial infarction
APACE	Advantageous Predictors of Acute Coronary Syndromes Evaluation
BEST	Bedside Evaluation of Sensitive Troponin
CAD	coronary artery disease
CADTH	Canadian Agency for Drugs and Technologies in Health
CDSR	Cochrane Database of Systematic Reviews
CE	Conformitè Europëenne
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CG	clinical guideline
CHD	coronary heart disease
CI	confidence interval
CoV	coefficient of variation
CRD	Centre for Reviews and Dissemination
cTn	cardiac troponin
cTnI	cardiac troponin I
cTnT	cardiac troponin T
DAR	diagnostic assessment report
DARE	Database of Abstracts of Reviews of Effects
DG	diagnostics guidance
DTA	diagnostic test accuracy
ECG	electrocardiogram
ED	emergency department
EDACS	Emergency Department Assessment of Chest Pain Score
eGFR	estimated glomerular filtration rate
ESC	European Society of Cardiology
FN	false negative
FP	false positive
GRACE	Global Registry of Acute Coronary Events
HEART	History ECG Age Risk factors Troponins
HES	Hospital Episode Statistics
High-STEACS	High-Sensitivity Troponin in the Evaluation of Patients With Acute Coronary Syndrome
High-US	High-Sensitivity Cardiac Troponin I Assays in the United States
HiSTORIC	High-Sensitivity Cardiac Troponin On Presentation to Rule Out Myocardial Infarction
hs-cTn	high-sensitivity cardiac troponin
hs-cTnI	high-sensitivity cardiac troponin I
hs-cTnT	high-sensitivity cardiac troponin T
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
IMPACT	Improved Assessment of Chest Pain Trial
IQR	interquartile range

LoB	limit of blank
LoD	limit of detection
MACE	major adverse cardiac event
MI	myocardial infarction
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NSTE-ACS	non-ST segment elevation acute coronary syndrome
NSTEMI	non-ST elevation myocardial infarction
OR	odds ratio
PROSPERO	International Prospective Register of Systematic Reviews
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
QUART	QUeensland Accelerated Risk Trial
RATPAC	Randomised Assessment of Treatment using Panel Assay of Cardiac Markers
RCT	randomised controlled trial
ROC	receiver operating characteristic
ROMI-3	Optimum Troponin Cutoffs for ACS in the ED
RR	relative risk
SD	standard deviation
SROC	summary receiver operating characteristic
STEMI	ST elevation myocardial infarction
TN	true negative
TP	true positive
TRAPID-AMI	High Sensitivity Cardiac Troponin T Assay for Rapid Rule-out of Acute Myocardial Infarction
TRUST	Triage Rule-out Using Sensitive Troponin
UA	unstable angina

Note

This monograph is based on the Diagnostic Assessment Report produced for NICE. The full report contained a considerable number of data that were deemed confidential. The full report was used by the Diagnostic Advisory Committee at NICE in their deliberations. The full report with each piece of confidential data removed and replaced by the statement 'confidential information (or data) removed' is available on the NICE website: www.nice.org.uk.

The present monograph presents as full a version of the report as is possible while retaining readability, but some sections, sentences, tables and figures have been removed. Readers should bear in mind that the discussion, conclusions and implications for practice and research are based on all the data considered in the original full NICE report.

Plain English summary

Heart disease is a leading cause of death in the UK, with myocardial infarction (heart attack) accounting for approximately 4% of all deaths recorded in 2018. Many people attend hospital with chest pain and suspected myocardial infarction, and chest pain has been reported as the most common cause of hospital admissions in the UK, accounting for approximately 5% of all emergency admissions in 2017–18. It is important to diagnose people who are suspected of having a myocardial infarction as early as possible to ensure quick and effective treatment. However, only around 20% of emergency admissions for chest pain will actually have an myocardial infarction and there are many other possible causes of chest pain (e.g. gastro-oesophageal disorders, muscle pain, anxiety or stable ischaemic heart disease). Current practice for ruling out myocardial infarction includes blood tests taken when the patient is first seen in the emergency department and repeated after 3–6 hours or 10–12 hours, depending on the test used. Tests that can quickly tell which patients do not have myocardial infarction could therefore avoid unnecessary hospital admissions and anxiety for many people.

We aimed to assess the clinical effectiveness and cost-effectiveness of high-sensitivity troponin tests, used as single tests or repeated over a short time, for the early rule out of myocardial infarction in people who present to hospital with chest pain.

We found that high-sensitivity troponin tests can safely rule out myocardial infarction within the 4-hour NHS emergency department target. Health economic analyses indicated that high-sensitivity tests may be considered value for money compared with standard troponin tests, which require repeat testing at 10–12 hours.

Scientific summary

Background

Coronary artery disease and myocardial infarction are a significant health burden in the UK. Many people attend hospital with chest pain and suspected myocardial infarction, with statistics showing that chest pain accounted for approximately 5% of emergency admissions in 2017–18. It is important to diagnose people suspected of having an myocardial infarction as early as possible to ensure quick and effective treatment. However, only around 20% of emergency admissions for chest pain will have an myocardial infarction and there are many other causes of chest pain. Tests that can quickly tell which patients do not have myocardial infarction could avoid unnecessary hospital admissions, waiting time and anxiety.

Cardiac troponins I and T are used as markers of acute myocardial infarction. They are intended for use in conjunction with clinical history and electrocardiography. ST segment elevation myocardial infarction can usually be diagnosed on presentation by electrocardiogram and therefore the main diagnostic challenge is the detection or rule out of non-ST segment elevation myocardial infarction. High-sensitivity cardiac troponin assays can detect lower levels of troponin in the blood than conventional assays and may enable non-ST segment elevation myocardial infarction to be ruled out at an earlier time after the onset of acute chest pain. National Institute for Health and Care Excellence guidance currently recommends the use of some high-sensitivity cardiac troponin assays [e.g. the Elecsys® Troponin-T high sensitive (Roche, Basel, Switzerland) and the ARCHITECT STAT High Sensitive Troponin-I (Abbott Laboratories, Abbott Park, IL, USA)] as options for the early rule out of non-ST segment elevation myocardial infarction in people presenting to an emergency department with chest pain and suspected acute coronary syndrome.

This update assessment was undertaken to ensure that guidance is based on current evidence (including new high-sensitivity cardiac troponin assays developed and marketed since the publication of National Institute for Health and Care Excellence guidance) and to facilitate the provision of more detailed, evidence-based recommendations on how to use high-sensitivity cardiac troponin assays (e.g. timing of testing and use of sequential testing strategies).

Objectives

This assessment aimed to assess the clinical effectiveness and cost-effectiveness of high sensitivity troponin tests, used as single tests or repeated over a short time, for the early (i.e. < 4 hours) rule out of myocardial infarction (and consequent early discharge) in people who present to hospital with chest pain.

Methods

This report contains reference to confidential information provided as part of the NICE appraisal process. This information has been removed from the report and the results, discussions and conclusions of the report do not include the confidential information. These sections are clearly marked in the report.

Assessment of clinical effectiveness

Sixteen databases, including MEDLINE, EMBASE, research registers and conference proceedings, were searched for relevant studies from 2013 (date of the previous assessment) to September 2019. Search results were screened for relevance independently by two reviewers. Full copies of all studies deemed potentially relevant were obtained and assessed independently by two reviewers. Any disagreements were resolved by consensus. Data extraction and quality assessment were conducted by one reviewer, and checked by a second. The methodological quality of included randomised controlled trials was assessed using the revised Cochrane Risk-of-Bias tool for Randomised Trials. The methodological quality of included diagnostic test accuracy studies was assessed using QUADAS-2 (for studies assessing a single high-sensitivity cardiac troponin assay) or QUADAS-2C (for studies comparing two or more high-sensitivity cardiac troponin assays).

The hierarchical summary receiver operating characteristic model was used to estimate summary sensitivity and specificity with 95% confidence intervals (CIs) and prediction regions around the summary points, and to derive hierarchical summary receiver operating characteristic curves for meta-analyses involving four or more studies. For meta-analyses with fewer than four studies, we estimated separate pooled estimates of sensitivity and specificity using random-effects logistic regression. Analyses were conducted separately for each high-sensitivity cardiac troponin assay. Analyses were stratified according to target condition (i.e. non-ST segment elevation myocardial infarction, any acute myocardial infarction or 30-day major adverse cardiac event), timing of collection of blood sample for testing and the threshold used to define a positive high-sensitivity cardiac troponin result.

Assessment of cost-effectiveness

We considered the long-term costs and quality-adjusted life-years associated with different troponin testing methods to diagnose or rule out non-ST segment elevation myocardial infarction for patients presenting at the emergency department with suspected non-ST segment elevation acute coronary syndrome. The de novo model consisted of a decision tree and a state–transition cohort model. The decision tree was used to model the 30-day outcomes after presentation, based on test results and the accompanying treatment decision. The long-term consequences in terms of costs and quality-adjusted life-years were estimated using a state–transition cohort model with a lifetime time horizon (i.e. 60 years). For the economic analyses, based on expert opinion, only high-sensitivity troponin tests that had a sensitivity of $\geq$ 97% were selected. A total of 22 unique testing strategies were included in the main economic analysis.

In the base case, it was assumed that standard troponin testing had perfect sensitivity and specificity (reference case) for diagnosing acute myocardial infarction, and that only those patients testing positive with the reference standard (standard troponin) were at increased risk for adverse events (myocardial infarction and mortality) and would benefit from immediate treatment. In a secondary analysis, a proportion of patients testing positive with a high-sensitivity cardiac troponin test and not testing positive with standard troponin (i.e. false positives) were assumed to be at increased risk of myocardial infarction and mortality. These patients were assumed to be treated for the high-sensitivity cardiac troponin assays and left untreated for the standard troponin test.

Results

Assessment of clinical effectiveness

Thirty-seven studies (123 publications) were included in the review. Thirty studies reported accuracy data for the Roche Elecsys Troponin-T high sensitive assay, nine studies reported accuracy data for the Abbott ARCHITECT STAT High Sensitive Troponin-I assay, two studies reported accuracy data for the Atellica® IM High-Sensitivity Troponin I (Siemens Healthcare, Erlangen, Germany), three studies reported accuracy data for the ADVIA Centaur® High-Sensitivity Troponin I (Siemens Healthcare, Erlangen, Germany), two studies reported accuracy data for the Access High Sensitivity Troponin I

(Beckman Coulter, Brea, CA, USA) and one study reported accuracy data for each of the Dimension Vista® High-Sensitivity Troponin I (Siemens Healthcare, Erlangen, Germany), VITROS® High Sensitivity Troponin I Assay (Ortho Clinical Diagnostics, Marlow, UK), VIDAS® High sensitive Troponin I (bioMérieux SA, Marcy l'Etoile, France) and TriageTrue High Sensitivity Troponin I Test (Quidel, San Diego, CA, USA). Seven studies reported accuracy data for more than one assay. We did not identify any studies of the Alinity i STAT high-sensitivity troponin I (Abbott Laboratories, Abbott Park, IL, USA) or Dimension® EXL™ hs-cTnI (Siemens Healthcare, Erlangen, Germany) that met the inclusion criteria for this review.

The high-sensitivity cardiac troponin test strategies evaluated by included studies are defined by the combination of four factors (i.e. assay, number and timing of tests, and threshold concentration), resulting in a large number of possible combinations. Clinical opinion, provided by the specialist committee members, indicated a minimum clinically acceptable sensitivity of 97%.

When considering single test strategies, only those using a threshold at or near to the limit of detection for the assay, in a sample taken at presentation, met the minimum clinically acceptable sensitivity criterion. The summary estimates of sensitivity and specificity for the target condition (i.e. non-ST segment elevation myocardial infarction) using the Roche Elecsys Troponin-T high sensitive assay (5 ng/l) were 99% (95% CI 97% to 100%) and 35% (95% CI 25% to 46%), respectively (six studies). The summary sensitivity and specificity estimates for the Abbott ARCHITECT STAT High Sensitive Troponin-I assay (2 ng/l) were 100% (95% CI 99% to 100%) and 21% (95% CI 16% to 26%), respectively (four studies). Of the remaining high-sensitivity cardiac troponin assays, only the Atellica IM High-Sensitivity Troponin I and ADVIA Centaur High-Sensitivity Troponin I assays were evaluated using a single presentation sample rule-out strategy, with a threshold at or near to the limit of detection for the assay. The limit of detection for both of these assays is 1.6 ng/l. Using a rule-out threshold of 2 ng/l, the sensitivity and specificity estimates were 100% (95% CI 99% to 100%) and 23% (95% CI 21% to 25%), respectively, for the ADVIA Centaur High-Sensitivity Troponin I, and 100% (95% CI 98% to 100%) and 26% (95% CI 24% to 28%), respectively, for the Atellica IM High-Sensitivity Troponin I assay.

The majority of the multiple test strategies meeting the minimum clinically acceptable sensitivity comprised an initial rule-out step, based on high-sensitivity cardiac troponin levels in a sample taken on presentation and a minimum symptom duration, and a second stage for patients not meeting the initial rule-out criteria, based on presentation levels of high-sensitivity cardiac troponin and absolute change in high-sensitivity cardiac troponin between presentation and a second sample taken after 1, 2 or 3 hours. The 2015 European Society of Cardiology guidelines for the management of acute coronary syndromes in patients presenting without persistent ST segment elevation included a 0/1-hour algorithm, which incorporates a rule-out pathway following this structure. Versions of the European Society of Cardiology 0/1-hour rule-out pathway have been evaluated using the following assays: Roche Elecsys Troponin-T high sensitive (sensitivity 99%, 95% CI 98% to 100%; specificity 68%, 95% CI 67% to 70%); Abbott ARCHITECT STAT High Sensitive Troponin-I assay (sensitivity 99%, 95% CI 98% to 100%; specificity 57%, 95% CI 56% to 59%) (summary estimate from two studies); Access High Sensitivity Troponin I (sensitivity 99%, 95% CI 94% to 100%; specificity 70%, 95% CI 66% to 74%); VITROS High Sensitivity Troponin I Assay (sensitivity 100%, 95% CI 95% to 100%; specificity 60%, 95% CI 55% to 64%); TriageTrue High Sensitivity Troponin I Test (sensitivity 100%, 95% CI 97% to 100%; specificity 66%, 95% CI 62% to 70%); ADVIA Centaur High-Sensitivity Troponin I (sensitivity 99%, 95% CI 95% to 100%; specificity 67%, 95% CI 61% to 72%). The High-Sensitivity Troponin in the Evaluation of Patients With Acute Coronary Syndrome (High-STEACS) pathway, which uses a later (3-hour) second sample, offers the potential to increase overall specificity and hence the proportion of patients in whom non-ST segment elevation myocardial infarction can be ruled out, without loss of sensitivity. Sensitivity and specificity estimates for the High-STEACS pathway were 99% (95% CI 97% to 100%) and 76% (95% CI 73% to 78%), respectively, using the Abbott ARCHITECT STAT High Sensitive Troponin-I assay, and 98% (95% CI 95% to 100%) and 74% (95% CI 72% to 76%), respectively, using the Atellica IM High-Sensitivity Troponin I assay.

Two randomised trials were included in the review. High-STEACS evaluated the implementation of an early rule-out pathway in hospitals in Scotland, which assessed rates of reclassification of patients, and subsequent incidence of myocardial infarction and cardiovascular death when high-sensitivity cardiac troponin I results were made available for patients previously classified using conventional cardiac troponin I results. The High-Sensitivity Cardiac Troponin On Presentation to Rule Out Myocardial Infarction (HiSTORIC) trial (confidential information has been removed) also evaluated the implementation of an early rule-out pathway in hospitals in Scotland. The primary outcomes were length of stay and myocardial infarction or cardiac death after discharge (at 30 days). In the High-STEACS study, the median length of stay was 7 (interquartile range 3–24) hours in the implementation phase and 4 (interquartile range 3–20) hours in the validation phase. In the HiSTORIC trial (confidential information has been removed). Both studies reported that the implementation of an early rule-out pathway was not associated with any increase in myocardial infarction or cardiac death after discharge, at 30 days or 1 year.

Assessment of cost-effectiveness

Base-case analysis

In the base-case analysis, standard troponin testing (at presentation and after 10–12 hours) was the most effective (probabilistic: 15.5331 life-years and 12.0825 quality adjusted life-years) and the most expensive strategy (£38,871). However, other testing strategies with a sensitivity of 100% (subject to uncertainty) were almost equally effective, resulting in the same life-year and quality-adjusted life-year gain at up to four decimal places. Comparisons based on the next best alternative showed that for willingness-to-pay values < £8455 per quality adjusted life-year, the Access High Sensitivity Troponin I [(symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 5 at 0 to 2 hours)] would be cost-effective. For thresholds between £8455 and £20,190 per quality-adjusted life-year, the Elecsys Troponin-T high sensitive (< 12 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours) would be cost-effective. For a threshold > £20,190 per quality-adjusted life-year, the Dimension Vista High-Sensitivity Troponin I (< 5 ng/l at 0 hours AND Δ < 2 ng/l at 0 to 1 hours) would be cost-effective.

Secondary analysis

In the secondary analysis, which assumed that a proportion of false positives in the high-sensitivity cardiac troponin testing strategies had an increased risk of adverse events (i.e. myocardial infarction and mortality), standard troponin (at presentation and after 10–12 hours) was the cheapest (£37,517) and least effective (11.334 quality-adjusted life-years) testing strategy (probabilistic analysis). The Access High Sensitivity Troponin I [European Society of Cardiology 0/1-hour pathway: (symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 4 ng/l at 0 to 1 hours)] was the most effective testing strategy (11.4725 quality-adjusted life-years) at higher costs (£38,077). All other strategies were (extendedly) dominated. The incremental cost-effectiveness ratio of the Access High Sensitivity Troponin I [European Society of Cardiology 0/1-hour pathway: (symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 4 ng/l at 0 to 1 hours)] compared with standard troponin (at presentation and after 10–12 hours) was £4043 per quality-adjusted life-year gained.

Sensitivity and scenario analyses

The following input parameters had a notable impact on the estimated cost-effectiveness: the 30-day mortality for untreated acute myocardial infarction, mortality 1 year after treated and untreated acute myocardial infarction, the discount rate used for outcomes, and the relative mortality for patients who tested true positive compared with those who tested false positive. Moreover, only scenario analysis 1 (i.e. increasing the costs for false positives) had a substantial impact on the cost-effectiveness.

Conclusions

There is evidence to indicate that high-sensitivity troponin assays can be used to rule out non-ST segment elevation myocardial infarction in adults presenting with acute chest pain, within the 4-hour NHS emergency department target. Test strategies that comprise an initial rule-out step, based on low high-sensitivity cardiac troponin levels in a sample taken on presentation and a minimum symptom duration, and a second stage for patients not meeting the initial rule-out criteria, based on low presentation levels of high-sensitivity cardiac troponin and small absolute change in high-sensitivity cardiac troponin between presentation and a second sample taken after 1, 2 or 3 hours, are likely to produce the highest rule-out rates while maintaining clinically acceptable sensitivity (i.e. very low rates of missed non-ST segment elevation myocardial infarction).

From a cost-effectiveness perspective, the Elecsys Troponin-T high sensitive (< 12 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours) and the Dimension Vista High-Sensitivity Troponin I (< 5 ng/l at 0 hours AND Δ < 2 ng/l at 0 to 1 hours) might be cost-effective for thresholds of £20,000 and £30,000 per quality-adjusted life-year gained, respectively (base case). For the secondary analysis, the Access High Sensitivity Troponin I [(symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 5 ng/l at 0 to 2 hours)] was considered cost-effective for these thresholds. The cost-effectiveness results should, however, be interpreted while noting that the differences between the strategies in both costs and quality-adjusted life-years were very small. Given these minimal differences in cost-effectiveness, it might be worthwhile to consider other aspects not captured in the economic assessment. Therefore, it is worth noting that the high-sensitivity test strategies with the highest true negatives (i.e. ≥ 65%) involve high-sensitivity tests strategies with a second test 2–3 hours after the initial test {i.e. Atellica IM High-Sensitivity Troponin I (High-STEACS pathway), ARCHITECT STAT High Sensitive Troponin-I assay (High-STEACS pathway), Elecsys Troponin-T high sensitive (99th centile) and Access High Sensitivity Troponin I [(symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 5 ng/l at 0 to 2 hours)]}.

Study registration

This study is registered as PROSPERO CRD42019154716.

Funding

This project was funded by the National Institute for Health Research (NIHR) Evidence Synthesis programme and will be published in full in *Health Technology Assessment*; Vol. 25, No. 33. See the NIHR Journals Library website for further project information.

Chapter 1 Objective

The overall objective of this project was to provide an update to National Institute for Health and Care Excellence (NICE) diagnostics guidance, published in October 2014, on early rule out of acute myocardial infarction (AMI) using high-sensitivity troponin tests [diagnostics guidance (DG) 15].[1] Some sections of this report have been reproduced from our previous publication.[2] This update summarises the current evidence on the clinical effectiveness and cost-effectiveness of high-sensitivity troponin assays (including new assays that have become available to the NHS since the publication of DG15[1]) for the management of adults presenting with acute chest pain, focusing on the early (i.e. within 4 hours of presentation) rule out of non-ST elevation myocardial infarction (NSTEMI). The following research questions were defined to address the objective of the review.

- What is the clinical effectiveness of high-sensitivity cardiac troponin (hs-cTn) assays (used singly or in series) compared with conventional diagnostic assessment for achieving early discharge (within 4 hours of presentation) when NSTEMI is excluded and without increase in adverse outcomes?
- What is the diagnostic performance of hs-cTn assays (used singly or in series, such that results are available within 3 hours of presentation) for the early rule out of NSTEMI in adults with acute chest pain?
- What is the accuracy of hs-cTn assays (used singly or in series, such that results are available within 3 hours of presentation) for the prediction of major adverse cardiac events (MACEs) [e.g. cardiac death, non-fatal myocardial infarction (MI), revascularisation or hospitalisation for myocardial ischaemia] during 30-day follow-up in adults with acute chest pain?
- What is the cost-effectiveness of using hs-cTn assays (used singly or in series, such that results are available within 3 hours of presentation) compared with the current standard of serial troponin T and/or I testing on admission and at 10–12 hours post admission?

These research questions were addressed as components of a single systematic review and associated cost-effectiveness modelling.

Chapter 2 Background and definition of the decision problem(s)

Population

The primary indication for this assessment is the early rule out of AMI and consequent early discharge in people presenting with acute chest pain and suspected, but not confirmed, NSTEMI.

Acute coronary syndrome (ACS) is the term used to describe a spectrum of conditions caused by coronary artery disease (CAD). ACS arises when atheromatous plaque ruptures or erodes, leading to vasospasm, thrombus formation and distal embolisation, obstructing blood flow through the coronary arteries. It incorporates three distinct conditions: (1) unstable angina (UA), (2) ST elevation myocardial infarction (STEMI) and (3) NSTEMI. CAD and MI are a significant health burden in the UK, with Office for National Statistics mortality data for 2018 showing 19,654 deaths from AMI and 59,995 deaths from ischaemic heart disease (AMI accounted for 3.6% of all deaths recorded in 2018 and ischaemic heart disease accounted for approximately 10.3% of all deaths recorded in 2018).[3]

Acute coronary syndrome usually presents as chest pain and chest pain has been reported as the most common cause of hospital admissions in the UK.[4] Hospital Episode Statistics (HES) for 2017–18 show 226,393 emergency admissions for chest pain, accounting for approximately 5% of all emergency admissions.[5] However, many people presenting with acute chest pain will have non-cardiac underlying causes, such as gastro-oesophageal disorders, muscle pain, anxiety or stable ischaemic heart disease. A 2003 study[6] on the impact of cardiology guidelines on the diagnostic classification of people with ACS in the UK reported that the majority of people admitted to hospital with chest pain have either no ischaemic heart disease or stable ischaemic heart disease.[6] HES for 2017–18 remain consistent with this observation, showing diagnoses of AMI in 45,163 emergency admissions and UA in 13,056 admissions (these represent approximately 20% and 6% of emergency admissions with chest pain, respectively).[5] Accurate and prompt differentiation of ACS (in particular AMI), stable CAD and other causes of chest pain is therefore vital to ensure appropriate and timely intervention when required and to avoid unnecessary hospital admissions.

ST elevation myocardial infarction can usually be diagnosed on presentation by electrocardiogram (ECG), hence the main diagnostic challenge in the investigation of suspected ACS is the detection or rule out of NSTEMI. Investigation of ACS can also involve identification of people with UA (i.e. CAD with worsening symptoms, but no evidence of myocardial necrosis).

Since the development of protein biomarkers of myocardial damage in the 1980s, the number of biomarker assays available has proliferated, cardiac specificity has increased and the role of biomarkers in the diagnostic work-up of acute chest pain has expanded. The most recent HES show that the number of emergency department (ED) attendances where the first recorded investigation was a cardiac biomarker has risen substantially from 13,743 in 2010–11 to 28,379 in 2011–12[7] (recorded in our previous report for DG15[2]) and then to 36,907 in 2017–18.[8] Cardiac troponin I (cTnI) and cardiac troponin T (cTnT), together with cardiac troponin (cTn) C, form the troponin–tropomyosin complex, which is responsible for regulating cardiac muscle contraction. cTnI and cTnT are used clinically as markers of cardiomyocyte necrosis, indicative of AMI. Troponin assays are intended for use in conjunction with clinical history taking and electrocardiography monitoring as, although specificity is high, troponins may also be elevated in many other conditions, including myocarditis, congestive heart failure, severe infections, renal disease and chronic inflammatory conditions of the muscle or skin. Standard biochemical diagnosis of NSTEMI is based on elevation of the cardiac biomarker troponin above the 99th centile of the reference range

for the normal population.[9] However, the optimal sensitivity of standard troponin assays for MI occurs several hours after the onset of symptoms[10] and, historically, this has been reflected in clinical guidelines (CGs), which recommended standard cTnI or cTnT testing at initial hospital assessment and again 10–12 hours after the onset of symptoms.[11,12] As the majority of people presenting with chest pain do not have NSTEMI, where presentation is within a few hours of symptom onset, delayed biomarker measurement may result in unnecessary periods of extended observation or hospitalisation, and associated costs. DG15 recommended the use of some hs-cTn assays [i.e. the Elecsys® Troponin-T high sensitive (Roche, Basel, Switzerland) and the ARCHITECT STAT High Sensitive Troponin-I (Abbott Laboratories, Abbott Park, IL, USA)] as options for the early rule out of NSTEMI in people presenting to an ED with chest pain and suspected ACS.[13] This recommendation was incorporated into the 2016 update to the NICE CG95.[14] High-sensitivity troponin assays are also now included in Scottish Intercollegiate Guidelines Network guidance on the management of ACS.[15] This updated assessment is being undertaken to ensure that guidance is based on current evidence (including new hs-cTn assays developed and marketed since the publication of DG15) and, where possible, to facilitate the provision of more detailed, evidence-based recommendations on how to use hs-cTn assays (e.g. timing of testing and use of sequential testing strategies).

Intervention technologies

High-sensitivity cTn assays that are able to detect lower levels of troponin in the blood are now available. Current generations of commercially available assays have analytical sensitivities up to 100 times greater than was the case for early troponin assays (1 ng/l vs. 100 ng/l).[16] Use of these high-sensitivity assays enables the detection of small changes in troponin levels, and may enable NSTEMI to be ruled out at an earlier time after the onset of acute chest pain. Use of the hs-cTn assays has the potential to facilitate earlier discharge for people with normal troponin levels. The recommended definition of a hs-cTn assay uses two criteria.[16,17]

1. The total imprecision, coefficient of variation (CoV), of the assay should be $\leq$ 10% at the 99th centile value for the healthy reference population.
2. The limit of detection (LoD) of the assay should be such as to allow measurable concentrations to be attainable for at least 50% (ideally >95%) of healthy individuals.

A number of high-sensitivity cardiac troponin I (hs-cTnI) and high-sensitivity cardiac troponin T (hs-cTnT) assays are currently available for use in the NHS in England and Wales, and all are designed for use in clinical laboratory settings.

ARCHITECT STAT High Sensitive Troponin-I assay (Abbott Diagnostics)

The ARCHITECT STAT High Sensitive Troponin-I assay can be used with the ARCHITECT i2000SR and i1000SR analysers (Abbott Laboratories, Abbott Park, IL, USA). The assay is a quantitative, chemiluminescent microparticle immunoassay for serum or plasma samples. Results are available within 16 minutes. The ARCHITECT STAT High Sensitive Troponin-I assay can detect cTnI in 96% of the reference population, and has a recommended 99th centile cut-off point of 26.2 ng/l with a CoV of 4%.[18] The assay is Conformitè Europëenne (CE) marked and available to the NHS.

Alinity i STAT High Sensitivity Troponin-I assay (Abbott Diagnostics)

The Alinity i STAT High Sensitive Troponin-I assay (Abbott Laboratories, Abbott Park, IL, USA) can be used with the Alinity i analyser (Abbott Laboratories, Abbott Park, IL, USA). It is a chemiluminescent microparticle immunoassay used for the quantitative determination of troponin I in plasma and serum samples. Results are available within 18 minutes. The Alinity i STAT High Sensitive Troponin-I assay has a recommended 99th centile cut-off point of 26.2 ng/l with a CoV of 4.6%. Sex-specific 99th centile cut off points of 15.6 ng/l for females (CoV of 5.0%) and 34.2 ng/l for males (CoV of 4.5%) are also provided.[19] The assay is CE marked and available to the NHS.

Access High Sensitivity Troponin I (Beckman Coulter)

The Access High Sensitivity Troponin I (Beckman Coulter, Brea, CA, USA) assay can be used with both the Access 2 and DxI/DxC analysers (Beckman Coulter, Brea, CA, USA). The assay is a quantitative, paramagnetic particle chemiluminescent immunoassay for serum or plasma samples. The turnaround time of the assay is 17 minutes. The Access High Sensitivity Troponin I assay has a recommended 99th centile cut-off point of 17.5 ng/l for the whole population, 11.6 ng/l for females and 19.8 ng/l for males, with a CoV of < 10%.[20] The assay can detect troponin I in > 50% of the reference population. The assay is CE marked and available to the NHS.

VIDAS High sensitive Troponin I assay (bioMérieux)

The VIDAS® High sensitive Troponin I (bioMérieux SA, Marcy l'Etoile, France) assay is designed for use in a laboratory setting on the following analysers: VIDAS, MINI VIDAS and VIDAS 3 (bioMérieux SA, Marcy l'Etoile, France). It is intended for the in vitro quantitative determination of troponin I in serum and plasma (lithium heparin) samples. Test results are available in 20 minutes. It has a recommended 99th centile cut-off point of 19 ng/l. Sex-specific 99th centile cut-off points of 11 ng/l for females and 25 ng/l for males are provided.[21] The assay is CE marked and available to the NHS.

VITROS High Sensitivity Troponin I Assay (Ortho Clinical Diagnostics)

The VITROS® High Sensitivity Troponin I Assay (Ortho Clinical Diagnostics, Marlow, UK) is designed for use in a laboratory setting on the following analysers: VITROS® ECi/ECiQ/3600 Immunodiagnostic Systems (Ortho Clinical Diagnostics, Marlow, UK) and the VITROS® 5600/XT 7600 Integrated System (Ortho Clinical Diagnostics, Marlow, UK). It is an immunometric immunoassay and is intended for the in vitro quantitative determination of troponin I in serum and plasma samples. Test results are available in 15 minutes. It has a recommended 99th centile cut-off point of 11 ng/l for both lithium heparin and serum samples. Sex-specific 99th centile cut-off points of 9 ng/l (in lithium heparin and serum) for females and 13 ng/l (in lithium heparin) and 12 ng/l (in serum) for males are provided.[22] The assay can detect troponin I in > 50% of the reference population. The assay is CE marked and available to the NHS.

TriageTrue High Sensitivity Troponin I Test (Quidel)

The TriageTrue High Sensitivity Troponin I Test (Quidel, San Diego, CA, USA) can be used in a near-patient setting (i.e. the point of care) or in a laboratory with the Triage MeterPro analyser Quidel, San Diego, CA, USA). It is a fluorescence immunoassay and is intended for the in vitro quantitative determination of troponin I in ethylenediaminetetraacetic acid, anticoagulated whole blood and plasma samples. Test results are available in < 20 minutes. It has a recommended 99th centile cut-off point of 20.5 ng/l with a CoV of < 10%. Sex-specific 99th centile cut-off points of 14.4 ng/l for females and 25.7 ng/l for males are provided.[23] The test can detect troponin I in > 50% of the reference population. The test is CE marked and available to the NHS.

Elecsys Troponin-T high sensitive assay (Roche)

The Elecsys Troponin-T high sensitive assay and Elecsys cTnT-hs STAT assay can be used on the cobas e 411, e 601, e 602 and e 801 analysers (Roche, Basel, Switzerland). The assay is a quantitative, sandwich electrochemiluminescence immunoassay for serum and plasma samples. Results are available within 18 minutes with the standard assay and within 9 minutes if the STAT assay is used. Both versions of the assay can detect cTnT in 57% of the reference population and have a recommended 99th centile cut-off point of 14 ng/l with a CoV of < 10%.[24–26] Both versions of the assay are CE marked and available to the NHS.

ADVIA Centaur High-Sensitivity Troponin I assay (Siemens Healthcare)

The ADVIA Centaur® High-Sensitivity Troponin I assay (Siemens Healthcare, Erlangen, Germany) can be used with the ADVIA Centaur XP and ADVIA Centaur XPT analysers (Siemens Healthcare, Erlangen, Germany). It is a magnetic latex particle chemiluminescent immunoassay and is intended for

the in vitro quantitative determination of cTnI in serum and plasma samples. Test results are available within 18 minutes. The assay has a recommended 99th centile cut-off point of 47.34 ng/l for the whole population in lithium heparin samples and of 46.47 ng/l in serum samples.[27] Sex-specific cut-off points of 36.99 ng/l for females and 57.27 ng/l for males are also recommended.[27] Each 99th centile has a CoV of < 10%. The assay can detect cTnI in > 50% of the reference population. The assay is CE marked and available to the NHS.

Atellica IM High-Sensitivity Troponin I (Siemens Healthcare)

The Atellica® IM High-Sensitivity Troponin I assay (Siemens Healthcare, Erlangen, Germany) can only be used with the Atellica® IM analyser (Siemens Healthcare, Erlangen, Germany). It is a magnetic latex particle chemiluminescent immunoassay and is intended for the in vitro quantitative determination of cTnI in serum and plasma samples. Test results are available within 10 minutes. The assay has a recommended 99th centile cut-off point of 45.2 ng/l for lithium heparin samples and 45.43 ng/l for serum samples. Each 99th centile has a CoV of < 10%.[28] The assay can detect cTnI in > 50% of the reference population. The assay is CE marked and available to the NHS.

Dimension® EXL™ hs-cTnI (Siemens Healthcare)

The Dimension® EXL™ hs-cTnI (Siemens Healthcare, Erlangen, Germany) assay is designed for use in a laboratory setting with the Dimension EXL analyser (Siemens Healthcare, Erlangen, Germany). It is a magnetic latex particle chemiluminescent immunoassay and is intended for the in vitro quantitative determination of troponin I in serum and plasma samples. Test results are available in 18 minutes. It has a recommended 99th centile cut-off point of 60.4 ng/l for lithium heparin and 58.2 ng/l for serum.[29] Sex-specific 99th centile cut-off points of 51.4 ng/l for females and 76.2 ng/l for males in lithium heparin and 47.8 ng/l for females and 71.8 ng/l for males in serum are provided.[29] Each 99th centile has a CoV of < 10%. The assay can detect troponin I in > 50% of the reference population. The assay is CE marked and available to the NHS.

Dimension Vista High-Sensitivity Troponin I assay (Siemens Healthcare)

The Dimension Vista® High-Sensitivity Troponin I assay (Siemens Healthcare, Erlangen, Germany) is designed for use in a laboratory setting with the Dimension Vista analysers (Siemens Healthcare, Erlangen, Germany). It is a magnetic latex particle chemiluminescent immunoassay and is intended for the in vitro quantitative determination of cTnI in serum and plasma samples. Test results are available within 10 minutes. The assay has a recommended 99th centile cut-off point of 58.9 ng/l for lithium heparin samples and 57.9 ng/l for serum samples.[30] Sex-specific 99th centile cut-off points of 53.77 ng/l for females and 78.5 ng/l for males are also recommended.[30] Each 99th centile has a CoV of < 10%. The assay can detect cTnI in > 50% of the reference population. The assay is CE marked and available to the NHS.

A summary of the product properties of hs-cTnI and hs-cTnT assays available in the NHS in England and Wales is provided in *Table 1*.

This assessment considers hs-cTn assays used singly or in series, up to 3 hours after the onset of chest pain or up to 3 hours after presentation (as reported) for serial troponin measurements. Data for both relative and absolute change in troponin levels and peak troponin are presented.

Comparator

The comparator for this technology appraisal is serial troponin T and/or I testing (using any method not defined as a hs-cTn test) on admission and at 10–12 hours after the onset of symptoms, as used in our previous diagnostic assessment report (DAR),[2] conducted to support the development of DG15.[13]

TABLE 1 Overview of cardiac biomarkers

Manufacturer	System and compatible analysers	Assay	99th centile (ng/l)	CoV at 99th centile (%)	Proportion of reference population in which cTn is detected (%)	Turnaround time (minutes)	LoD (ng/l)	LoQ (ng/l)
Abbott Diagnostics	ARCHITECT i1000sr and i2000sr	ARCHITECT hs-cTnI[18]	Overall: 26.2 Female: 15.6 Male: 34.2	Overall: 4.0 Female: 5.3 Male: 3.5	96[31]	18[a]	1.9	4.7 (10% CoV); 1.3 (20% CoV)
Abbott Diagnostics	Alinity i	Alinity hs-cTnI[19]	Overall: 26.2 Female: 15.6 Male: 34.2	Overall: 4.6 Female: 5.0 Male: 4.5	96[31]	18[a]	1.6	3.7 (10% CoV); 2.1 (20% CoV)
Beckman Coulter	Access 2, DxI 600/800, DxC 600i/880i/860i/680i/660i	Access hs-cTnI[20]	Lithium heparin – Overall: 17.5 Female: 11.6 Male: 19.8 Serum – Overall: 18.2 Female: 11.8 Male: 19.7	Lithium heparin – Overall: 3.7 Female: 4.2 Male: 3.6 Serum – Overall: 6.0 Female: 6.9 Male: 5.8	> 50	17[a]	2.3	2.3
bioMérieux	VIDAS, MINI VIDAS, VIDAS 3	VIDAS hs-cTnI[a]	Overall: 19 Female: 11 Male: 25			20		

continued

TABLE 1 Overview of cardiac biomarkers (*continued*)

Manufacturer	System and compatible analysers	Assay	99th centile (ng/l)	CoV at 99th centile (%)	Proportion of reference population in which cTn is detected (%)	Turnaround time (minutes)	LoD (ng/l)	LoQ (ng/l)
Ortho Clinical Diagnostics	VITROS ECi/ECiQ/3600 Immunodiagnostic Systems and the VITROS 5600/XT 7600 Integrated System	VITROS hs-cTnI[22]	Lithium heparin – Overall: 11 Female: 9 Male: 13 Serum – Overall: 11 Female: 9 Male: 12	≤ 10[a]	> 50	15[a]	0.39–0.86	1.23
Quidel	Triage MeterPro	TriageTrue hs-cTnI[23]	Overall: 20.5 Female: 14.4 Male: 25.7	Overall: < 10	> 50	< 20[a]	Plasma: 1.6 Whole blood: 1.9	Plasma: 8.4 (10% CoV); 3.6 (20% CoV) Whole blood: 6.2 (10% CoV); 2.8 (20% CoV)
Roche	200 test pack: cobas e 411, e 601, e 602 300 test pack: cobas e 801	Elecsys hs-cTnT[24,25]	Overall: 14 Female: 9 Male: 16.8	< 10	57	18	3 (cobas e 801) 5 (all others)	2.97–6.60
Roche	100 test pack: cobas e 411, e 601, e 602, 300 test pack: cobas e 801	Elecsys hs TnT STAT[26]	Overall: 14 Female: 9 Male: 16.8	< 10	57	9	3 (cobas e 801) 5 (all others)	13

Manufacturer	System and compatible analysers	Assay	99th centile (ng/l)	CoV at 99th centile (%)	Proportion of reference population in which cTn is detected (%)	Turnaround time (minutes)	LoD (ng/l)	LoQ (ng/l)
Siemens Healthcare	Atellica	Atellica IM hs-cTnI[28]	Lithium heparin – Overall: 45.2 Female: 34.11 Male: 53.48 Serum – Overall: 45.43 Female: 38.64 Male: 53.53	< 4	75	10	1.6	2.5
Siemens Healthcare	Dimension EXL	Dimension EXL hs-cTnI[29]	Lithium heparin – Overall: 60.4 Female: 51.4 Male: 76.2 Serum – Overall: 58.2 Female: 47.8 Male: 71.8	< 5	> 50	10	2.7	4.0

continued

TABLE 1 Overview of cardiac biomarkers (*continued*)

Manufacturer	System and compatible analysers	Assay	99th centile (ng/l)	CoV at 99th centile (%)	Proportion of reference population in which cTn is detected (%)	Turnaround time (minutes)	LoD (ng/l)	LoQ (ng/l)
Siemens Healthcare	Dimension Vista	Dimension Vista hs-cTnI[30]	Lithium heparin – Overall: 58.9 Female: 53.7 Male: 78.5 Serum – Overall: 57.9 Female: 51.1 Male: 74.9	< 5	> 50	10	2.0	3.0
Siemens Healthcare	ADVIA Centaur XP and ADVIA Centaur XPT	ADVIA Centaur hs-cTnI[27]	Lithium heparin – Overall: 47.34 Female: 36.99 Male: 57.27 Serum – Overall: 46.47 Female: 39.59 Male: 58.05	< 4.9	63	18	1.6	2.5 (20% CoV)

LoQ, limit of quantitation.
a Information supplied to NICE by the manufacturer.

Care pathway

Diagnostic assessment

The assessment of patients with suspected ACS is described in NICE CG95.[11] This has been updated since the publication of DG15[13] to include recommendations on the use of high-sensitivity troponin assays.[14] The guideline specifies that initial assessment should include a resting 12-lead ECG, along with a clinical history, a physical examination and biochemical marker analysis. For people in whom a regional ST segment elevation or presumed new left branch bundle block is seen on the ECG, management should follow NICE CG167.[32] People without persistent ST elevation changes on the ECG [i.e. those with non-ST segment elevation acute coronary syndrome (NSTE-ACS)] should receive further investigation using cardiac biomarkers, with the aim of distinguishing NSTEMI from UA. NICE CG95 makes the following recommendations on the use of cardiac biomarkers.[14]

- Do not use high-sensitivity troponin tests for people in whom ACS is not suspected.
- For people at high or moderate risk of MI (as indicated by a validated tool), perform high-sensitivity troponin tests, as recommended in the NICE diagnostics guidance on MI (DG15).
- For people at low risk of MI (as indicated by a validated tool):
    - perform a second high-sensitivity troponin test, as recommended in the NICE diagnostics guidance on MI (DG15), if the first troponin test at presentation is positive
    - consider performing a single high-sensitivity troponin test at presentation to rule out NSTEMI if the first troponin test is below the lower LoD (i.e. negative).
- Ensure that patients understand that a detectable troponin on the first high-sensitivity test does not necessarily indicate that they have had an MI. Do not use biochemical markers, such as natriuretic peptides and high-sensitivity C-reactive protein, to diagnose an ACS.
- Do not use biochemical markers of myocardial ischaemia (such as ischaemia-modified albumin) as opposed to markers of necrosis when assessing people with acute chest pain.
- When interpreting high-sensitivity troponin measurements, take into account:
    - the clinical presentation
    - the time from onset of symptoms
    - the resting 12-lead ECG findings
    - the pre-test probability of NSTEMI
    - the length of time since the suspected ACS
    - the probability of chronically elevated troponin levels in some people
    - that 99th centile thresholds for troponin I and T may differ between sexes.

Clinical guideline 95 recommends that a diagnosis of NSTEMI should be made using the universal definition of MI, which states that AMI is defined as a change in cardiac biomarker concentration and at least one cardiac biomarker concentration value above the 99th centile for the reference population, accompanied by symptoms of ischemia, an abnormal ECG, evidence of myocardial damage on imaging, or an intracoronary thrombus identified by angiography or at autopsy.[11]

The Scottish Intercollegiate Guidelines Network guideline 148 provides the following recommendations in relation to cTns.[15]

- In patients with suspected ACS, serum troponin concentration should be measured at presentation to guide appropriate management and treatment.
- Serum troponin concentration should be measured 12 hours from the onset of symptoms to establish a diagnosis of MI.

- In patients with suspected ACS, measurement of cTn at presentation and at 3 hours after presentation with a high-sensitivity assay should be considered as an alternative to serial measurement over 10–12 hours with a standard troponin assay to rule out MI.
- Sex-specific thresholds of cTn should be used for the diagnosis of MI in men and women.

Guidelines from the European Society of Cardiology (ESC) on the management of ACS in patients presenting without persistent ST segment elevation recommend that 'measurement of cardiac troponins with sensitive or high-sensitivity assays to obtain results within 60 minutes'.[33] The guideline also describes 0/1- and 0/3-hour rule-out algorithms, which incorporate both high-sensitivity troponin assays and clinical risk scores.[33] For the 0/1-hour algorithm, additional troponin testing after 3–6 hours is recommended if the first two measurements are inconclusive and the clinical condition is still suggestive of ACS.[33]

The guideline from the American College of Cardiology (ACC)/American Heart Association (AHA) on the management of patients with NSTE-ACS does not include any specific recommendations about the use of high-sensitivity troponin assays.[34] However, the guideline does note that 'For patients with a TIMI [thrombolysis in myocardial infarction] risk score of 0 and normal high-sensitivity cardiac troponin 2 hours after presentation, accelerated diagnostic protocols have been developed that predict a very low rate of 30-day MACE'.[34]

The 2017 publication *Asia-Pacific Consensus Statement on the Optimal Use of High-Sensitivity Troponin Assays in Acute Coronary Syndromes Diagnosis: Focus on hs-cTnI* makes nine recommendations.[35]

1. Troponin is the preferred cardiac biomarker for diagnostic assessment of ACS and is indicated for patients with symptoms of possible ACS.
2. hs-cTn assays are recommended.
3. Serial testing is required for all patients.
4. Testing should be performed at presentation and 3 hours later.
5. Sex-specific cut-off point values should be used for hs-cTnI assays.
6. A hs-cTnI level > 10 times the upper limit of normal should be considered to 'rule in' a diagnosis of ACS.
7. Dynamic change > 50% in hs-cTnI level from presentation to 3-hour retest identifies patients at high risk for ACS.
8. When only point-of-care testing is available, patients with elevated readings should be considered at high risk, whereas patients with low/undetectable readings should be retested after 6 hours or sent for laboratory testing.
9. Regular education on the appropriate use of troponin tests is essential.

The rapidly expanding evidence base on hs-cTns, together with their increasing uptake and inclusion in CGs, means that an update to the NICE diagnostics guidance on early rule out of AMI using high-sensitivity troponin tests (DG15), published in October 2014,[13] is now considered necessary.

Management/treatment

The NICE CG94[36] provides recommendations on the management of people with suspected NSTE-ACS. The guideline states that initial treatment should include a combination of antiplatelet (e.g. aspirin, clopidogrel and glycoprotein IIb/IIIa inhibitors) and antithrombin therapy, and should take into account contraindications, risk factors and the likelihood of percutaneous coronary intervention. The following NICE guidelines are being combined and updated: *Unstable Angina and NSTEMI: The Early Management of Unstable Angine and Non-ST-Segment-Elevation Myocardial Infarction* (CG94),[36] *Myocardial Infarction: Cardiac Rehabilitation and Prevention of Further Cardiovascular Disease* (CG172)[37] and *Myocardial Infarction with ST-segment Elevation: The Acute Management of Myocardial Infarction with ST-Segment Elevation* (CG167).[32] The new guideline will be titled Acute Coronary Syndromes when published, and publication is expected in November 2020.

Longer-term follow-up of people who have had an AMI is described in full in NICE CG48 *Secondary Prevention in Primary and Secondary Care for Patients Following a Myocardial Infarction*.[38] This includes recommendations on lifestyle changes, cardiac rehabilitation programmes, drug therapy (including a combination of angiotensin-converting enzyme inhibitors, aspirin, beta-blockers and statins) and further cardiological assessment to determine whether or not coronary revascularisation is required.[38]

A list of NICE guideline documents relevant to the management of suspected ACS is provided in *Appendix 9*.

Chapter 3 Assessment of clinical effectiveness

This report contains reference to confidential information provided as part of the NICE Diagnostic Assessment process. This information has been removed from the report and the results, discussions and conclusions of the report do not include the confidential information. These sections are clearly marked in the report.

In addition, text in this chapter has been reproduced from Westwood *et al.*,[2] which contains information licensed under the Non-Commercial Government Licence v2.0.

Systematic review methods followed the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care,[39] the NICE *Diagnostics Assessment Programme Manual*[40] and the Cochrane *Handbook for DTA Reviews*.[41] A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist for this review is provided in *Appendix 10*. All data for studies included in our previous DAR,[2] conducted to support the development of DG15,[13] were taken directly from that report.

Systematic review methods

Search strategy

Search strategies utilised in the original report[2] were updated with any new interventions identified in the NICE scope. Search strategies were based on the intervention (i.e. high-sensitivity troponin assays) and target condition, as recommended in the CRD's guidance for undertaking reviews in health care[39] and the Cochrane *Handbook for DTA Reviews*.[41]

Search strategies were developed specifically for each database and the keywords associated with hs-cTnT or hs-cTnI were adapted according to the configuration of each database. No language restrictions were applied.

The following databases were searched between 20 September 2019 and 26 September 2019 for relevant studies from 2013 to the present:

- MEDLINE ALL (Ovid) – 1946 to 24 September 2019
- EMBASE (Ovid) – 1974 to 25 September 2019
- Cochrane Database of Systematic Reviews (CDSR) (Wiley) – Issue 9/September 2019
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley) – Issue 9/September 2019
- Database of Abstracts of Reviews of Effects (DARE) (CRD) – up to March 2015
- Health Technology Assessment (HTA) database (CRD) – up to March 2018
- Science Citation Index (SCI) (Web of Science) – 1988 to 24 September 2019
- Conference Proceedings Citation Index – Science (CPCI-S) (Web of Science) – 1990 to 24 September 2019
- Latin American and Caribbean Health Sciences Literature (LILACS) (internet) – 2013 to 20 September 2019
- National Institute for Health Research HTA programme (internet) – up to 26 September 2019
- PROSPERO (International Prospective Register of Systematic Reviews) (internet) – up to 20 September 2019.

Completed and ongoing trials were identified by searches of the following resources (2013–present):

- National Institutes of Health ClinicalTrials.gov (URL: www.clinicaltrials.gov/) – first posted from 1 January 2013 to 31 December 2019.
- World Health Organization International Clinical Trials Registry Platform (URL: www.who.int/ictrp/en/) – date of registration 1 January 2013 to 25 September 2019.

The following key conference proceedings are indexed in EMBASE and so will be covered in the EMBASE search detailed above:

- AHA Scientific Sessions.
- American Association for Clinical Chemistry.
- ESC.

The following conference abstracts were manually searched to compliment those conference abstracts indexed in EMBASE:

- American Association for Clinical Chemistry (2018, 2019).
- AHA Scientific Sessions 2017–19.
- ESC 2019.

References in retrieved articles and relevant systematic reviews were checked.

Searches took into account generic and other product names for the intervention. All search strategies are provided in *Appendix 1*. The main EMBASE strategy was independently peer reviewed by a second information specialist, using the Canadian Agency for Drugs and Technologies in Health (CADTH) peer review checklist.[42]

Inclusion and exclusion criteria

Inclusion criteria for each of the clinical effectiveness questions are summarised in *Table 2*. Studies that fulfilled these criteria were eligible for inclusion in the review. Studies that were included in our previous DAR,[2] conducted to support the development of DG15,[13] were also included in this review.

Inclusion screening and data extraction

Two out of three reviewers (MW, DF and GW) independently screened the titles and abstracts of all reports identified by searches and any discrepancies were discussed and resolved by consensus. Full copies of all studies deemed potentially relevant were obtained and the same two reviewers independently assessed these for inclusion. Any disagreements were resolved by consensus. Details of studies excluded at the full-paper screening stage are presented in *Appendix 5*.

Studies cited in materials provided by the manufacturers of hs-cTn assays were first checked against the project reference database (in EndNote X8, Clarivate Analytics, Philadelphia, PA, USA) and any studies not already identified by our searches were screened for inclusion following the process described above.

The following data were extracted: study details, inclusion and exclusion criteria, participant characteristics (demographic characteristics and cardiac risk factors), target condition (NSTEMI or AMI), details of the hs-cTnT or hs-cTnI test strategy (manufacturer, number and timing of tests, and definition of positive diagnostic threshold), details of reference standard [manufacturer, timing, diagnostic threshold for conventional troponin T or I testing, clinical and imaging components of the reference standard, method of adjudication (e.g. two independent clinicians)], incidence of a MACE during 30-day follow-up and test performance outcome measures [numbers of true-positive (TP), false-positive (FP), false-negative (FN) and true-negative (TN) test results]. When studies reported data

TABLE 2 Inclusion criteria

Question	What is the diagnostic performance of hs-cTn assays (used singly or in series, such that results are available within 3 hours of presentation) for the early rule out of NSTEMI in adults with acute chest pain?	What is the accuracy of hs-cTn assays (used singly or in series, such that results are available within 3 hours of presentation) for the prediction of a MACE (e.g. cardiac death, non-fatal MI, revascularisation or hospitalisation for myocardial ischaemia) during 30-day follow-up in adults with acute chest pain?	What is the effectiveness of hs-cTn assays (used singly or in series) compared with conventional diagnostic assessment for achieving successful early discharge of adults with acute chest pain within 4 hours of presentation?
Participants	Adults (aged ≥ 18 years) presenting with acute 'pain, discomfort or pressure in the chest, epigastrium, neck, jaw, or upper limb without an apparent non-cardiac source'[34] due to a suspected, but not proven, AMI		
Setting	Secondary or tertiary care		
	Interventions (index test)	Any hs-cTnT or hs-cTnI test,[a] listed in *Table 1*, or hs-cTn assays (used singly or in series,[b] such that results were available within 3 hours of presentation)	
Comparators	Any other hs-cTn test or test sequence, as specified above, or no comparator		Troponin T or I measurement on presentation and 10–12 hours after the onset of symptoms
Reference standard	The third or fourth universal definition of AMI,[43] including measurement of troponin T or I (using any method) on presentation and 3–6 hours later, or occurrence of a MACE (any definition used in identified studies) during 30-day follow-up		Not applicable
Outcomes[c]	Test accuracy (i.e. the numbers of TP, FN, FP and TN test results)		Early discharge (i.e. ≤ 4 hours after initial presentation) without a MACE during follow-up; incidence of a MACE during follow-up; reattendance at or readmission to hospital during follow-up; time to discharge; patient satisfaction or HRQoL measures
Study design	Diagnostic cohort studies		RCTs (CCTs will be considered if no RCTs are identified)

CCT, controlled clinical trial; FN, false negative; FP, false positive; HRQoL, health-related quality of life; RCT, randomised controlled trial; TN, true negative; TP, true positive.

a A high-sensitivity assay is defined as one that has a CoV ≤ 10% at the 99th centile value for the healthy reference population, and where the LoD allows measurable concentrations to be attained for at least 50% of healthy individuals.

b For serial hs-cTn assays, both data on relative or absolute change in troponin levels and peak troponin values were considered.

c Any estimates of the relative accuracy/effectiveness of different hs-cTnT or hs-cTnI tests were derived from direct, within study comparisons.

for the development and validation of hs-cTn test strategy, data were extracted for the validation cohort only. Data were extracted by one reviewer, using the data extraction forms from the original systematic review.[2] A second reviewer checked data extraction and any disagreements were resolved by consensus or discussion with a third reviewer. Full data extraction tables are provided in *Appendix 2*.

Quality assessment

The methodological quality of included randomised controlled trials (RCTs) was assessed using the revised Cochrane Risk-of-Bias Tool for Randomised Trials.[44] The methodological quality of included diagnostic test accuracy (DTA) studies that evaluated a single hs-cTn assay for the target conditions NSTEMI, AMI or MACEs was assessed using QUADAS-2.[45] Studies that provided data for two or more

hs-cTn assays were assessed using QUADAS-2C,[46] a version of the QUADAS tool that has been developed specifically for the assessment of comparative DTA studies (this tool is currently undergoing piloting and is not yet published). Quality assessments were undertaken by one reviewer and checked by a second (MW, DF and GW). Any disagreements were resolved by consensus.

The results of the quality assessments are summarised and presented in *Tables 4–6* and are presented in full, by study, in *Appendices 3* and *4*.

Methods of analysis/synthesis

Sensitivity and specificity were calculated for each set of 2 × 2 data and plotted in receiver operating characteristic (ROC) space. The hierarchical summary receiver operating characteristic (SROC) model was used to estimate summary sensitivity and specificity with 95% confidence intervals (CIs) and prediction regions around the summary points, and to plot hierarchical SROC curves. Pooled results were obtained only from meta-analyses involving four or more studies.[47–49] This approach allows for between-study heterogeneity in sensitivity and specificity, and for the trade-off (negative correlation) between sensitivity and specificity commonly seen in diagnostic meta-analyses. For meta-analyses with fewer than four studies, we estimated separate pooled estimates of sensitivity and specificity using random-effects logistic regression.[50] Heterogeneity was assessed visually using SROC plots and assessed statistically using the variance of logit (sensitivity) and logit (specificity), where 'logit' indicates the logistic function (the smaller these values were, the less heterogeneity there was between studies). Analyses were performed in Stata 13 (StataCorp LP, College Station, TX, USA), mainly using the *metandi* command. For analyses with fewer than four studies, we used MetaDisc.[51]

Analyses were conducted separately for each hs-cTn assay. Analyses were stratified according to target condition (e.g. NSTEMI, any AMI or 30-day MACE), timing of collection of blood sample for testing and the threshold used to define a positive hs-cTn result. Stratified analyses were conducted for all time points and thresholds for which sufficient data were available.

When possible, we compared the accuracy of the included hs-cTn assays by tabulating the summary estimates from analyses for common time points and thresholds assessed for multiple assays.

Results of the assessment of clinical effectiveness assessment

The literature searches of bibliographic databases conducted for this update identified 9379 new references. After the initial screening of titles and abstracts, 212 papers were considered potentially relevant and were ordered for full-paper screening. Of these, one study[52] could not be obtained from The British Library and 80 were included in the review.[53–132] In addition, 37 publications, taken from the assessment report conducted for DG15,[2] were carried forward and included in this review.[133–169] All potentially relevant studies cited in documents supplied by the test manufacturers had already been identified by bibliographic database searches. Four additional publications, not identified because their publication post-dated our searches,[170–173] and two further studies, which were unpublished at that time,[174,175] were provided (academic in confidence) by specialist committee members. *Figure 1* shows the flow of studies through the review process and *Appendix 5* provides details, with reasons for exclusions, of all publications excluded at the full-paper screening stage.

Overview of included studies

Based on the update searches and inclusion screening described above and information taken from the assessment report conducted for DG15,[2] a total of 123 publications[53–175] of 37 studies[56,58,61,62,64,68,72,80,84,87–89,96,100–102,110,115,117,121,133,135,137,139,141,142,144,147,148,150,157,159,161,165,171,175,176] were included in the review.

The results section of this report cites studies using the primary publication and, where this is different, the publication in which the referenced data were reported. Thirty studies reported accuracy data for the

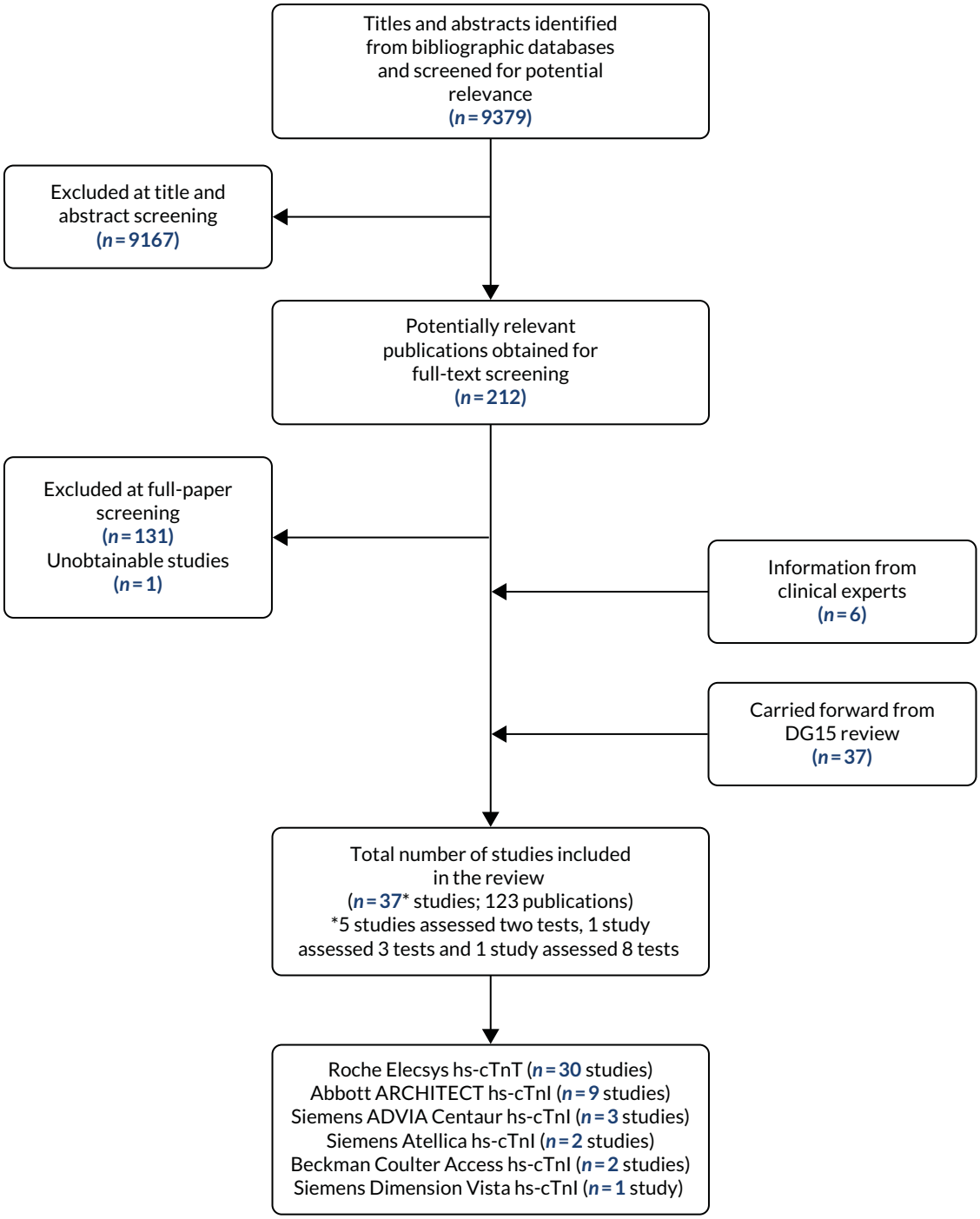

FIGURE 1 Flow of studies through the review process.

Roche Elecsys hs-cTnT assay,[56,58,61,62,64,68,72,80,87–89,100–102,115,117,121,133,135,137,139,142,144,147,148,150,157,159,161,165] nine studies reported accuracy data for the Abbott ARCHITECT hs-cTnI assay,[58,61,64,68,84,96,101,110,141] two studies reported accuracy data for Siemens Healthcare Atellica hs-cTnI,[61,176] three studies reported accuracy data for Siemens Healthcare ADVIA Centaur hs-cTnI,[58,115,176] two studies reported accuracy data for Beckman Coulter ACCESS hs-cTnI[58,171] and one study reported accuracy data for each of Siemens Healthcare Dimension Vista hs-cTnI,[58] Ortho VITROS hs-cTnI,[58] bioMérieux VIDAS hs-cTnI[58] and Quidel Cardiovascular TriageTrue hs-cTnI.[58] Seven studies reported accuracy data for more than one assay.[58,61,64,68,101,115,176]

We did not identify any studies of the Abbott Alinity hs-cTnI and the Siemens Healthcare Dimension EXL hs-cTnI, which also met the inclusion criteria for this review. The High-Sensitivity Troponin in the Evaluation of Patients With Acute Coronary Syndrome (High-STEACS) trial,[61] which contributed multiple diagnostic accuracy data sets, was a stepped-wedge cluster RCT that evaluated implementation of an early rule-out pathway in hospitals in Scotland. This trial assessed rates of reclassification of patients, and subsequent incidence of MI and cardiovascular death when hs-cTnI results were made available for patients previously classified based on cTnI results (these results have been included).[99] A second stepped-wedge cluster RCT, the High-Sensitivity Cardiac Troponin On Presentation to Rule Out Myocardial Infarction (HiSTORIC) trial (unpublished report provided AiC),[175] evaluated the implementation of an early rule-out pathway in hospitals in Scotland. The primary outcomes were length of stay, and MI or cardiac death after discharge (at 30 days). Publications reporting new data were identified for three of the studies included in the assessment report conducted for DG15:[2] ADAPT (2-Hour Accelerated Diagnostic Protocol to Assess Patients With Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarker),[68] APACE (Advantageous Predictors of Acute Coronary Syndromes Evaluation)[58] and QUART (QUeensland Accelerated Risk Trial).[88] *Table 3* provides a summary of the included studies and related publications.

Twenty two[56,58,61,62,64,84,102,110,115,121,133,135,137,141,142,144,148,150,157,159,161,175] of the 37 included studies were conducted in Europe (seven in the UK[56,61,64,115,159,161,175]), five were conducted in Australia and New Zealand,[68,88,139,147,171] six were conducted in the USA,[87,89,101,165,176,177] three were conducted in East Asia[72,100,117] and one was a worldwide study.[80] Twenty seven of the 37 included studies reported receiving some support from test manufacturers, including supply of assay kits[56,58,61,64,68,72,80,84,87-89,96,101,115,133,135,139,141,142,144,147,148,150,157,165,171,176] and three studies did not report any information on funding.[62,102,110]

TABLE 3 Overview of included DTA studies

Study	Country(s)	*n*	Target condition(s) reported	Subgroup(s) reported
Abbott ARCHITECT hs-cTnI				
BACC	Germany	1040	NSTEMI	None
[a]**Neumann *et al.* 2016**[84]				
Neumann *et al.* 2017[85]				
Neumann *et al.* 2017[86]				
[a,b]**Keller *et al.* 2011**[141]	Germany	1818	AMI	None
[b]Keller *et al.* 2011[163]				
UTROPIA	USA	1631	NSTEMI	
Dodd *et al.* 2019[125]				
Sandoval *et al.* 2017[95]				
[a]**Sandoval *et al.* 2017**[96]				
Venge *et al.* 2017[110]	Germany, France Austria and the Netherlands	450	AMI	None
Abbott Alinity hs-cTnI				
No studies identified				
Beckman Coulter ACCESS hs-cTnI				
ADAPT/IMPACT	Australia	1280	NSTEMI	None
Nestelberger *et al.* 2019[171]				

TABLE 3 Overview of included DTA studies (*continued*)

Study	Country(s)	*n*	Target condition(s) reported	Subgroup(s) reported
Siemens Healthcare Dimension EXL hs-cTnI				
No studies identified				
Roche Elecsys hs-cTnT				
[a,b]**Aldous *et al.* 2012**[139]	New Zealand	939	NSTEMI; AMI	None
[b]**Aldous *et al.* 2012**[134]				
[b]**Aldous *et al.* 2011**[143]				
[b]**Aldous *et al.* 2011**[147]	New Zealand	382	AMI	None
[b]Aldous *et al.* 2011[162]				
[b]Aldous *et al.* 2010[155]				
[a,b]**Body *et al.* 2011**[161]	UK	703	AMI	None
[b]Body *et al.* 2011[153]				
[b]Body *et al.* 2010[169]				
Body *et al.* 2015[56]	UK	463	AMI; 30-day MACE	None
Cappellini *et al.* 2019[62]	Italy	3318	NSTEMI	Sex
[b]**Christ *et al.* 2010**[150]	Germany	137	AMI	None
CORE	Sweden	1138	30-day MACE	
Borna *et al.* 2018[116]				
Mokhtari *et al* 2016[119]				
[a]**Mokhtari *et al.* 2016**[121]				
Mokhtari *et al* 2017[120]				
FASTER I and FAST II	Sweden	360	NSTEMI	None
[b]**Eggers *et al.* 2012**[137]				
[a,b] **Freund *et al.* 2011**[142]	France	317	AMI	Low/moderate vs. high pre-test probability
[b]Freund *et al.* 2010[166]				
[a]**Huang *et al.* 2015**[72]	China	3458	AMI	Renal function
Guangquan *et al.* 2016[73]				
[b]**Kurz *et al.* 2011**[148]	Germany	94	NSTEMI	None
Lin *et al.* 2019[117]	Singapore	2444	30-day MACE	None
[a,b]**Melki *et al.* 2011**[144]	Sweden	233	NSTEMI	None
[b]Melki *et al.* 2010[154]				
[a]**Peacock *et al.* 2018**[89]	USA	1600	AMI	None
Chang *et al.* 2018[124]				
PITAGORAS	Spain	446	NSTEMI; 30-day MACE	None
[b]**Sanchis *et al.* 2012**[135]				

continued

TABLE 3 Overview of included DTA studies (*continued*)

Study	Country(s)	*n*	Target condition(s) reported	Subgroup(s) reported
QUART	Australia	764	AMI	None
[b]Parsonage *et al.* 2013[151]				
Parsonage *et al.* 2013[131]				
[a]**Parsonage *et al.* 2014**[88]				
RATPAC (point-of-care arm)	UK	850	NSTEMI; 30-day MACE	None
[a,b]**Collinson *et al.* 2013**[159]				
[b]Collinson *et al.* 2012[164]				
[b]Collinson *et al.* 2012[152]				
REACTION-US	USA	569	NSTEMI	None
[a]**Nowak 2018**[87]				
Nowak 2018[127]				
[b]**Saenger *et al.* 2010**[165]	USA	288	AMI	None
[b]**Sebbane *et al.* 2013**[157]	France	248	NSTEMI	None
Shiozaki *et al.* 2017[100]	Japan	413	NSTEMI	None
Slagman *et al.* 2017[102]	Germany	3423	NSTEMI	None
TRAPID-AMI		1282	NSTEMI; AMI; 30-day MACE	Sex and age (< 65 years vs. ≥ 65 years)
Body *et al.* 2015[122]				
Body *et al.* 2016[114]				
McCord *et al.* 2017[126]				
[a]**Mueller *et al.* 2016**[80]				
Mueller-Hennessen *et al.* 2016[81]				
Mueller-Hennessen *et al.* 2017[82]				
Mueller-Hennessen *et al.* 2019[83]				
TUSCA	Spain	358	NSTEMI	None
[b]**Santaló 2013**[133]				
Abbott ARCHITECT hs-cTnI and Roche Elecsys hs-cTnT				
ADAPT	Australia and New Zealand		NSTEMI; AMI; 30-day MACE	None
Aldous *et al.* 2014[53]				
Boeddinghaus *et al.* 2016[57]				
[b]**Cullen *et al.* 2013**[156]				
[a]**Cullen *et al.* 2014**[68]				
Eggers *et al.* 2016[69]				
Greenslade *et al.* 2015[71]				
Meller *et al.* 2015[118]				
Parsonage *et al.* 2013[130]				
van der Linden *et al.* 2018[109]				
Wildi *et al.* 2017[112]				

TABLE 3 Overview of included DTA studies (*continued*)

Study	Country(s)	*n*	Target condition(s) reported	Subgroup(s) reported
ROMI-3	USA	1137	NSTEMI	Renal function
Kavasak *et al.* 2017[76]				
[a]**Shortt *et al.* 2017**[101]				
TRUST	UK	963 (867 Abbott hs-cTnI, 959 Roche hs-cTnT)	NSTEMI	None
[a]**Carlton *et al.* 2015**[64]				
Carlton *et al.* 2015[63]				
Abbott ARCHITECT hs-cTnI, Siemens Healthcare Atellica hs-cTnI and Roche Elecsys hs-cTnT				
High-STEACS	UK (Scotland)	32,837	NSTEMI; 30-day MACE	Sex, age (< 65 years vs. ≥ 65 years), history of ischaemic heart disease
[a]**Bularga *et al.* 2019**[61]				
Chapman *et al.* 2017[65]				
Chapman *et al.* 2018[66]				
Chapman *et al.* 2019[67]				
Miller-Hodges *et al.* 2018[79]				
Shah *et al.* 2015[98]				
Chapman *et al.* 2020[174]				
Roche Elecsys TnT and Siemens ADVIA Centaur hs-cTnI				
BEST	UK	665	NSTEMI	None
[a]**Body *et al.* 2019**[115]				
Body *et al.* 2020[172]				
Siemens Healthcare Atellica hs-cTnI and ADVIA Centaur hs-cTnI				
High-US	USA	2212	NSTEMI; 30-day MACE	None
Nowak *et al.* 2019[128]				
Nowak *et al.* 2019[129]				
[a]**Sandoval *et al.* 2019**[176]				
Abbott ARCHITECT hs-cTnI, Roche Elecsys hs-cTnT, Siemens Healthcare ADVIA Centaur hs-cTnI, Siemens Healthcare Dimension Vista hs-cTnI, Beckman Coulter ACCESS hs-cTnI, Ortho VITROS hs-cTnI, bioMérieux VIDAS hs-cTnI and Quidel Cardiovascular TriageTrue hs-cTn				
APACE			NSTEMI; AMI; 30-day MACE	Sex, age (≤ 70 years vs. > 70 years), previous CAD, renal function
Badertscher *et al.* 2018[54]				
Badertscher *et al.* 2018[6]				
[a]**Boeddinghaus *et al.* 2017**[58]				
Boeddinghaus *et al.* 2018[59]				
Boeddinghaus *et al.* 2019[60]				
Boeddinghaus *et al.* 2019[123]				
Boeddinghaus *et al.* 2019[170]				

continued

TABLE 3 Overview of included DTA studies (*continued*)

Study	Country(s)	*n*	Target condition(s) reported	Subgroup(s) reported
Boeddinghaus *et al.* 2020[173]				
[b]Cullen *et al.* 2013[156]				
[b]Hoeller *et al.* 2013[168]				
[b]Haaf *et al.* 2012[136]				
[b]Hochholzer *et al.* 2011[149]				
[b]Irfan *et al.* 2013[158]				
Jaeger *et al.* 2016[2]				
Kaier *et al.* 2017[75]				
Lindahl *et al.* 2017[132]				
[b]Potocki *et al.* 2012[140]				
Reichlin *et al.* 2015[90]				
Reichlin *et al.* 2015[91]				
[b]Reiter *et al.* 2011[146]				
[b]Reiter *et al.* 2012[138]				
[b]Reichlin *et al.* 2009[167]				
[b]Reichlin *et al.* 2011[145]				
Rubini Gimenez *et al.* 2014[70]				
Rubini Gimenez *et al.* 2015[92]				
Rubini Gimenez *et al.* 2015[93]				
Rubini Giménez *et al.* 2016[94]				
Twerenbold *et al.* 2017[105]				
Twerenbold *et al.* 2017[103]				
Twerenbold *et al.* 2017[104]				
Twerenbold *et al.* 2018[106]				
Twerenbold *et al.* 2018[107]				
Twerenbold *et al.* 2019[108]				
Wildi *et al.* 2016[111]				
Wildi *et al.* 2019[113]				

BACC, Biomarkers in Acute Cardiac Care; BEST, Bedside Evaluation of Sensitive Troponin; CORE, Clinical Objective Rule-out Evaluation; FAST II, Fast Assessment of Thoracic Pain II; FASTER I, Fast Assessment of Thoracic Pain by nEuRal networks I; High-US, High-Sensitivity Cardiac Troponin I Assays in the United States; IMPACT, Improved Assessment of Chest Pain Trial; RATPAC, Randomised Assessment of Treatment using Panel Assay of Cardiac Markers; REACTION-US, Rapid Evaluation of Acute Myocardial Infarction in the United States; ROMI-3, Optimum Troponin Cutoffs for ACS in the ED; TRAPID-AMI, High Sensitivity Cardiac Troponin T Assay for Rapid Rule-out of Acute Myocardial Infarction; TRUST, Triage Rule-out Using Sensitive Troponin; TUSCA, UltraSensitive Troponin in Acute Coronary syndromes; UTROPIA, Use of TROPonin In Acute coronary syndromes.

a Primary publication for citation.

b Publication included in the assessment report for DG15.[2]

Note

Publications in bold have provided data for inclusion in this assessment.

For DTA studies, full details of the characteristics of study participants, study inclusion and exclusion criteria, hs-cTn assay used and reference standard, and detailed results are reported in the data extraction tables presented in *Appendix 2* (see *Tables 35–37*).

Study quality

We conducted a quality assessment of the two RCTs included in this assessment, using the revised Cochrane Risk-of-Bias Tool for Cluster Randomised Trials.[44] The results are shown in *Table 4*.

Overall, the trials were well conducted with procedures to ensure randomisation and blinding. Patients were unaware of the intervention in both the High-STEACS[99] and HiSTORIC trials.[175]

The methodological quality of the included DTA studies that evaluated a single hs-cTn assay was assessed using QUADAS-2.[45] Studies that provided data for two or more hs-cTn assays were assessed using QUADAS-2C.[46] The main potential sources of bias in the included DTA studies relate to patient spectrum and patient flow. There were also concerns regarding the applicability of the patient population. There were concerns regarding the applicability of the reference standard for some studies in the previous systematic review,[2] but this was not the case for any of the new studies identified for this update. The results of the QUADAS-2 and QUADAS-2C assessments are summarised in *Tables 5* and *6* (full QUADAS-2 and QUADAS-2C assessments for each study are provided in *Appendices 3* and *4*, respectively). A summary of the risks of bias and applicability concerns within each QUADAS-2 and QUADAS-2C domain is provided below.

Patient spectrum

Eight studies[87,88,100,117,121,135,139,144] assessed using QUADAS-2 were rated as having a high risk of bias for patient selection. A further nine studies[80,89,102,110,137,148,157,161,165] were rated as having an unclear risk of bias because they did not provide sufficient details to make a judgement on whether or not appropriate steps were taken to minimise bias when enrolling patients. Five studies[88,117,121,139,144] enrolled patients at certain times only (e.g. during office hours). This was considered to have the potential to lead to the inclusion of a different spectrum of patients than if consecutive patients had been enrolled. Two studies[87,100] were rated as having a high risk of bias for patient selection because they excluded patients for reasons that were not specified in their reported methods. The last study[135] that was judged as having a high risk of bias for patient enrolment excluded certain patient groups, including those with a troponin elevation in any two serial determinations and those with a prior diagnosis of ischemic heart disease, structural heart disease, concomitant heart failure or significant bradyarrhythmia.

TABLE 4 Quality assessment of High-STEACS and HiSTORIC

Quality assessment	High-STEACS trial[99]	HiSTORIC trial[175]
Bias arising from the randomisation process	Low	NI
Bias arising from the timing of intervention and recruitment of individual participants in relation to randomisation	Low	Low
Bias due to deviations from intended interventions	Low	Low
Bias due to missing outcome data	Low	Low
Bias in measurement of the outcome	Low	Low
Bias in selection of the reported result	Low	Low
Overall bias	Low	Low

NI, no information.

TABLE 5 QUADAS-2 results for studies of single hs-cTn assays

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
ADAPT/IMPACT, Nestelberger *et al.* 2019[171]	✓	✓	✓	✓	✓	✓	✓
[a]Aldous *et al.* 2011[147]	✓	✓	✓	✗	✗	✓	✗
[a]Aldous *et al.* 2012[139]	✗	✓	✓	✓	✓	✓	✗
BACC, Neumann *et al.* 2016[84]	✓	✓	✓	✓	✓	✓	✓
[a]Body *et al.* 2011[161]	?	✓	✓	✓	✗	✓	✗
Body *et al.* 2015[56]	✓	✓	✓	✓	✗	✓	✓
Cappellini *et al.* 2019[62]	✓	✗	?	?	✓	✓	✓
[a]Christ *et al.* 2010[150]	✓	✓	?	✓	✗	✓	✗
CORE, Mokhtari *et al.* 2016[119,121]	✗	✓	✓	✓	✗	✓	✓
[a]FASTER I and FAST II, Eggers *et al.* 2012[137]	?	✓	?	✗	✗	✓	✗
[a]Freund *et al.* 2011[142]	✓	✓	✓	✓	✗	✓	✗
Huang *et al.* 2015[72]	✓	✓	✓	✓	✓	✓	✓
[a]Keller *et al.* 2011[141]	✓	✓	✓	✗	✗	✓	✗
[a]Kurz *et al.* 2011[148]	?	✓	✓	✓	✗	✓	✗
Lin *et al.* 2019[117]	✗	✗	✗	✓	✗	✓	✓
[a]Melki *et al.* 2011[144]	✗	✓	✓	✓	✗	✓	✓
Peacock *et al.* 2018[89]	?	✓	✓	✓	✗	✓	✓
[a]PITGORAS, Sanchis *et al.* 2012[135]	✗	✓	?	✓	✗	✓	✓
QUART, Parsonage *et al.* 2014[88]	✗	✓	✓	✓	✗	✓	✓
[a]RATPAC (point-of-care arm), Collinson *et al.* 2013[159]	✓	✓	✓	✗	✗	✓	✓
REACTION-US, Nowak *et al.* 2018[87]	✗	✓	✓	✓	✗	✓	✓
[a]Saenger *et al.* 2010[165]	?	✓	?	?	✗	✓	✗
[a]Sebbane *et al.* 2013[157]	?	✓	✓	✗	✓	✓	✗
Shiozaki *et al.* 2017[100]	✗	✓	?	✓	✗	✓	✓
Slagman *et al.* 2017[102]	?	✓	✗	?	?	✓	?
TRAPID-AMI, Mueller *et al.* 2016[80]	?	✓	✓	✓	✓	✓	✓
[a]TUSCA, Santaló *et al.* 2013[133]	✓	✓	?	✓	✓	✓	?
UTROPIA, Sandoval *et al.* 2017[96]	✓	✓	✗	✓	✓	✓	✓
Venge *et al.* 2017[110]	?	✓	?	✗	✗	✓	✓

✗, high risk; ✓, low risk; ?, unclear risk; BACC, Biomarkers in Acute Cardiac Care; CORE, Clinical Objective Rule-out Evaluation; FAST II, Fast Assessment of Thoracic Pain II; FASTER I, Fast Assessment of Thoracic Pain by nEuRal networks I; IMPACT, Improved Assessment of Chest Pain Trial; RATPAC, Randomised Assessment of Treatment; REACTION-US, Rapid Evaluation of Acute Myocardial Infarction in the United States; TRAPID-AMI, High Sensitivity Cardiac Troponin T Assay for Rapid Rule-out of Acute Myocardial Infarction using Panel Assay of Cardiac Markers; TUSCA, UltraSensitive Troponin in Acute Coronary syndromes; UTROPIA, Use of TROPonin In Acute coronary syndromes.
a Information taken from our previous systematic review.[2]

TABLE 6 QUADAS-2C results for studies providing comparative accuracy data for multiple hs-cTn assays

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
***ADAPT*, Cullen et al. 2014[68]**							
Abbott ARCHIRECT hs-cTnI	✓	?	✓	✓	✓	✓	✓
Roche Elecsys hs-cTnT	✓	?	✓	✓	✓	✓	✓
Abbott ARCHIRECT hs-cTnI vs. Roche Elecsys hs-cTnT	✓	?	✓	✓			
***APACE*, Boeddinghaus et al. 2018,[59] *Boeddinghaus* et al. 2019,[170] *Boeddinghaus* et al. 2019[178] (comparison of assays using ESC 0/1-hour pathway or equivalent)**							
Abbott ARCHIRECT hs-cTnI	✓	✓	✗	✓	✓	✓	✓
Beckman Coulter ACCESS hs-cTnI	✓	✓	✗	✓	✓	✓	✓
Ortho VITROS hs-cTnI	✓	✓	✗	✓	✓	✓	✓
Roche Elecsys hs-cTnT	✓	✓	✗	✓	✓	✓	✓
Siemens ADVIA Centaur hs-cTnI	✓	✓	✗	✓	✓	✓	✓
Quidel TriageTrue hs-cTnI	✓	✓	✗	✓	✓	✓	✓
Comparison of Abbott ARCHITECT hs-cTnI, Roche Elecsys hs-cTnT and Siemens ADVIA Centaur hs-cTnI	?	?	✗	✓			
Comparison of all tests	?	?	✗	✗			
***BEST*, *Body* et al. 2019,[115] *Body* et al. 2020[172]**							
Roche Elecsys hs-cTnT	✓	✓	✗	✓	✓	✓	✓
Siemens ADVIA Centaur hs-cTnI	✓	✓	✓	✓	✓	✓	✓
Roche Elecsys hs-cTnT vs. Siemens ADVIA Centaur hs-cTnI	✗	?	✗	✗			
***High-STEACS*, *Chapman* et al. 2018,[66] *Chapman* et al. 2019[67] (comparison of assays using ESC 0/1-hour pathway, ESC 0/3-hour pathway and High-STEACS 0/3-hour pathway)**							
ARCHITECT hs-cTnI	✓	✓	?	✓	✓	✓	✓
Siemens Atellica hs-cTnI	✓	✓	?	✓	✓	✓	✓
ARCHITECT hs-cTnI vs. Siemens Atellica hs-cTnI	?	?	?	✗			
***High-US*, *Sandoval* et al. 2019[176]**							
Siemens Atellica hs-cTnI	✓	✓	✓	✓	✓	✓	✓
Siemens ADVIA Centaur hs-cTnI	✓	✓	✓	✓	✓	✓	✓
Siemens Atellica hs-cTnI vs. Siemens ADVIA Centaur hs-cTnI	✓	?	✓	✓			
***ROMI-3*, *Shortt* et al. 2017[101]**							
Abbott ARCHIRECT hs-cTnI	✓	✓	✓	✓	✓	✓	✓
Roche Elecsys hs-cTnT	✓	✓	✓	✓	✓	✓	✓
Abbott ARCHIRECT hs-cTnI vs. Roche Elecsys hs-cTnT	✓	?	✓	✓			

continued

TABLE 6 QUADAS-2C results for studies providing comparative accuracy data for multiple hs-cTn assays (*continued*)

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
***TRUST*, Carlton et al. *2015*[64]**							
Abbott ARCHIRECT hs-cTnI	✓	✓	✗	✗	✓	✓	✓
Roche Elecsys hs-cTnT	✓	✓	✗	✓	✓	✓	✓
Abbott ARCHIRECT hs-cTnI vs. Roche Elecsys hs-cTnT	✓	✓	✗	✗			

✗, high risk; ✓, low risk; ?, unclear risk; BEST, Bedside Evaluation of Sensitive Troponin; High-US, High-Sensitivity Cardiac Troponin I Assays in the United States; ROMI-3, Optimum Troponin Cutoffs for ACS in the ED; TRUST, Triage Rule-out Using Sensitive Troponin.

All studies assessed using QUADAS-2C were rated as having a low risk of bias for patient selection for all individual index tests. However, one study, for which data for two hs-cTn assays were reported in separate publications,[115,172] was rated as having a high risk of bias for patient selection for the comparison of the two assays. This was because the study did not set out to conduct both tests in all patients or to randomly allocate patients to one of the two tests. A further two studies, APACE[59,170,178] and the High-STEACS trial,[66,67] were rated as having an unclear risk of bias with respect to the comparison between hs-cTn assays.

As with our previous systematic review,[2] this assessment included studies that enrolled both mixed populations (i.e. when the target condition was any AMI) and studies restricted to our primary focus of populations where patients with STEMI were excluded (i.e. target condition NSTEMI). Studies not restricted to this specific patient group were therefore considered to have high concerns regarding applicability. Only seven studies[133,137,139,144,148,157,159] from our previous systematic review were restricted to patients in whom STEMI had been excluded. Three of these studies[137,144,148] were restricted to patients admitted to coronary care/chest patients units, and so were considered to represent patients with more severe disease, and a further study[159] had strict inclusion criteria that resulted in the inclusion of a very low-risk population. These four studies[137,144,148,159] were not considered to be representative of the spectrum of patients with chest pain presenting to the ED, and so were also rated as having high concerns regarding applicability. This assessment includes a further 13 studies[58,61,62,64,68,72,80,84,96,101,115,171,176] that were restricted to patients in whom STEMI had been excluded.

Index test

All but three of the studies[62,68,117] were rated as having a low risk of bias for the index, as they reported data for at least one threshold that was prespecified. Two studies[62,117] were rated as having a high risk of bias in this domain because they reported data for optimised thresholds that were derived in the same population. As the reference standard (i.e. the diagnosis of AMI or a MACE) was generally interpreted after the high sensitivity troponin test, blinding was not considered important for these studies. However, all but one of the studies[64] that compared two or more hs-cTn assays were rated as having an unclear risk of bias with respect to the comparison, using QUADAS-2C, as no information was provided about whether or not index tests were interpreted blind to the results of other index tests. Inclusion criteria were very tightly defined in terms of the high-sensitivity troponin assays that we were interested in, and so all studies were considered to have low concerns regarding the applicability of the index test.

Reference standard

Nine studies[61,62,100,110,133,135,137,150,165] were rated as having an unclear risk of bias for the reference standard because it was unclear whether or not the diagnosis of NSTEMI/AMI/MACEs was made without

knowledge of the high-sensitivity troponin results. One study,[115] assessed using QUADAS-2C, was rated as having a high risk of bias for one of the two hs-cTn assays assessed and for the comparison between assays (this was because the results of one of the hs-cTn assays were available to clinicians adjudicating the final diagnosis). Ten of the studies[137,139,141,142,147,148,150,157,161,165] taken from our previous systematic review had high concerns regarding the applicability of the reference standard. All new studies identified for this assessment had low concerns regarding the applicability of the reference standard.

Patient flow

Six of the studies[110,137,141,147,157,159] that reported data for a single hs-cTn assay, assessed using QUADAS-2, were considered as having a high risk of bias for patient flow and a further three studies[62,102,165] were considered as having an unclear risk of bias. In all cases, this was related to withdrawals from the study. Verification bias was not considered to be a problem in any of the studies. All of the studies assessed using QUADAS-2C were rated as having a low risk of bias for patient flow, with respect to the individual hs-cTn assays that they assessed. However, four of these studies [APACE,[59,170,178] BEST (Bedside Evaluation of Sensitive Troponin),[115,172] High-STEACS[66,67] and TRUST (Triage Rule-out Using Sensitive Troponin)[64]] were rated as having a high risk of bias with respect to at least one between-assay comparison and in all cases this was because the number of patients for whom hs-cTn results were available differed between assays.

Randomised controlled trials comparing high-sensitivity troponin assays with conventional troponin assays

Study details

Two RCTs were identified.[99,175] The High-STEACS trial, which contributed multiple diagnostic accuracy data sets, was a stepped-wedge cluster RCT that evaluated implementation of an early rule-out pathway in hospitals in Scotland. This trial assessed rates of reclassification of patients and subsequent incidence of MI and cardiovascular death when hs-cTnI results were made available for patients previously classified based on cTnI results.[99] A second stepped-wedge cluster RCT, the HiSTORIC trial (unpublished report provided AiC)[175] also evaluated the implementation of an early rule-out pathway in hospitals in Scotland. The primary outcomes were length of stay and MI or cardiac death after discharge (at 30 days). A summary of study details for the High-STEACS and HiSTORIC trials is provided in *Table 7*.

Both studies[99,175] had large sample sizes and reported power calculations for the primary outcome. Both women and men were represented in the trials. The mean age of patients in the High-STEACS trial[99] was 61 years and the mean age of patients in the HiSTORIC trial[175] was 59 years. The HiSTORIC trial[175] excluded patients with STEMI but the High-STEACS trial[99] did not. As both trials[99,175] were conducted in Scotland, they are likely to be highly relevant to UK practice.

Both trials[99,175] used the Abbott ARCHITECT high-sensitivity assay. In the High-STEACS trial,[99] during the validation phase of the trial (6–12 months), results of the hs-cTnI assay were concealed from the attending clinician and a contemporary cTn assay was used to guide care. A high-sensitivity test was introduced after 6 months (early implementation) or 12 months (late implementation).[99] The HiSTORIC trial[175] also had a validation phase where troponin testing was performed at presentation and repeated 6–12 hours after the onset of symptoms, if indicated. In the validation phase of the HiSTORIC trial,[175] the High-STEACS trial[99] early rule-out pathway was used. A range of outcomes were investigated in both trials. Both trials[99,175] considered MI and cardiac death at 1 year and length of stay in hospital. The HiSTORIC trial[175] also investigated MI or cardiac death at 30 days.

Efficacy results

In the High-STEACS trial,[99] patients reclassified by the high-sensitivity test were older [mean age 75 years, standard deviation (SD) 14 years] than those identified by a cTnI assay (mean age 70 years, SD 15 years) and more likely to be women (83% vs. 41%). They were less likely to show myocardial ischaemia on the electrocardiograph (14% vs. 36%). Other baseline characteristics were similar.

TABLE 7 Summary of study details for included RCTs

Study detail	High-STEACS trial[99]	HiSTORIC trial[175]
Number of patients	48,282 (47% female)	31,492 (45% female)
Location and setting	Ten secondary and tertiary care hospitals in Scotland	Seven acute hospitals in Scotland
Trial design	Stepped-wedge cluster RCT	
Study dates	June 2013 to March 2016	December 2014 to December 2016
Participant inclusion criteria	Patients presenting with suspected ACS and with paired cTn measurements from standard care and trial assay	Consecutive patients with suspected ACS and a normal troponin concentration at presentation
Participant exclusion criteria	Patients previously admitted during the trial period or not resident in Scotland	Patients presenting with an out-of-hospital cardiac arrest or STEMI, previously admitted during the trial or not resident in Scotland
High-sensitivity assay	hs-cTnI (Abbott ARCHITECT) CoV < 10% at 4.7 ng/l, and 99th centile URL of 34 ng/l in men and 16 ng/l in women	
Contemporary assay	cTnI (Abbott) CoV < 10% at 40 ng/l (seven sites) and 50 ng/l (three sites) at 6 and 12 hours	Serial testing at presentation and repeated 6–12 hours after onset of symptoms if indicated
Primary outcome	Subsequent MI (type 1 or type 4b) or cardiovascular death within 1 year following initial presentation to hospital	Length of stay (i.e. length of time from presentation to the ED until discharge from hospital) MI (type 1, type 4b or type 4c) or cardiac death at 30 days (primary) and 1 year (secondary)
Other outcomes	Duration of hospital stay, MI (type 1 or 4b), unplanned coronary revascularisation, all-cause death, death from cardiovascular causes, hospital admission for heart failure and ischaemic stroke, major haemorrhage, unplanned hospital admission (excluding ACS and non-cardiovascular death)	Proportion of patients discharged from the ED, MI, cardiac death, cardiovascular death, all-cause death, unplanned coronary revascularisation and revisits for any reason after discharge at 1 year

URL, upper reference limit.

In the High-STEACS trial,[99] 2586 (5%) patients had MI or death from cardiovascular causes at 1 year. Of the 1771 patients reclassified by the hs-cTnI assay, 105 of 720 (15%) were in the validation phase and 131 of 1051 (12%) were in the implementation phase. The adjusted odds ratio (OR) for implementation compared with validation was 1.10 (95% CI 0.75 to 1.61).[99] In the HiSTORIC trial[175] (confidential information has been removed).

In the High-STEACS trial,[99] patients reclassified using the high-sensitivity test, there were no differences in any of the secondary efficacy and safety outcome measures between phases, including MI (type 1 or 4b), unplanned coronary revascularisation, all-cause death, death from cardiovascular causes (cardiac and non-cardiac), hospital admission for heart failure and ischaemic stroke.[99]

In the High-STEACS trial,[99] the median length of stay was 7 [interquartile range (IQR) 3–24] hours in the implementation phase and 4 (IQR 3–20) hours in the validation phase. In the HiSTORIC trial[175] (confidential information has been removed).[175]

The authors of the High-STEACS trial[99] concluded that although implementation of a hs-cTn assay resulted in reclassification of 17% of 10,360 patients with myocardial injury or infarction, only one-third had a diagnosis of type 1 MI and the incidence of subsequent MI or death from cardiovascular causes within 1 year was not affected by use of this assay.[99] (Confidential information has been removed.)[175]

Diagnostic accuracy of the Roche Elecsys hs-cTnT assay

Study details

Thirteen diagnostic cohort studies,[133,135,137,139,142,144,147,148,150,157,159,161,165] taken from our previous systematic review,[2] and a further 17 studies,[56,58,61,62,64,68,72,80,87–89,100–102,115,117,121] newly identified or updated (i.e. new publications since our previous systematic review), provided data on the diagnostic performance of the Roche Elecsys hs-cTnT assay. One of these studies[89] assessed the STAT version of the assay. Twenty seven[56,58,61,62,64,68,72,80,87–89,100–102,115,133,137,139,142,144,147,148,150,157,159,161,165] of the 30 studies in this section assessed the diagnostic performance of the Roche Elecsys hs-cTnT assay for the detection of AMI, three studies[117,121,135] assessed performance for the prediction of a MACE within 30 days of the index presentation and four studies[56,58,64,89] provided data for both AMI and 30-day MACE. Eighteen studies[58,62,64,68,72,80,87,100-102,115,133,137,139,144,148,157,159] provided data specific to the population of interest for this assessment (i.e. participants with STEMI were excluded and the target condition was NSTEMI rather than any AMI).

All but one[62] of the 26 studies that assessed diagnostic performance for the detection of AMI reported data on the diagnostic performance of a single sample taken on presentation for at least one threshold. Twenty-two studies[56,64,68,70,72,88,100–102,114,133,137,139,142,144,147,148,150,157,159,161,165] reported data for the 99th centile for the general population and 14 of these studies[64,68,70,72,100–102,133,137,139,144,148,157,159] provided data for the target condition NSTEMI. Nine studies[56,63,75,87,101,114,115,139,147] assessed the diagnostic performance of a LoD threshold (5 ng/l) in a single sample taken on presentation and six of these studies[63,75,87,101,115,139] provided data for the target condition NSTEMI. Similarly, eight studies[56,63,101,114,139,150,161,167] assessed the diagnostic performance of a limit of blank (LoB) threshold (3 ng/l) in a single sample taken on presentation and three of these studies[63,101,139] provided data for the target condition NSTEMI. Studies assessing the diagnostic performance of the Roche Elecsys hs-cTnT assay for the detection of AMI (any AMI or NSTEMI) reported data for a total of 33 different testing strategies (with different combinations of sample timing and threshold). *Table 8* provides summary estimates of the diagnostic performance of all combinations of population, diagnostic threshold and hs-cTnT test timing that were assessed by more than one study. Diagnostic performance estimates are also provided where combinations assessed by a single study have been selected for inclusion in the cost-effectiveness modelling conducted for this assessment. Key results used in the cost-effectiveness modelling conducted for this assessment are highlighted in bold. *Table 6* also includes diagnostic performance estimates for prespecified clinical subgroups taken from single studies. Full results (including numbers of TP, FP, FN and TN test results) for all studies and all data sets are provided in *Appendix 2*, *Table 37*.

TABLE 8 Accuracy of the Roche hs-cTnT assay: summary estimates (95% CI)

Test strategy	Population	Target condition	Number of studies	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
Single sample strategies					
99th centile threshold (14 ng/l) at 0 hours	All	Any AMI	22	90 (85 to 94)	78 (72 to 83)
	All	NSTEMI	14	90 (85 to 94)	77 (68 to 84)
	All	MACE	2	81 (75 to 86)	78 (76 to 81)
	Age ≤ 70 years	Any AMI	1[146]	88 (78 to 94)	86 (83 to 89)
	Age > 70 years	Any AMI	1[146]	97 (92 to 99)	49 (44 to 55)
	Patients with pre-existing CAD	Any AMI	1[140]	93 (85 to 97)	60 (55 to 65)
	Patients without pre-existing CAD	Any AMI	1[140]	94 (88 to 97)	82 (79 to 85)

continued

TABLE 8 Accuracy of the Roche hs-cTnT assay: summary estimates (95% CI) (*continued*)

Test strategy	Population	Target condition	Number of studies	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
	Mixed; low to moderate pre-test probability	Any AMI	1[142]	89 (70 to 97)	85 (79 to 89)
	Mixed; high pre-test probability	Any AMI	1[142]	94 (77 to 99)	66 (50 to 79)
	Female	NSTEMI	1[94]	91 (85 to 96)	79 (76 to 82)
	Male	NSTEMI	1[94]	91 (87 to 94)	79 (76 to 81)
	Patients with an eGFR < 30 ml/minute/1.73 m^2	NSTEMI	1[72]	100 (83 to 100)	13 (4 to 29)
	Patients with an eGFR 30–59 ml/minute/1.73 m^2	NSTEMI	1[72]	100 (96 to 100)	47 (39 to 55)
	Patients with an eGFR 60–89 ml/minute/1.73 m^2	NSTEMI	1[72]	96 (91 to 98)	72 (68 to 76)
	Patients with an eGFR > 90 ml/minute/1.73 m^2	NSTEMI	1[72]	92 (83 to 97)	84 (80 to 87)
LoD (< 5 ng/l) at 0 hours	All	Any AMI	9	99 (97 to 99)	36 (28 to 45)
	All	**NSTEMI**	**6**	**99 (97 to 100)**	**35 (25 to 46)**
	All	MACE	3	98 (95 to 99)	32 (30 to 34)
LoB (< 3 ng/l) at 0 hours	All	Any AMI	8	100 (98 to 100)	19 (11 to 31)
	All	NSTEMI	3	98 (96 to 99)	21 (19 to 22)
	All	MACE	3	96 (93 to 98)	17 (15 to 19)
99th centile threshold (14 ng/l) at 2 hours	All	NSTEMI	2	95 (92 to 96)	81 (79 to 82)
Multiple sample strategies					
ESC 0/1 hour pathway: (symptoms > 3 hours AND < 5 ng/l at 0 hours) OR (< 12 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours)	**All**	**NSTEMI**	**1[104]**	**99 (98 to 100)**	**68 (67 to 70)**
	All	MACE	2	99 (97 to 100)	62 (61 to 64)
	Patients with normal renal function	NSTEMI	1[106]	99 (97 to 100)	78 (76 to 80)
	Patients with impaired renal function (eGFR < 60 ml/minute/1.73 m^2)	NSTEMI	1[106]	100 (98 to 100)	26 (22 to 31)
(< 14 ng/l at 0 hours AND 2 hours) AND Δ < 4 ng/l	All	NSTEMI	2	98 (96 to 99)	74 (72 to 76)
< 12 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours	**All**	**NSTEMI**	**3**	**98 (97 to 99)**	**73 (71 to 74)**
< 8 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 0.5 hours	**All**	**NSTEMI**	**1[87]**	**100 (93 to 100)**	**45 (40 to 49)**
99th centile threshold (< 14 ng/l at 0 hours AND 3 hours)	**All**	**NSTEMI**	**1[148]**	**100 (89 to 100)**	**77 (58 to 90)**

eGFR, estimated glomerular filtration rate.
Note
Key results used in the cost-effectiveness modelling are highlighted in bold.

Single sample strategies

The summary estimates of sensitivity and specificity, where the diagnostic threshold was defined as the 99th centile for the general population, were 90% (95% CI 85% to 94%) and 78% (95% CI 72% to 83%), respectively, based on data from 22 studies[56,64,68,70,72,88,100–102,114,133,137,139,142,144,147,148,150,157,159,161,165] The SROC curve for this analysis is shown in *Figure 2*. These estimates were similar when the analysis was restricted to studies that excluded participants with STEMI[64,68,70,72,100-102,133,137,139,144,148,157,159] [summary estimates of sensitivity and specificity were 90% (95% CI 85% to 94%) and 77% (95% CI 68% to 84%), respectively]. The SROC curve is shown in *Figure 3*. Based on these data, it is unlikely that hs-cTnT testing on a single admission sample, using the 99th centile diagnostic threshold, would be considered adequate for rule out

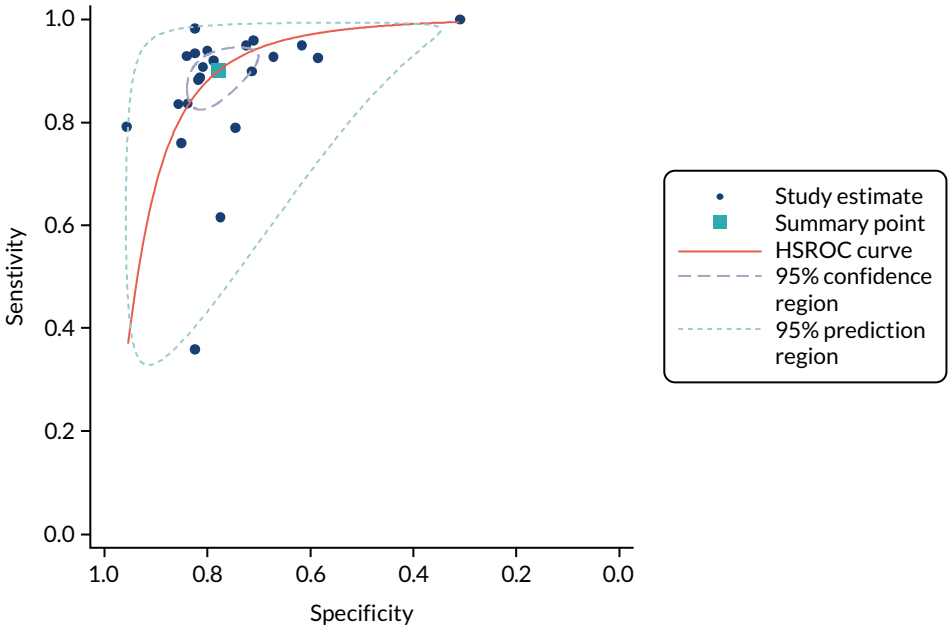

FIGURE 2 A SROC for the Roche Elecsys hs-cTnT assay using the 99th centile threshold and a presentation sample, target condition any AMI (22 studies[56,64,68,70,72,88,100–102,114,133,137,139,142,144,147,148,150,157,159,161,165]).

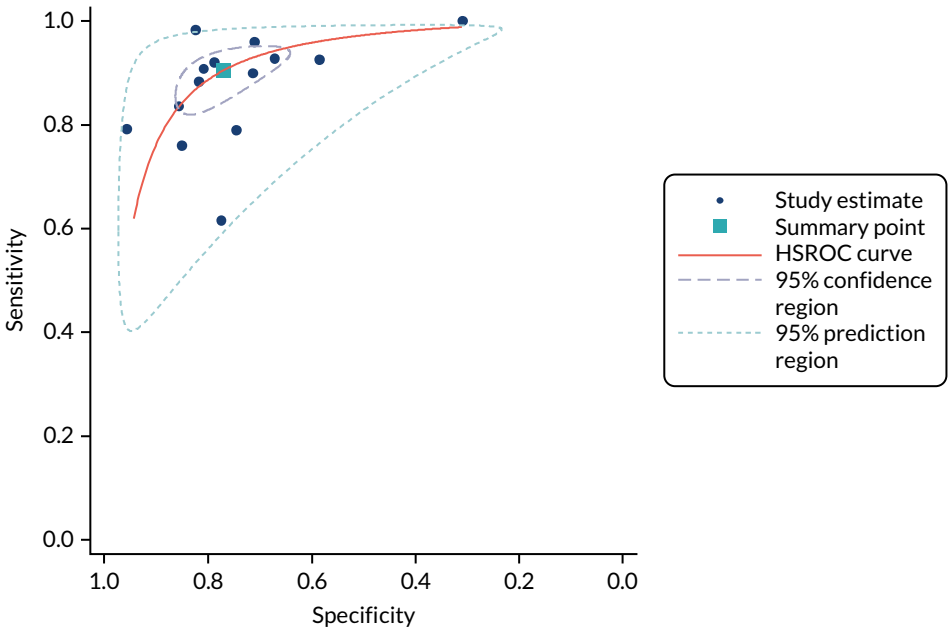

FIGURE 3 A SROC for the Roche Elecsys hs-cTnT assay using the 99th centile threshold and a presentation sample, target condition NSTEMI (14 studies[64,68,70,72,100-102,133,137,139,144,148,157,159]).

of any AMI or NSTEMI. The summary estimates of sensitivity and specificity, where the diagnostic threshold was defined as the 99th centile for the general population but the sample was taken 2 hours after presentation, were 95% (95% CI 92% to 96%) and 81% (95% CI 79% to 82%), respectively, based on data from three studies[68,139,144] in which the target condition was NSTEMI. Later sampling appears to be associated with improved rule-out performance at this threshold.

In our previous systematic review, limited data were identified on additional clinical subgroups [i.e. age > 70 years vs. ≤ 70 years,[146] without pre-existing CAD vs. with pre-existing CAD[140] and high vs. low to moderate pre-test probability (determined by clinical judgement and based on cardiovascular risk factors, type of chest pain, physical findings and ECG abnormalities)[142]]. None of these studies excluded participants with STEMI. The study[146] that stratified participants by age reported a higher estimate of sensitivity (97%, 95% CI 92% to 99%) in participants aged > 70 years than for patients aged ≤ 70 years (88%, 95% CI 78% to 94%). The estimate of sensitivity for people aged > 70 years was also higher than the corresponding summary estimates derived from all 22 studies[56,64,68,70,72,88,100–102,114,133,137,139,142,144,147,148,150,157,159,161,165] that used the 99th centile diagnostic threshold. A similar pattern was apparent for people with a high pre-test probability compared with those with a low to moderate pre-test probability[142] and for participants without pre-existing CAD compared with those with pre-existing CAD[140] (see *Table 8*). As with the age stratification, the estimates of sensitivity were higher than the corresponding summary estimates derived from the 22 studies[56,64,68,70,72,88,100–102,114,133,137,139,142,144,147,148,150,157,159,161,165] that used the 99th centile diagnostic threshold, for people with a high pre-test probability and for people without pre-existing CAD. *Figure 4* illustrates the variation in performance characteristics of a single admission sample, using the 99th centile diagnostic threshold, when used in different clinical subgroups. These data provide some indication that hs-cTnT testing on a single admission sample, using the 99th centile diagnostic threshold, may be adequate for rule out of AMI in certain selected populations [i.e. older people (aged ≥ 70 years), those without pre-existing CAD and people classified by clinical judgement as having a high pre-test probability].

In addition to these studies, the current assessment identified one further study[72] that reported data on how the diagnostic performance of a single sample taken on presentation, and using the 99th centile for the general population as the cut-off point, varies with renal function (see *Table 8*). These data[72] show a marked decrease in specificity as renal function decreases.

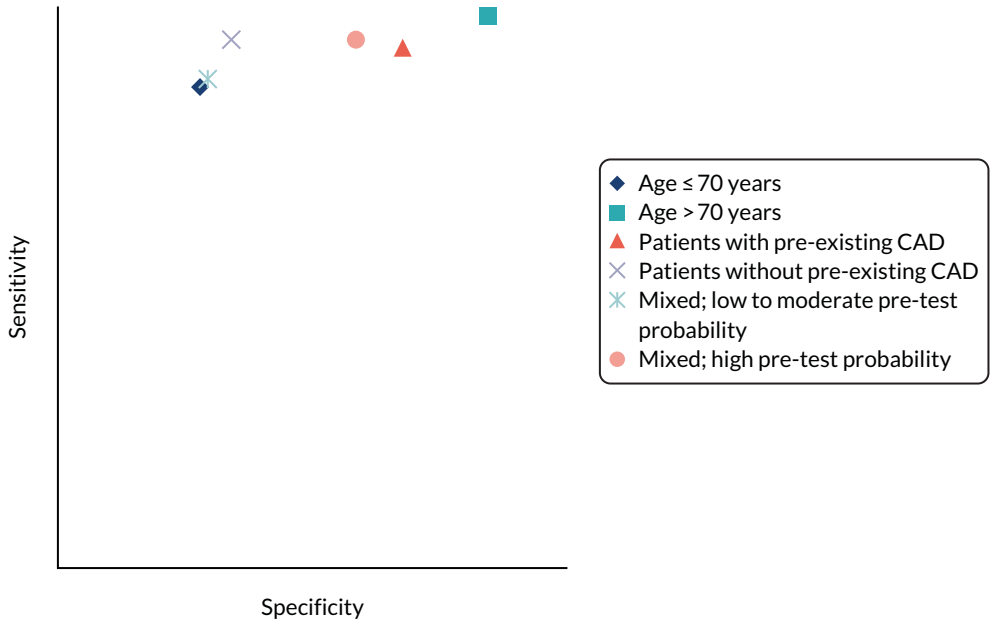

FIGURE 4 A ROC space plot for the Roche Elecsys hs-cTnT assay using the 99th centile threshold and a presentation sample in different clinical subgroups. Reproduced from Westwood *et al.*[2] Contains information licensed under the Non-Commercial Government Licence v2.0.

Nine studies[56,63,75,87,101,114,115,139,147] assessed the diagnostic performance of a LoD threshold (5 ng/l) in a single sample taken on presentation. The summary estimates of sensitivity and specificity using this threshold were 99% (95% CI 97% to 99%) and 36% (95% CI 28% to 45%), respectively (the SROC curve for this analysis is shown in *Figure 5*). The summary estimates of sensitivity and specificity were similar [99% (95% CI 97% to 100%) and 35% (95% CI 25% to 46%), respectively] when the analysis was restricted to the six studies[63,75,87,101,115,139] providing data for the target condition NSTEMI (the SROC curve for this analysis is shown in *Figure 6*). The eight studies[56,63,101,114,139,150,161,167] that assessed the diagnostic performance of a LoB threshold (3 ng/l) in a single sample taken on presentation gave a similarly high summary estimate of sensitivity (100%, 95% CI 98% to 100%), which was associated with reduced specificity (19%, 95% CI 11% to 31%) (the SROC curve for this analysis is shown in *Figure 7*).

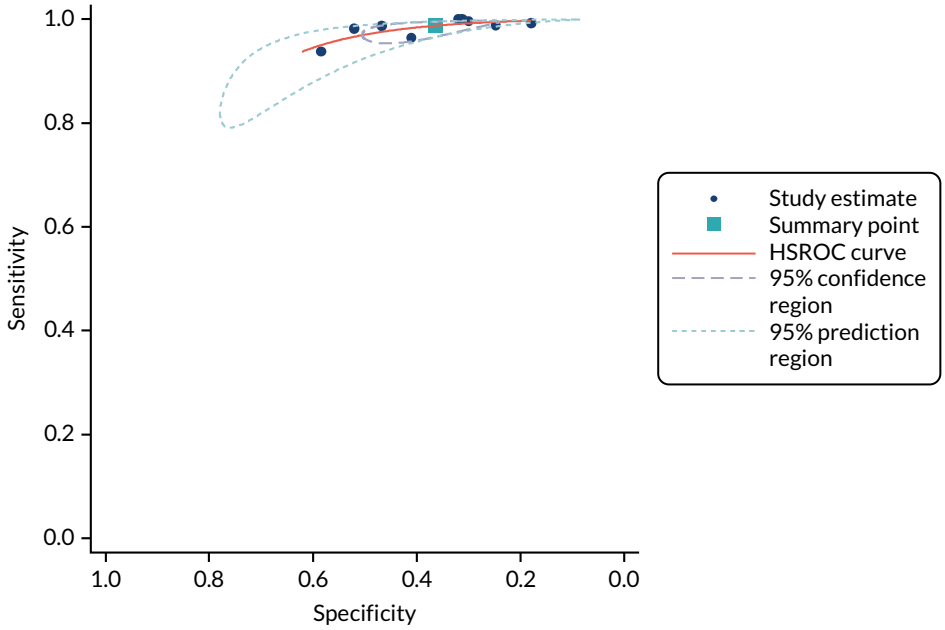

FIGURE 5 A SROC for the Roche Elecsys hs-cTnT assay using the LoD threshold and a presentation sample, target condition any AMI (nine studies[56,63,75,87,101,114,115,139,147]).

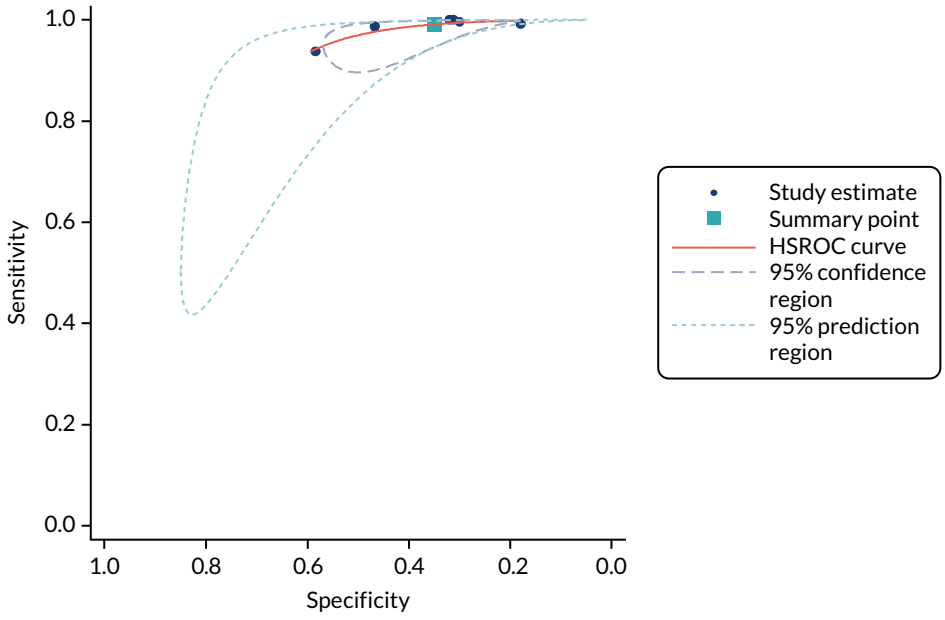

FIGURE 6 A SROC for the Roche Elecsys hs-cTnT assay using the LoD threshold and a presentation sample, target condition any NSTEMI (six studies[63,75,87,101,115,139]).

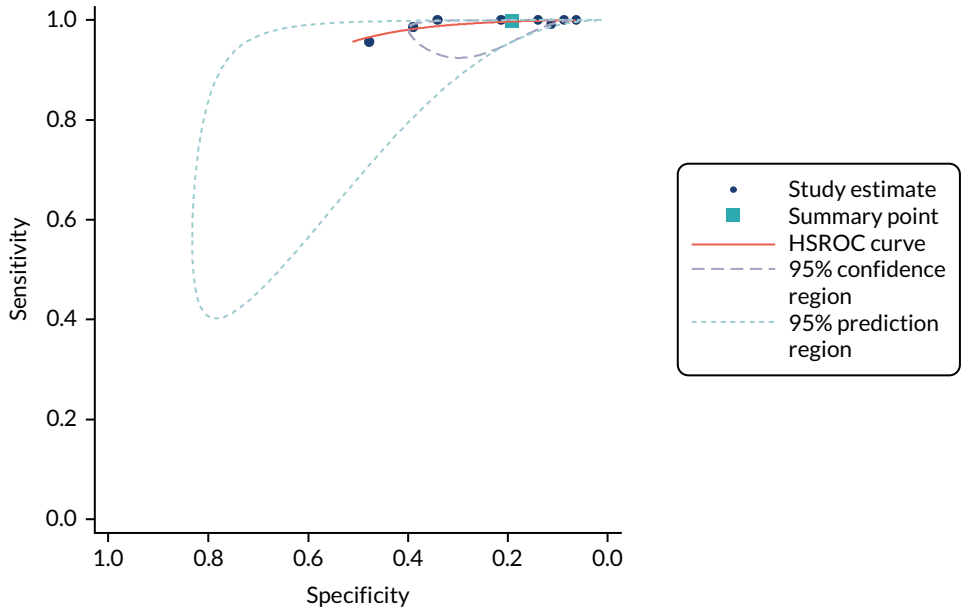

FIGURE 7 A SROC for the Roche Elecsys hs-cTnT assay using the LoB threshold and a presentation sample, target condition any AMI (eight studies[56,63,101,114,139,150,161,167]).

Again, restricting the analysis to those studies that provided data for the target condition NSTEMI[63,101,139] did not substantially change the summary estimates of sensitivity (98%, 95% CI 96% to 99%) and specificity (21%, 95% CI 19% to 22%). These data add to the data for these thresholds included in our previous systematic review,[2] and provide some indication that hs-cTnT testing on a single admission sample may be adequate to rule out any AMI or NSTEMI when a lower diagnostic threshold (5 ng/l or 3 ng/l) is used.

Multiple sample strategies

The number of multiple sample strategies/rule-out algorithms that have been evaluated has substantially increased since our previous systematic review.[2] Our previous systematic review[2] included eight studies[133,139,143,145,151,158,165,168] that provided data on the performance of a variety of strategies involving multiple sampling, most commonly involving a combination of a peak hs-cTn value above the 99th centile diagnostic threshold and a 20% change in hs-cTnT over 2 or 3 hours following presentation. The current assessment includes data for a total of 23 distinct multiple sample strategies that used the Roche Elecsys hs-cTnT assay (including six for the STAT version of the assay), of which 14 were evaluated in populations that excluded patients with STEMI (target condition NSTEMI). Most strategies were evaluated by a single study (the summary sensitivity and specificity estimates for strategies that were evaluated by more than one study are provided in *Table 8*). Diagnostic performance estimates are also provided when combinations assessed by a single study have been selected for inclusion in the cost-effectiveness modelling conducted for this assessment. Key results used in the cost-effectiveness modelling conducted for this assessment are highlighted in bold (see *Table 8*). Full results for all multiple sample strategies evaluated are provided in *Appendix 2*, *Table 37*. In general, the use of multiple sample strategies appears to offer increased specificity compared with a single sample on presentation and a very low (LoD or LoB) threshold, without substantial loss of sensitivity (see *Table 6*).

The ESC 0/1-hour rule-out pathway combines an initial sample and a very low (LoD of 5 ng/l) threshold in patients reporting a minimum symptom duration of 3 hours, with repeat testing at 1 hour for patients in whom the initial hs-cTnT is < 12 ng/l and in whom symptom duration is < 3 hours (i.e. it uses an 'or' combination). The sensitivity and specificity estimates for this strategy were 99% (95% CI 98% to 100%) and 68% (95% CI 67% to 70%), respectively, for the target condition NSTEMI (taken from the APACE study[104]). The overall rule-out rate for this strategy was 56.9%. It was not clear in what proportion of participants NSTEMI was ruled out using the presentation sample alone.[104] Based on data from the

same study,[104] the ESC 0/1-hour rule-out pathway would miss 5 of 746 (0.67%) people with NSTEMI. A further publication of the APACE study[108] reported data for the performance of the ESC 0/1-hour rule-out pathway for both the target condition NSTEMI and the target condition MACE at 30-day follow-up (including MI at index admission). Data from this publication indicated that, although the ESC 0/1-hour rule-out pathway did not miss any participants with NSTEMI at the index admission, 3 of 1420 (0.21%) participants who met the rule-out criteria experienced a MACE during 30 days' follow-up.[108]

Similar estimates of diagnostic performance were obtained for strategies involving an 'AND' combination of initial hs-cTnT level and absolute change. The summary estimates of sensitivity and specificity for a hs-cTnT level below the 99th centile (< 14 ng/l) on presentation and at 2 hours combined with an absolute change of < 4 ng/l were 98% (95% CI 96% to 99%) and 74% (95% CI 72% to 76%), respectively (based on data from two studies[57,90]). Similarly, the summary estimates of sensitivity and specificity for a hs-cTnT level of < 12 ng/l on presentation combined with an absolute change of < 3 ng/l at 1 hour were 98% (95% CI 97% to 99%) and 73% (95% CI 71% to 74%), respectively (based on data from three studies[80,91,100]). It should be noted that this strategy is equivalent to the rule-out threshold used in the repeat testing component of the ESC 0/1-hour pathway. Comparing the sensitivity and specificity estimates for these two strategies, we can see that, although the additional very early rule-out step (i.e. hs-cTnT < 5 ng/l on presentation) in the ESC 0/1-hour pathway may facilitate earlier discharge for some patients, it does not appear to improve overall diagnostic performance.

Prognostic accuracy

A total of nine studies[56,63,81,89,108,117,121,135,174] assessed the performance of one or more testing strategies using the Roche Elecsys hs-cTnT assay for the prediction of a MACE within 30 days of the index presentation. As for the target conditions any AMI and NSTEMI, *Table 8* provides summary estimates of the diagnostic performance of all combinations of population, diagnostic threshold and hs-cTnT test timing that were assessed by more than one study. The sensitivity estimates for single sample strategies and the target condition (i.e. a MACE) were generally slightly lower than those for the target conditions any AMI or MACE, and specificity estimates were similar or lower. The sensitivity estimates for the ESC 0/1-hour rule-out strategy were similar for the target conditions MACE and NSTEMI, and the specificity estimate was lower for MACE than for NSTEMI (see *Table 8*).

Diagnostic accuracy of the Abbott ARCHITECT hs-cTnI assay

Study details

Nine diagnostic cohort studies[58,61,64,68,84,96,101,110,141] provided data on the diagnostic performance of the Abbott ARCHITECT hs-cTnI assay, one[141] of which was taken directly from our previous systematic review.[2] The remaining studies were newly identified or updated (i.e. new publications since our previous systematic review[2]). All studies in this section assessed the accuracy of the Abbott ARCHITECT hs-cTnI assay for the detection of AMI and seven studies[58,61,64,68,84,96,101] provided data specific to the population of interest for this assessment (i.e. participants with STEMI excluded). Three studies[58,61,68] also assessed the performance of the Abbott ARCHITECT hs-cTnI assay for the prediction of a MACE within 30 days of the index presentation.

All nine studies[58,61,64,68,84,96,101,110,141] in this section reported data on the diagnostic performance of a single sample taken on presentation, for at least one threshold. Five studies[58,64,68,101,110] reported data for the 99th centile for the general population and four[58,64,68,101] of these studies provided data for the target condition NSTEMI. Four studies[58,68,96,101] assessed the diagnostic performance of a LoD threshold (2 ng/l) in a single sample taken on presentation, all of which were for the target condition NSTEMI. Studies assessing the diagnostic performance of the Abbott ARCHITECT hs-cTnI assay for the detection of AMI (i.e. any AMI or NSTEMI) reported data for a total of 33 different testing strategies (i.e. different combinations of sample timing and threshold). *Table 9* provides summary estimates of the diagnostic performance of all combinations of population, diagnostic threshold and hs-cTnI test timing that were assessed by more than one study. Diagnostic performance estimates are also provided when

TABLE 9 Accuracy of the Abbott ARCHITECT hs-cTnI assay: summary estimates (95% CI)

Test strategy	Population	Target condition	Number of studies	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
Single sample strategies					
99th centile threshold (26.2 ng/l) at 0 hours	All	Any AMI	5	75 (65 to 82)	94 (91 to 96)
		NSTEMI	4	75 (64 to 84)	94 (90 to 96)
Sex-specific 99th centile threshold (females 16 ng/l and males 34 ng/l at 0 hours)	Patients with an eGFR < 60 ml/minute/1.73 m^2	NSTEMI	1[79]	99 (96 to 100)	71 (67 to 74)
	Patients with an eGFR ≥ 60 ml/minute/1.73 m^2		1[79]	99 (97 to 100)	92 (91 to 93)
	Patients aged ≥ 65 years with an eGFR ≥ 60 ml/minute/1.73 m^2		1[79]	98 (96 to 100)	86 (84 to 88)
	Patients aged ≥ 65 years with an eGFR < 60 ml/minute/1.73 m^2		1[79]	98 (95 to 100)	69 (65 to 73)
	Patients aged < 65 years with an eGFR ≥ 60 ml/minute/1.73 m^2		1[79]	99 (97 to 100)	96 (95 to 97)
	Patients aged < 65 years with an eGFR < 60 ml/minute/1.73 m^2		1[79]	100 (88 to 100)	82 (72 to 89)
LoD (< 2ng/l) at 0 hours	**All**	**NSTEMI**	**4**	**100 (99 to 100)**	**21 (16 to 26)**
	All	MACE	1[61]	97 (95 to 98)	39 (39 to 40)
< 4 ng/l at 0 hours	**All**	**NSTEMI**	**2**	**99 (97 to 100)**	**50 (48 to 52)**
< 5 ng/l at 0 hours	All	NSTEMI	3	97 (95 to 98)	58 (57 to 59)
Multiple sample strategies					
ESC 0/1-hour pathway: (symptoms > 3 hours AND < 2 ng/l at 0 hours) OR (< 5 ng/l at 0 hours AND Δ < 2 ng/l at 0 to 1 hours)	**All**	**NSTEMI**	**2**	**99 (98 to 100)**	**57 (56 to 59)**
	Normal renal function	NSTEMI	1[106]	99 (97 to 100)	66 (64 to 68)
	Impaired renal function (eGFR < 60 ml/minute/1.73 m^2)	NSTEMI	1[106]	99 (95 to 100)	25 (20 to 30)
High-STEACS trial[79] pathway: (symptoms ≥ 2 hours AND < 5 ng/l at 0 hours) OR (≤ 16 ng/l (F) ≤ 34 ng/l (M) at 3 hours AND Δ < 3 ng/l at 0 to 3 hours)	**All**	**NSTEMI**	**1[66]**	**99 (97 to 100)**	**76 (73 to 78)**
	Male	NSTEMI	1[65]	98 (93 to 100)	88 (85 to 91)
	Female			98 (92 to 100)	87 (83 to 90)
	Aged < 65 years			99 (93 to 100)	94 (92 to 96)
	Aged ≥ 65 years			97 (92 to 99)	78 (74 to 82)
	Known ischaemic heart disease			96 (89 to 99)	82 (78 to 86)
	No known ischaemic heart disease			100 (97 to 100)	92 (89 to 94)
	All	MACE	1[66]	98 (97 to 99)	81 (79 to 83)

eGFR, estimated glomerular filtration rate.
Note
Key results used in the cost-effectiveness modelling are highlighted in bold.

combinations assessed by a single study have been selected for inclusion in the cost-effectiveness modelling conducted for this assessment. Key results used in the cost-effectiveness modelling conducted for this assessment are highlighted in bold. *Table 9* also includes diagnostic performance estimates for prespecified clinical subgroups taken from single studies. Full results (including numbers of TP, FP, FN and TN test results) for all studies and all data sets are provided in *Appendix 2*, *Table 37*.

Single sample strategies

The summary estimates of sensitivity and specificity where the diagnostic threshold was defined as the 99th centile for the general population were 75% (95% CI 65% to 82%) and 94% (95% CI 94% to 96%), respectively, based on data from five studies[58,64,68,101,110] (the SROC curve for this analysis is shown in *Figure 8*). These estimates were similar when the analysis was restricted to studies that excluded participants with STEMI. For these studies,[58,64,68,101] the summary estimates of sensitivity and specificity were 75% (95% CI 64% to 84%) and 94% (95% CI 90% to 96%), respectively (the SROC curve for this analysis is shown in *Figure 9*). Based on these data, it is unlikely that hs-cTnI testing on a single admission sample using the 99th centile diagnostic threshold would be considered adequate for either rule out or rule in of any AMI or NSTEMI.

The results of subgroup analyses, using data from the High-STEACS study,[79] appear to indicate that the sensitivity of a single sample taken on presentation can be markedly increased by using sex-specific 99th centile cut-off points (see *Table 9*). Data from this study also indicated that specificity is lower in patients with impaired renal function [estimated glomerular filtration rate (eGFR) < 60 ml/minute/1.73 m^2].

Four studies[58,68,96,101] assessed the diagnostic performance of a LoD threshold (2 ng/l) in a single sample taken on presentation, all of which were for the target condition NSTEMI. The summary estimates of sensitivity and specificity using this threshold were 100% (95% CI 99% to 100%) and 21% (95% CI 16% to 26%), respectively (the SROC curve for this analysis is shown in *Figure 10*). These data provide some indication that hs-cTnI testing on a single admission sample may be adequate to rule out NSTEMI when a lower diagnostic threshold (2 ng/l) is used.

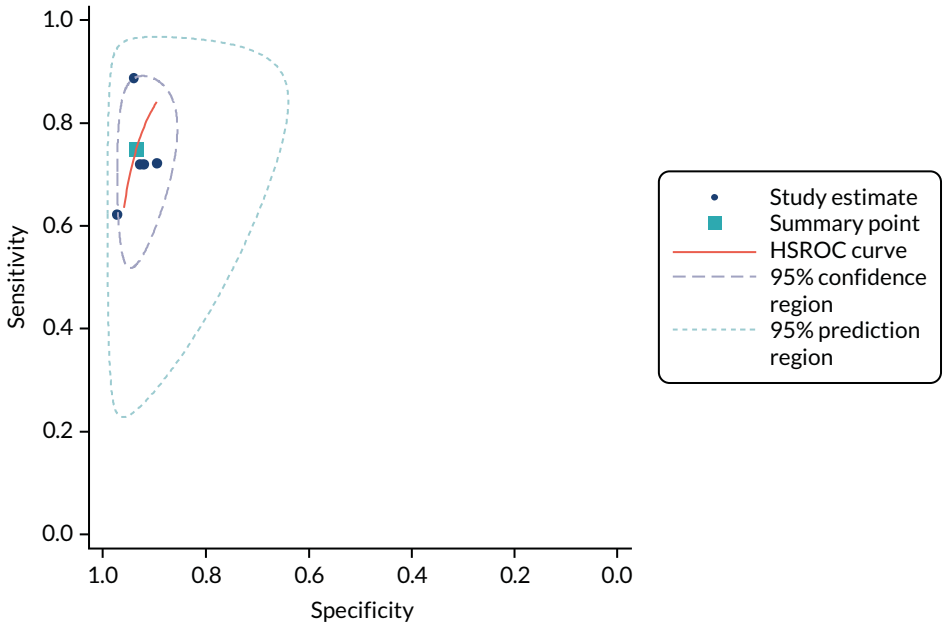

FIGURE 8 A SROC for the Abbott ARCHITECT hs-cTnI assay using the 99th centile threshold and a presentation sample, target condition any AMI (five studies[58,64,68,101,110]).

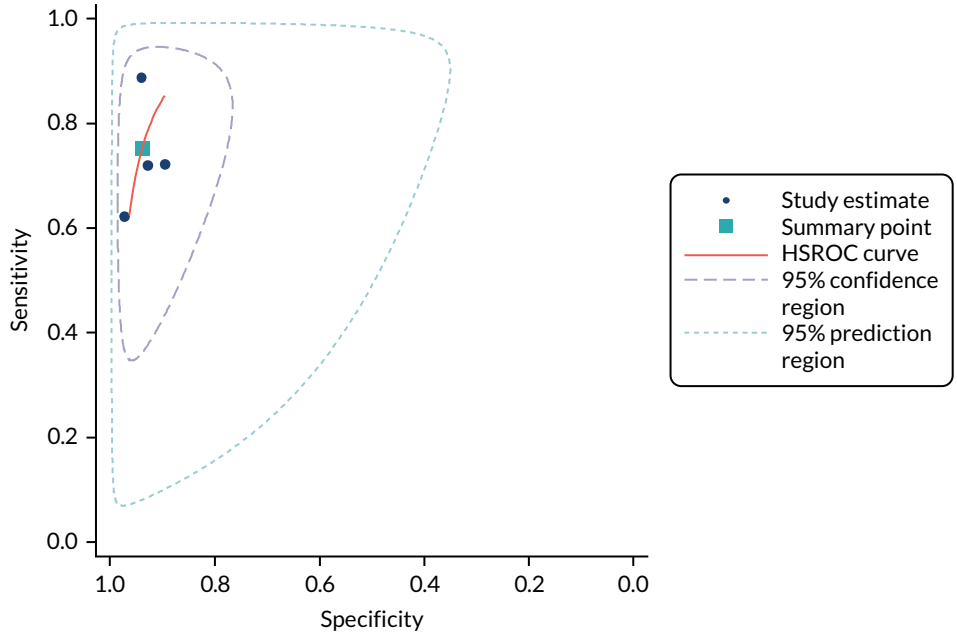

FIGURE 9 A SROC for the Abbott ARCHITECT hs-cTnI assay using the 99th centile threshold and a presentation sample, target condition any NSTEMI (four studies[58,64,68,101]).

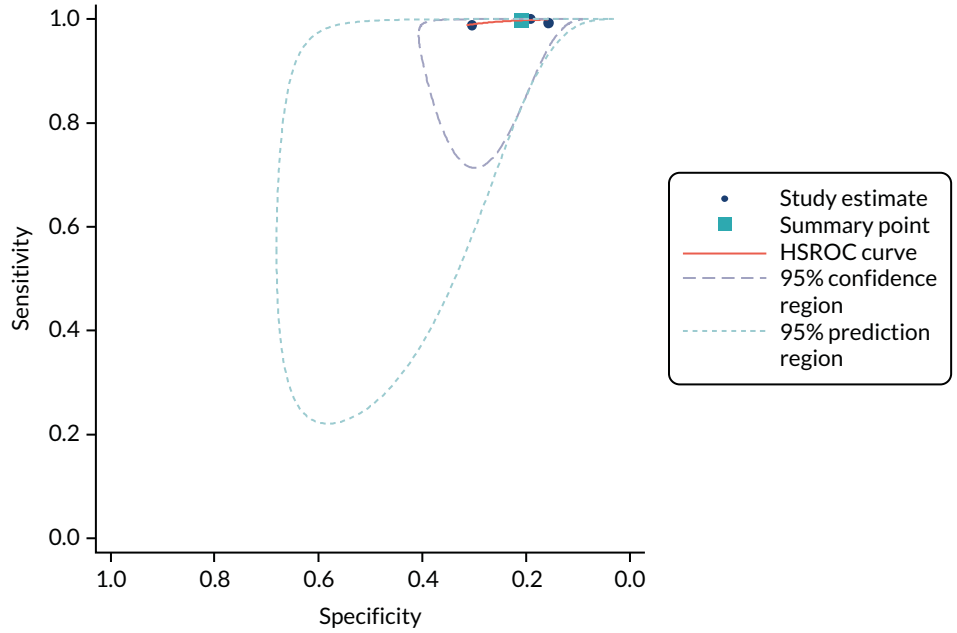

FIGURE 10 A SROC for the Abbott ARCHITECT hs-cTnI assay using the LoD threshold and a presentation sample, target condition any NSTEMI (four studies[58,68,96,101]).

Multiple sample strategies

The number of multiple sample strategies/rule-out algorithms that have been evaluated has substantially increased since our previous systematic review.[2] Our previous systematic review[2] included only two studies[141,151] that provided data on the performance of strategies involving multiple sampling. The current assessment includes data for a total of 17 distinct multiple sample strategies using the Abbott ARCHITECT hs-cTnI assay, of which 12 were evaluated in populations that excluded patients with STEMI (target condition NSTEMI). Most strategies were evaluated by a single study and the summary sensitivity and specificity estimates for strategies that were evaluated by more than one study are

provided in *Table 9*. Diagnostic performance estimates are also provided when combinations assessed by a single study have been selected for inclusion in the cost-effectiveness modelling conducted for this assessment. Key results used in the cost-effectiveness modelling conducted for this assessment are highlighted in bold (see *Table 9*). Full results for all multiple sample strategies evaluated are provided in *Appendix 2*, *Table 37*. In general, the use of multiple sample strategies appears to offer increased specificity compared with a single sample on presentation and a very low (LoD or LoB) threshold, without substantial loss of sensitivity (see *Table 7*).

The ESC 0/1-hour rule-out pathway combines an initial sample and a very low (LoD of 2 ng/l) threshold in patients reporting a minimum symptom duration of 3 hours, with repeat testing at 1 hour for patients in whom the initial hs-cTnI level is <5 ng/l and in whom symptom duration is < 3 hours (i.e. it uses an 'or' combination). The summary sensitivity and specificity estimates for this strategy were 99% (95% CI 98% to 100%) and 57% (95% CI 56% to 59%), respectively, for the target condition NSTEMI (two studies[66,104]). Based on data from one of these studies,[66] the overall rule-out rate for this strategy was 71.4% and NSTEMI was ruled out using the single presentation sample alone in 37.7% of participants. In one study,[66] no participants with NSTEMI were missed using the ESC 0/1-hour rule-out criteria, and in the second study,[104] 8 of 740 (1.08%) people with NSTEMI were missed, based on the ESC 0/1-hour rule-out criteria. Subgroup analysis indicated a marked reduction in specificity (25%, 95% CI 20% to 30%) when this strategy was used in people with impaired renal function (eGFR 60 ml/minute/1.73 m^2).[106] The High-STEACS trial pathway utilises an initial rule-out step, based on a low (5 ng/l) threshold in a sample taken at presentation, in patients reporting a minimum symptom duration of 2 hours. Repeat testing at a later time point (3 hours) is then undertaken for patients in whom the initial hs-cTnI level is less than the sex-specific 99th centile (16 ng/l for females and 34 ng/l for males) and in whom symptom duration was < 2 hours at presentation. The High-STEACS trial pathway appears to offer a further increase in specificity for the target condition NSTEMI [the sensitivity and specificity estimates for this strategy were 99% (95% CI 97% to 100%) and 76% (95% CI 73% to 78%), respectively].[66] The overall rule-out rate for this pathway was 64.9% and it was not clear in what proportion of participants NSTEMI was ruled-out using the presentation sample alone.[66] Based on data from the same study,[66] the High-STEACS pathway would miss 2 of 275 (0.73%) patients with NSTEMI. The same publication also provided data for the target condition of a MACE at 30-day follow-up (including MI at index admission), showing that a further four participants of those who met the rule-out criteria (i.e. 4/1244, 0.32%) experienced a MACE during the follow-up period.[66]

Subgroup analyses reported in a further publication of the High-STEACS trial[65] indicted that the sensitivity of this pathway was consistently high (≥ 97%) across all clinical subgroups assessed (see *Table 9*).

Prognostic accuracy

Three studies[58,61,68] assessed the performance of one or more testing strategies using the Abbott ARCHITECT hs-cTnI assay for the prediction of a MACE within 30 days of the index presentation. No single or multiple sample strategy was assessed by more than one study. Where available, sensitivity and specificity estimates from single studies for strategies corresponding to those selected for inclusion in cost-effectiveness modelling with the target condition NSTEMI estimates from single studies, have been included in *Table 7*. Sensitivity estimates for 30-day MACE were similar to those for NSTEMI, whereas specificity estimates were higher (see *Table 7*).

Diagnostic accuracy of the Beckman Coulter Access hs-cTnI assay

Study details

Two studies, the APACE study[58] and ADAPT/IMPACT (Improved Assessment of Chest Pain Trial),[171] provided data on the diagnostic performance of the Beckman Coulter Access hs-cTnI assay.[60,171] In both studies, patients with STEMI were excluded (i.e. the target condition was NSTEMI).

Single sample strategies

No single sample test strategies were assessed.

Multiple sample strategies

The two[60,171] studies evaluating the Beckman Coulter Access hs-cTnI assay each assessed a different multiple sample strategy. One study[60] reported data for a strategy that followed the structure of the ESC 0/1-hour rule-out pathway [i.e. an initial sample with a low threshold (4 ng/l) followed by repeat testing at 1 hour in patients whose initial troponin level was < 5 ng/l and who did not report a minimum symptom duration of 3 hours]. The sensitivity and specificity estimates for this strategy were 99% (95% CI 94% to 100%) and 70% (95% CI 66% to 74%), respectively.[60] The overall rule-out rate for this strategy was 60%, with NSTEMI being ruled out in 32% of participants based on the presentation sample alone.[60] In this study, 1 of 96 (1.04%) participants with NSTEMI were missed using the ESC 0/1-hour rule-out criteria.[60] The second study[64] assessed a similar strategy, but with repeat testing at 2 hours. The sensitivity estimates were similar for the two strategies, but the specificity of the 2-hour repeat testing strategy was higher than that of the 1-hour strategy (*Table 10*). Full results (including the numbers of TP, FP, FN and TN test results) are provided in *Appendix 2*, *Table 37*. Both strategies were selected for inclusion in our cost-effectiveness modelling.

Diagnostic accuracy of the bioMérieux VIDAS hs-cTnI assay

Study details

One diagnostic cohort study,[132] which formed part of the APACE study,[58] provided data on the diagnostic performance of the bioMérieux VIDAS hs-cTnI assay. This study excluded patients with STEMI (i.e. the target condition was NSTEMI).

Single sample strategies

No single sample test strategies were assessed.

Multiple sample strategies

The study[132] evaluating the bioMérieux VIDAS hs-cTnI assay assessed the performance of a repeat testing strategy, with samples taken on presentation and at 2 hours (*Table 11*). This strategy was selected for inclusion in our cost-effectiveness modelling, as it was the only strategy evaluated for the bioMérieux VIDAS hs-cTnI assay. The reported sensitivity and specificity estimates were 98% (95% CI 92% to 100%) and 64% (95% CI 59% to 68%), respectively (see *Table 11*). The overall rule-out rate for this strategy was 54.6%, with NSTEMI being ruled out in 32.6% of participants, based on the presentation sample alone.[132] Using this strategy, 2 of 87 (2.29%) participants with NSTEMI were missed.[132] Full results (including the numbers of TP, FP, FN and TN test results) are provided in *Appendix 2*, *Table 37*.

TABLE 10 Accuracy of the Beckman Coulter hs-cTnI assay: summary estimates (95% CI)

Test strategy	Population	Target condition	Number of studies	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
Multiple sample strategies					
ESC 0/1-hour pathway: (symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 4 ng/l at 0 to 1 hours)	**All**	**NSTEMI**	**1[60]**	**99 (94 to 100)**	**70 (66 to 74)**
(symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 5 ng/l at 0 to 2 hours)			**1[171]**	**98 (92 to 100)**	**83 (81 to 86)**

Note
Key results used in the cost-effectiveness modelling are highlighted in bold.

TABLE 11 Accuracy of the bioMérieux VIDAS hs-cTnI assay: summary estimates (95% CI)

Test strategy	Population	Target condition	Number of studies	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
Multiple sample strategies					
< 2 ng/l at 0 hours OR (< 6 ng/l at 0 AND 2 hours)	**All**	**NSTEMI**	**1**[132]	**98 (92 to 100)**	**64 (59 to 68)**

Note
Key results used in the cost-effectiveness modelling are highlighted in bold.

Diagnostic accuracy of the Ortho VITROS hs-cTnI assay

Study details

One diagnostic cohort study,[170] which formed part of the APACE study,[58] provided data on the diagnostic performance of the Ortho VITROS hs-cTnI assay.[170] This study assessed the accuracy of the Ortho VITROS hs-cTnI assay for the detection of AMI. Participants with STEMI were excluded (i.e. the target condition was NSTEMI rather than any AMI).

Single sample strategies

No single sample test strategies were assessed.

Multiple sample strategies

The study of Ortho VITROS hs-cTnI assay[170] assessed the performance of a strategy incorporating measurements performed at baseline and at 1 hour. The strategy followed the structure of the ESC 0/1-hour rule-out pathway. The threshold used to rule out AMI was < 1 ng/l at presentation with a minimum symptom duration of 3 hours, OR < 2 ng/l at presentation together with an absolute change within 1 hour of < 1 ng/l for patients with symptom duration < 3 hours. The reported sensitivity of this strategy was 100% (95% CI 95% to 100%) and the specificity was 60% (95% CI 55% to 64%) (*Table 12*). The overall rule-out rate for this strategy was 52.9%, with NSTEMI being ruled out in 18% of participants based on the presentation sample alone.[170] No participants with NSTEMI were missed.[170] Full results (including the numbers of TP, FP, FN and TN test results) are provided in *Appendix 2*, *Table 37*. This strategy was selected for inclusion in our cost-effectiveness modelling, as it was the only strategy evaluated for the Ortho VITROS hs-cTnI assay.

TABLE 12 Accuracy of the Ortho VITROS hs-cTnI assay: summary estimates (95% CI)

Test strategy	Population	Target condition	Number of studies	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
Multiple sample strategies					
ESC 0/1-hour pathway: (symptoms > 3 hours AND < 1 ng/l at 0 hours) OR (< 2 ng/l at 0 hours AND Δ < 1 ng/l at 0 to 1 hours)	**All**	**NSTEMI**	**1**[170]	**100 (95 to 100)**	**60 (55 to 64)**

Note
Key results used in the cost-effectiveness modelling are highlighted in bold.

Diagnostic accuracy of the Quidel TriageTrue hs-cTnI assay

Study details

One diagnostic cohort study,[173] which formed part of the APACE study,[58] provided data on the diagnostic performance of the Quidel TriageTrue hs-cTnI assay. This study assessed the accuracy of the Quidel TriageTrue hs-cTnI assay for the detection of AMI. Participants with STEMI were excluded (i.e. the target condition was NSTEMI rather than any AMI).

Single sample strategies

No single sample test strategies were assessed.

Multiple sample strategies

One study[170] assessed the performance of a Quidel TriageTrue hs-cTnI assay strategy, incorporating measurements performed at baseline and at 1 hour. The strategy followed the structure of the ESC 0/1-hour rule-out pathway. The threshold used to rule out AMI was < 4 ng/l at presentation with a minimum symptom duration of 3 hours, OR < 5 ng/l at presentation together with an absolute change within 1 hour of < 3 ng/l for patients with symptom duration < 3 hours. The reported sensitivity of this strategy was 100% (95% CI 97% to 100%) and the specificity was 66% (95% CI 62% to 70%) (*Table 13*). The overall rule-out rate for this strategy was 55.4%, with NSTEMI being ruled out in 45% of participants based on the presentation sample alone.[170] No participants with NSTEMI were missed.[170] Full results (including the numbers of TP, FP, FN and TN test results) are provided in *Appendix 2*, *Table 37*. This strategy was selected for inclusion in our cost-effectiveness modelling, as it was the only strategy evaluated for the Quidel TriageTrue hs-cTnI assay.

Diagnostic accuracy of the Siemens ADVIA Centaur hs-cTnI assay

Study details

Three studies, APACE,[58] BEST[115] and High-US (High-Sensitivity Cardiac Troponin I Assays in the United States),[176] provided data on the diagnostic performance of the Siemens Healthcare ADVIA Centaur hs-cTnI assay. All three studies reported data for the target condition NSTEMI[59,172,176] and one study[176] also assessed the performance of the Siemens ADVIA Centaur hs-cTnI assay for the prediction of a MACE within 30 days of index presentation.

Single sample strategies

The BEST study[172] assessed the diagnostic performance of a single sample taken at presentation and a low rule-out threshold (3 ng/l) for the target condition NSTEMI. The High-US study[176] assessed the performance of three different thresholds (2 ng/l, 3 ng/l and 5 ng/l) in a single sample taken at presentation for both NSTEMI and MACEs. The 2-ng/l and the 5-ng/l thresholds were selected for inclusion in our cost-effectiveness modelling. Sensitivity and specificity estimates for these thresholds and summary estimates for the 3 ng/l threshold are provided in *Table 14*.

TABLE 13 Accuracy of the Quidel TriageTrue hs-cTnI assay: summary estimates (95% CI)

Test strategy	Population	Target condition	Number of studies	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
Multiple sample strategies					
ESC 0/1-hour pathway: (symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours)	**All**	**NSTEMI**	**1[173]**	**100 (97 to 100)**	**66 (62 to 70)**

Note
Key results used in the cost-effectiveness modelling are highlighted in bold.

TABLE 14 Accuracy of the Siemens ADVIA Centaur hs-cTnI assay: summary estimates (95% CI)

Test strategy	Population	Target condition	Number of studies	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
Single sample strategies					
< 2 ng/l at 0 hours	**All**	**NSTEMI**	**1**[176]	**100 (99 to 100)**	**23 (21 to 25)**
< 2 ng/l at 0 hours	All	MACE	1[176]	100 (98 to 100)	23 (22 to 25)
< 3 ng/l at 0 hours	All	NSTEMI	2	99 (98 to 100)	35 (33 to 36)
< 3 ng/l at 0 hours	All	MACE	1[176]	99 (97 to 100)	36 (33 to 38)
< 5 ng/l at 0 hours	**All**	**NSTEMI**	**1**[176]	**99 (97 to 100)**	**52 (50 to 54)**
< 5 ng/l at 0 hours	All	MACE	1[176]	99 (96 to 100)	52 (50 to 54)
Multiple sample strategies					
ESC 0/1-hour pathway: (symptoms > 3 hours AND < 3 ng/l at 0 hours) OR (< 6 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours)	**All**	**NSTEMI**	**1**[59]	**99 (95 to 100)**	**56 (52 to 60)**
< 3 ng/l at 0 hours OR (< 8 ng/l at 0 hours AND Δ < 7 ng/l at 0 to 2 hours)	**All**	**NSTEMI**	**1**[59]	**100 (95 to 100)**	**67 (61 to 72)**

Note
Key results used in the cost-effectiveness modelling are highlighted in bold.

Multiple sample strategies

The APACE study[59] evaluated two different multiple sample strategies using the Siemens ADVIA Centaur hs-cTnI assay. One strategy followed the structure of the ESC 0/1-hour rule-out pathway [i.e. an initial sample with a low threshold (3 ng/l) followed by repeat testing at 1 hour in patients whose initial troponin level was < 6 ng/l and who did not report a minimum symptom duration of 3 hours].[59] The sensitivity and specificity estimates for this strategy were 99% (95% CI 95% to 100%) and 56% (95% CI 52% to 60%), respectively. The overall rule-out rate for this strategy was 46.4%, with NSTEMI being ruled out in 16% of participants based on the presentation sample alone.[59] Based on data from this study, use of the ESC 0/1-hour pathway would miss 1 of 114 (0.88%) people with NSTEMI.[59] The second study[59] assessed a similar strategy, but with higher thresholds and repeat testing at 2 hours. The sensitivity estimates were similar for the two strategies, but the specificity of the 2-hour repeat testing strategy was higher than that of the 1-hour strategy (see *Table 14*). Full results are provided in *Appendix 2*, *Table 37*. Both strategies were selected for inclusion in our cost-effectiveness modelling.

Diagnostic accuracy of the Siemens Atellica hs-cTnI assay

Study details

Two studies, the High-STEACS trial[61] and High-US,[176] provided data on the diagnostic performance of the Siemens Healthcare Atellica hs-cTnI assay. Both studies[67,176] reported data for the target condition NSTEMI and one study[176] also assessed the performance of the Siemens Atellica hs-cTnI assay for the prediction of a MACE within 30 days of the index presentation.

Single sample strategies

The High-US study[176] assessed the performance of three different thresholds (2 ng/l, 3 ng/l and 5 ng/l) in a single sample taken at presentation, for both NSTEMI and MACEs. The 2 ng/l threshold was selected for inclusion in our cost-effectiveness modelling. The sensitivity and specificity estimates for this threshold were 100% (95% CI 98% to 100%) and 26% (95% CI 24% to 28%), respectively (*Table 15*).

TABLE 15 Accuracy of the Siemens Atellica hs-cTnI assay: summary estimates (95% CI)

Test strategy	Population	Target condition	Number of studies	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
Single sample strategies					
< 2 ng/l at 0 hours	**All**	**NSTEMI**	**1**[176]	**100 (98 to 100)**	**26 (24 to 28)**
< 2 ng/l at 0 hours	All	MACE	1[176]	99 (97 to 100)	26 (24 to 28)
Multiple sample strategies					
ESC 0/1-hour pathway: (symptoms ≥ 3 hours AND < 3 ng/l at 0 hours) OR (< 6 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours)	All	NSTEMI	1[67]	94 (79 to 99)	69 (64 to 74)
ESC 0/3-hour pathway: [symptoms ≥ 6 hours AND ≤ 34 ng/l (females), ≤ 53 ng/l (males) at 0 hours] OR [≤ 34 ng/l (females), ≤ 53 ng/l (males) at 0 and 3 hours] OR Δ < 50% of 99th centile at 0–3 hours	All	NSTEMI	1[67]	91 (87 to 94)	74 (72 to 77)
High-STEACS pathway: (symptoms ≥ 2 hours AND < 5 ng/l at 0 hours) OR [≤ 34 ng/l (F) ≤ 53 ng/l (M) at 3 hours AND Δ < 3 ng/l at 0 to 3 hours]	**All**	**NSTEMI**	**1**[67]	**98 (95 to 99)**	**74 (72 to 76)**

Note
Key results used in the cost-effectiveness modelling are highlighted in bold.

Multiple sample strategies

The High-STEACS study[67] assessed the diagnostic performance of three different multiple testing strategies for the target condition NSTEMI. One strategy, defined as the ESC 0/1-hour pathway, used a combination of a minimum symptom duration of 3 hours and a low rule-out threshold (3 ng/l) on presentation, OR repeat testing in patients with a presentation troponin level < 6 ng/l AND symptom duration < 3 hours. A second strategy, defined as the ESC 0/3-hour pathway, used a combination of a minimum symptom duration of 6 hours and sex-specific thresholds, OR relative difference at 3 hours. Neither of the two ESC pathways for this assay met the minimum clinically acceptable sensitivity criterion for inclusion in cost-effectiveness modelling. The sensitivity and specificity estimates for these two strategies are provided in *Table 15*. The High-STEACS pathway combined an initial sample and a low (5 ng/l) threshold in patients reporting a minimum symptom duration of 2 hours with repeat testing at a later time point (3 hours) for patients in whom the initial hs-cTnI is less than the sex-specific 99th centile (i.e. 34 ng/l for females and 53 ng/l for males) and in whom symptom duration was < 2 hours. The High-STEACS pathway was selected for inclusion in our cost-effectiveness modelling. The sensitivity and specificity estimates for this strategy were 98% (95% CI 95% to 99%) and 74% (95% CI 72% to 76%), respectively.[67] The overall rule-out rate for this strategy was 64.5%, with NSTEMI being ruled out in 29.7% of participants based on the presentation sample alone.[67] In this study, application of the High-STEACS pathway missed 6 of 278 (2.16%) participants with NSTEMI.[67]

Diagnostic accuracy of the Siemens Healthcare Dimension Vista hs-cTnI assay

Study details

One diagnostic cohort study,[74] which formed part of the APACE study,[58] provided data on the diagnostic performance of the Siemens Healthcare Dimension Vista hs-cTnI assay. This study[74] assessed the accuracy of the Siemens Healthcare Dimension Vista hs-cTnI assay for the detection of AMI. Participants with STEMI were excluded (i.e. the target condition was NSTEMI rather than any AMI).

Single sample strategies

No single sample test strategies were assessed.

Multiple sample strategies

The study of Siemens Healthcare Dimension Vista hs-cTnI[74] assessed the performance of a strategy incorporating measurements performed at baseline and absolute change within 1 hour. The threshold used to rule out AMI was < 5 ng/l at presentation and a change within the hour of < 2 ng/l, which was derived from a cohort of 750 patients. The strategy was validated with a further 750 patients. This strategy was selected for inclusion in our cost-effectiveness modelling, as it was the only strategy evaluated for the Siemens Dimension Vista hs-cTnI assay (*Table 16*).

The sensitivity of the strategy was 100% (95% CI 97% to 100%) and specificity was 66% (95% CI 62% to 69%). Results were provided separately for male and female participants. Sensitivity for males was 95% (95% CI 87% to 99%) and for females it was 100% (95% CI 89% to 100%). Specificity for males was 62% (95% CI 57% to 66%) and for females it was 73% (95% CI 66% to 79%). Full results (including the numbers of TP, FP, FN and TN test results) are provided in *Appendix 2*, *Table 37*.

Comparative diagnostic accuracy for test strategies assessed for more than one assay in the same study

Seven studies[58,61,64,68,101,115,176] reported accuracy data for more than one assay.

Four studies, ADAPT,[68] APACE,[58] ROMI-3 (Optimum Troponin Cutoffs for ACS in the ED),[101] and TRUST,[64] provided data to support a direct comparison between the Roche Elecsys hs-cTnT assay and the Abbott ARCHITECT hs-cTnI assay, using either the 99th centile for the general population, or LoD threshold and a single sample at presentation or both, for the target condition NSTEMI. As data for these combinations of assay threshold and timing are reported individually by a number of additional studies (see *Diagnostic accuracy of the Roche Elecsys hs-cTnT assay* and *Diagnostic accuracy of the Abbott ARCHITECT hs-cTnI assay*), it is possible to compare the estimates of relative sensitivity and specificity derived from indirect comparisons of summary estimates with those derived from direct, within-study comparisons (*Table 17*). Although the sensitivity estimates for the Roche Elecsys hs-cTnT assay, using the 99th centile for the general population threshold and a single sample at presentation, were higher than those for the Abbott ARCHITECT hs-cTnI assay (direct or indirect comparisons), neither assay achieved the minimum clinically acceptable sensitivity (97%). Based on these data, it is unlikely that using the 99th centile diagnostic threshold and a single sample at presentation would be considered adequate for rule out of NSTEMI. When the LoD threshold was used with a single sample at presentation, sensitivity estimates were comparable for the Roche Elecsys hs-cTnT assay and the Abbott ARCHITECT hs-cTnI assay (direct or indirect comparisons) and the sensitivity estimates were always ≥ 99%. The indirect comparison (based on summary estimates and one[75] of the two direct comparisons) indicated that specificity was higher for the Roche Elecsys hs-cTnT assay (30%, 95% CI 27% to 33%) than for the Abbott ARCHITECT hs-cTnI assay (18%, 95% CI 16% to 21%).[75] The second direct comparison gave

TABLE 16 Accuracy of the Siemens Healthcare Dimension Vista hs-cTnI assay: summary estimates (95% CI)

Test strategy	Population	Target condition	Number of studies	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
Multiple sample strategies					
< 5 ng/l at 0 hours AND Δ < 2 ng/l at 0 to 1 hours	**All**	**NSTEMI**	**1**[74]	**100 (97 to 100)**	**66 (62 to 69)**
	Male	NSTEMI	1[74]	95 (87 to 99)	62 (57 to 66)
	Female			100 (89 to 100)	73 (66 to 79)

Note
Key results used in the cost-effectiveness modelling are highlighted in bold.

TABLE 17 Comparison between assays (single presentation sample strategies): sensitivity and specificity (95% CI) for the target condition NSTEMI

		Indirect comparison		Direct comparison							
				ADAPT[68]		APACE[70,75]		ROMI-3[101]		TRUST[64]	
Assay (threshold)	*n*	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
Roche Elecsys hs-cTnT (99th centile, 14 ng/l)	14	90 (85 to 94)	77 (68 to 84)	91 (86 to 94)	81 (79 to 83)	92 (89 to 94)	79 (77 to 81)	92 (87 to 96)	58 (55 to 62)	84 (74 to 94)	86 (83 to 88)
Abbott ARCHITECT hs-cTnI (99th centile, 26.2 ng/l)	4	75 (64 to 84)	94 (90 to 96)	89 (84 to 93)	94 (93 to 95)	72 (67 to 76)	93 (91 to 94)	72 (64 to 80)	90 (87 to 91)	62 (49 to 74)	97 (96 to 98)
Roche Elecsys hs-cTnT (LoD, 5 ng/l)	6	99 (97 to 100)	35 (25 to 46)	NR		100 (97 to 100)	30 (27 to 33)	99 (96 to 100)	18 (16 to 20)	NR	
Abbott ARCHITECT hs-cTnI (LoD, 2 ng/l)	4	100 (99 to 100)	21 (16 to 26)			100 (99 to 100)	18 (16 to 21)	99 (96 to 100)	16 (14 to 18)		

NR, not reported.

similar specificities for the Roche Elecsys hs-cTnT assay (18%, 95% CI 16% to 20%) and the Abbott ARCHITECT hs-cTnI assay (16%, 95% CI 14% to 18%).[101] These data indicate that the LoD threshold and a single sample at presentation is likely to be adequate for ruling out NSTEMI, using either the Roche Elecsys hs-cTnT assay or the Abbott ARCHITECT hs-cTnI assay. There is no clear evidence to support the choice of one assay over the other.

The APACE study[58] provided data on the performance of the ESC 0/1-hour pathway using the rule-out thresholds specified for the Roches Elecsys hs-cTnT assay[59,104] and the Abbott ARCHITECT hs-cTnI assay[59,104] in the ESC 2015 guidelines for the management of ACSs in patients presenting without persistent ST segment elevation.[33] The APACE study also provided data on the performance of the ESC 0/1-hour pathway using rule-out thresholds derived for the Beckman Coulter ACCESS hs-cTnI,[60] Siemens ADVIA Centaur hs-cTnI,[59] Ortho VITROS hs-cTnI[170] and Quidel TriageTrue hs-cTnI [173] assays. Although all six assay ESC 0/1-hour pathways were evaluated in participants from the APACE trial, only the Roche Elecsys hs-cTnT, Abbott ARCHITECT hs-cTnI and Siemens ADVIA Centaur hs-cTnI assays were evaluated in the same patient subgroup (reported in a single publication[59]). For this reason, the comparison of Roche Elecsys hs-cTnT, Abbott ARCHITECT hs-cTnI and Siemens ADVIA Centaur hs-cTnI assays has been rated as having a low risk of bias with respect to the flow and timing domain of QUADAS-2C, whereas the all tests comparison was rated as having a high risk of bias (see *Table 6*). The comparative sensitivity and specificity estimates for the rule-out threshold of the ESC 0/1-hour pathway are provided in *Table 18*, with those estimates that were derived from the same participant subgroup of the APACE study highlighted in bold. Data from the APACE study[58] indicate that the ESC 0/1-hour rule-out pathway performs consistently across all six hs-cTn assays evaluated (sensitivity estimates were always ≥ 98%).

The High-STEACS study[61] provided data on the rule-out performance of the ESC 0/1-hour pathway, the ESC 0/3-hour pathway and the High-STEACS 0/3-hour pathway, using the Abbott ARCHITECT hs-cTnI assay[66] and the Siemens Atellica hs-cTnI assay.[67] As results for the two assays were published separately[66,67] and neither assay was evaluated in all participants in the High-STEACS study,[61] it is not clear that the same group of study participants received both assays. For this reason, the comparison has been rated as having a high risk of bias with respect to the flow and timing domain of QUADAS-2C, whereas the all tests comparison was rated high risk of bias (see *Table 6*). The comparative sensitivity and specificity estimates for the rule-out thresholds of each pathway and assay combination are provided in *Table 19*. Data from this study indicated that the sensitivity of the ESC 0/1-hour pathway

TABLE 18 Comparison between assays from the APACE study[58] (ESC 0/1-hour rule-out pathway): sensitivity and specificity (95% CI) for the target condition NSTEMI

Assay	Threshold	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
Roche Elecsys hs-cTnT	(symptoms > 3 hours AND < 5 ng/l at 0 hours) OR (< 12 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours)	**99 (95 to 100)**	**69 (65 to 73)**
Abbott ARCHITECT hs-cTnI	(symptoms > 3 hours AND < 2 ng/l at 0 hours) OR (< 5 ng/l at 0 hours AND Δ < 2 ng/l at 0 to 1 hours)	**98 (94 to 100)**	**65 (60 to 69)**
Beckman Coulter ACCESS hs-cTnI	(symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 4 ng/l at 0 to 1 hours)	99 (94 to 100)	70 (66 to 74)
Ortho VITROS hs-cTnI	(symptoms > 3 hours AND < 1 ng/l at 0 hours) OR (< 2 ng/l at 0 hours AND Δ < 1 ng/l at 0 to 1 hours)	100 (95 to 100)	60 (55 to 64)
Quidel TriageTrue hs-cTnI	(symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours)	100 (97 to 100)	66 (62 to 70)
Siemens ADVIA Centaur hs-cTnI	(symptoms > 3 hours AND < 3 ng/l at 0 hours) OR (< 6 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours)	**99 (95 to 100)**	**56 (52 to 60)**

Note
Bold indicates estimates derived from the same participant subgroup of the APACE study.[59]

TABLE 19 Comparison between assays from the High-STEACS study[61] (ESC 0/1-hour rule-out pathway, ESC 0/3-hour pathway and High-STEACS 0/3-hour pathway): sensitivity and specificity (95% CI) for the target condition NSTEMI

Assay	Pathway: threshold	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
Abbott ARCHITECT hs-cTnI	ESC 0/1-hour pathway: (symptoms > 3 hours AND < 2 ng/l at 0 hours) OR (< 5 ng/l at 0 h AND Δ < 2 ng/l at 0 to 1 hours)	100 (91 to 100)	78 (73 to 82)
Siemens Atellica hs-cTnI	ESC 0/1-hour pathway: (symptoms ≥ 3 hours AND < 3 ng/l at 0 hours) OR (< 6 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours)	94 (79 to 99)	69 (64 to 74)
Abbott ARCHITECT hs-cTnI	ESC 0/3-hour pathway: [symptoms ≥ 6 hours AND ≤ 16 ng/l (F) ≤ 34 ng/l (M) at 0 hours] OR [≤ 16 ng/l (F) ≤ 34 ng/l (M) at 3 hours] OR Δ < 50% of 99th centile at 0 to 3 hours	91 (87 to 94)	74 (72 to 77)
Siemens Atellica hs-cTnI	ESC 0/3-hour pathway: [symptoms ≥ 6 hours AND ≤ 34 ng/l (F) ≤ 53 ng/l (M) at 0 hours] OR [≤ 34 ng/l (F) ≤ 53 ng/l (M) at 3 hours] OR Δ < 50% of 99th centile at 0 to 3 hours	90 (86 to 93)	81 (79 to 82)
Abbott ARCHITECT hs-cTnI	High-STEACS 0/3-hour pathway: (symptoms ≥ 2 hours AND < 5 ng/l at 0 hours) OR [≤ 16 ng/l (F) ≤ 34 ng/l (M) at 3 hours AND Δ < 3 ng/l]	99 (97 to 100)	76 (73 to 78)
Siemens Atellica hs-cTnI	High-STEACS 0/3-hour pathway: (symptoms ≥ 2 hours AND < 5 ng/l at 0 hours) OR [≤ 34 ng/l (F) ≤ 53 ng/l (M) at 3 hours AND Δ < 3 ng/l at 0 to 3 hours]	98 (95 to 99)	74 (72 to 76)

was lower using the rule-out thresholds developed for the Siemens Atellica hs-cTnI assay (94%, 95% CI 79% to 99%)[67] than using the recommended ESC recommended rule-out thresholds[33] for the Abbott ARCHITECT hs-cTnI assay 100% (95% CI 91% to 100%).[66] The sensitivity ESC 0/1-hour rule-out pathway developed for the Siemens Atellica hs-cTnI assay did not reach the specified minimum clinically acceptable value of 97% and therefore this strategy was not included in our cost-effectiveness modelling. The sensitivity and specificity estimates for the ESC 0/3-hour rule-out pathway were similar using either the Abbott ARCHITECT hs-cTnI assay[66] or the Siemens Atellica hs-cTnI assay;[67] however, neither reached the specified minimum clinically acceptable value of 97%. The sensitivity and specificity estimates for the High-STEACS 0/3-hour rule-out pathway were also similar using either the Abbott ARCHITECT hs-cTnI assay[66] or the Siemens Atellica hs-cTnI assay[67] and both were ≥ 98%, indicating that the High-STEACS pathway is likely to be adequate for ruling out NSTEMI.

The High-US study compared the performance of two Siemens hs-cTnI assays (the Atellica and ADVIA Centaur) using three low thresholds and a single sample at presentation, for the target condition NSTEMI.[176] All three of the thresholds assessed were above the LoD (1.6 ng/l) for the assays. *Table 20* provides comparative sensitivity and specificity estimates for the two assays. The results of this study indicate consistent performance between the two Siemens assays evaluated for all three thresholds.

TABLE 20 Comparison between assays from the High-US study (single sample at presentation): sensitivity and specificity (95% CI) for the target condition NSTEMI

Assay	Threshold	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
Siemens Atellica hs-cTnI	2 ng/l	100 (98 to 100)	26 (24 to 28)
Siemens ADVIA Centaur hs-cTnI	2 ng/l	100 (99 to 100)	23 (21 to 25)
Siemens Atellica hs-cTnI	3 ng/l	99 (97 to 100)	37 (35 to 40)
Siemens ADVIA Centaur hs-cTnI	3 ng/l	99 (97 to 100)	35 (33 to 37)
Siemens Atellica hs-cTnI	5 ng/l	99 (97 to 100)	53 (51 to 55)
Siemens ADVIA Centaur hs-cTnI	5 ng/l	99 (97 to 100)	52 (50 to 54)

The sensitivity estimates were ≥ 99% for both assays at all three thresholds, indicating that a single sample at presentation and a low threshold (above the LoD) is likely to be adequate for ruling out NSTEMI.

The BEST study[172] provided data to compare the rule-out performance two single sample at presentation strategies based on different assays, the Siemens ADVIA Centaur assay using a threshold of 3 ng/l[172] and the Roche Elecsys hs-cTnT assay using the LoD (5 ng/l) threshold.[115] Data for the two assays were reported in separate publications with different numbers of participants (subgroups of the BEST study population) and for this reason the comparison has been rated as having a high risk of bias with respect to the flow and timing domain of QUADAS-2C (see *Table 6*). The sensitivity estimates were similar for the Roche Elecsys hs-cTnT assay (99%, 95% CI 93% to 100%)[115] and the Siemens ADVIA hs-cTnI assay (99%, 95% CI 96% to 100%),[172] whereas the Roche Elecsys hs-cTnT assay had higher specificity (47%, 95% CI 43% to 51%)[115] than the Siemens ADVIA Centaur hs-cTnI assay (33%, 95% CI 30% to 36%).[172]

Selection of test strategies for inclusion in cost-effectiveness modelling

Test strategies for each hs-cTn assay were selected for inclusion in cost-effectiveness modelling based on optimal diagnostic performance, as indicated by data from the systematic review. Data from studies that excluded patients with STEMI (i.e. where the target condition was NSTEMI) were preferentially selected.

Each test strategy is defined by a combination of four factors: (1) assay, of which there are nine, (2) number of tests (up to two), (3) timing of tests (between 0 and 3 hours) and (4) threshold concentration, of which there are many. This implies that there are many tens of possible strategies to compare in the cost-effectiveness analysis (CEA), which would be of questionable feasibility to construct, analyse and present as a full incremental analysis. It is also unnecessary to compare strategies that could be determined to be dominated before conducting the CEA. Therefore, all dominated strategies were eliminated by considering the factors that might affect either the total cost or quality-adjusted life-years (QALYs) [i.e. sensitivity, specificity, assay (assume a different cost for each one) and number and timing of tests (the greater number and later administration implies a higher cost)]. According to these criteria, the final number of non-dominated strategies was > 40, and so deemed to be still too high. Therefore, given that the main basis of considering these strategies was the idea that they might facilitate the safe rule out of those without a NSTEMI, the clinical experts on the specialist committee for this assessment were consulted to determine whether or not there was a minimum acceptable sensitivity (i.e. a maximum FN rate). They were asked the following.

> *We have now reached the stage, with this assessment, where decisions need to be made regarding which test strategies will be included in our cost effectiveness modelling.*
>
> *This is problematic because, as I'm sure you will be aware, the volume of data has increased markedly since our previous assessment and there remains a lack of consistency with respect to test strategies evaluated; our final data set comprises over 60 distinct combinations of assay, threshold and timing.*
>
> *Given the very large number of possible strategies, we considered limiting the strategies to be included in the CEA model to those for which it can be determined, before CEA, that they are not dominated. This approach would be based on criteria that might affect either the total cost or QALYs [quality-adjusted life years]:*
>
> 1. *sensitivity*
> 2. *specificity*
> 3. *assay – assume different cost for each one*
> 4. *number and timing of tests – greater number and later administration implies higher cost.*

However, using this approach still results in around 40 non-dominated strategies.

Even if it were feasible to model this number of strategies, interpretation of CE [cost-effectiveness] results with this many comparators is very challenging, particularly where, as in this case, the differences are likely to be small.

Therefore, we would like to request your input to determine a minimum clinically acceptable sensitivity which we will then use as an initial criterion to select strategies for CE modelling. In this context, please could you provide your opinion on what should constitute the minimum sensitivity.

On the basis of the responses of the clinical experts (see *Appendix 6*), an additional criterion, minimum sensitivity of 97%, was applied. As a result of this, the number of strategies was reduced to a manageable number of 21 (*Table 21*).

TABLE 21 Test strategies selected for cost-effectiveness modelling

Test strategy	Number of studies	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
Roche Elecsys hs-cTnT			
LoD (< 5 ng/l) at 0 hours	6[63,75,87,101,115,139]	99 (97 to 100)	35 (25 to 46)
ESC 0/1-hour pathway: (symptoms > 3 hours AND < 5 ng/l at 0 hours) OR (< 12 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours)	1[104]	99 (98 to 100)	68 (67 to 70)
< 12 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours	3[80,91,100]	98 (97 to 99)	73 (71 to 74)
< 8 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 0.5 hours	1[87]	100 (93 to 100)	45 (40 to 49)
99th centile threshold (< 14 ng/l at 0 hours AND 3 hours)	1[148]	100 (89 to 100)	77 (58 to 90)
Abbott ARCHITECT hs-cTnI			
LoD (< 2 ng/l) at 0 hours	4[58,71,96,101]	100 (99 to 100)	21 (16 to 26)
< 4 ng/l at 0 hours	2[71,101]	99 (97 to 100)	50 (48 to 52)
ESC 0/1-hour pathway: (symptoms > 3 hours AND < 2 ng/l at 0 hours) OR (< 5 ng/l at 0 hours AND Δ < 2 ng/l at 0 to 1 hours)	2[66,104]	99 (98 to 100)	57 (56 to 59)
High-STEACS pathway: (symptoms ≥ 2 hours AND < 5 ng/l at 0 hours) OR [≤ 16 ng/l (F) ≤ 34 ng/l (M) at 3 hours AND Δ < 3 ng/l at 0 to 3 hours]	1[66]	99 (97 to 100)	76 (73 to 78)
Beckman Coulter Access hs-cTnI			
ESC 0/1-hour pathway: (symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 4 ng/l at 0 to 1 hours)	1[60]	99 (94 to 100)	70 (66 to 74)
(symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 5 ng/l at 0 to 2 hours)	1[171]	98 (92 to 100)	83 (81 to 86)
bioMérieux VIDAS hs-cTnI			
< 2 ng/l at 0 hours OR (< 6 ng/l at 0 AND 2 hours)	1[132]	98 (92 to 100)	64 (59 to 68)
Ortho VITROS hs-cTnI			
ESC 0/1-hour pathway: (symptoms > 3 hours AND < 1 ng/l at 0 hours) OR (< 2 ng/l at 0 hours AND Δ < 1 ng/l at 0 to 1 hours)	1[170]	100 (95 to 100)	60 (55 to 64)
Quidel TriageTrue hs-cTnI			
ESC 0/1-hour pathway: (symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours)	1[173]	100 (97 to 100)	66 (62 to 70)

TABLE 21 Test strategies selected for cost-effectiveness modelling (*continued*)

Test strategy	Number of studies	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
Siemens ADVIA Centaur hs-cTnI			
< 2 ng/l at 0 hours	1[176]	100 (99 to 100)	23 (21 to 25)
< 5 ng/l at 0 hours	1[176]	99 (97 to 100)	52 (50 to 54)
ESC 0/1-hour pathway: (symptoms > 3 hours AND < 3 ng/l at 0 hours) OR (< 6 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours)	1[59]	99 (95 to 100)	56 (52 to 60)
< 3 ng/l at 0 hours OR (< 8 ng/l at 0 hours AND Δ < 7 ng/l at 0 to 2 hours)	1[59]	100 (95 to 100)	67 (61 to 72)
Siemens Atellica hs-cTnI			
< 2 ng/l at 0 hours	1[176]	100 (98 to 100)	26 (24 to 28)
High-STEACS pathway: (symptoms ≥ 2 hours AND < 5 ng/l at 0 hours) OR [≤ 34 ng/l (F) ≤ 53 ng/l (M) at 3 hours AND Δ < 3 ng/l at 0 to 3 hours]	1[67]	98 (95 to 99)	74 (72 to 76)
Siemens Dimension Vista hs-cTnI			
< 5 ng/l at 0 hours AND Δ < 2 ng/l at 0 to 1 hours	1[74]	100 (97 to 100)	66 (62 to 69)

Chapter 4 Assessment of cost-effectiveness

This chapter explores the cost-effectiveness of hs-cTn assays (used up to 4 hours from the onset of chest pain/presentation) compared with the current standard of serial troponin T and/or I testing on admission and at 10–12 hours after the onset of symptoms for the early rule out of AMI in people with acute chest pain.

Review of economic analyses of hs-cTn assays

Search strategy

The search strategies used to identify clinical effectiveness studies, detailed in *Chapter 3*, *Search strategy*, were also employed to identify any cost studies since 2013. Details of the databases searched for this update are provided in *Chapter 3*, *Search strategy*, and full strategies are provided *in Appendix 1*. Search strategies utilised in the original report[2] were updated with any new interventions identified in the NICE scope. Search strategies were based on intervention (high-sensitivity troponin assays) and target condition, as recommended in the CRD guidance for undertaking reviews in health care[39] and the Cochrane *Handbook for DTA Reviews*.[41]

Additional top-up searches were run to identify any specific cost studies from the UK that utilise a cost filter together with the NICE UK geographic filter;[179,180] these strategies and the filters used are also detailed in *Appendix 1*.

The following databases were searched on 10 January 2020 for relevant UK cost studies from 2013 to the present:

- MEDLINE ALL (Ovid): 1946 to 9 January 2020
- EMBASE (Ovid): 1974 to 9 January 2020
- American Economic Association's electronic bibliography (EconLit) (EBSCO*host*): 2013 to 9 January 2020
- NHS Economic Evaluation Database (NHS EED) (URL: www.crd.york.ac.uk/CRDWeb/): 2013 to March 2015.

Inclusion criteria

Studies reporting a full economic analysis that explicitly related to the cost-effectiveness of hs-cTn or standard cTn (with cTn implying either cTnI or cTnT) testing, with survival and/or QALYs as an outcome measure, were eligible for inclusion. Specifically, one of the strategies had to include cTn testing. Studies that reported a cost analysis of cTn testing only were not included in the review.

Results

Five studies, identified in our previous assessment report,[2] are described below and summarised in *Table 22*.

Goodacre *et al.*[181] and Fitzgerald *et al.*[182]

The study by Fitzgerald *et al.*[182] was based on the RATPAC (Randomised Assessment of Treatment using Panel Assay of Cardiac Markers) multicentre pragmatic controlled trial.[181] An economic evaluation was undertaken to assess the cost-effectiveness of management based on testing with a panel of point-of-care cardiac markers compared with management without point-of-care panel assessment. The included population consisted of patients presenting to hospital with chest pain due to suspected, but not proven, AMI and no other potentially serious alternative pathology or comorbidity. The analysis was performed from an NHS perspective, using trial data to estimate the mean costs per patient of chest pain-related care and the mean number of QALYs accrued by patients in each arm of

TABLE 22 Summary of included cost-effectiveness studies

	Included study				
Study detail	**Goodacre *et al.*;[181] Fitzgerald *et al.*[182]**	**Vaidya *et al.*[183]**	**Thokala *et al.*;[184] Goodacre *et al.*[185]**	**CADTH report[186]**	**Collinson *et al.*[159]**
Population	People presenting to hospital with chest pain due to suspected, but not proven, AMI and no other potentially serious alternative pathology or comorbidity	Patients presenting to the hospital with chest pain	Patients attending hospital with symptoms suggesting MI, but a normal or non-diagnostic ECG and no major comorbidities requiring hospital treatment	65-year-old patients presenting to an ED with ischemic chest pain, without an ST segment elevation ECG who require cTn testing for diagnosis of NSTEMI	Patients presenting to hospital with symptoms suggestive of MI but with no diagnostic ECG changes (ST deviation > 1 mm or T-wave inversion > 3mm), no known history of CHD and no major comorbidities requiring inpatient treatment
Time horizon	Lifetime	Lifetime	Lifetime	Lifetime	Lifetime
Objective	Estimate the cost-effectiveness of the PoC panel in terms of mean costs and QALYs accrued compared with standard care	Assess the cost-effectiveness of a hs-cTnT, alone or combined with the H-FABP assay, in comparison with the cTnT assay for the diagnosis of AMI	Estimate the incremental cost per QALY of delayed troponin testing compared with presentation testing and no testing to determine which diagnostic strategy should be recommended	To investigate the cost-effectiveness of hs-cTnT and hs-cTnI assays compared with each other, as well as with cTnI assays, in patients with suspected ACS symptoms in the ED	Assess the cost-effectiveness of measuring a combination of biomarkers compared with measurement of cTn alone
Source of effectiveness information	Data from within the trial up to 3 months and, beyond this, lifetime costs and QALY estimates were used from a previous economic evaluation	No information	Sensitivity and specificity were taken from the meta-analysis, as reported in the Goodacre *et al.* report;[185] the RATPAC trial[159] was used for sampling patient characteristics; the Mills *et al.* report[187] was used to assess risk of reinfarction and death, and Polanczyk *et al.*[188] was used for life expectancy of patients with MI and myocardial re-infarction	Sensitivity and specificity from review performed in same report. Proportion of UA and mortality estimated based on published studies, and one unpublished study. Utility decrements based on published study	Sensitivity and specificity data derived from data from the HTA (RATPAC) itself, short-term survival and probability of reinfarction based on Mills *et al.*[187] Source for long-term survival and QALYs not specified

Study detail	Included study				
	Goodacre *et al.*;[181] Fitzgerald *et al.*[182]	Vaidya *et al.*[183]	Thokala *et al.*;[184] Goodacre *et al.*[185]	CADTH report[186]	Collinson *et al.*[159]
Comparators	Diagnostic assessment using the PoC biochemical marker panel Conventional diagnostic assessment without the panel	Conventional cTnT hs-cTnT hs-cTnT combined with the H-FABP assay	No biochemical testing: discharge all patients without treatment (hypothetical) Standard troponin assay measured at presentation using the 10% CoV as the threshold for positivity Standard troponin assay measured at presentation using the 99th centile threshold High-sensitivity troponin assay measured at presentation using the 99th centile threshold Standard troponin assay measured at presentation and 10 hours after symptom onset using the 99th centile threshold	hs-cTnT hs-cTnI cTnI	No testing: discharge all patients without treatment hs-cTn at presentation: discharge home if test is negative or admit to hospital for troponin testing at 10–12 hours if positive hs-cTn and a combination of cytoplasmic or neurohormone biomarkers at presentation: discharge home if both tests are negative or admit to hospital for troponin testing at 10–12 hours if either test is positive hs-cTn at presentation and at 90 minutes, as in the RATPAC protocol: discharge home if both tests are negative or admit to hospital for troponin testing at 10–12 hours if either test is positive Standard troponin testing at 10–12 hours
Unit costs	Microcosting study within RATPAC and PSSRU unit costs	No information	Admission and treatment were based on the national tariff. Lifetime costs for MI patients were taken from Ward *et al.*[189] The price of a troponin test was taken from Goodacre *et al.*[181]	Costs of hospital admission were based on the Ontario Case Costing Initiative database and the Ontario Schedule of Benefits for Physician Services. Costs of ED visits were based on a hospital in Soutwestern Ontario, Canada, and the Ontario Schedule of Benefits. Unit prices of cTn tests were based on information provided by the manufacturers	Hospital stay and treatment for MI based on NHS reference cost and biochemical testing based on Goodacre *et al.*[181]

continued

TABLE 22 Summary of included cost-effectiveness studies (*continued*)

Study detail	Included study				
	Goodacre *et al.*;[181] Fitzgerald *et al.*[182]	Vaidya *et al.*[183]	Thokala *et al.*;[184] Goodacre *et al.*[185]	CADTH report[186]	Collinson *et al.*[159]
Measure of benefit	QALYs	AMI survivor	QALYs	QALYs	QALYs
Study type	Trial-based economic evaluation up to 3 months, decision tree lifetime, cost–utility analysis	Model-based cost-effectiveness and cost–utility study	Model-based cost–utility analysis	Model-based cost–utility analysis	Model-based cost–utility study
Model assumptions	2-hour delay between sampling and results available 4 hours after presentation at ED patients moves to inpatient department 1-hour delay between presentation and start of biomarker sampling After a short term (test–treatment–outcome), progress depends on whether or not patient had MI and whether or not this was treated only	No information	10-hour troponin testing has perfect sensitivity and specificity (as it is the reference standard) 2-hour delay from the time at which sampling could be performed to results available For presentation testing strategies, decision made within 1 hour of results available For 10-hour testing strategies, decision made according to scenario applied Diagnostic strategy influences outcomes among patients with MI only	Non-NSTEMI patients are further classified into UA or non-ACS, with consequences for costs and outcome There is a small survival benefit (relative risk of 1-year mortality 1.01) of treating early compared with treating late (presentation testing vs. standard testing)	10-hour troponin testing has perfect sensitivity and specificity (as it is the reference standard) Presentation blood tests taken in ED, and results available and decision made within 2 hours of sampling For testing at 10–12 hours, delays according to scenario used
Perspective	NHS	Health care	NHS	Publicly funded health-care system	NHS in England and Wales
Discount rate	No information	No information	No information	5% discount rate applied to costs and QALYs	No information

Study detail	Included study				
	Goodacre *et al.*;[181] Fitzgerald *et al.*[182]	Vaidya *et al.*[183]	Thokala *et al.*;[184] Goodacre *et al.*[185]	CADTH report[186]	Collinson *et al.*[159]
Uncertainty around cost-effectiveness ratio expressed	Incremental cost-effectiveness plane and probability of strategy being dominated/ cost-effective	CEACs (not shown in abstract)	CEACs for PSA results, per scenario	As reported in outcomes of one-way sensitivity analyses,[186] and also (for the PSA) in CEACs	CEACs
Sensitivity analysis	PSA	One way and probabilistic	One-way sensitivity analyses, scenario analyses (doctor on demand, twice-daily ward round and once-daily ward round) and PSA	One way and probabilistic	Secondary analysis using cTnI instead of cTnT, scenario analysis (doctor on demand, once-daily ward round, twice-daily ward round) and PSA
Outcome (cost and life-years/QALYs) per comparator	Empirical 3 months - PoC: £1217; QALY 0.158 Standard care: £1006; QALY 0.161 For the model, no outcomes per comparator were reported	No information	For doctor-on-demand scenario, per 1000 patients without known CAD No testing: £965,994; QALY 26,227 Presentation standard troponin: 10% CoV; £1,560,361; QALY 26,345 Presentation standard troponin, 99th percentile: £1,609,760; QALY 26,352 Presentation high-sensitivity troponin, 99th percentile: £1,806,910; QALY 26,279 10-hour troponin: £2,016,540; QALY 26,286	cTnI: CA$2018; QALY 8.1385 hs-cTnI: CA$2082; QALY 3.1389 hs-cTnT: CA$2186; QALY 8.1399	For doctor-on-demand scenario, per 1000 patients: No testing: £965,994; QALY 26,227 hs-cTnT at presentation: £1,581,263; QALY 26,349 hs-cTnT at presentation and 90 minutes: £1,715,526; QALY 26,354 hs-cTnT and H-FABP at presentation: £1,682,362; QALY 26,359 10-hour troponin: £2,016,540; QALY 26,386

continued

TABLE 22 Summary of included cost-effectiveness studies (*continued*)

Study detail	Included study				
	Goodacre *et al.*;[181] Fitzgerald *et al.*[182]	Vaidya *et al.*[183]	Thokala *et al.*;[184] Goodacre *et al.*[185]	CADTH report[186]	Collinson *et al.*[159]
Summary of incremental analysis	Empirical 3 months: Increment PoC vs. standard care: £211; QALY −0.00282 Probability PoC cost-effective at £20,000/QALY = 0.4% Decision model 3 months: Increment PoC vs. standard care: £169; QALY −0.002 Probability PoC cost-effective at £20,000/QALY = 22.3% Decision model lifetime: Increment PoC vs. standard care: £329; QALY −0.087 Probability PoC cost-effective at £20,000/QALY = 33.6%	hs-cTnT vs. cTnT: incremental cost €111; 16/17 lives per 1000 AMI; ICER €3748/QALY hs-cTnT + H-FABP vs. cTnT: incremental cost €178; ICER €5717/QALY	For doctor-on-demand scenario: Presentation standard troponin: 10% CoV vs. no testing; £5030/QALY Presentation standard troponin 99th percentile vs. presentation standard troponin: 10% CoV; £6518/QALY Presentation high-sensitivity troponin 99th percentile vs. presentation standard troponin 99th percentile: £7487/QALY 10-hour troponin vs. presentation high-sensitivity troponin 99th percentile: £27,546/QALY	cTnI reference hs-cTnI: incremental costs CA$64; incremental QALYs 0.000352 dominated (by extension) hs-cTnT: incremental costs CA$168; incremental QALYs 0.001408; ICER CA$119,377/QALY	No testing: reference strategy hs-cTnT compared vs. testing: ICER £5012/QALY hs-cTnT at presentation and at 90 minutes: dominated hs-cTnT and H-FABP vs. hs-cTnT at presentation: ICER £11,026/QALY (as reported, but correct value should be £10,871) 10-hour troponin vs. hs-cTnT and H-FABP: ICER £12,090/QALY Conclusion: if a rapid rule-out strategy with a sensitivity of 95% (and a specificity of around 90%) is available, then a 10-hour troponin strategy does not seem cost-effective

CEAC, cost-effectiveness acceptability curve; CHD, coronary heart disease; H-FABP, heart-type fatty acid-binding protein; ICER, incremental cost-effectiveness ratio; PoC, point of care; PSA, probabilistic sensitivity analysis; PSSRU, Personal Social Services Research Unit; RATPAC, Randomised Assessment of Treatment using Panel Assay of Cardiac Markers.

the trial, with a time horizon of 3 months. In addition, a decision-analytic model was constructed to duplicate (validate) trial results and extrapolate results to a longer time horizon.

Resource use data were collected for all patients. Cost and outcome data were collected using patient notes and self-completed questionnaires. Unit prices were based partly on a micro-costing study on a sample of patients, partly on a study previously undertaken by the investigators, and partly on purchase price and national unit costs. QALYs were calculated based on EuroQol-5 Dimensions measurements. In a sensitivity analysis, productivity costs were included, as reported by the patients.

As it was anticipated that the trial would have limited power to detect a difference in major adverse events, the decision-analytic model was intended to explore whether or not uncertainty around the effect of the intervention on the major adverse event rate could influence the potential cost-effectiveness of the intervention. The model used trial data to estimate costs and QALYs for up to 3 months. Beyond this, lifetime cost and QALYs were estimated from a previous study.[190] It was assumed that patients who had died at 3 months would accrue no further costs or QALYs. Those who had survived non-fatal MI would accrue costs and QALYs associated with coronary heart disease (CHD) (estimated at £10,079 and 6.829, respectively). Those without CHD were assigned zero costs and 20 QALYs.

Empirical results showed that the point-of-care test strategy was dominated by standard care, which delivered slightly more QALYs at a lower cost. The probability that point-of-care testing would be more cost-effective than standard care at a willingness-to-pay threshold of £20,000 per QALY was < 1%. The decision-analytic model, again, resulted in higher costs and less effect for the point-of-care panel assay compared with standard care, and also when extrapolated to lifetime survival. The probability of the point-of-care panel assay being cost-effective for the 3-month and lifetime model was 22.3% and 33.6%, respectively.

The main conclusion was that point-of-care panel assay testing is unlikely to be considered cost-effective in the NHS, with an 89% probability that standard care is dominant. Cost-effectiveness was mainly driven by differences in mean cost, with point estimates suggesting that, per patient, point-of-care panel assessment was £211 more expensive than standard care.

Vaidya *et al.*[183]

Vaidya *et al.*[183] aimed to assess the cost-effectiveness of an hs-cTnT assay, alone or in combination with the heart-type fatty acid-binding protein (H-FABP), in comparison with the conventional cTnT assay for the diagnosis of AMI in patients presenting to hospital with chest pain. A decision-analytic model was developed to perform both a cost–utility analysis (cost per QALY gained) and a CEA (cost per life-year gained and cost per AMI averted), using a health-care perspective and a lifetime time horizon. One-way and probabilistic sensitivity analyses (PSAs) were conducted.

The incremental cost-effectiveness ratio (ICER) for hs-cTnT compared with conventional cTnT was €3748 per QALY gained. For hs-cTnT in combination with H-FABP compared with conventional cTnT, the ICER was €5717 per QALY gained. For life-years and AMI averted, no ICERs were reported in the abstract. The PSA showed the hs-cTnT assay to be the preferable strategy, with a probability of > 90% at a ceiling ratio of €4800 per QALY. This led to the conclusion that the hs-cTnT assay is very cost-effective relative to the conventional cTnT assay. Combining hs-cTnT with H-FABP did not seem to offer any additional economic or health benefit over the hs-cTnT test alone.

Goodacre *et al.*[185] and Thokala *et al.*[184]

Goodacre *et al.*[185] and Thokala *et al.*[184] aimed to estimate the cost-effectiveness of using alternative biomarker strategies to diagnose MI, and using biomarkers, computed tomography coronary angiography and exercise electrocardiography to risk-stratify troponin-negative patients. As the second aim was outside the scope of this review, we have summarised the analysis that compares the biomarker strategies for diagnosing MI only, referred to in the HTA report as ‘the diagnostic phase model’.

The different diagnostic strategies were applied to a hypothetical cohort of patients attending the ED with suspected, but not proven, ACS. Patient characteristics were defined using data from the RATPAC trial,[191] as well as patients' arrival times during the day at the ED. The model assigned each patient a probability of reinfarction or death, depending on their characteristics and whether or not they had treatment. The model took a lifetime time horizon. The economic perspective was that of the NHS in England and Wales.

The following strategies were applied to each patient.

- No testing [discharge all patients without treatment (hypothetical)].
- Standard troponin assay measured at presentation using the 10% CoV as the threshold for positivity.
- Standard troponin assay measured at presentation using the 99th centile threshold.
- High-sensitivity troponin assay measured at presentation using the 99th centile threshold.
- Standard troponin assay measured at presentation and 10 hours after symptom onset using the 99th centile threshold.

Blood tests at presentation were assumed to be taken in the ED and so a decision could be made within 1 hour of the test results becoming available. For the 10–12 hours troponin measurement, three different scenarios were tested:

1. the 'doctor-on-demand' scenario, with medical staff available 24 hours a day to make a disposition decision within 1 hour of the results being available
2. the twice-daily ward round scenario, with medical staff only available at twice-daily ward rounds to make disposition decisions
3. the once-daily ward round scenario, with medical staff only available at a once-daily ward round to make disposition decisions.

Sensitivity and specificity estimates for the presentation troponin tests were obtained by performing a meta-analysis of estimates from individual primary studies included in the accompanying review. The 10-hour troponin test was assumed to have perfect sensitivity and specificity, as it was the reference standard for the review. This implies that patients with a FP test on the hs-cTn testing at presentation will still be discharged home after the 10- to 12-hour troponin test, but patients with a FN test will be discharged home without treatment. The 'discharge without testing or treatment' by definition has perfect specificity, but a sensitivity of 0%.

The risk of reinfarction and death for patients with MI was based on a study by Mills *et al.*[187] Life expectancy of patients with MI and MI with reinfarction was estimated from Polanczyk *et al.*,[188] and the utility of patients with MI was based on Ward *et al.*[189] The utility of patients with reinfarction was estimated by using a multiplicative factor of 0.8 for patients with MI (expert opinion). Patients without MI were assigned the life expectancy and utility scores of the general population. Lifetime costs for patients with MI were based on Ward *et al.*[189] One-way sensitivity analyses were performed, as well as a PSA. In a secondary analysis, a strategy was added that involved alternative biomarkers in combination with the presentation troponin testing.

The results showed that measuring a 10-hour troponin level in all patients was the most effective strategy (ICER £27,546–103,560). However, at a threshold of £30,000 per QALY, the optimal strategy in all but one scenario was measurement of high-sensitivity troponin at presentation, with a 10-hour troponin test if positive and discharge home if negative (ICER £7487–17,191/QALY). The exception was a scenario involving patients without known CAD and a doctor available on demand to discharge the patient, when, using the £30,000 per QALY threshold, the strategy of measuring a 10-hour troponin level in all patients was optimal (ICER of £27,546/QALY). Sensitivity analyses showed the optimal strategy to vary with different levels of sensitivity and timing of the tests.

The report concluded that the additional costs that are likely to be incurred by measuring a 10-hour troponin level, compared with a presentation high-sensitivity troponin level, are unlikely to represent a cost-effective use of NHS resources in most of the scenarios tested.

CADTH optimal use report[186]

The CADTH report[186] aimed to determine the cost-effectiveness of hs-cTnT and hs-cTnI assays compared with each other, as well as with cTnI assays in patients with suspected ACS symptoms in the ED. For this purpose, three comparators were considered: (1) hs-cTnT, (2) hs-cTnI and (3) cTnI. As cTnT is no longer available in Canada, it was not taken into account in the analysis. The target population consisted of patients aged 65 years presenting to the ED, without ST segment elevation, who required cTn testing for diagnosis of NSTEMI. For the economic evaluation, a decision tree was constructed that calculated lifetime cost per QALY from the perspective of a publicly funded health-care system.

The model consisted of a short-term part (which had a time horizon of 1 year) and a long-term part. The short-term part incorporated the testing and treatment procedures and short-term outcomes. Patients were tested at presentation at the ED and if they were not admitted to hospital after the first test they were tested again after 6 hours. When the patient was admitted after the first test, treatment was said to be initiated early, and when a patient was admitted after the second test, treatment was late. One year mortality depended on whether or not a patient had NSTEMI and whether they were treated early, treated late or untreated (in the case of FN test results). Those not suffering from NSTEMI were further stratified into UA or not having ACS. The annual probability of death in the long-term part of the model was dependent on patient age, gender and whether they had suffered an NSTEMI, UA or did not have any type of ACS in the short-term part of the model.

The sensitivity and specificity for each cTn test at presentation to the ED was derived from the systematic review that was also part of this study. In the model, patients with a negative cTn test at presentation were assumed to be observed and have a second cTn test 6 hours later. After the second cTn test, 90% of these FNs were assumed to become TPs.

Short-term mortality rates and relative risks (RRs) for treated/non-treated patients were taken from published clinical studies and one non-referenced study. The relative risk for late treatment compared with early treatment was derived from expert opinion. Long-term mortality rates were taken from published clinical studies and one non-referenced study. QALYs were calculated by incorporating an age-specific utility decrement for patients with NSTEMI. A number of one-way sensitivity analyses were performed, as well as a PSA.

The base-case results indicated that hs-cTnI was dominated by hs-cTnT, when compared to cTnI, at an ICER of CA$119,377 per QALY. The PSA showed that for willingness-to-pay thresholds up to CA$124,000, cTnI had the highest probability of being cost-effective. For willingness-to-pay thresholds > CA$124,000, hs-cTnT had the highest probability of being cost-effective. The hs-cTnI test was not likely to be cost-effective for any value of the threshold.

The authors concluded that hs-cTnT would be considered the most cost-effective testing strategy if willingness to pay for a QALY is ≥ CA$119,377, otherwise cTnI would be the most cost-effective test. However, there was a lot of uncertainty in results when model assumptions were changed.

Collinson *et al.*[159]

Collinson *et al.*[159] used a decision tree developed in the related HTA by Goodacre *et al.*[185] to compare the cost-effectiveness of five diagnostic strategies for a hypothetical cohort of patients presenting to hospital with symptoms suggestive of MI but with no diagnostic ECG changes, no known history of CHD and no major comorbidities requiring inpatient treatment. Essentially, this was a substudy of the point-of-care arm of the RATPAC trial. All methods and model inputs were identical to the study by

Thokala *et al.*[184] and the HTA report by Goodacre *et al.*,[185] but with slightly different strategies applied to the cohort of patients.

1. No testing: discharge all patients without treatment (theoretical 'zero' option).
2. hs-cTnT at presentation: discharge home if test is negative or admit to hospital for troponin testing at 10–12 hours if positive.
3. hs-cTnT and H-FABP at presentation: discharge home if both tests are negative or admit to hospital for troponin testing at 10–12 hours if either test is positive.
4. hs-cTnT at presentation and at 90 minutes, as in the RATPAC protocol: discharge home if both tests are negative or admit to hospital testing at 10–12 hours if either test is positive.
5. Standard troponin testing at 10–12 hours.

The difference with the other studies is in the addition of H-FABP in the third strategy, and in the second high-sensitive troponin test at 90 minutes in the fourth strategy. In a secondary analysis, cTnT was replaced by cTnI. Sensitivity and specificity of presentation biochemical testing were estimated using data from within the study (RATPAC). Standard troponin testing at 10–12 hours was assumed to have perfect sensitivity and specificity, as this was the reference standard.

At the £20,000 per QALY threshold, 10-hour troponin testing was cost-effective (£12,090/QALY) in the doctor-on-demand scenario, but not in the other scenarios (once-daily ward round and twice-daily ward rounds), where hs-cTnT and H-FABP measurement at presentation was cost-effective. At the £30,000 per QALY threshold, 10-hour troponin testing was cost-effective in the doctor-on-demand scenario and twice-daily ward rounds scenario (£24,600/QALY), whereas the hs-cTnT and H-FABP measurement at presentation strategy was cost-effective (£14,806/QALY) in the once-daily ward round scenario. Secondary analysis using cTnI instead of cTnT showed that cTnI testing at presentation and at 90 minutes was cost-effective in all three scenarios at the £20,000 per QALY threshold and in two of the scenarios at the £30,000 per QALY threshold, with 10-hour troponin being cost-effective in the doctor-on-demand scenario only (£24,327/QALY). The overall conclusion was that 10-hour troponin testing is only likely to be cost-effective compared with rapid rule-out strategies if patients can be discharged as soon as a negative result is available and a £30,000 per QALY threshold is used.

The targeted literature search conducted for this assessment retrieved 98 records. After removing 63 duplicates, this resulted in 35 remaining records. After initial screening of titles and abstracts, one paper[192] was considered to be potentially relevant. Hand-searching identified an additional seven potentially relevant papers, but after title and abstract screening these were excluded as they were not full cost-effectiveness studies ($n = 4$)[193–196] or were cost-effectiveness studies not focused on the UK ($n = 3$).[197–199]

Ambavane *et al.*[192]

The Ambavane *et al.*[192] study used patients [enrolled in the TRAPID-AMI (High Sensitivity Cardiac Troponin T Assay for Rapid Rule-out of Acute Myocardial Infarction) study] who presented to the ED with acute chest pain to assess the cost-effectiveness of a 1-hour rule-out and rule-in algorithm, using hs-cTnT testing, in comparison with standard care. The study reported that the 1-hour algorithm had higher sensitivity (87% vs. 69%) but lower specificity (96% vs. 97%) than standard care. Total costs were reduced for the 1-hour algorithm compared with standard care (£2480 vs. £4561) and this was mainly driven by a shorter length of stay in the ED.

Summary of studies included in the cost-effectiveness review

Most of the studies identified in this review found that the question of whether or not hs-cTn testing is cost-effective cannot be answered unequivocally. In favour of hs-cTn testing, the abstract by Vaidya *et al.*[183] concluded that hs-cTnT testing is 'very cost effective' and the study by Goodacre *et al.*[185] concluded that 'the optimal strategy in all but one scenario was high-sensitivity troponin at presentation, with a 10 hour troponin test if positive and discharge home if negative'.[185] The other papers reported

ICERs that were considerably higher and with substantial uncertainty. The accuracy of high-sensitive tests and the efficiency of decision-making based on test results were important drivers of cost-effectiveness.

Model structure and methodology

Troponin testing strategies considered in the model

The health economic analysis will estimate the cost-effectiveness of different troponin testing strategies for diagnosing or ruling out NSTEMI in patients presenting at the ED with suspected NSTE-ACS who have no major comorbidities requiring hospitalisation (e.g. as heart failure or arrhythmia) and in whom STEMI has been ruled out. Those diagnosed with NSTEMI will then be admitted to the hospital for AMI treatment and those diagnosed as without NSTEMI can be discharged without AMI treatment and further hospital stay. AMI treatment might include aspirin, statins and angiotensin-converting enzyme inhibitors, and consideration of coronary revascularisation for high-risk cases.[185] Initiating AMI treatment for NSTEMI will reduce the probability of MACEs, particularly cardiac death and reinfarction.

Standard serial troponin testing for patients with acute chest pain due to possible ACS does not achieve optimal sensitivity in detecting AMI until 10–12 hours after onset of symptoms. Waiting for 10–12 hours after symptoms onset is burdensome for patients and induces additional health-care costs. Therefore, various alternatives have been proposed that use more sensitive troponin tests for the early rule out of NSTEMI (within the 4-hour NHS ED target).[200]

Chapter 3 of this report summarises evidence about the clinical effectiveness of the various hs-cTn test strategies reported in the literature and describes the process used to select strategies for inclusion in the economic model. For the economic model, only those high-sensitivity troponin tests that had a sensitivity of $\geq$ 97% were selected (based on expert opinion indicating that sensitivity should minimally be 97% to be acceptable for clinicians). This resulted in the following high-sensitivity troponin strategies being evaluated in the economic model.

- Roche Elecsys hs-cTnT:
  - 99th centile threshold (< 14 ng/l at 0 hours AND 3 hours)
  - LoD (< 5 ng/l) at 0 hours
  - ESC 0/1-hour pathway – (symptoms > 3 hours AND < 5 ng/l at 0 hours) OR (< 12 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours)
  - (< 8 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 0.5 hours)
  - (< 12 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours).
- Siemens Dimension Vista hs-cTnI:
  - (< 5 ng/l at 0 hours AND Δ < 2 ng/l at 0 to 1 hours).
- Abbott ARCHITECT hs-cTnI:
  - LoD (< 2 ng/l) at 0 hours
  - ESC 0/1-hour pathway – (symptoms > 3 hours AND < 2 ng/l at 0 hours) OR (< 5 ng/l at 0 hours AND Δ < 2 ng/l at 0 to 1 hours)
  - High-STEACS pathway – (symptoms $\geq$ 2 hours AND < 5 ng/l at 0 hours) OR [$\leq$ 16 ng/l (F) $\leq$ 34 ng/l (M) at 3 hours AND Δ < 3 ng/l]
  - < 4 ng/l at 0 hours.

- Siemens ADVIA Centaur hs-cTnI:
  - < 2 ng/l at 0 hours
  - < 3 ng/l at 0 hours OR (< 8 ng/l at 0 hours AND Δ < 7 ng/l at 0–2 hours)
  - ESC 0/1-hour pathway – (symptoms > 3 hours AND < 3 ng/l at 0 hours) OR (< 6 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours)
  - < 5 ng/l at 0 hours.
- Siemens Atellica hs-cTnI:
  - < 2 ng/l at 0 hours
  - High-STEACS pathway – (symptoms ≥ 2 hours AND < 5 ng/l at 0 hours) OR [≤ 34 ng/l (F) ≤ 53 ng/l (M) at 3 hours AND Δ < 3 ng/l].
- Beckman Coulter Access hs-cTnI:
  - ESC 0/1-hour pathway – (symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 4 ng/l at 0 to 1 hours)
  - [(symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 5 ng/l at 0 to 2 hours)].
- Ortho VITROS hs-cTnI:
  - ESC 0/1-hour pathway – (symptoms > 3 hours AND < 1 ng/l at 0 hours) OR (< 2 ng/l at 0 hours AND Δ < 1 ng/l at 0 to 1 hours).
- bioMérieux VIDAS hs-cTnI:
  - < 2 ng/l at 0 hours OR (< 6 ng/l at 0 AND 2 hours).
- Quidel TriageTrue hs-cTnI:
  - ESC 0/1-hour pathway – (symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours).

In the base case, it was assumed that standard troponin had perfect sensitivity and specificity (reference case) for diagnosing AMI. Using this assumption, all patients testing positive on a hs-cTn test but negative on the standard troponin would be classified as FPs. This implies that their risk for adverse events would be the same as for those patients testing negative on both the hs-cTn test and the standard troponin, and that they ought to be discharged home without further immediate treatment. However, there is evidence to suggest that patients with a negative standard troponin and a positive hs-cTn may be at higher long-term risk for adverse events than patients who test negative on both the standard and the high-sensitive troponin.[201] A secondary analysis was therefore performed, which attributed a higher risk of adverse events (e.g. MI and mortality) to a proportion of patients testing FP on the hs-cTn test.

Based on the available evidence, two analyses were performed.

1. The base-case analysis.
2. A secondary analysis. This analysis assumes that patients testing FP in the hs-cTn testing strategies do not have the same risk for adverse events as patients testing TN. Instead, these patients were assigned a higher risk for (re)infarction and death to reflect the idea that, when the hs-cTn test gives a positive result, in some cases this must be caused by a disease process, whether or not the strict definition of AMI is met. The risk of adverse events in patients testing positive on a hs-cTn test but negative on the standard troponin is higher than the risk of adverse events for patients testing negative on both the hs-cTn test and the standard troponin, and lower than the risk of adverse events in patients diagnosed with NSTEMI (i.e. testing positive on both a hs-cTn and standard troponin).

Model structure

An identical model structure to the one reported in the initial DAR[2] is used. This model structure was developed using the HTA report by Goodacre *et al.*[185] as a starting point and adapted to better fit the scope of the current assessment. In the health economic model, the mean expected costs (NHS and Personal Social Services perspective) and QALYs were calculated for each alternative strategy. These long-term consequences were estimated based on the accuracy of the different testing strategies followed by AMI treatment or discharge from the hospital without AMI treatment for patients presenting at the ED with suspected NSTE-ACS, including patients with NSTEMI and patients without NSTEMI, who are further subdivided into 'no ACS, no UA' and 'UA'. For this purpose, a decision tree and a state–transition model were developed. The decision tree was used to model the 30-day outcomes after presentation, based on test results and the accompanying treatment decision. These outcomes consisted of 'no ACS, no UA', 'UA', 'non-fatal AMI (untreated)', 'non-fatal AMI (treated)' and 'death'. The decision tree is shown in *Figure 11* and the state–transition model is shown in *Figure 12*.

The long-term consequences in terms of costs and QALYs were estimated using a state–transition cohort model (see *Figure 15*) with a lifetime time horizon (60 years). The cycle time was 1 year, except for the first cycle, which was adjusted to 335.25 days (i.e. 365.25 days – 30 days) to ensure that the decision tree period (30 days) and the first cycle summed to 1 year. The following health states were included:

- no ACS and no UA
- UA
- post AMI (treated and untreated)
- post AMI with reinfarction
- death.

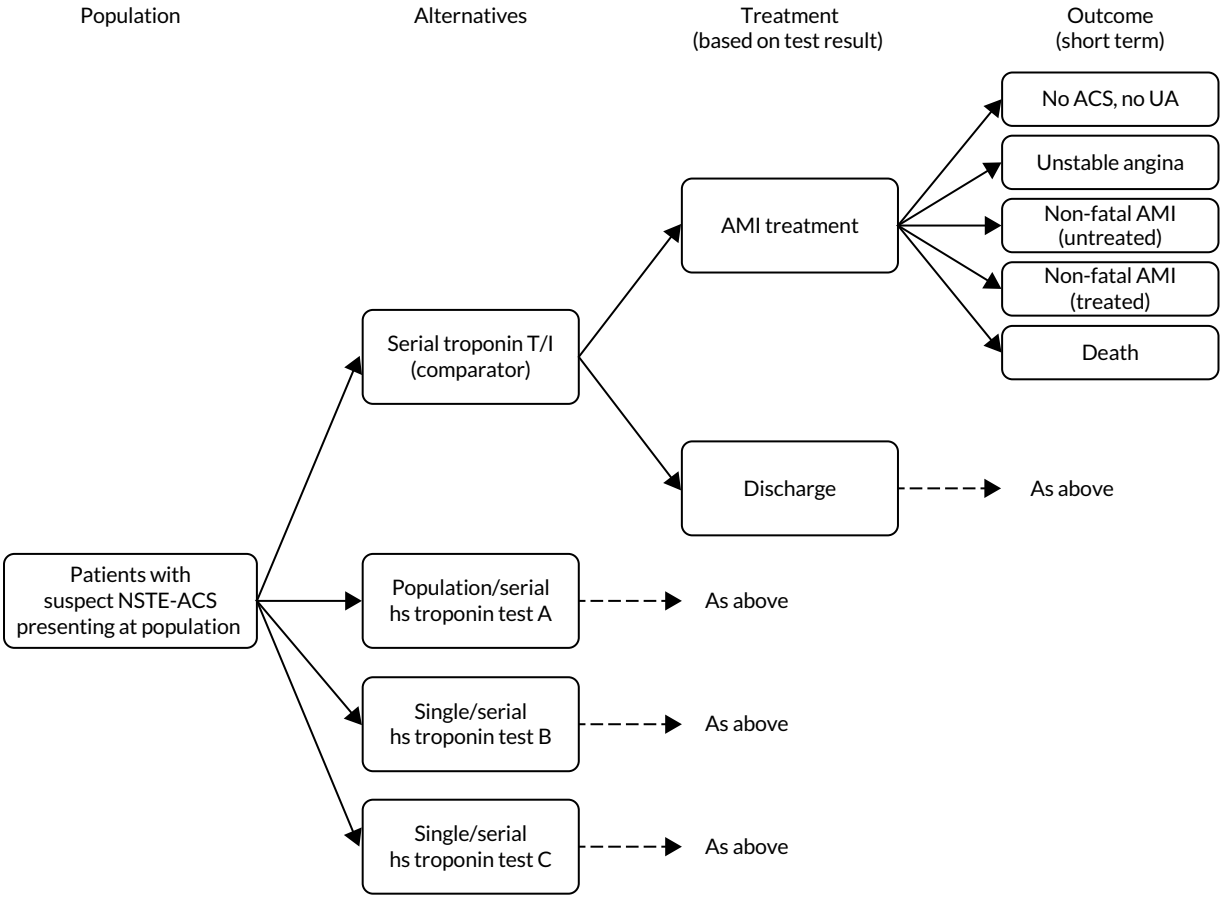

FIGURE 11 Decision tree structure.

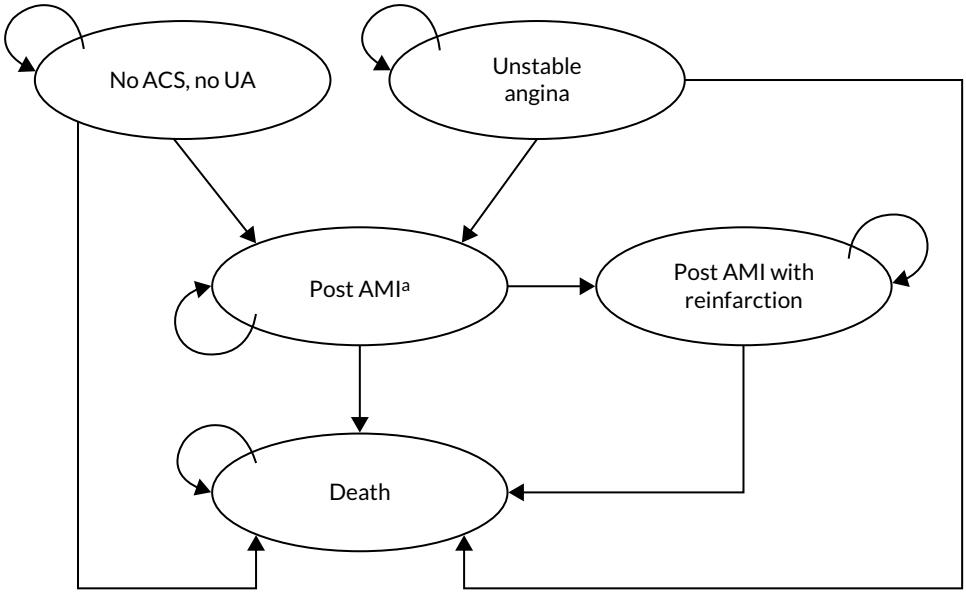

FIGURE 12 State–transition model structure. During the first year post AMI a distinction is made between treated and untreated AMI.

In short, patients presenting at the ED with suspected NSTEMI were classified as TP, FP, FN or TN. TP patients were considered to be correctly treated for AMI, whereas TNs were considered not to be treated for AMI (TN patients can be with or without UA). FP patients were considered to be those who have no AMI, but who did not meet early rule-out criteria. It was assumed that FP patients would remain in the hospital longer (i.e. as long as it would take for the standard troponin test results to become available), but would not be treated for AMI. Consequently, the life expectancy and quality of life for FP patients was, in the base-case analysis, equal to the life expectancy and quality of TN patients. Finally, FN patients were assumed to have untreated AMI with consequently increased reinfarction and mortality probabilities for 1 year.

Model parameters

Estimates for the model input parameters were retrieved from the literature and by consulting experts. Accuracy estimates were derived from the systematic review component of this assessment (see *Chapter 3*).

Transition probabilities

An overview of transition probabilities is provided in *Table 23*.

TABLE 23 Transition probabilities

Transition probability	Estimate	SE/95% CI	Distribution	Source
Decision tree (short term)				
Proportion of AMI of all chest pain emergency admissions	0.199	0.001	Beta	HES[5]
Proportion of NSTEMIs of all confirmed cases of heart attack	0.613	0.002	Beta	Healthcare Quality Improvement Programme[202]
NSTEMI prevalence[a]	0.122			Calculated
Proportion of UA (of all non-NSTEMI patients)	0.160	0.038	Beta	CADTH report[186]

TABLE 23 Transition probabilities (*continued*)

Transition probability	Estimate	SE/95% CI	Distribution	Source
Decision tree (30-day) probabilities				
Mortality: treated AMI	0.097	0.012	Beta	Pope *et al.*[203]
Mortality: untreated AMI	0.105	0.069	Beta	Pope *et al.*[203]
Mortality: treated UA	0.021	0.005	Beta	Pope *et al.*[203]
Mortality: no ACS	[b]		Fixed	ONS[204]
State–transition model (long term)				
AMI incidence	[c]		Fixed	British Heart Foundation[205]
Annual reinfarction (treated)[d]	0.023	0.001	Beta	Smolina *et al.*[206]
RR reinfarction (untreated vs. treated)[e]	2.568	1.366 to 5.604	Log-normal	Mills *et al.*[187]
Annual mortality no ACS	[b]		Fixed	ONS[204]
Annual mortality post MI[d]	0.066	0.000	Beta	Smolina *et al.*[206]
Annual mortality post reinfarction[d]	0.142	0.002	Beta	Smolina *et al.*[206]
HR mortality (UA vs. NSTEMI)	0.781	0.581 to 1.053	Log-normal	Allen *et al.*[207]
RR mortality (untreated vs. treated)[d]	1.877	0.951 to 4.239	Log-normal	Mills *et al.*[187]
Secondary analysis (adjusted RR for patients tested FP)				
OR: AMI[f]	1.210	0.830 to 1.760	Log-normal	Liplinski *et al.*[201]
OR: death[f]	1.600	1.140 to 2.240	Log-normal	Liplinski *et al.*[201]
Proportion of AMI[g]	0.109	0.011	Beta	Liplinski *et al.*[201]
Proportion of death[g]	0.110	0.011	Beta	Liplinski *et al.*[201]
RR: AMI[f,h]	0.842		Calculated	Liplinski *et al.*[201]
RR: death[f,h]	0.652		Calculated	Liplinski *et al.*[201]

HR, hazard ratio; ONS, Office for National Statistics; RR, relative risk; SE, standard error.
a Prevalence was used to calculate the proportions of TPs, FPs, TNs and TPs based on test accuracy.
b Based on age-dependent mortality from the general population.
c Age-dependent incidence from the general population.
d Weighted average based on gender (58.1% males).[185]
e Increased reinfarction and mortality risk for untreated (vs. treated) was assumed for the first year after presentation at ED, after which no increased risk was assumed (RR 1.0).
f For patients with both positive hs-cTn and standard troponin tests vs. patients with positive hs-cTn and negative standard troponin tests.
g Proportion for patients with both positive hs-cTn and standard troponin tests. This proportion is used only to convert ORs to RRs.
h ORs were converted to RRs using the method described by Zhang and Yu.[208]

Decision tree

The proportions of patients testing positive or negative (and therefore commencing AMI treatment or being discharged from the hospital) were based on the estimated accuracy of the testing strategies considered (*Table 24*) and the estimated prevalence of NSTEMI in the UK (12.2%) (see *Table 23*). The proportion of TPs, FPs, FNs and TNs were calculated (*Table 25*) as follows:

- TP = NSTEMI prevalence × sensitivity.
- FP = (1 – NSTEMI prevalence) × (1 – specificity).
- FN = NSTEMI prevalence × (1 – sensitivity).
- TN = (1 – NSTEMI prevalence) × specificity.

TABLE 24 Test accuracy

Test strategy	Sensitivity (SE)[a]	Specificity (SE)[a]	Distribution	Source
Standard troponin (at presentation and after 10–12 hours)	1.00 (–)	1.00 (–)	Fixed	Assumption
1. Roche Elecsys hs-cTnT: 99th centile	1.00 (0.03)	0.77 (0.08)	Multivariate normal	See *Chapter 3*
2. Roche Elecsys hs-cTnT: LoD	0.99 (0.01)	0.35 (0.05)	Multivariate normal	See *Chapter 3*
3. Roche Elecsys hs-cTnT: ESC pathway	0.99 (0.01)	0.68 (0.01)	Multivariate normal	See *Chapter 3*
4. Roche Elecsys hs-cTnT (< 8 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 0.5 hours)	1.00 (0.02)	0.45 (0.02)	Multivariate normal	See *Chapter 3*
5. Roche Elecsys hs-cTnT: (< 12 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours)	0.98 (0.01)	0.73 (0.01)	Multivariate normal	See *Chapter 3*
6. Siemens Dimension Vista hs-cTnI: (< 5 ng/l at 0 hours AND Δ < 2 ng/l at 0 to 1 hours)	1.00 (0.02)	0.66 (0.02)	Multivariate normal	See *Chapter 3*
7. Abbott ARCHITECT hs-cTnI: LoD	1.00 (0.00)	0.21 (0.03)	Multivariate normal	See *Chapter 3*
8. Abbott ARCHITECT hs-cTnI: ESC pathway	0.99 (0.00)	0.57 (0.01)	Multivariate normal	See *Chapter 3*
9. Abbott ARCHITECT hs-cTnI: High-STEACS pathway	0.99 (0.01)	0.76 (0.01)	Multivariate normal	See *Chapter 3*
10. Abbott ARCHITECT hs-cTnI: < 4 ng/l at 0 hours	0.99 (0.01)	0.50 (0.01)	Multivariate normal	See *Chapter 3*
11. Siemens ADVIA Centaur hs-cTnI: < 2 ng/l at 0 hours	1.00 (0.00)	0.23 (0.01)	Multivariate normal	See *Chapter 3*
12. Siemens ADVIA Centaur hs-cTnI: [< 3 ng/l at 0 hours OR (< 8 ng/l at 0 hours AND Δ < 7 ng/l at 0 to 2 hours)]	1.00 (0.01)	0.67 (0.03)	Multivariate normal	See *Chapter 3*
13. Siemens ADVIA Centaur hs-cTnI: ESC pathway	0.99 (0.01)	0.56 (0.02)	Multivariate normal	See *Chapter 3*
14. Siemens ADVIA Centaur hs-cTnI: < 5 ng/l at 0 hours	0.99 (0.01)	0.52 (0.01)	Multivariate normal	See *Chapter 3*
15. Siemens Atellica hs-cTnI: < 2 ng/l at 0 hours	1.00 (0.01)	0.26 (0.01)	Multivariate normal	See *Chapter 3*
16. Siemens Atellica hs-cTnI: High-STEACS pathway	0.98 (0.01)	0.74 (0.01)	Multivariate normal	See *Chapter 3*
17. Beckman Coulter ACCESS hs-cTnI: ESC pathway	0.99 (0.02)	0.70 (0.02)	Multivariate normal	See *Chapter 3*
18. Beckman Coulter ACCESS hs-cTnI: [(symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 5 ng/l at 0 to 2 hours)]	0.98 (0.02)	0.83 (0.01)	Multivariate normal	See *Chapter 3*
19. Ortho VITROS hs-cTnI: ESC pathway	1.00 (0.01)	0.60 (0.02)	Multivariate normal	See *Chapter 3*
20. bioMérieux VIDAS hs-cTnI: [< 2 ng/l at 0 hours OR (< 6 ng/l at 0 AND 2 hours)]	0.98 (0.02)	0.64 (0.02)	Multivariate normal	See *Chapter 3*
21. Quidel TriageTrue hs-cTnI: ESC pathway	1.00 (0.01)	0.66 (0.02)	Multivariate normal	See *Chapter 3*

SE, standard error.

a Correlation between sensitivity and specificity was calculated to be –0.655 based on the covariance matrix from the output for Roche Elecsys hs-cTnT LoD (see *Chapter 3*). This correlation was assumed to be equal for other tests.

TABLE 25 Test outcomes

Test strategy	TP	FP	FN	TN	PPV	NPV
Standard troponin (at presentation and after 10–12 hours)	0.12	0.00	0.00	0.88	1.00	1.00
1. Roche Elecsys hs-cTnT: 99th centile	0.12	0.20	0.00	0.68	0.38	1.00
2. Roche Elecsys hs-cTnT: LoD	0.12	0.57	0.00	0.31	0.18	1.00
3. Roche Elecsys hs-cTnT: ESC pathway	0.12	0.28	0.00	0.60	0.30	1.00
4. Roche Elecsys hs-cTnT: (< 8 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 0.5 hours)	0.12	0.48	0.00	0.40	0.20	1.00
5. Roche Elecsys hs-cTnT: (< 12 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours)	0.12	0.24	0.00	0.64	0.33	1.00
6. Siemens Dimension Vista hs-cTnI: (< 5 ng/l at 0 hours AND Δ < 2 ng/l at 0 to 1 hours)	0.12	0.30	0.00	0.58	0.29	1.00
7. Abbott ARCHITECT hs-cTnI: LoD	0.12	0.69	0.00	0.18	0.15	1.00
8. Abbott ARCHITECT hs-cTnI: ESC pathway	0.12	0.38	0.00	0.50	0.24	1.00
9. Abbott ARCHITECT hs-cTnI: High-STEACS pathway	0.12	0.21	0.00	0.67	0.36	1.00
10. Abbott ARCHITECT hs-cTnI: < 4 ng/l at 0 hours	0.12	0.44	0.00	0.44	0.22	1.00
11. Siemens ADVIA Centaur hs-cTnI: < 2 ng/l at 0 hours	0.12	0.68	0.00	0.20	0.15	1.00
12. Siemens ADVIA Centaur hs-cTnI: [< 3 ng/l at 0 hours OR (< 8 ng/l at 0 hours AND Δ < 7 ng/l at 0 to 2 hours)]	0.12	0.29	0.00	0.59	0.30	1.00
13. Siemens ADVIA Centaur hs-cTnI: ESC pathway	0.12	0.39	0.00	0.49	0.24	1.00
14. Siemens ADVIA Centaur hs-cTnI: < 5 ng/l at 0 hours	0.12	0.42	0.00	0.46	0.22	1.00
15. Siemens Atellica hs-cTnI: < 2 ng/l at 0 hours	0.12	0.65	0.00	0.23	0.16	1.00
16. Siemens Atellica hs-cTnI: High-STEACS pathway	0.12	0.23	0.00	0.65	0.34	1.00
17. Beckman Coulter ACCESS hs-cTnI: ESC pathway	0.12	0.26	0.00	0.61	0.31	1.00
18. Beckman Coulter ACCESS hs-cTnI: [(symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 5 ng/l at 0 to 2 hours)]	0.12	0.15	0.00	0.73	0.45	1.00
19. Ortho VITROS hs-cTnI: ESC pathway	0.12	0.35	0.00	0.53	0.26	1.00
20. bioMérieux VIDAS hs-cTnI: [< 2 ng/l at 0 hours OR (< 6 ng/l at 0 AND 2 hours)]	0.12	0.32	0.00	0.56	0.27	1.00
21. Quidel TriageTrue hs-cTnI: ESC pathway	0.12	0.30	0.00	0.58	0.29	1.00

NPV, negative predictive value; PPV, positive predictive value.

After treatment, TP patients in the decision tree were allocated to 'non-fatal AMI (treated)' and FP patients were further subdivided between 'no ACS, no UA' and 'UA' (based on the proportion of UA among non-NSTEMI patients) (see *Table 23*). After being discharged, TN patients were also subdivided between 'no ACS, no UA' and 'UA', whereas FN patients were allocated to 'non-fatal AMI (untreated)'. The proportions of FNs (reported in *Table 25*) can be considered as the proportion of AMIs that would have been missed when assuming that standard troponin testing had perfect accuracy. Finally, to calculate the total number of deaths in the decision tree, the probability of 30-day mortality was assigned based on above mentioned subdivision (see *Table 23*). It was assumed that UA was always correctly diagnosed and therefore the mortality probability for treated UA was used.

State–transition model

The age-dependent AMI incidence in the UK[205] was used to model the occurrence of AMI for patients in the health states 'no ACS,' and 'UA'. It was assumed that all AMIs in the state–transition model were diagnosed correctly and therefore received treatment. For patients in the 'post-MI' health state, the probability of reinfarction after treated AMI was retrieved from a UK record linkage study ($n = 387,452$) that assessed long-term survival and recurrence after AMI.[206] For this purpose, the probabilities for females and males were weighted according to the estimated proportion of females and males in the population (males = 58.1%).[185] The reinfarction probability for the 'post-MI with reinfarction' health state is equal to the reinfarction probability for the 'post-MI' health state. The reinfarction relative risk (RR) for people with untreated compared with treated AMI was calculated from a study by Mills *et al.*[187] and based on patients with a troponin concentration of 5–19 ng/l. This RR was assumed for the first year after presentation at ED only, after which no increased risk was assumed (i.e. RR equals 1.0 for untreated vs. treated AMI after year 1).

Age-dependent mortality from the general population was used for patients in the 'no ACS, no UA' health state.[204] For the 'post-MI' and 'post-MI with reinfarction' health states, mortality was extracted from the record linkage study.[206] Again, the study by Mills *et al.*[187] was used to calculate the mortality RR for untreated compared with treated AMI for the first year, after which an RR of 1.0 was used. Finally, a multivariate adjusted mortality hazard ratio for UA compared with NSTEMI was retrieved from a study by Allen *et al.*[207] to calculate mortality after UA.

All input parameters for the state–transition model are reported in *Table 23*.

Health state utilities

Age-dependent utility scores from the UK general population were calculated for patients in the 'no ACS, no UA' health state based on a linear regression model.[189] These age-dependent utility scores were combined with age-dependent disutilities for AMI[186] to calculate utilities for the 'post-MI' health states (with or without reinfarction). Utility scores for the 'UA' health state were calculated based on post-MI utility scores and a utility increment of 0.010[189] (*Table 26*).

Resource use and costs

Test-specific resource use consisted of the number of tests performed and the duration of hospital stay (hours) before discharge/AMI treatment (*Table 27*). For test strategies that involved a subsequent test conditional on the outcomes of the first test, the rule-out rate for the presentation sample was used to calculate number of subsequent tests.

TABLE 26 Utility scores

Utility score	Estimate	SE	Distribution	Source
No ACS, no UA				
Intercept	1.060	0.029	Normal	Ward *et al.*[189]
Disutility for age	0.004	0.001	Normal	Ward *et al.*[189]
Post MI (disutility vs. no ACS by age in years)				
45	0.060	0.001	Normal	Ward *et al.*[189]
55	0.051	0.001	Normal	Ward *et al.*[189]
65	0.025	0.001	Normal	Ward *et al.*[189]
75	0.007	0.001	Normal	Ward *et al.*[189]
UA				
Utility increment vs. AMI	0.010	0.042	Normal	Ward *et al.*[189]

SE, standard error.

TABLE 27 Resource use (test specific)

Test	Estimate	Range	Distribution	Source
Number of tests				
Standard troponin (at presentation and after 10–12 hours)	2.00		Fixed	Assumption
1. Roche Elecsys hs-cTnT: 99th centile	2.00		Fixed	Assumption
2. Roche Elecsys hs-cTnT: LoD	1.00		Fixed	Assumption
3. Roche Elecsys hs-cTnT: ESC pathway	1.75		Fixed	Assumption
4. Roche Elecsys hs-cTnT: (< 8 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 0.5 hours)	2.00		Fixed	Assumption
5. Roche Elecsys hs-cTnT: (< 12 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours)	2.00		Fixed	Assumption
6. Siemens Dimension Vista hs-cTnI: (< 5 ng/l at 0 hours AND Δ < 2 ng/l at 0 to 1 hours)	2.00		Fixed	Assumption
7. Abbott ARCHITECT hs-cTnI: LoD	1.00		Fixed	Assumption
8. Abbott ARCHITECT hs-cTnI: ESC pathway	1.62		Fixed	Assumption
9. Abbott ARCHITECT hs-cTnI: High-STEACS pathway	1.41		Fixed	Assumption
10. Abbott ARCHITECT hs-cTnI: < 4 ng/l at 0 hours	1.00		Fixed	Assumption
11. Siemens ADVIA Centaur hs-cTnI: < 2 ng/l at 0 hours	1.84		Fixed	Assumption
12. Siemens ADVIA Centaur hs-cTnI: [< 3 ng/l at 0 hours OR (< 8 ng/l at 0 hours AND Δ < 7 ng/l at 0 to 2 hours)]	1.84		Fixed	Assumption
13. Siemens ADVIA Centaur hs-cTnI: ESC pathway	2.00		Fixed	Assumption
14. Siemens ADVIA Centaur hs-cTnI: < 5 ng/l at 0 hours	1.00		Fixed	Assumption
15. Siemens Atellica hs-cTnI: < 2 ng/l at 0 hours	1.00		Fixed	Assumption
16. Siemens Atellica hs-cTnI: High-STEACS pathway	1.70		Fixed	Assumption
17. Beckman Coulter ACCESS hs-cTnI: ESC pathway	1.68		Fixed	Assumption
18. Beckman Coulter ACCESS hs-cTnI: [(symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l and Δ < 5 ng/l at 0 to 2 hours)]	1.68		Fixed	Assumption
19. Ortho VITROS hs-cTnI: ESC pathway	1.82		Fixed	Assumption
20. bioMérieux VIDAS hs-cTnI: [< 2 ng/l at 0 hours OR (< 6 ng/l at 0 AND 2 hours)]	1.67		Fixed	Assumption
21. Quidel TriageTrue hs-cTnI: ESC pathway	1.55		Fixed	Assumption
Hospital stay (hours) before discharge/AMI treatment[a]				
Standard troponin (at presentation and after 10–12 hours)	14	13–15	Beta PERT	Assumption
1. Roche Elecsys hs-cTnT: 99th centile	6		Fixed	Assumption
2. Roche Elecsys hs-cTnT: LoD	3		Fixed	Assumption
3. Roche Elecsys hs-cTnT: ESC pathway	4		Fixed	Assumption
4. Roche Elecsys hs-cTnT: (< 8 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 0.5 hours)	3.5		Fixed	Assumption
5. Roche Elecsys hs-cTnT: (< 12 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours)	4		Fixed	Assumption
6. Siemens Dimension Vista hs-cTnI: (< 5 ng/l at 0 hours AND Δ < 2 ng/l at 0 to 1 hours)	4		Fixed	Assumption
7. Abbott ARCHITECT hs-cTnI: LoD	3		Fixed	Assumption

continued

TABLE 27 Resource use (test specific) (*continued*)

Test	Estimate	Range	Distribution	Source
8. Abbott ARCHITECT hs-cTnI: ESC pathway	4		Fixed	Assumption
9. Abbott ARCHITECT hs-cTnI: High-STEACS pathway	6		Fixed	Assumption
10. Abbott ARCHITECT hs-cTnI: < 4 ng/l at 0 hours	3		Fixed	Assumption
11. Siemens ADVIA Centaur hs-cTnI: < 2 ng/l at 0 hours	3		Fixed	Assumption
12. Siemens ADVIA Centaur hs-cTnI: [< 3 ng/l at 0 hours OR (< 8 ng/l at 0 hours AND Δ < 7 ng/l at 0 to 2 hours)]	5		Fixed	Assumption
13. Siemens ADVIA Centaur hs-cTnI: ESC pathway	4		Fixed	Assumption
14. Siemens ADVIA Centaur hs-cTnI: < 5 ng/l at 0 hours	3		Fixed	Assumption
15. Siemens Atellica hs-cTnI: < 2 ng/l at 0 hours	3		Fixed	Assumption
16. Siemens Atellica hs-cTnI: High-STEACS pathway	6		Fixed	Assumption
17. Beckman Coulter ACCESS hs-cTnI: ESC pathway	4		Fixed	Assumption
18. Beckman Coulter ACCESS hs-cTnI: [(symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 5 ng/l at 0 to 2 hours)]	5		Fixed	Assumption
19. Ortho VITROS hs-cTnI: ESC pathway	4		Fixed	Assumption
20. bioMérieux VIDAS hs-cTnI: [< 2 ng/l at 0 hours OR (< 6 ng/l at 0 AND 2 hours)]	5		Fixed	Assumption
21. Quidel TriageTrue hs-cTnI: ESC pathway	4		Fixed	Assumption

a Includes delay from the time at which sampling could be performed to the time at which results became available (2 hours), and delay between arrival at hospital and troponin assessment commencing (1 hour).

Health state costs were retrieved from a study published by Danese *et al.*,[209] which was a retrospective cohort study using Clinical Practice Research Datalink records to identify UK individuals who had their first cardiovascular event between 2006 and 2012. Direct medical costs were estimated for 24,093 patients.

Additionally, costs of fatal events were accumulated for all fatal AMIs. For this purpose, it was assumed that all 30-day deaths after 'true' NSTEMIs were due to a fatal AMI event. To calculate the hospital stay costs for patients, based on the number of hours before the test results become available, non-elective inpatient stays (i.e. short stays) were retrieved from the Personal Social Services Research Unit and divided by 24 (to calculate hourly costs). For the calculation of hospital stay duration, it was assumed that doctors were available on demand and the time to discharge was delayed because of the time between arrival at the ED and the start of first sampling (1 hour), and the time between sampling and the results being available (2 hours). In the case of multiple testing, the 1-hour delay between arrival at the ED and start of sampling was applied to the first test only; however, this also affected the timing of the second test, if applicable. The 2-hour delay before test results become available applies to all tests performed.

Although information was provided by test manufacturers to calculate test-dependent costs, based on clinical expert input, it was assumed that the costs per test would be identical for all tests (i.e. £2.50, which is consistent with the test cost information submitted by the manufacturers), except for the point-of-care test (i.e. Quidel). For this test, we assumed a cost of £25.00 (based on cost information submitted by the manufacturers). However, scenario analyses were performed using test-specific costs. For these scenario analyses it should be noted that the information received from the manufacturers did not allow us to incorporate costs related to the analyser (e.g. capital, service, maintenance and training costs) nor the personnel costs (implicitly assuming that these costs would be identical for all test strategies).

All costs were inflated to the 2018–19 price level (*Table 28*).

TABLE 28 Health state costs, event costs and unit prices

Cost	Estimate (£)	SE/range (£)	Distribution	Source
Health state costs				
No ACS, no UA first year	2403.70	175.36	Gamma	Danese *et al.*[209]
No ACS, no UA subsequent year	2403.70	175.36	Gamma	Danese *et al.*[209]
UA first year	4427.02	74.54	Gamma	Danese *et al.*[209]
UA subsequent year	2208.02	69.16	Gamma	Danese *et al.*[209]
Post MI first year	6865.23	151.42	Gamma	Danese *et al.*[209]
Post MI subsequent years	2493.13	176.95	Gamma	Danese *et al.*[209]
Post re-MI first year	8197.80	611.91	Gamma	Danese *et al.*[209]
Post re-MI subsequent years	4123.37	968.43	Gamma	Danese *et al.*[209]
Event costs				
AMI treatment costs	2496.48		Fixed	*NHS Reference Costs 2017–18*[210]
Costs of fatal AMI	1539.75	10.56	Gamma	Walker *et al.*[211]
Unit prices				
Hospital stay costs (per hour)[c]	26.08		Fixed	PSSRU[212]
Test costs[a]	2.50	1.85–6.00	Beta PERT	Expert opinion, information submitted by manufacturer and assumptions
Test costs (point of care)	25.00	1.85–26.00	Beta PERT	

PSSRU, Personal Social Services Research Unit; SE, standard error.

Overview of main model assumptions

The main assumptions in the health economic analyses are as follows.

- Serial troponin testing (comparator) has perfect accuracy (sensitivity = 1.0 and specificity = 1.0).
- The life expectancy, quality of life and cost for FP patients is, in the base-case analysis, equal to the life expectancy, quality of life and cost of TN patients. This assumption was amended in the secondary and sensitivity analyses.
- In contrast with AMIs occurring during the decision tree period, all AMIs (either first or reinfarction) occurring in the state–transition model are diagnosed correctly and therefore treated.
- UA is always correctly diagnosed and therefore treated.
- The reinfarction probability for the 'post MI with reinfarction' health state is equal to the reinfarction probability for the 'post-MI' health state.
- The increased post-MI reinfarction and mortality probabilities for untreated AMI were assumed to last 1 year and afterwards a RR of 1.0 was applied (for untreated vs. treated AMI).
- There is no additional benefit of starting treatment early and so treatment effect for high-sensitive strategies is equal to treatment effect for standard troponin strategy.
- All 30-day deaths (after presentation at the ED) are due to fatal AMI events and will receive the associated costs.

Model analyses

Expected costs, life-years and QALYs were estimated for all strategies. Discount rates of 3.5% and a half-cycle correction were applied for both costs and effects. Incremental cost and QALYs for each strategy compared with standard troponin and with the next best alternative were calculated. The ICER was then calculated by dividing the incremental costs by the incremental QALYs. PSAs (10,000 simulations) were performed and cost-effectiveness acceptability curves (CEACs) were constructed.

Secondary analysis

For the base case, it was assumed that patients who tested negative on standard troponin and positive on hs-cTn tests would experience life expectancy and quality of life equal to TN patients. This assumption is, however, debatable. A meta-analysis by Liplinski *et al.*[201] showed that patients with a negative standard troponin test and positive hs-cTn test have an increased risk of (re)infarction and mortality compared with those who test negative on both the standard troponin and hs-cTn tests. Although this risk was not as high as in patients with both positive standard troponin and positive hs-cTn tests, it could still be considered prognostically important. Therefore, in this secondary analysis, the risk of MI and mortality was adjusted for patients who tested FP (see *Table 23*). It was assumed for this proportion of patients that the relative treatment benefit would be equal to that for TP patients. As the prevalence of this 'higher-risk subgroup' is likely to be the same for all comparators, it was assumed that this proportion was equal to the lowest proportion of FP patients for all hs-cTn tests (0.15) (see *Table 25*). This 'higher-risk subgroup' was assumed to be treated for all hs-cTn tests (as they tested positive with these tests) and untreated for the standard troponin test (as they tested negative with this test), therefore affecting the probability of adverse outcomes (according to the RR of reinfarction and mortality) (see *Table 23*) and treatment costs (see *Table 28*). In addition, the post-MI utility and health state costs were used for this 'higher-risk subgroup'.

Sensitivity and scenario analysis

For both the base-case and the secondary analyses, one-way sensitivity analyses were performed and included all probabilistic parameters (NHS reference costs were included by ± 20%), creating tornado diagrams for the relevant comparisons on the cost-effectiveness frontier. Additionally, the following scenario analyses were performed.

- AMI treatment costs (£2496 based on NHS reference costs) are applied for patients who tested FP rather than using no treatment costs, as assumed in the base-case analysis.
- The assumption that the increased post AMI reinfarction and mortality probabilities for untreated AMI lasts for only 1 year was replaced by the assumption that these probabilities would remain elevated for a lifetime.
- The assumption of equal test costs was relaxed and test-dependent costs were incorporated (based on the information provided by manufacturers). The assay-specific test costs were (unit price per test):

    - Roche Elecsys hs-TnT – £6.05
    - Abbott ARCHITECT hs-TnI – £4.17
    - Siemens ADVIA Centaur hs-TnI – £2.00
    - Siemens Atellica hs-TnI – £2.00
    - Siemens Dimension Vista hs-TnI – £2.00
    - Beckman Coulter ACCESS hs-TnI – £2.75
    - Ortho VITROS hs-TnI – £1.85
    - BioMérieux VIDAS hs-TnI – £6.05
    - Quidel TriageTrue hs-TnI (point of care) – £25.00.

In addition to the abovementioned scenario analyses, the base-case and secondary analyses results were also considered in comparing different strategies per assay (in case of multiple strategies).

Results of cost-effectiveness analyses

This section describes the results using deterministic and probabilistic analyses for the base-case analysis and the secondary analysis. Scenario analyses (deterministic) and sensitivity analyses are described here and results of these are presented in tabulated form in *Appendices 6* and *7*.

Base-case analysis

The base-case analysis includes 22 test strategies. *Tables 29* and *30* show the deterministic and probabilistic cost-effectiveness results of these comparisons, respectively. Standard troponin (at presentation and after 10–12 hours) testing was the most effective (probabilistic 15.5331 life-years; 12.0825 QALYs) and the most expensive strategy (£38,871). However, other testing strategies with a sensitivity of 100% (subject to uncertainty) were almost equally as effective, resulting in the same life-year and QALY gain at up to four decimal places. These were (starting with the cheapest) Siemens Dimension Vista hs-cTnI (< 5 ng/l at 0 hours AND Δ < 2 ng/l at 0 to 1 hours); Ortho VITROS hs-cTnI [ESC 0/1-hour pathway: (symptoms > 3 hours AND < 1 ng/l at 0 hours) OR (< 2 ng/l at 0 hours AND Δ < 1 ng/l at 0 to 1 hours)]; Siemens ADVIA Centaur hs-cTnI [< 3 ng/l at 0 hours OR (< 8 ng/l at 0 hours AND Δ < 7 ng/l at 0 to 2 hours)]; Roche Elecsys hs-cTnT [99th centile threshold (< 14 ng/l at 0 hours AND 3 hours)]; Quidel TriageTrue hs-cTnI [ESC 0/1-hour pathway: (symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours)]; Roche Elecsys hs-cTnT (< 8 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 0.5 hours); Siemens Atellica hs-cTnI (< 2 ng/l at 0 hours); and Siemens ADVIA Centaur hs-cTnI (< 2 ng/l at 0 hours). Owing to the few differences in outcomes between these strategies, some of these appear to be on the cost-effectiveness frontier, even when they are not (*Figure 13*). The CEAC for the base-case analysis is shown in *Figure 14*.

TABLE 29 Deterministic results for base-case analysis: costs and QALYs

Strategy	Cost (£)	QALY	Compared with standard troponin			Full incremental ICER: Δ costs/ Δ QALYs
			Δ Costs (£)	Δ QALYs	Δ Costs/ Δ QALYs (£)	
18. Beckman Coulter ACCESS hs-cTnI: [(symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 5 ng/l at 0 to 2 hours)]	38,666	12.0763	−210	−0.0011	188,819	Cheapest
5. Roche Elecsys hs-cTnT: (< 12 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours)	38,669	12.0765	−206	−0.0009	218,065	Extendedly dominated
17. Beckman Coulter ACCESS hs-cTnI: ESC pathway	38,678	12.0768	−198	−0.0006	355,439	£22,200
3. Roche Elecsys hs-cTnT: ESC pathway	38,683	12.0768	−193	−0.0006	346,892	Dominated
6. Siemens Dimension Vista hs-cTnI: (< 5 ng/l at 0 hours AND Δ < 2 ng/l at 0 to 1 hours)	38,693	12.0774	−183	0.0000	328,961,202	£26,504
14. Siemens ADVIA Centaur hs-cTnI: < 5 ng/l at 0 hours	38,702	12.0768	−173	−0.0006	311,539	Dominated
16. Siemens Atellica hs-cTnI: High-STEACS pathway	38,704	12.0763	−171	−0.0011	154,010	Dominated
9. Abbott ARCHITECT hs-cTnI: High-STEACS pathway	38,705	12.0768	−171	−0.0006	307,326	Dominated
20. bioMérieux VIDAS hs-cTnI: [< 2 ng/l at 0 hours OR (< 6 ng/l at 0 AND 2 hours)]	38,705	12.0763	−171	−0.0011	153,650	Dominated

continued

TABLE 29 Deterministic results for base-case analysis: costs and QALYs (*continued*)

Strategy	Cost (£)	QALY	Compared with standard troponin			Full incremental ICER: Δ costs/ Δ QALYs
			Δ Costs (£)	Δ QALYs	Δ Costs/ Δ QALYs (£)	
19. Ortho VITROS hs-cTnI: ESC pathway	38,706	12.0774	−170	0.0000	305,073,895	Dominated
10. Abbott ARCHITECT hs-cTnI: < 4 ng/l at 0 hours	38,706	12.0767	−170	−0.0007	234,660	Dominated
8. Abbott ARCHITECT hs-cTnI: ESC pathway	38,708	12.0768	−168	−0.0006	302,200	Dominated
12. Siemens ADVIA Centaur hs-cTnI: [< 3 ng/l at 0 hours OR (< 8 ng/l at 0 hours AND Δ < 7 ng/l at 0 to 2 hours)]	38,709	12.0774	−167	0.0000	300,489,458	Dominated
1. Roche Elecsys hs-cTnT: 99th centile	38,709	12.0774	−167	0.0000	299,391,873	Dominated
13. Siemens ADVIA Centaur hs-cTnI: ESC pathway	38,711	12.0768	−165	−0.0006	296,376	Dominated
21. Quidel TriageTrue hs-cTnI: ESC pathway	38,726	12.0774	−149	0.0000	268,289,079	Dominated
4. Roche Elecsys hs-cTnT: (< 8 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 0.5 hours)	38,734	12.0774	−142	0.0000	254,650,046	Dominated
2. Roche Elecsys hs-cTnT: LoD	38,746	12.0769	−130	−0.0005	259,678	Dominated
15. Siemens Atellica hs-cTnI: < 2 ng/l at 0 hours	38,773	12.0774	−103	0.0000	185,244,726	Dominated
11. Siemens ADVIA Centaur hs-cTnI: < 2 ng/l at 0 hours	38,782	12.0774	−93	0.0000	167,886,624	Dominated
7. Abbott ARCHITECT hs-cTnI: LoD	38,784	12.0772	−92	−0.0002	550,577	Dominated
Standard troponin (at presentation and after 10–12 hours)	38,876	12.0774	0	0.0000	NA	£328,961,202

TABLE 30 Probabilistic results for base-case analysis: costs and QALYs

Strategy	Cost (£)	QALY	Compared with standard troponin			Full incremental ICER: Δ costs/ Δ QALYs
			Δ Costs (£)	Δ QALYs	Δ Costs/ Δ QALYs (£)	
18. Beckman Coulter ACCESS hs-cTnI: [(symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 5 ng/l at 0 to 2 hours)]	38,625	12.0768	−246	−0.0058	42,753	Cheapest
17. Beckman Coulter ACCESS hs-cTnI: ESC pathway	38,650	12.0790	−221	−0.0036	62,121	Extendedly dominated
3. Roche Elecsys hs-cTnT: ESC pathway	38,662	12.0798	−209	−0.0027	77,589	Extendedly dominated

TABLE 30 Probabilistic results for base-case analysis: costs and QALYs (*continued*)

Strategy	Cost (£)	QALY	Compared with standard troponin			Full incremental ICER: Δ costs/ Δ QALYs
			Δ Costs (£)	Δ QALYs	Δ Costs/ Δ QALYs (£)	
20. bioMérieux VIDAS hs-cTnI: [< 2 ng/l at 0 hours OR (< 6 ng/l at 0 AND 2 hours)]	38,662	12.0764	−209	−0.0061	34,307	Dominated
5. Roche Elecsys hs-cTnT: (< 12 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours)	38,663	12.0813	−208	−0.0012	169,682	£8455
14. Siemens ADVIA Centaur hs-cTnI: < 5 ng/l at 0 hours	38,678	12.0794	−193	−0.0032	60,899	Dominated
9. Abbott ARCHITECT hs-cTnI: High-STEACS pathway	38,681	12.0795	−190	−0.0030	63,659	Dominated
13. Siemens ADVIA Centaur hs-cTnI: ESC pathway	38,684	12.0791	−187	−0.0034	54,645	Dominated
6. Siemens Dimension Vista hs-cTnI: (< 5 ng/l at 0 hours AND Δ < 2 ng/l at 0 to 1 hours)	38,688	12.0825	−183	0.0000	36,842,603	£20,190
16. Siemens Atellica hs-cTnI: High-STEACS pathway	38,698	12.0811	−173	−0.0014	119,994	Dominated
10. Abbott ARCHITECT hs-cTnI: < 4 ng/l at 0 hours	38,699	12.0815	−171	−0.0010	169,198	Dominated
19. Ortho VITROS hs-cTnI: ESC pathway	38,701	12.0825	−170	0.0000	28,179,082	Dominated
8. Abbott ARCHITECT hs-cTnI: ESC pathway	38,702	12.0818	−169	−0.0007	233,736	Dominated
12. Siemens ADVIA Centaur hs-cTnI: [< 3 ng/l at 0 hours OR (< 8 ng/l at 0 hours AND Δ < 7 ng/l at 0 to 2 hours)]	38,704	12.0825	−167	0.0000	25,072,373	Dominated
1. Roche Elecsys hs-cTnT: 99th centile	38,706	12.0825	−165	0.0000	15,661,356	Dominated
21. Quidel TriageTrue hs-cTnI: ESC pathway	38,721	12.0825	−149	0.0000	28,167,521	Dominated
4. Roche Elecsys hs-cTnT: (< 8 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 0.5 hours)	38,729	12.0825	−142	0.0000	17,442,604	Dominated
2. Roche Elecsys hs-cTnT: LoD	38,738	12.0817	−132	−0.0008	169,952	Dominated
15. Siemens Atellica hs-cTnI: < 2 ng/l at 0 hours	38,768	12.0825	−103	0.0000	21,210,686	Extendedly dominated
11. Siemens ADVIA Centaur hs-cTnI: < 2 ng/l at 0 hours	38,777	12.0825	−94	0.0000	31,584,800	Extendedly dominated
7. Abbott ARCHITECT hs-cTnI: LoD	38,778	12.0823	−93	−0.0002	381,602	Dominated
Standard troponin (at presentation and after 10–12 hours)	38,871	12.0825	0	0.0000	NA	£36,842,603

NA, not applicable.

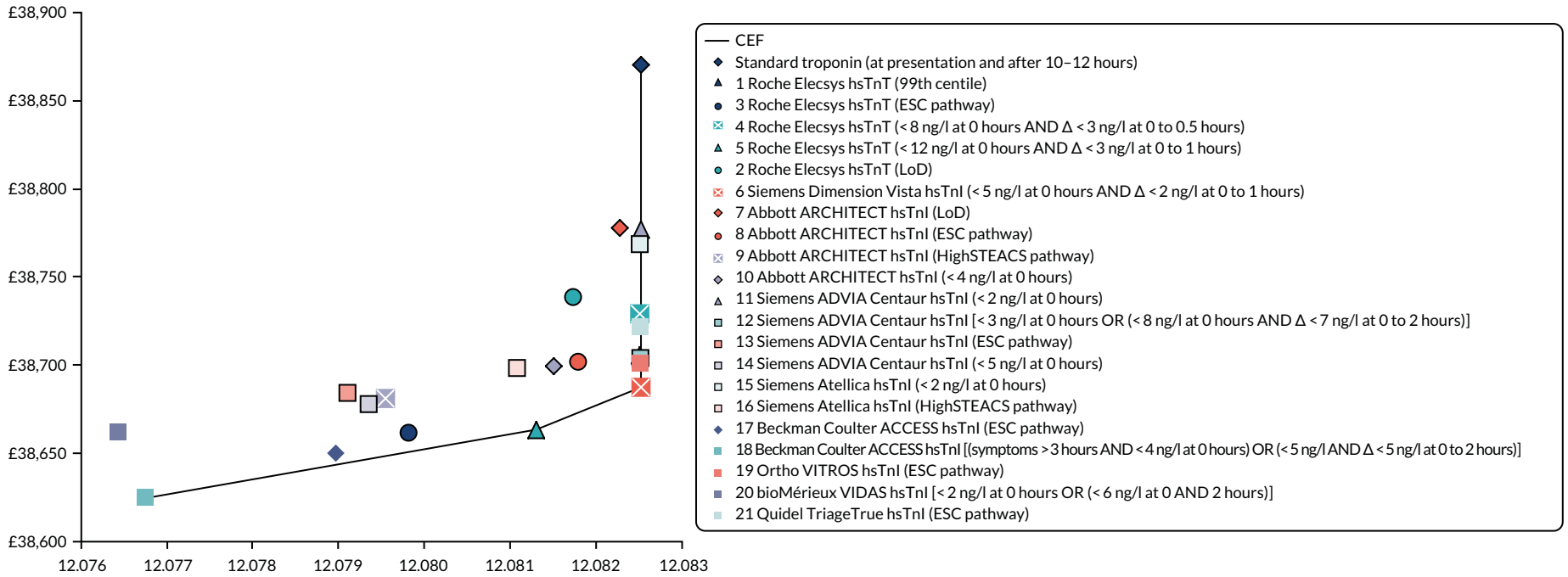

FIGURE 13 The cost-effectiveness frontier for the base-case analysis (based on PSA). CEF, cost-effectiveness frontier.

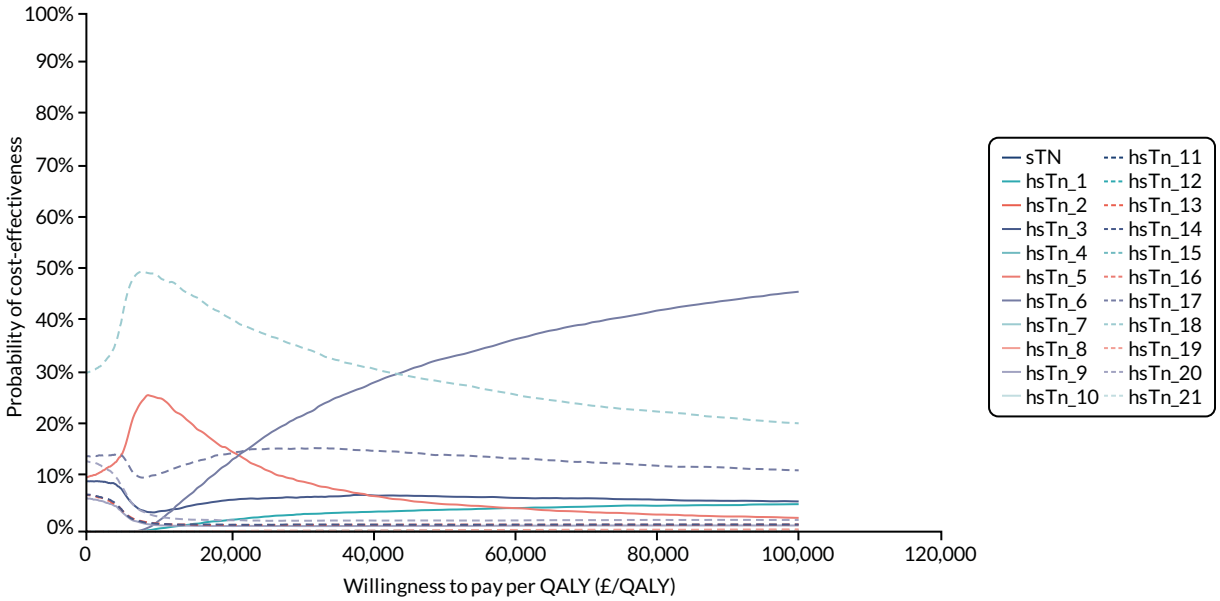

FIGURE 14 A CEAC for the base-case analysis.

Beckman Coulter ACCESS hs-cTnI (symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 5 ng/l at 0 to 2 hours), the test strategy with the highest specificity [83 (95% CI 81 to 86)], was the cheapest (probabilistic analysis £38,625), but it was also amongst the least effective (15.5254 life-years and 12.0768 QALYs), owing to a sensitivity of 98 (95% CI 92 to 100). Compared with standard troponin testing, hs-cTn testing resulted in probabilistic ICERs ranging between £34,307 and £36,842,603 savings per QALY lost.

Comparisons based on the next best alternative showed that for willingness-to-pay values < £8455 per QALY, the Beckman Coulter ACCESS hs-TnI [(symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 5 ng/l at 0 to 2 hours)] would be cost-effective. For willingness-to-pay thresholds between £8455 and £20,190 per QALY, the Roche Elecsys hs-TnT (< 12 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours) was cost-effective. For a willingness-to-pay threshold of > £20,190 per QALY, the Siemens Dimension Vista hs-TnI (< 5 ng/l at 0 hours AND Δ < 2 ng/l at 0 to 1 hours) would be cost-effective (see *Table 30*).

At a willingness-to-pay threshold of £20,000 and £30,000 per QALY, the Beckman Coulter ACCESS hs-cTnI [ESC 0/1 hour-pathway: (symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 4 ng/l at 0 to 1 hours)] had a probability of being cost-effective of 41% and 36%, respectively. At these thresholds, the Siemens Dimension Vista hs-cTnI (< 5 ng/l at 0 hours AND Δ < 2 ng/l at 0 to 1 hours) had a probability of being cost-effective of 13% and 22%, respectively.

Secondary analysis

The secondary analysis includes the same test strategies. This analysis assumed that in a proportion of patients with a FP hs-cTn test (i.e. positive hs-cTn test and a negative standard troponin test), there is prognostic significance [i.e. it is associated with an increased risk of adverse events (e.g. mortality and MI)], which can be reduced by testing positive using the hs-cTn test (*Tables 31* and *32*).

In the secondary analysis, standard troponin (at presentation and after 10–12 hours) was the cheapest (£37,517) and the least effective (11.334 QALYs) testing strategy (probabilistic analysis). Beckman Coulter ACCESS hs-cTnI [ESC 0/1-hour pathway: (symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 4 ng/l at 0 to 1 hours)] was the most effective testing strategy (11.4725 QALYs) at higher costs (£38,077). All other strategies were (extendedly) dominated. The ICER of Beckman Coulter ACCESS hs-cTnI [ESC 0/1-hour pathway: (symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 4 ng/l at 0 to 1 hours)] compared with standard troponin (at presentation and after 10–12 hours) was £4043 per QALY gained.

TABLE 31 Deterministic results for secondary analysis: costs and QALYs

Strategy	Cost (£)	QALY	Compared with standard troponin			Full incremental ICER: Δ costs/ΔQALYs
			Δ Cost (£)	Δ QALY	Δ Costs/Δ QALYs (£)	
Standard troponin (at presentation and after 10–12 hours)	37,503	11.3230	0	0.0000	NA	Cheapest
7. Abbott ARCHITECT hs-cTnI: LoD	38,017	11.4014	514	0.0784	6559	Extendedly dominated
15. Siemens Atellica hs-cTnI: < 2 ng/l at 0 hours	38,022	11.4064	519	0.0835	6216	Extendedly dominated
11. Siemens ADVIA Centaur hs-cTnI: < 2 ng/l at 0 hours	38,022	11.4035	519	0.0805	6445	Dominated
2. Roche Elecsys hs-cTnT: LoD	38,023	11.4147	520	0.0918	5668	Extendedly dominated
10. Abbott ARCHITECT hs-cTnI: < 4 ng/l at 0 hours	38,030	11.4291	527	0.1062	4967	Extendedly dominated
14. Siemens ADVIA Centaur hs-cTnI: < 5 ng/l at 0 hours	38,033	11.4313	530	0.1083	4894	Extendedly dominated
4. Roche Elecsys hs-cTnT: (< 8 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 0.5 hours)	38,042	11.4250	540	0.1020	5290	Dominated
8. Abbott ARCHITECT hs-cTnI: ESC pathway	38,054	11.4361	551	0.1132	4867	Extendedly dominated
13. Siemens ADVIA Centaur hs-cTnI: ESC pathway	38,054	11.4352	551	0.1122	4910	Dominated
19. Ortho VITROS hs-cTnI: ESC pathway	38,061	11.4396	559	0.1167	4789	Extendedly dominated
3. Roche Elecsys hs-cTnT: ESC pathway	38,063	11.4469	561	0.1239	4523	Extendedly dominated
5. Roche Elecsys hs-cTnT: (< 12 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours)	38,064	11.4510	562	0.1280	4387	Extendedly dominated
17. Beckman Coulter ACCESS hs-cTnI: ESC pathway	38,065	11.4488	562	0.1259	4465	Dominated
6. Siemens Dimension Vista hs-cTnI: (< 5 ng/l at 0 hours AND Δ < 2 ng/l at 0 to 1 hours)	38,067	11.4455	564	0.1225	4605	Dominated
20. bioMérieux VIDAS hs-cTnI: [< 2 ng/l at 0 hours OR (< 6 ng/l at 0 AND 2 hours)]	38,073	11.4424	570	0.1195	4771	Dominated
12. Siemens ADVIA Centaur hs-cTnI: [< 3 ng/l at 0 hours OR (< 8 ng/l at 0 hours AND Δ < 7 ng/l at 0 to 2 hours)]	38,086	11.4465	583	0.1235	4722	Dominated
18. Beckman Coulter ACCESS hs-cTnI: [(symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 5 ng/l at 0 to 2 hours)]	38,093	11.4610	590	0.1380	4278	£4278
21. Quidel TriageTrue hs-cTnI: ESC pathway	38,101	11.4455	598	0.1225	4880	Dominated
16. Siemens Atellica hs-cTnI: High-STEACS pathway	38,104	11.4522	601	0.1292	4650	Dominated
9. Abbott ARCHITECT hs-cTnI: High-STEACS pathway	38,110	11.4547	608	0.1317	4612	Dominated
1. Roche Elecsys hs-cTnT: 99th centile	38,118	11.4562	615	0.1333	4615	Dominated

NA, not applicable.

TABLE 32 Probabilistic results for secondary analysis: costs and QALYs

Strategy	Cost (£)	QALY	Compared with standard troponin			Full incremental ICER: Δ costs/ Δ QALYs
			Δ Costs (£)	Δ QALYs	Δ Costs/ Δ QALYs	
Standard troponin (at presentation and after 10–12 hours)	37,517	11.3340	0	0.0000	NA	Cheapest
14. Siemens ADVIA Centaur hs-cTnI: < 5 ng/l at 0 hours	38,039	11.4463	522	0.1123	4648	Extendedly dominated
7. Abbott ARCHITECT hs-cTnI: LoD	38,046	11.4201	529	0.0861	6148	Dominated
2. Roche Elecsys hs-cTnT: LoD	38,050	11.4328	532	0.0988	5389	Dominated
15. Siemens Atellica hs-cTnI: < 2 ng/l at 0 hours	38,051	11.4249	534	0.0909	5868	Dominated
11. Siemens ADVIA Centaur hs-cTnI: < 2 ng/l at 0 hours	38,051	11.4221	534	0.0881	6064	Dominated
10. Abbott ARCHITECT hs-cTnI: < 4 ng/l at 0 hours	38,055	11.4466	538	0.1126	4778	Extendedly dominated
13. Siemens ADVIA Centaur hs-cTnI: ESC pathway	38,057	11.4497	540	0.1157	4662	Extendedly dominated
20. bioMérieux VIDAS hs-cTnI: [< 2 ng/l at 0 hours OR (< 6 ng/l at 0 AND 2 hours)]	38,060	11.4547	543	0.1207	4500	Extendedly dominated
17. Beckman Coulter ACCESS hs-cTnI: ESC pathway	38,066	11.4628	548	0.1288	4258	Extendedly dominated
4. Roche Elecsys hs-cTnT: (< 8 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 0.5 hours)	38,070	11.4430	553	0.1089	5072	Dominated
3. Roche Elecsys hs-cTnT: ESC pathway	38,072	11.4619	555	0.1279	4337	Dominated
18. Beckman Coulter ACCESS hs-cTnI: [(symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 5 ng/l at 0 to 2 hours)]	38,077	11.4725	560	0.1385	4043	£4043
8. Abbott ARCHITECT hs-cTnI: ESC pathway	38,079	11.4535	562	0.1195	4699	Dominated
19. Ortho VITROS hs-cTnI: ESC pathway	38,087	11.4571	570	0.1231	4630	Dominated
5. Roche Elecsys hs-cTnT: (< 12 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours)	38,088	11.4678	570	0.1338	4263	Dominated
6. Siemens Dimension Vista hs-cTnI: (< 5 ng/l at 0 hours AND Δ < 2 ng/l at 0 to 1 hours)	38,092	11.4627	575	0.1287	4467	Dominated
12. Siemens ADVIA Centaur hs-cTnI: [< 3 ng/l at 0 hours OR (< 8 ng/l at 0 hours AND Δ < 7 ng/l at 0 to 2 hours)]	38,111	11.4636	594	0.1296	4580	Dominated
9. Abbott ARCHITECT hs-cTnI: High-STEACS pathway	38,115	11.4691	598	0.1351	4425	Dominated
21. Quidel TriageTrue hs-cTnI: ESC pathway	38,126	11.4627	609	0.1287	4729	Dominated
16. Siemens Atellica hs-cTnI: High-STEACS pathway	38,126	11.4689	609	0.1349	4517	Dominated
1. Roche Elecsys hs-cTnT: 99th centile	38,139	11.4718	622	0.1378	4514	Dominated

NA, not applicable.

At a willingness-to-pay threshold of £20,000 and £30,000 per QALY, the Beckman Coulter ACCESS hs-cTnI [ESC 0/1-hour pathway: (symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 4 ng/l at 0–1 hour)] had a probability of being cost-effective of 67% and 64%, respectively (*Figures 15* and *16*).

Scenario analyses

Three scenario analyses were performed deterministically and conditional on both the base-case and the secondary analyses. Results are shown in *Appendix 7*. Scenario 1 (see *Table 39* and *Figure 17*) assumed that patients who tested FP would receive treatment and a treatment cost would be incurred for these patients. In this scenario and conditional on the base case, the Beckman Coulter ACCESS hs-cTnI (symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 5 ng/l at 0 to 2 hours), the test strategy with the highest specificity [83 (95% CI 81 to 86)], was the cheapest. The Roche Elecsys hs-cTnT [99th centile threshold (< 14 ng/l at 0 hours AND 3 hours)] was cost-effective for thresholds > £57,659 per QALY gained and standard troponin (at presentation and after 10–12 hours) would be cost-effective at thresholds > £157,505,897 per QALY gained.

Scenario 1 was conditional on the secondary analysis (see *Table 40* and *Figure 18*) and resulted in standard troponin (at presentation and after 10–12 hours) being the cheapest strategy. The Beckman Coulter ACCESS hs-cTnI (symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 5 ng/l at 0 to 2 hours) was cost-effective at and above a threshold of £4698 per QALY gained and all other test strategies were more costly and less effective.

Scenario 2 (see *Table 41* and *Figure 19*) assumed a lifetime RR of higher mortality and reinfarction rate for those who tested FN (instead of an increased 1-year risk). Conditional on the base case, the Beckman Coulter ACCESS hs-cTnI (symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 5 ng/l at 0 to 2 hours) remained the cheapest, and the Beckman Coulter ACCESS hs-cTnI [ESC 0/1-hour pathway: (symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 4 ng/l at 0 to 1 hours)] and Siemens Dimension Vista hs-cTnI (< 5 ng/l at 0 hours AND Δ < 2 ng/l at 0 to 1 hours) were cost-effective at thresholds > £6962 and £7874 per QALY gained, respectively. Standard troponin (at presentation and after 10–12 hours) would be cost-effective thereafter, over thresholds of almost £70 M only.

Scenario 2 (see *Table 42* and *Figure 20*), conditional on the secondary analysis, resulted in standard troponin (at presentation and after 10–12 hours) being the cheapest strategy. The Beckman Coulter ACCESS hs-cTnI (symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 5 ng/l at 0 to 2 hours) was cost-effective above a threshold of £3362 per QALY gained, and all other test strategies were less effective and therefore dominated or extendedly dominated.

Scenario 3 (see *Table 43* and *Figure 21*) assumed differential test costs for all tests, based on information provided by the manufacturers. Conditional on the base case, the Beckman Coulter ACCESS hs-cTnI (symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 5 ng/l at 0 to 2 hours) remained the cheapest, and the Beckman Coulter ACCESS hs-cTnI [ESC 0/1-hour pathway: (symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 4 ng/l at 0 to 1 hours)] and Siemens Dimension Vista hs-cTnI (< 5 ng/l at 0 hours AND Δ < 2 ng/l at 0 to 1 hours) were cost-effective over thresholds of £22,200 and £23,949 per QALY gained, respectively. Standard troponin (at presentation and after 10–12 hours) would be cost-effective thereafter, above thresholds of approximately £330 M.

In scenario 3 (see *Table 44* and *Figure 22*), conditional on the secondary analysis, standard troponin (at presentation and after 10–12 hours) remained the cheapest strategy. The Beckman Coulter ACCESS hs-cTnI (symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 5 ng/l at 0 to 2 hours) was cost-effective up to a threshold of £4281 per QALY gained, and all other test strategies were less effective and therefore dominated or extendedly dominated.

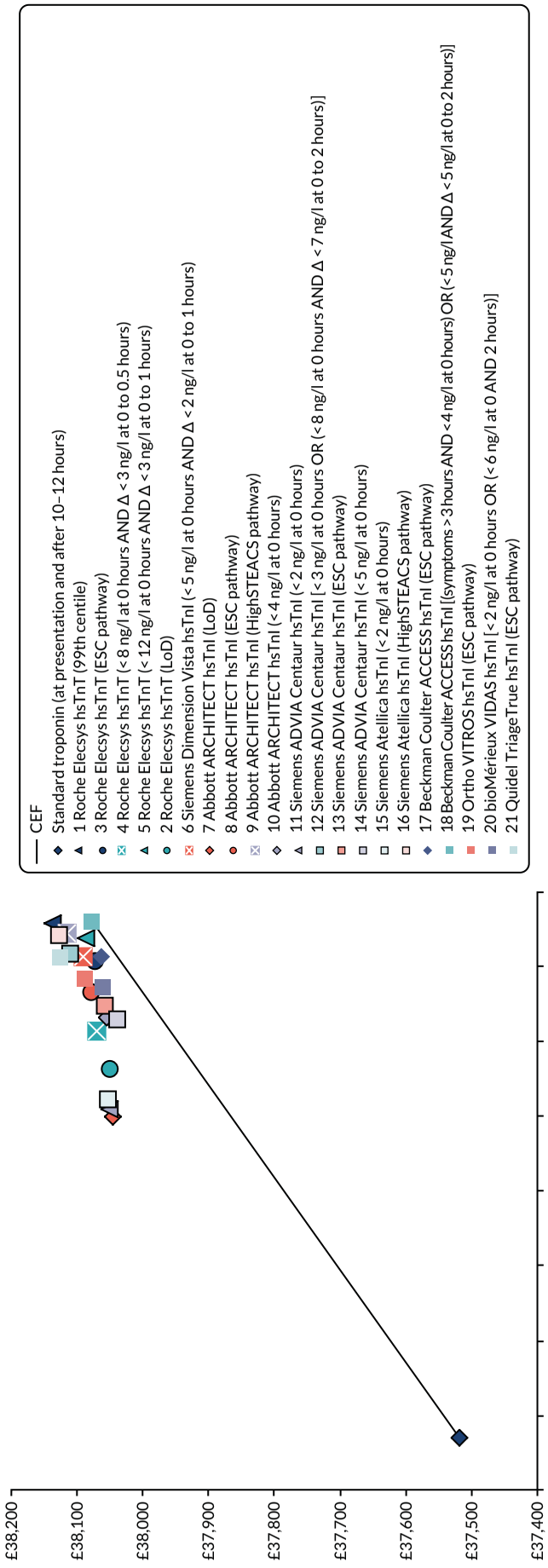

FIGURE 15 The cost-effectiveness frontier for the secondary analysis (based on PSA). CEF, cost-effectiveness frontier.

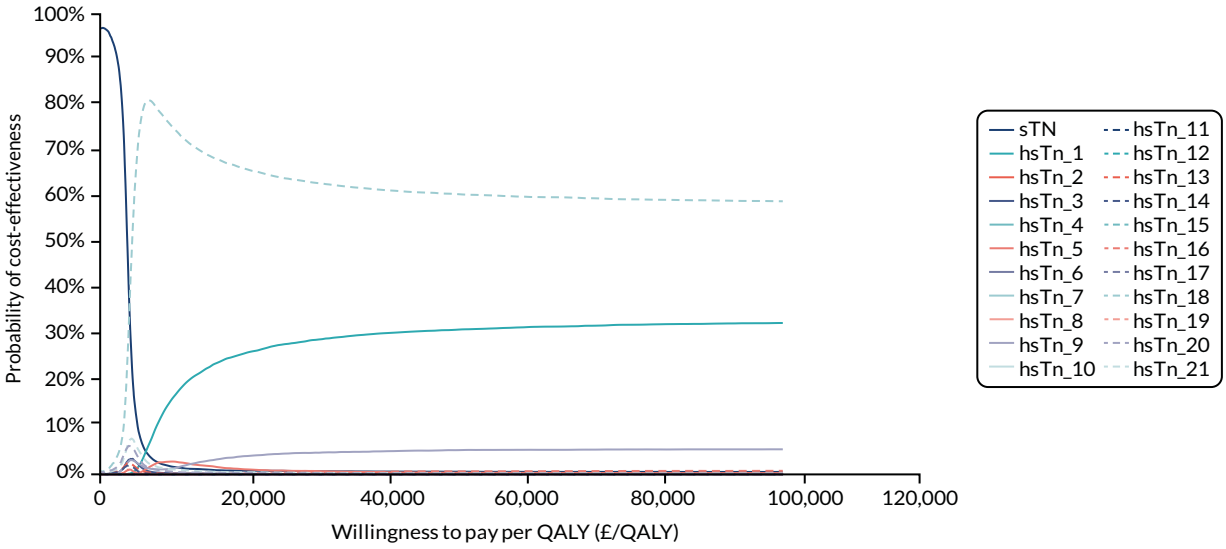

FIGURE 16 A CEAC for the secondary analysis.

Sensitivity analyses

The following input parameters had a noticeable impact on the estimated cost-effectiveness in the base-case analysis: the 30-day mortality for untreated and treated AMI (decision tree) and the mortality 1 year after treated and untreated AMI (Markov trace). Varying the remaining parameters did not have a substantial impact on the results in the comparisons between the Siemens Dimension Vista hs-cTnI (< 5 ng/l at 0 hours AND Δ < 2 ng/l at 0 to 1 hours), the Roche Elecsys hs-cTnT [ESC 0/1-hour pathway: (symptoms > 3 hours AND < 5 ng/l at 0 hours) OR (< 12 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours)] and the Beckman Coulter ACCESS hs-cTnI [(symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 5 ng/l at 0 to 2 hours)] (see *Figures 23* and *24*). In the comparison between the Siemens Dimension Vista hs-cTnI (< 5 ng/l at 0 hours AND Δ < 2 ng/l at 0 to 1 hours) and standard troponin (at presentation and after 10–12 hours) (see *Figure 25*), and in addition to parameters in the other comparisons, the parameters with the most impact on results were the proportions of AMI in emergency admissions and the proportions of NSTEMI in patients with heart attack (see *Appendix 8*).

In the secondary analysis, the parameters with notable impact on the estimated cost-effectiveness were the 30-day mortality for untreated AMI, the mortality 1 year after treated and untreated AMI, the discount rate used for outcomes and the relative mortality for patients who tested TP compared with those who tested FP {comparison of the Beckman Coulter ACCESS hs-cTnI [ESC 0/1-hour pathway: (symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 4 ng/l at 0 to 1 hours)] vs. standard troponin (at presentation and after 10–12 hours) testing} (see *Appendix 8*, *Figure 26*).

Incremental analyses per assay

Base-case analysis

The per assay analyses (*Table 33*) indicate that at willingness-to-pay thresholds of £20,000 and £30,000 per QALY gained, the following test strategies would be the most cost-effective use of the particular assays: Roche Elecsys hs-cTnT (< 12 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours), Abbott ARCHITECT hs-cTnI (ESC pathway), Siemens ADVIA Centaur hs-cTnI [< 3 ng/l at 0 hours OR (< 8 ng/l at 0 hours AND Δ < 7 ng/l at 0 to 2 hours)], Siemens Atellica hs-cTnI (High-STEACS pathway) and Beckman Coulter ACCESS hs-cTnI (ESC pathway).

TABLE 33 Probabilistic results for base-case analysis: per assay

Strategy	Cost (£)	QALY	ICER
Roche Elecsys hs-cTnT assay			
3. Roche Elecsys hs-cTnT: ESC pathway	38,662	12.0798	Cheapest
5. Roche Elecsys hs-cTnT: (< 12 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours)	38,663	12.0813	£1040
1. Roche Elecsys hs-cTnT: 99th centile	38,706	12.0825	£35,140
4. Roche Elecsys hs-cTnT: (< 8 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 0.5 hours)	38,729	12.0825	£9,658,481
2. Roche Elecsys hs-cTnT: LoD	38,738	12.0817	Dominated
Abbott ARCHITECT hs-cTnI assay			
9. Abbott ARCHITECT hs-cTnI: High-STEACS pathway	38,681	12.0795	Cheapest
10. Abbott ARCHITECT hs-cTnI: < 4 ng/l at 0 hours	38,699	12.0815	Extendedly dominated
8. Abbott ARCHITECT hs-cTnI: ESC pathway	38,702	12.0818	£9,183
7. Abbott ARCHITECT hs-cTnI: LoD	38,778	12.0823	£158,972
Siemens ADVIA Centaur hs-cTnI assay			
14. Siemens ADVIA Centaur hs-cTnI: < 5 ng/l at 0 hours	38,678	12.0794	Cheapest
13. Siemens ADVIA Centaur hs-cTnI: ESC pathway	38,684	12.0791	Dominated
12. Siemens ADVIA Centaur hs-cTnI: [< 3 ng/l at 0 hours OR (< 8 ng/l at 0 hours AND Δ < 7 ng/l at 0 to 2 hours)]	38,704	12.0825	£8213
11. Siemens ADVIA Centaur hs-cTnI: < 2 ng/l at 0 hours	38,777	12.0825	£19,868,699
Siemens Atellica hs-cTnI assay			
16. Siemens Atellica hs-cTnI: High-STEACS pathway	38,698	12.0811	Cheapest
15. Siemens Atellica hs-cTnI: < 2 ng/l at 0 hours	38,768	12.0825	£48,675
Beckman Coulter ACCESS hs-cTnI assay			
18. Beckman Coulter ACCESS hs-cTnI: [(symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 5 ng/l at 0 to 2 hours)]	38,625	12.0768	Cheapest
17. Beckman Coulter ACCESS hs-cTnI: ESC pathway	38,650	12.0790	£11,522

Secondary analysis

The per assay analyses (*Table 34*) indicate that at willingness-to-pay thresholds of £20,000 and £30,000 per QALY gained, the following test strategies would be the most cost-effective use of the particular assays: Roche Elecsys hs-cTnT (99th centile), Abbott ARCHITECT hs-cTnI (High-STEACS pathway), Siemens ADVIA Centaur hs-cTnI [< 3 ng/l at 0 hours OR (< 8 ng/l at 0 hours AND Δ < 7 ng/l at 0 to 2 hours)], Siemens Atellica hs-cTnI (High-STEACS pathway) and Beckman Coulter ACCESS hs-cTnI [(symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 5 ng/l at 0 to 2 hours)].

TABLE 34 Probabilistic results for secondary analysis: per assay

Strategy	Cost (£)	QALY	ICER
Roche Elecsys hs-cTnT assay			
2. Roche Elecsys hs-cTnT: LoD	38,050	11.4328	Cheapest
4. Roche Elecsys hs-cTnT: (< 8 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 0.5 hours)	38,070	11.4430	Extendedly dominated
3. Roche Elecsys hs-cTnT: ESC pathway	38,072	11.4619	£769
5. Roche Elecsys hs-cTnT: (< 12 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours)	38,088	11.4678	£2658
1. Roche Elecsys hs-cTnT: 99th centile	38,139	11.4718	£12,797
Abbott ARCHITECT hs-cTnI assay			
7. Abbott ARCHITECT hs-cTnI: LoD	38,046	11.4201	Cheapest
10. Abbott ARCHITECT hs-cTnI: < 4 ng/l at 0 hours	38,055	11.4466	£326
8. Abbott ARCHITECT hs-cTnI: ESC pathway	38,079	11.4535	Extendedly dominated
9. Abbott ARCHITECT hs-cTnI: High-STEACS pathway	38,115	11.4691	£2666
Siemens ADVIA Centaur hs-cTnI assay			
14. Siemens ADVIA Centaur hs-cTnI: < 5 ng/l at 0 hours	38,039	11.4463	Cheapest
11. Siemens ADVIA Centaur hs-cTnI: < 2 ng/l at 0 hours	38,051	11.4221	Dominated
13. Siemens ADVIA Centaur hs-cTnI: ESC pathway	38,057	11.4497	Extendedly dominated
12. Siemens ADVIA Centaur hs-cTnI: [< 3 ng/l at 0 hours OR (< 8 ng/l at 0 hours AND Δ < 7 ng/l at 0 to 2 hours)]	38,111	11.4636	£4140
Siemens Atellica hs-cTnI assay			
15. Siemens Atellica hs-cTnI: < 2 ng/l at 0 hours	38,051	11.4249	Cheapest
16. Siemens Atellica hs-cTnI: High-STEACS pathway	38,126	11.4689	£1719
Beckman Coulter ACCESS hs-cTnI assay			
17. Beckman Coulter ACCESS hs-cTnI: ESC pathway	38,066	11.4628	Cheapest
18. Beckman Coulter ACCESS hs-cTnI: [(symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 5 ng/l at 0 to 2 hours)]	38,077	11.4725	£1197

Chapter 5 Discussion

Statement of principal findings

Clinical effectiveness

The evidence base relating to the use of hs-cTn assays for the early rule out of AMI in people presenting with chest pain has expanded rapidly since the publication of our previous systematic review,[2] which was conducted to support the development of DG15.[13] Update searches of bibliographic databases (from 2013 to October 2019) conducted for this assessment identified a total of 9379 unique references, compared with a total of 6766 unique references identified for the 9-year period (2005 to October 2013) covered by the searches conducted for our previous systematic review.[2] This current assessment includes a total of 123 publications relating to 37 studies, compared with the 37 publications relating to 18 studies included in our previous systematic review.[2]

The main areas of change are an expansion of the number of hs-cTn assays available for use in the UK NHS, an increase in the number of studies comparing the performance of different hs-cTn assays and a proliferation of studies considering how to operationalise hs-cTn assays in clinical practice (previously, the majority of studies assessed the diagnostic accuracy of a single test).

This assessment includes nine assays that were not included in the scope for DG15:[13] (1) Abbott Alinity hs-cTnI, (2) Beckman Coulter Access hs-cTnI, (3) bioMérieux VIDAS hs-cTnI, (4) Ortho Clinical Diagnostics VITROS hs-cTnI, (5) Quidel Cardiovascular TriageTrue hs-cTnI, (6) Siemens Healthcare Atellica hs-cTnI, (7) Siemens Healthcare Dimension EXL hs-cTnI, (8) Siemens Healthcare Dimension Vista hs-cTnI and (9) Siemens Healthcare ADVIA Centaur hs-cTnI. One assay that was included in DG15 (i.e. the Beckman Coulter AccuTnI+3 hs-cTnI assay) is no longer available and therefore it is not included in this current assessment. As was the case in our previous systematic review,[2] most results relate to two assays, the Roche Elecsys hs-cTnT assay and the Abbott Architect hs-cTnI assay. Of the studies included in this assessment, 30 provided data on the Roche Elecsys hs-cTnT assay, nine provided data on the Abbott ARCHITECT hs-cTnI assay, three provided data on the Siemens ADVIA Centaur hs-cTnI assay, two provided data on each of the Siemens Atellica hs-cTnI assay and the Beckman Coulter Access hs-cTnI assay, and one study provided data on each of the Siemens Dimension Vista hs-cTnI assay, the Ortho VITROS hs-cTnI assay, the bioMérieux VIDAS hs-cTnI assay and the Quidel TriageTrue hs-cTnI assay. We did not identify any studies that evaluated testing strategies using either the Abbott Alinity hs-cTnI assay or the Siemens Dimension EXL hs-cTnI assay.

The APACE study was the only study included in our previous systematic review[2] to evaluate more than one hs-cTn assay[168] (i.e. to provide data to support direct comparisons of performance between assays). This assessment includes 25 new publications,[54,55,58–60,70,74,75,90–94,103–108,111,113,123,132,170,173] relating to the APACE study, which have been published since our previous systematic review. Of particular significance is the fact that eight different hs-cTn assays (i.e. the Roche Elecsys hs-cTnT, Abbott ARCHITECT hs-cTnI, the Beckman Coulter Access hs-cTnI, the bioMérieux VIDAS hs-cTnI, the Ortho VITROS hs-cTnI, the Quidel TriageTrue hs-cTnI, the Siemens ADVIA Centaur hs-cTnI and the Siemens Dimension Vista hs-cTnI) have now been evaluated in subgroups of the APACE study population. Five further studies that are included in this assessment (ADAPT,[68] BEST,[115] High-US,[176] ROMI-3[101] and TRUST[64]) evaluated two hs-cTn assays and one study (High-STEACS[61]) evaluated three assays.

Our previous systematic review included theoretical optimal testing strategies for the Roche Elecsys hs-cTnT assay and for the Abbott ARCHITECT hs-cTnI assay. These strategies used a two-step repeat-testing process, providing two potential opportunities to rule out NSTEMI and hence to discharge

patients within the 4-hour window specified in the scope. Our estimates of the clinical effectiveness and cost-effectiveness of these strategies were limited by the assumption that the diagnostic performance of the second step is the same when used in people in whom NSTEMI is not ruled out by the first step, as it is when used in the whole population. This assumption was necessary because no combined test performance data were available for the proposed strategies. Indeed, there were few studies of any multiple test strategies. By contrast, this current assessment includes data for a very large number of different test strategies (e.g. unique combinations of assay, threshold and timing), which are dominated by multiple testing strategies (59 distinct multiple testing strategies). Therefore, the construction of theoretical optimised testing strategies has been rendered obsolete, and the problem has become one of determining which of the large number of strategies that have been proposed and evaluated are likely to be considered clinically acceptable and cost-effective. The process of selecting test strategies for inclusion in cost-effectiveness modelling is described in detail in *Chapter 3, Selection of test strategies for inclusion in cost-effectiveness modelling.*

With respect to single test strategies, the results of our previous systematic review[2] indicated that very low hs-cTn levels (below a threshold that is at or near the LoD) in a single sample, taken on presentation, may be considered adequate to rule out NSTEMI. At the time of our previous review, data for an LoD threshold rule-out strategy and the target condition NSTEMI were available for the Roche Elecsys hs-cTnT assay only (threshold 5 ng/l). One study[141] evaluated a LoD threshold for the Abbott ARCHITECT hs-cTnI assay (2 ng/l) for the target condition any AMI. The number of included studies reporting data for the performance of a single presentation sample rule-out strategy, using a threshold at or near to the LoD for the assay, has increased in this assessment. The summary estimates of sensitivity and specificity for the target condition NSTEMI, using the Roche Elecsys hs-cTnT assay and a threshold of 5 ng/l in a single presentation sample, were 99% (95% CI 97% to 100%) and 35% (95% CI 25% to 46%), respectively, based on data from six studies[63,75,87,101,115,139] (see *Table 8*). The corresponding summary sensitivity and specificity estimates for the Abbott ARCHITECT hs-cTnI assay, using a 2 ng/l threshold, were 100% (95% CI 99% to 100%) and 21% (95% CI 16% to 26%), respectively, based on data from four studies[58,68,96,101] (see *Table 9*). Of the remaining hs-cTn assays included in this assessment, only the Siemens Atellica hs-cTnI assay and the Siemens ADVIA Centaur hs-cTnI assay were evaluated using a single presentation sample rule-out strategy, with a threshold at or near to the LoD for the assay. The LoD for both of these assays is 1.6 ng/l and both assays were evaluated by the High-US study,[176] using a rule-out threshold of 2 ng/l. The sensitivity and specificity estimates were 100% (95% CI 99% to 100%) and 23% (95% CI 21% to 25%), respectively, for the Siemens ADVIA Centaur hs-cTnI assay (see *Table 14*), and 100% (95% CI 98% to 100%) and 26% (95% CI 24% to 28%), respectively, for the Siemens Atellica hs-cTnI assay (see *Table 15*).[176]

The majority of the multiple test strategies selected for inclusion in our cost-effectiveness modelling (see *Table 21*) comprised an initial rule-out step, based on hs-cTn levels in a sample taken on presentation and a minimum symptom duration, and a second stage (for patients not meeting the initial rule-out criteria), based on presentation levels of hs-cTn and absolute change in hs-cTn between presentation and a second sample taken after 1, 2 or 3 hours. The 2015 ESC guidelines[33] for the management of ACSs in patients presenting without persistent ST segment elevation included 0/3- and 0/1-hour algorithms for rule-in and rule-out of AMI using hs-cTn assays. The ESC 0/1-hour algorithm incorporates separate rule-out and rule-in pathways and an intermediate 'observe' zone.[33] The rule-out pathway comprises an initial rule-out step, based on hs-cTn levels in a sample taken on presentation for patients who have a minimum symptom duration of 3 hours, and a second stage (for patients not meeting the initial rule-out criteria), based on presentation levels of hs-cTn and absolute change in hs-cTn between presentation and a second sample taken after 1 hour. The published ESC 0/1-hour algorithm specifies rule-out thresholds to be used with the Roche Elecsys hs-cTnT assay, the Abbott ARCHITECT hs-cTnI assay and the Siemens Dimension Vista hs-cTnI assay.[33] Subsequently, ESC 0/1-hour algorithm rule-out thresholds have been published for the Beckman Coulter Access hs-cTnI assay,[60] the Ortho VITROS hs-cTnI assay,[170] the Quidel TriageTrue hs-cTnI assay[173] and the Siemens ADVIA Centaur hs-cTnI assay.[59] Data on the rule-out performance of the ESC 0/1-hour algorithm for

the target condition NSTEMI that are included in this assessment were calculated by dichotomising at the rule-out threshold (i.e. study participants in the observe or the rule-in categories were classified as test positive). Unsurprisingly, the addition of a second rule-out step appears to offer consistently higher specificity than rule-out strategies based on very low hs-cTn levels in a single sample taken on presentation alone, and sensitivity estimates remained high. Sensitivity and specificity estimates for the ESC 0/1-hour rule-out pathways included in this assessment were:

- 99% (95% CI 98% to 100%) and 68% (95% CI 67% to 70%), respectively, for the Roche Elecsys hs-cTnT assay [rule-out threshold: (symptoms > 3 hours AND < 5 ng/l at 0 hours) OR (< 12 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours)][104]
- 99% (95% CI 98% to 100%) and 57% (95% CI 56% to 59%), respectively, for the Abbott ARCHITECT hs-cTnI assay (summary estimate based on two studies[66,104]) [rule-out threshold: (symptoms > 3 hours AND < 2 ng/l at 0 hours) OR (< 5 ng/l at 0 hours AND Δ < 2 ng/l at 0 to 1 hours)][104,213]
- 99% (95% CI 94% to 100%) and 70% (95% CI 66% to 74%), respectively, for the Beckman Coulter Access hs-cTnI assay [rule-out threshold: (symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 4 ng/l at 0 to 1 hours)][60]
- 100% (95% CI 95% to 100%) and 60% (95% CI 55% to 64%) for the Ortho VITROS hs-cTnI assay [rule out threshold: (symptoms > 3 hours AND < 1 ng/l at 0 hours) OR (< 2 ng/l at 0 hours AND Δ < 1 ng/l at 0 to 1 hours)][170]
- 100% (95% CI 97% to 100%) and 66% (95% CI 62% to 70%) for the Quidel TriageTrue hs-cTnI assay [rule-out threshold: (symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours)][173]
- 99% (95% CI 95% to 100%) and 67% (95% CI 61% to 72%) for the Siemens ADVIA Centaur hs-cTnI assay [rule-out threshold: (symptoms > 3 hours AND < 3 ng/l at 0 hours) OR (< 6 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours)].[59]

All of these test strategies were selected for inclusion in our cost-effectiveness modelling. Using a hypothetical cohort of 1000 patients and an NSTEMI prevalence of 12.2%, calculated by combining the HES 2017–18 prevalence of AMI in people presenting to the ED with chest pain[117] and the ratio of NSTEMI to STEMI from the Myocardial Ischemia National Audit Project,[202] application of the ESC 0/1-hour rule-out pathway would result in the discharge of between 500 and 615 people (depending on the hs-cTn assay used) within 2 hours of presentation (allowing for a 1-hour assay turnaround time), with a maximum of one instance of NSTEMI missed per 1000 people. Thresholds for the ESC 0/1-hour pathway using the Siemens Atellica hs-cTnI assay have also been published (rule-out threshold: (symptoms > 3 hours AND < 3 ng/l at 0 hours) OR (< 6 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours).[67] However, this strategy did not reach the specified minimum clinically acceptable sensitivity of 97%. The sensitivity and specificity estimates were 94% (95% CI 79% to 99%) and 69% (95% CI 64% to 74%), respectively, and therefore it was not included in our cost-effectiveness modelling. Two-step rule-out strategies, such as High-STEACS,[61] which use a later (3-hour) second sample, offer the potential to further increase overall specificity. The sensitivity and specificity estimates for the High-STEACS pathway that have been included in this assessment were:

- 99% (95% CI 97% to 100%) and 76% (95% CI 73% to 78%), respectively, for the Abbott ARCHITECT hs-cTnI assay {rule-out threshold: (symptoms ≥ 2 hours AND < 5 ng/l at 0 hours) OR [≤ 16 ng/l (females) ≤ 34 ng/l (males) at 3 hours AND Δ < 3 ng/l at 0 to 3 hours]}[66]
- 98% (95% CI 95% to 100%) and 74% (95% CI 72% to 76%), respectively, for the Siemens Atellica hs-cTnI assay {rule-out threshold: (symptoms ≥ 2 hours AND < 5 ng/l at 0 hours) OR [≤ 34 ng/l (females) ≤ 53 ng/l (males) at 3 hours AND Δ < 3 ng/l at 0 to 3 hours]}.[67]

Based on the hypothetical cohort of 1000 patients, described above, application of the High-STEACS rule-out pathway would result in the discharge of between 650 and 667 patients within 4 hours (allowing for a 1-hour assay turnaround time), with up to two patients with NSTEMI being erroneously discharged for every 1000 people presenting with chest pain. These findings are consistent with the

conclusions from a recently published large individual patient-level analysis,[214] which took data from 15 international patient cohorts ($n = 22,651$ patients) and used a derivation-validation design to assess multiple hs-cTn test strategies and inform the development of a risk assessment tool. This study found that patients at low risk for MI were likely to have very low concentrations of hs-cTn at presentation and small absolute changes on serial sampling, and that these patients were also at very low risk for MI or death from any cause at 30 days.[214]

In addition to the changes in the evidence about diagnostic accuracy described above, two major RCTs (i.e. the High-STEACS trial[99] and the unpublished HiSTORIC trial[175]) are included in this assessment. Both trials were stepped-wedge cluster RCTs that evaluated implementation of an early rule-out pathway in hospitals in Scotland. The primary outcomes were length of stay, and MI or cardiac death after discharge (at 30 days).[99,175] Both trials used the Abbott ARCHITECT hs-cTnI assay. In the High-STEACS trial,[99] during the validation phase of the trial (6–12 months), results of the hs-cTnI assay were concealed from the attending clinician and a contemporary cTn assay was used to guide care. A high-sensitivity test was introduced after 6 months (early implementation) or 12 months (late implementation).[99] The HiSTORIC trial[175] also had a validation phase where troponin testing was performed at presentation and repeated 6–12 hours after the onset of symptoms, if indicated.[175] In the validation phase of HiSTORIC trial, the High-STEACS early rule-out pathway was used.[99,175] In the High-STEACS trial, of 1771 patients reclassified by the hs-cTnI assay, 105 of 720 (15%) patients were in the validation phase and 131 of 1051 (12%) patients were in the implementation phase. The adjusted OR for implementation compared with validation was 1.10 (95% CI 0.75 to 1.61).[99] In the HiSTORIC trial[175] (confidential information has been removed). In the High-STEACS trial,[99] the median length of stay was 7 (IQR 3–24) hours in the implementation phase and 4 (IQR 3–20) hours in the validation phase. In the HiSTORIC trial[175] (confidential information has been removed). The authors of the High-STEACS trial[99] concluded that although implementation of a hs-cTn assay resulted in reclassification of 17% of 10,360 patients with myocardial injury or infarction, only one-third of the patients had a diagnosis of type 1 MI and the incidence of subsequent MI or death from cardiovascular causes within 1 year was not affected by use of this assay.[99] (Confidential information has been removed.)[175] These studies represent direct, real-world evidence about the effects of implementing an early rule-out strategy based on a hs-cTn assay obtained in a UK setting.

We identified a further RCT, the RAPID-TnT (Rapid Assessment of Possible ACS In the emergency Department with high sensitivity Troponin T),[215] conducted in Australia, which did not meet the inclusion criteria for this assessment as it did not compare testing with a hs-cTn assay with testing with a conventional cTn assay. Participants in the RAPID-TnT trial ($n = 3378$) were randomised to either the 0/1-hour Roche Elecsys hs-cTnT [reported to the LoD (< 5ng/l)] or masked Roche Elecsys hs-cTnT [reported to ≤ 29 ng/l evaluated at 0/3 hours (standard arm)]. The 30-day primary end point was all-cause death and MI.[215] Participants in the 0/1-hour arm were more likely to be discharged from the ED (45.1% vs. 32.3%) and the median length of ED stay was also shorter in the 0/1-hour arm [4.6 (IQR 3.4–6.4) hours vs. 5.6 (IQR 4.0–7.1) hours].[215] The 0/1-hour Roche Elecsys hs-cTnT protocol was not inferior to standard care, with respect to 30-day all-cause mortality and MI [17/1646 (1.0%) in the 0/1-hour arm vs. 16/1642 (1.0%) in the standard arm, incidence rate ratio 1.06 (95% CI 0.53 to 2.11); non-inferiority was an absolute margin of 0.5% determined by poisson regression].[215]

Cost-effectiveness

In our health economic analysis, the cost-effectiveness of different testing strategies involving hs-cTn for the early rule out of AMI in people with acute chest pain presenting to the ED with suspected ACS and STEMI ruled out was assessed. In the base case, standard troponin testing at 10–12 hours was considered the reference standard, assuming perfect sensitivity and specificity. In addition to the base-case analysis, given some evidence that FPs compared with this reference standard also have an increased mortality and MI probability, a secondary analysis was conducted that assumed an increased risk of adverse events (i.e. MI and mortality) for patients with a FP hs-cTn test result.

In the base-case analysis, standard troponin testing was both most effective and most costly. The strategies considered cost-effective, depending on ICER thresholds, were the Beckman Coulter ACCESS hs-TnI [(symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 5 ng/l at 0 to 2 hours)] for willingness-to-pay thresholds of < £8455 per QALY gained, the Roche Elecsys hs-cTnT [ESC 0/1-hour pathway: (symptoms > 3 hours AND < 5 ng/l at 0 hours) OR (< 12 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours)] for thresholds between £8455 and £20,190 per QALY gained and the Siemens Dimension Vista hs-cTnI (< 5 ng/l at 0 hours AND Δ < 2 ng/l at 0 to 1 hours) for thresholds > £20,190 per QALY gained.

The above mentioned results should, however, be interpreted while noting that the differences between the strategies in both costs and QALYs were very small. Given these minimal differences in cost-effectiveness, it might be worthwhile to consider other aspects not captured in the economic assessment. This might include differences in the proportion of patients who are correctly ruled out (i.e. TNs). Although the cost consequences of the early rule out have been considered in the cost-effectiveness assessment, early rule out might have benefits not captured by the model (e.g. preventing unnecessary anxiety in patients without MI and making hospital resources available for other patients). It is noticeable that, in the base-case analysis, the high-sensitivity test strategies with the highest TN rates (i.e. ≥ 65%) involve high-sensitivity test strategies with a second test 2–3 hours after the initial test {i.e. the Siemens Atellica hs-cTnI (High-STEACS pathway), the Abbott ARCHITECT hs-cTnI (High-STEACS pathway), the Roche Elecsys hs-cTnT (99th centile) and the Beckman Coulter ACCESS hs-cTnI [(symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 5 ng/l at 0 to 2 hours)]}.

Strengths and limitations of assessment

Clinical effectiveness

Extensive literature searches were conducted in an attempt to maximise retrieval of relevant studies. These included electronic searches of a variety of bibliographic databases, as well as screening of clinical trials registers and conference abstracts, to identify unpublished studies. Owing to the known difficulties in identifying test accuracy studies using study design-related search terms,[216] search strategies were developed to maximise sensitivity at the expense of reduced specificity. Therefore, large numbers of citations were identified and screened, relatively few of which met the inclusion criteria of the review.

The possibility of publication bias remains a potential problem for all systematic reviews. Considerations may differ for systematic reviews of test accuracy studies. It is relatively simple to define a positive result for studies of treatment (e.g. a significant difference between the treatment and control groups that favours treatment). This is not the case for test accuracy studies, which measure agreement between index test and reference standard. It would seem likely that studies finding greater agreement (i.e. high estimates of sensitivity and specificity) will be published more often. In addition, test accuracy data are often collected as part of routine clinical practice or by retrospective review of records. Test accuracy studies are not subject to the formal registration procedures applied to RCTs and are therefore more easily discarded when results appear unfavourable. The extent to which publication bias occurs in studies of test accuracy remains unclear; however, simulation studies have indicated that the effect of publication bias on meta-analytic estimates of test accuracy is minimal.[217] Formal assessment of publication bias in systematic reviews of test accuracy studies remains problematic and reliability is limited.[41] We did not undertake a statistical assessment of publication bias in this review. However, our search strategy included a variety of routes to identify unpublished studies and resulted in the inclusion of a number of conference abstracts.

Clear inclusion criteria were specified in the protocol for this review. The review has been registered on PROSPERO (CRD42019154716) and the protocol is available from URL: www.nice.org.uk/guidance/indevelopment/gid-dg10035/documents (accessed 20 October 2020). The eligibility of studies for

inclusion is therefore transparent. In addition, we have provided specific reasons for exclusion for all of the studies that were considered potentially relevant at initial citation screening and were subsequently excluded on assessment of the full publication (see *Appendix 5*). The review process followed recommended methods to minimise the potential for error and/or bias.[39] Studies were independently screened for inclusion by two reviewers and data extraction and quality assessment were carried out by one reviewer and checked by a second (MW, DF and GW). Any disagreements were resolved by consensus.

Diagnostic cohort studies included in this review were assessed for risk of bias and applicability using the QUADAS-2 tool developed by the authors[45] and recommended by the Cochrane Collaboration.[41] QUADAS-2 is structured into four key domains: (1) participant selection, (2) index test, (3) reference standard and (4) the flow of patients through the study (including timing of tests). Each domain is rated for risk of bias (low, high or unclear), and the participant selection, index test and reference standard domains are also rated separately for concerns regarding the applicability of the study to the review question (low, high or unclear). Studies that provided data for two or more hs-cTn assays were assessed using QUADAS-2C,[46] in place of QUADAS-2. QUADAS-2C is a version of the QUADAS tool that has been developed specifically for the assessment of comparative DTA studies. This tool is currently undergoing piloting and is not yet published. The results of the QUADAS-2 and QUADAS-2C assessments are reported, in full, for all included studies in *Appendices 3* and *4*, and are summarised in *Chapter 3*, *Study quality*. The methodological quality of included RCTs was assessed using the revised Cochrane Risk-of-Bias Tool for Randomised Trials.[44] The main potential sources of bias in the studies included in this assessment were related to participant spectrum and participant flow (domains 1 and 4 of QUADAS-2 and QUADAS-2C). The most common feature of studies rated as having a 'high risk of bias' for patient selection was the inclusion of participants based on staffing or work flow considerations (e.g. participants were excluded if they presented at night or during busy periods).[88,117,121,139,144] This was considered to have the potential to lead to the inclusion of a different spectrum of patients than if consecutive patients had been enrolled. All studies assessed using QUADAS-2C were rated as having a low risk of bias for patient selection for all individual index tests. However, one study, for which data for two hs-cTn assays were reported in separate publications,[115,172] was rated as having a high risk of bias for participant selection for the comparison of the two assays. This was because the study did not set out to conduct both tests in all patients or to randomly allocate patients to one of the two tests. Six of the studies[110,137,141,147,157,159] that reported data for a single hs-cTn assay, assessed using QUADAS-2, were considered as having a high risk of bias for patient flow and a further three studies[62,102,165] were considered as having an unclear risk of bias. In all cases, this was related to withdrawals from the study. Verification bias was not considered to be a problem in any of the studies. All of the studies assessed using QUADAS-2C were rated as having a low risk of bias for participant flow, with respect to the individual hs-cTn assays that they assessed. However, four of these studies (APACE,[59,170,178] BEST,[115,172] High-STEACS[66,67] and TRUST[64]) were rated as having a high risk of bias for participant flow, with respect to at least one between-assay comparison. In all cases, this was because the number of participants for whom hs-cTn results were available differed between assays.

As with our previous systematic review,[2] this assessment included studies that enrolled both mixed populations (i.e. when the target condition was any AMI) and studies restricted to populations where patients with STEMI were excluded (i.e. the target condition was NSTEMI). Our primary focus remained the population of patients with STEMI excluded. Studies not restricted to this specific patient group were therefore considered to have high concerns regarding applicability. Seven studies[133,137,139,144,148,157,159] from our previous systematic review were restricted to patients in whom STEMI had been excluded. This assessment includes a further 13 studies[58,61,62,64,68,72,80,84,96,101,115,171,176] that were restricted to patients in whom STEMI had been excluded.

The most recent systematic review[218] identified during this assessment aimed to compare the diagnostic performance of various accelerated algorithms using hs-cTn assays, for patients with symptoms suggestive of AMI. This review, by Lee *et al.*,[218] reported summary estimates of sensitivity and specificity for a '0-hour algorithm', 1-hour algorithm, 2-hour algorithm and 0- to 1-hour delta algorithm. Separate estimates were reported for hs-cTnT and hs-cTnI; however, no distinction was

made between different hs-cTnI assays. None of the summary estimates of sensitivity reported in the systematic review by Lee *et al.*[218] reached the minimum clinically acceptable sensitivity (97%) defined for this assessment.

We believe that our assessment provides information of direct relevance to UK clinical practice, as we focus on the performance of hs-cTn within the 4-hour time window corresponding to the target for NHS EDs, which specifies a maximum ED waiting time of 4 hours before admission, transfer or discharge.[200]

This assessment represents an advance on our previous systematic review,[2] conducted to support the development of DG15,[13] in that we are now able to include data on the diagnostic performance of two-stage rule-out algorithms, which have been taken directly from large diagnostic cohort studies. In our previous systematic review, we proposed strategies for how hs-cTn assays might be applied and interpreted to maximise diagnostic performance. These strategies were devised with consideration to test timing, diagnostic threshold and interpretation of combinations of multiple test results. However, because there was no direct evidence of the performance of such strategies, our estimates of their effectiveness and cost-effectiveness relied on the assumption that the diagnostic performance of the second step would be the same when used in people in whom NSTEMI was not ruled out by the first step, as when used in the whole population.[2]

A limitation of this assessment, with respect to the evaluation of the ESC 0/1-hour pathway, is our use of the rule-out threshold to dichotomise data. This approach classifies all patients in both the observe and the rule-in arms of the ESC 0/1-hour pathway as test positive and therefore does not account for potential differences in the care pathway for these two patient groups.

This assessment was further limited in that the scope[21] did not include studies evaluating the use of hs-cTn assays as part of or in combination with a clinical risk score.

Our searches identified two recent systematic reviews that evaluated the History ECG Age Risk factors Troponins (HEART) score[219] for risk stratification of patients presenting to the ED with chest pain[220,221] and that included an assessment of the effect of using hs-cTn (vs. conventional troponins) in the heart score. Both studies used the low-risk HEART score (0–3) to define the rule-out threshold and reported accuracy data using 30-day to 6-week (short-term) MACEs as the reference standard. Van Den Verg and Body[220] reported summary estimates of sensitivity and specificity of the HEART score, based on nine studies using either conventional or high-sensitivity troponin assays. The summary sensitivity estimate was 97% (95% CI 94% to 98%) and the summary specificity estimate was 47% (95% CI 41% to 54%).[220] None of the studies in this review compared the performance of the HEART score using a hs-cTn assay compared with conventional troponins. However, the review authors noted that the two studies that used a high-sensitivity assay (Roche Elecsys hs-cTnT), with the original HEART score definition and a target condition of short-term MACEs, reported differing estimates of sensitivity [93% (95% CI 84% to 98%) and 100% (95% CI 98% to 100%)]. Laureano-Phillips *et al.*[221] reported summary sensitivity and specificity estimates for the original HEART score and the target condition short-term MACEs using either conventional or high-sensitivity troponin assays. The summary sensitivity estimate was 97% (95% CI 94% to 98%) and the summary specificity estimate was 38% (95% CI 33% to 43%); however, the number of studies included in this analysis was unclear.[221] The only estimates of the sensitivity and specificity of the HEART score using high-sensitivity troponins, provided in this review, were for a different target condition (i.e. all-time frame MACEs).[221] The findings of these two reviews[220,221] suggest that further work may be needed to validate the use of high-sensitivity troponin assays in the context of the HEART score and, potentially, other clinical risk scores that include a cTn component.

The potential use of clinical risk scores in combination with hs-cTn test strategies is distinct from the integration of hs-cTn assays into existing clinical risk scores, in place of conventional troponin assays. One of the publications of the High-STEACS study[66] included in this assessment reported data on the performance of the High-STEACS pathway, using the Abbott ARCHITECT hs-cTnI assay and the

rule-out threshold (symptoms ≥ 2 hours AND < 5 ng/l at 0 hours) OR [≤ 16 ng/l (F) ≤ 34 ng/l (M) at 3 hours AND Δ < 3 ng/l at 0 to 3 hours], alone and in combination validated clinical risk scores [a HEART score of ≤ 3,[219] a Global Registry of Acute Coronary Events (GRACE) score of ≤ 108,[222] a Thrombolysis Myocardial Infarction score of 0 or 1,[223] or and Emergency Department Assessment of Chest Pain Score (EDACS) of < 16[224]]. The High-STEACS pathway alone classified 1244 of 1917 (64.9%) participants as low risk (rule out) and missed instances of NSTEMI at index presentation and one further instance during the 30-day follow-up.[66] Combining the High-STEACS pathway with clinical risk scores reduced the proportion of people classified as low risk (rule out) in all instances (HEART 24.3%, GRACE 47%, Thrombolysis In Myocardial Infarction 44% and EDACS 41%) and the addition of a clinical risk score did not improve the negative predictive value of the High-STEACS pathway.[66] The same pattern was observed when the ESC 0/1-hour pathway, using the Abbott ARCHITECT hs-cTnI assay and the rule-out threshold (symptoms > 3 hours AND < 2 ng/l at 0 hours) OR (< 5 ng/l at 0 hours AND Δ < 2 ng/l at 0 to 1 hours) was assessed alone and in combination with the same set of clinical risk scores.[66] These data provide an indication that the addition of clinical risk scores to the key hs-cTn multiple test strategies considered in this assessment would be likely to reduce the proportion of patients discharged within 4 hours (ruled out), without improving safety.

Our assessment was less comprehensive for the Beckman Coulter Access hs-cTnI, bioMérieux VIDAS hs-cTnI, Ortho Clinical Diagnostics VITROS hs-cTnI, Quidel Cardiovascular TriageTrue hs-cTnI, Siemens Healthcare Atellica hs-cTnI, Siemens Healthcare Dimension Vista hs-cTnI and Siemens Healthcare ADVIA Centaur hs-cTnI assays than for the Roche Elecsys hs-cTnT and the Abbott ARCHITECT hs-cTnI assays, because available data were limited for these six assays. Furthermore, we were unable to identify any studies of either the Abbott Alinity hs-cTnI assay or the Siemens Healthcare Dimension EXL hs-cTnI assay.

Cost-effectiveness

Our CEA is, to the best of our knowledge, the most comprehensive to date in terms of the number of relevant hs-cTn test strategies for the early rule out of AMI in people presenting to the ED with acute chest pain and suspected ACS. The model was informed by a comprehensive, high-quality systematic review of DTA.

As in any economic model, a number of major and minor assumptions had to be made. It is important to understand the impact of these assumptions to correctly interpret the results of the model. The impact of most assumptions has been explored in sensitivity and scenario analyses. However, one major assumption that was maintained throughout all analyses was the conservative assumption of no health benefit of early treatment in the hs-cTn strategies, compared with 'late' treatment in the standard cTn strategy. Although many experts believe that there must be a benefit, at least to some extent, of treating patients early, there is no evidence to support or quantify a timing effect as of yet. In addition, there may well be adverse effects associated with early treatment (e.g. the risk of bleeding, unnecessary percutaneous coronary interventions, etc.). The Canadian HTA report[186] identified in the economic review did include an advantage for early versus late treatment, based on one study, which investigated the effect of a 36-hour treatment delay.[225] The RR found in this study was then recalculated, assuming a constant effect of timing on treatment benefit, to a RR of 1.035 of mortality for a treatment delay of 6 hours versus early treatment, which was again adjusted to 1.01 based on expert opinion. Any possible adverse effect of early treatment was not considered in this analysis. A similar approach would have been possible in the present model but, in our view, this would not be informative, given the level of uncertainty underlying this final estimate. Therefore, it was decided to leave out a possible effect of timing of treatment. This could be considered a conservative approach, but even this is uncertain.

The assumption that standard troponin, as the reference standard, has perfect sensitivity and specificity was also maintained throughout all analyses. However, there is evidence that the prognostic performance of standard troponin testing may be imperfect. For example, a negative troponin test

might correctly assess that a patient is not experiencing a NSTEMI, but some patients with negative test results may still benefit from treatment. A secondary analysis was performed to take this possibility into account, which resulted in the standard troponin strategy being less effective than the hs-cTn testing strategies.

In addition to the abovementioned strategies, it should be noted that not all test strategies presented in *Chapter 3* are considered in the CEAs (see *Chapter 3* for an overview of all high-sensitivity troponin strategies that were identified in the literature). For the economic model, only those high-sensitivity troponin tests that had a sensitivity of ≥ 97% were selected. Although some of the test strategies with lower sensitivity might potentially be cost-effective, it would be questionable whether or not these strategies would be considered acceptable for clinicians.

Uncertainties

Clinical effectiveness

A recent systematic review of sex-specific and overall 99th centiles of hs-cTnI and hs-cTnT derived from healthy reference populations[226] found that 14 of 16 (87.5%) hs-cTnI studies and 11 of 18 (61.1%) hs-cTnT studies reported lower female-specific thresholds than the overall threshold for the population. Conversely, male-specific thresholds were reported as being 'generally in line with currently used overall thresholds'.[226] In addition, the product information leaflets for all of the hs-cTn assays included in this assessment report separate female and male, as well as overall, 99th centile for the general population (see *Table 1*). Despite this, the clinical effectiveness and cost-effectiveness of using sex-specific thresholds for hs-cTn assay remains unclear. Although there are some subgroup data comparing the performance of a common threshold in males and females,[62,65,74,79,81,94] few studies have evaluated the diagnostic performance of sex-specific thresholds. Considering those test strategies included in this assessment, which were selected for inclusion in our cost-effectiveness modelling, only the High-STEACS pathway utilises sex-specific thresholds.[66,67] It remains unclear whether or not the use of sex-specific thresholds in the High-STEACS pathway offers any advantage over the use of a single general population threshold, as no equivalent pathway (using a single general population threshold) has been evaluated.

Our previous systematic review[2] identified some data on the diagnostic performance of hs-cTn testing in clinically important subgroups (e.g. older people[146,168] and people with and without pre-existing CAD).[140,168] However, these data were very limited and were available for the Roche Elecsys hs-cTnT assay only. The current assessment includes some additional data about the performance of hs-cTn test strategies in people with normal renal function and those with impaired renal function,[72,79,106] people with known ischemic heart disease and those with no known ischemic heart disease,[65] and people aged ≥ 65 years compared with those aged < 65 years.[65] Of particular note are the renal function subgroup data for the ESC 0/1-hour pathway, using the Abbott ARCHITECT hs-cTnI assay,[106] which indicate that the sensitivity of the rule-out pathway is high for both people with normal renal function (99%, 95% CI 97% to 100%) and those with impaired renal function (i.e. an eGFR < 60 ml/minute/1.73 m^2) (99%, 95% CI 94% to 100%). However, the specificity of this test strategy was markedly lower in patients with impaired renal function (25%, 95% CI 20% to 30%) than in those with normal renal function (66%, 95% CI 64% to 68%).[106] Based on the hypothetical cohort of 1000 patients, described above, these data indicate that the use of the ESC 0/1-hour rule-out strategy in people with impaired renal function would not lead to any additional instances of NSTEMI being missed, but would reduce the number of people discharged within 4 hours to approximately 220. Subgroup data for the High-STEACS pathway, also using the Abbott ARCHITECT hs-cTnI assay,[65] indicate that this test strategy may fall bellow the clinically acceptable threshold for sensitivity (97%) defined from this assessment, when used in people with known ischemic heart disease [96% (95% CI 89% to 99%) vs. those with no known ischemic heart disease, 100% (95% CI 97% to 100%)]. There remains some uncertainty about how the diagnostic performance of individual hs-cTn assays may vary in clinically relevant subgroups, as well as what may constitute the optimal testing strategy in these groups.

It should be noted that the performance of any test strategy that incorporates the 99th centile for the general population in the diagnostic threshold will be dependent on the characteristics of the reference population from which this value was derived. The High-STEACS pathway using the Abbott ARCHITECT hs-cTnI assay {rule-out threshold: (symptoms $\geq$ 2 hours AND < 5 ng/l at 0 hours) OR [$\leq$ 16 ng/l (F) $\leq$ 34 ng/l (M) at 3 hours AND Δ < 3 ng/l at 0 to 3 hours]}[66] and the High-STEACS pathway using the Siemens Atellica hs-cTnI assay {rule-out threshold: (symptoms $\geq$ 2 hours AND < 5 ng/l at 0 hours) OR [$\leq$ 34 ng/l (F) $\leq$ 53 ng/l (M) at 3 hours AND Δ < 3 ng/l at 0 to 3 hours]}[67] were the only two strategies, selected for inclusion in our cost-effectiveness modelling, to incorporate 99th centile thresholds. The product information leaflet for the Abbott ARCHITECT hs-cTnI assay describes the 99th centile as derived from a healthy US population of 1531 individuals, who had normal BNP (B-type natriuretic peptide), glycated haemoglobin and eGFR values. The leaflet also recommends that laboratories should establish their own 99th centile that is applicable to their population.[18] Similarly, the product information leaflet for the Siemens Atellica hs-cTnI assay describes the 99th centile as derived from a healthy US population of 2007 individuals, aged between 22 and 91 years. The leaflet also recommends that laboratories should establish their own 99th centile that is applicable to their population and that reflects their institutional criteria for the diagnosis of AMI.[28]

Cost-effectiveness

The main uncertainties for the CEA lie in the model assumptions, particularly regarding the effect of actual clinical practice in terms of both other diagnostic information and treatment, given this information. Although many of these assumptions have been varied in one-way sensitivity analyses, the precise implication of FN test results, where patients are discharged without essential treatment, or of FP test results, where patients stay in hospital and may receive unnecessary interventions, is unknown. Given this, as well as the minimal differences between the test strategies, the results of the CEA should be interpreted in the context of potential cost and benefits (i.e. FNs/FPs) that are not captured in the economic model.

Chapter 6 Conclusions

Implications for service provision

There is evidence to indicate that high-sensitivity troponin assays can be used to rule out NSTEMI in adults presenting with acute chest pain within the 4-hour NHS ED target. Test strategies that comprise an initial rule-out step, based on low hs-cTn levels in a sample taken on presentation and a minimum symptom duration, and a second stage (for patients not meeting the initial rule-out criteria), based on low presentation levels of hs-cTn and small absolute change in hs-cTn between presentation and a second sample taken after 1, 2 or 3 hours, are likely to produce the highest rule-out rates while maintaining clinically acceptable sensitivity (very low rates of missed NSTEMI). There is a lack of evidence about the clinical effectiveness of two of the intervention technologies included in the scope of this assessment (i.e. the Abbott Alinity hs-cTnI assay and the Siemens Dimension EXL hs-cTnI assay).

From a cost-effectiveness perspective, the Roche Elecsys hs-cTnT (< 12 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours) and Siemens Dimension Vista hs-cTnI (< 5 ng/l at 0 hours AND Δ < 2 ng/l at 0 to 1 hours) might be cost-effective for thresholds of £20,000 and £30,000 per QALY gained, respectively (base case). For the secondary analysis, the Beckman Coulter ACCESS hs-cTnI [(symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 5 ng/l at 0 to 2 hours)] was considered to be cost-effective for these thresholds. The cost-effectiveness results should, however, be interpreted while noting that the differences between the strategies in both costs and QALYs were very small. Given these minimal differences in cost-effectiveness, it might be worthwhile to consider other aspects not captured in the economic assessment. Therefore, it is worth noting that the high-sensitivity tests strategies with the highest TNs (i.e. ≥ 65%) involve high-sensitivity tests strategies with a second test 2–3 hours after the initial test {i.e. the Siemens Atellica hs-cTnI (High-STEACS pathway), the Abbott ARCHITECT hs-cTnI (High-STEACS pathway), the Roche Elecsys hs-cTnT (99th centile) and the Beckman Coulter ACCESS hs-cTnI [(symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 5 ng/l at 0 to 2 hours)]}.

Suggested research priorities

If adoption of either the Abbott Alinity hs-cTnI assay or the Siemens Dimension EXL hs-cTnI assay is to be considered, then studies are needed to evaluate the diagnostic performance of these assays and to determine optimum test strategies and thresholds.

Further diagnostic cohort studies or subgroup analyses of existing data sets are needed to fully explore possible variation in the accuracy of hs-cTn assays and the optimal testing strategies for these assays in relevant demographic and clinical subgroups (e.g. sex, age, ethnicity, renal function, previous CAD, previous AMI).

Multivariable prediction modelling studies may be useful to assess the independent prognostic value of a positive hs-cTn test result, in the context of other clinical risk factors and tests, in patients who do not have a confirmed AMI at the index presentation.

Acknowledgements

The authors acknowledge the clinical advice and expert opinion provided by Professor Rick Body, Clinical Professor of Emergency Medicine, Manchester Royal Infirmary/University of Manchester; Professor Nick Mills, Professor of Cardiology and Consultant Cardiologist, University of Edinburgh; Professor Adam Timmis, Professor of Clinical Cardiology, Queen Mary University of London and St Bartholomew's Hospital, London; Professor Paul Collinson, Professor of Cardiovascular Biomarkers, St George's University Hospitals NHS Foundation Trust; and Mr Alan Reid, scheme organiser UK NEQAS Cardiac Markers (Glasgow, UK) and principal clinical scientist, Queen Elizabeth University Hospital, Glasgow. Finally, the authors would like to thank the lay members of the NICE Diagnostics Advisory Committee and Assessment Subgroup for providing input on the patients' perspective at key stages of the assessment process.

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Publication

Westwood ME, Armstrong N, Worthy G, Fayter D, Ramaekers BLT, Grimm S, *et al.* Optimizing the use of high-sensitivity troponin assays for the early rule-out of myocardial infarction in patients presenting with chest pain: a systematic review. *Clin Chem* 2021;**67**:237–44.

Data-sharing statement

Requests for access to data should be addressed to the corresponding author.

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Appendix 1 Literature search strategies

EMBASE (Ovid)

Dates searched: 1974 to 25 September 2019.

Date of search: 26 September 2019.

Search strategy

1. "high sensitivity cardiac troponin T"/or high sensitivity troponin t assay/(90)
2. "high sensitivity cardiac troponin I"/or high sensitivity troponin i assay/ (44)
3. (Hstnt or hs-tnt or hsctnt or hs-ctnt or tnt-hs or tnths or ctnths or ctnt-hs).ti,ab,ot. (2939)
4. (Hstni or hs-tni or hsctni or hs-ctni or tni-hs or tnihs or ctnihs or ctni-hs or ctni-ultra).ti,ab,ot. (1194)
5. ((troponin t or tnt or ctnt or tropt or trop t) adj2 (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive)).ti,ab,ot,hw. (4206)
6. ((troponin I or tni or ctni or tropI or trop I) adj2 (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive)).ti,ab,ot,hw. (2415)
7. (troponin$ adj2 (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive)).ti,ab,ot,hw. (6601)
8. (troponin$ adj5 (architect or elecsys or access or centaur or vidas or vitros or dimension or vista or triagetrue or triage-true or atellica or alinity or advia)).ti,ab,hw,ot. (396)
9. ("dimension exl" or "atellica IM" or atellica-im or "alinity i" or alinity-i or "advia centaur" or "dimension vista").ti,ab,hw,ot. (1300)
10. troponin$.mv,my. (65)
11. (elecsys$ or architect$ or centaur or vidas or vitros or atellica or alinity).dv. (2819)
12. (advia or advia120 or advia1800 or advia2120i or advia2400 or adviacentaur).dv. (972)
13. or/1-12 (12,098)
14. troponin t/or troponin I/or (60304-72-5 or 77108-40-8).rn. (38,060)
15. (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive).ti,ab,ot,hw. (9,837,120)
16. 14 and 15 (21,639)
17. 13 or 16 (27,778)
18. thorax pain/ (84,161)
19. ((chest or thorax or thoracic) adj2 (pain$ or discomfort or tight$ or pressure)).ti,ab,ot,hw. (110,352)
20. acute coronary syndrome/ (54,220)
21. (acute adj2 coronary adj2 syndrome$).ti,ab,ot,hw. (67,681)
22. exp heart muscle ischemia/ (91,534)
23. exp heart infarction/ (365,052)
24. exp Unstable-Angina-Pectoris/ (23,610)
25. (preinfarc$ Angina$ or pre infarc$ Angina$).ti,ab,ot,hw. (410)
26. Unstable angina$.ti,ab,ot. (19,196)
27. ((heart$ or myocardi$ or cardiac or coronary) adj2 (preinfarc$ or infarc$ or attack$ or arrest$ or occlusion$ or isch?emia$)).ti,ab,ot,hw. (554,354)
28. (MI or ACS or STEMI or NSTE-ACS or NSTEACS or nonSTEMI or NSTEMI or AMI or UAP or OMI).ti,ab,ot,hw. (163,966)
29. or/18-28 (719,484)
30. 17 and 29 (14,259)
31. animal/ (1,431,471)
32. animal experiment/ (2,438,936)

33. (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (6,574,496)
34. or/31-33 (6,574,496)
35. exp human/ (20,203,276)
36. human experiment/ (469,138)
37. or/35-36 (20,204,702)
38. 34 not (34 and 37) (5,073,475)
39. 30 not 38 (13,490)
40. limit 39 to yr = "2013 -Current" (8169)

MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily (Ovid)

Dates searched: 1946 to 24 September 2019.

Date of search: 26 September 2019.

Search strategy

1. (Hstnt or hs-tnt or hsctnt or hs-ctnt or tnt-hs or tnths or ctnths or ctnt-hs).ti,ab,ot. (1169)
2. (Hstni or hs-tni or hsctni or hs-ctni or tni-hs or tnihs or ctnihs or ctni-hs or ctni-ultra or accutni or accu-tni).ti,ab,ot. (561)
3. ((troponin t or tnt or ctnt or tropt or trop t) adj2 (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive)).ti,ab,ot. (1967)
4. ((troponin I or tni or ctni or tropI or trop I) adj2 (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive)).ti,ab,ot. (1117)
5. (troponin$ adj2 (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive)).ti,ab,ot. (3072)
6. (troponin$ adj5 (architect or elecsys or access or centaur or vidas or vitros or dimension or vista or triagetrue or triage-true or atellica or alinity or advia)).ti,ab,hw,ot. (138)
7. ("dimension exl" or "atellica IM" or atellica-im or "alinity i" or alinity-i or "advia centaur" or "dimension vista").ti,ab,hw,ot. (398)
8. or/1-7 (4229)
9. troponin t/or troponin I/or (60304-72-5 or 77108-40-8).rn. (12,105)
10. (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive).ti,ab,ot. (7,169,880)
11. 9 and 10 (6385)
12. 8 or 11 (8437)
13. chest pain/ (12,556)
14. ((chest or thorax or thoracic) adj2 (pain$ or discomfort or tight$ or pressure)).ti,ab,ot,hw. (40,643)
15. exp myocardial ischemia/ (419,151)
16. (acute adj2 coronary adj2 syndrome$).ti,ab,ot. (29,162)
17. (preinfarc$ Angina$ or pre infarc$ Angina$).ti,ab,ot. (321)
18. Unstable angina$.ti,ab,ot. (12,789)
19. ((heart$ or myocardi$ or cardiac or coronary) adj2 (preinfarc$ or infarc$ or attack$ or arrest$ or occlusion$ or isch?emia$)).ti,ab,ot. (260,414)
20. (MI or ACS or STEMI or NSTE-ACS or NSTEACS or nonSTEMI or NSTEMI or AMI or UAP or OMI).ti,ab,ot. (89,398)
21. or/13-20 (570,108)
22. 12 and 21 (4465)
23. animals/not (animals/and humans/) (4,585,749)

24. 22 not 23 (4245)
25. limit 24 to yr = "2013 -Current" (2104)

Cochrane Database of Systematic Reviews (Wiley)

Dates searched: Issue 9/September 2019.

The CDSR search retrieved four references.

Cochrane Central Register of Controlled Trials (Wiley)

Dates searched: Issue 9/September 2019

Date of search: 26 September 2019.

The CENTRAL search retrieved 567 references (436 when trials and pre 2013 records removed).

Search strategy

#1 (Hstnt or hs-tnt or hsctnt or hs-ctnt or tnt-hs or tnths or ctnths or ctnt-hs):ti,ab,kw (259)
#2 (Hstni or hs-tni or hsctni or hs-ctni or tni-hs or tnihs or ctnihs or ctni-hs or ctni-ultra):ti,ab,kw (108)
#3 ((troponin t or tnt or ctnt or tropt or trop t) near/2 (sensitiv* or hs or early or initial or rapid or present* or ultra or high performance or ultrasensitive)):ti,ab,kw (1608)
#4 ((troponin I or tni or ctni or tropI or trop I) near/2 (sensitiv* or hs or early or initial or rapid or present* or ultra or high performance or ultrasensitive)):ti,ab,kw (2893)
#5 (troponin* near/2 (sensitiv* or hs or early or initial or rapid or present* or ultra or high performance or ultrasensitive)):ti,ab,kw (623)
#6 (troponin* near/5 (architect or elecsys or access or unicel or centaur or vidas or vitros or dimension or vista or triagetrue or triage-true or atellica or alinity or advia)):ti,ab,kw (17)
#7 #1 or #2 or #3 or #4 or #5 or #6 (3902)
#8 MeSH descriptor: [Troponin T] this term only (432)
#9 MeSH descriptor: [Troponin I] this term only (506)
#10 #8 or #9 (897)
#11 (sensitiv* or hs or early or initial or rapid or present* or ultra or "high performance" or ultrasensitive):ti,ab,kw (401,488)
#12 #10 and #11 (436)
#13 #7 or #12 (4184)
#14 MeSH descriptor: [Chest Pain] this term only (428)
#15 ((chest or thorax or thoracic) near/2 (pain* or discomfort or tight* or pressure)):ti,ab,kw (5686)
#16 (acute near/2 coronary near/2 syndrome*):ti,ab,kw (6420)
#17 MeSH descriptor: [Myocardial Ischemia] explode all trees (26,176)
#18 (preinfarc* Angina* or pre infarc* Angina*):ti,ab,kw (349)
#19 (Unstable angina*):ti,ab,kw (3941)
#20 ((heart* or myocardi* or cardiac or coronary) near/2 (preinfarc* or infarc* or attack* or arrest* or occlusion* or isch?emia*)):ti,ab,kw (41,934)
#21 (MI or ACS or STEMI or NSTE-ACS or NSTEACS or nonSTEMI or NSTEMI or AMI or UAP or OMI):ti,ab,kw (17,551)
#22 #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 (63,623)
#23 #13 and #22 with Cochrane Library publication date Between Sep 2013 and Dec 2019 (571)

Latin American and Caribbean Health Sciences Literature

Dates searched: 2013 to 20 September 2019.

Date of search: 20 September 2019.

URL: http://regional.bvsalud.org/php/index.php?lang=en

Search strategy

Terms	Records
tw:((troponin* OR mh:d05.750.078.730.825.925 OR mh:d12.776.210.500.910.925 OR mh: d12.776.220.525.825.925 OR mh:d05.750.078.730.825.962 OR mh:d12.776.210.500.910.962 OR mh: d12.776.220.525.825.962 OR mh:d05.750.078.730.825 OR mh:d12.776.210.500.910 OR mh: d12.776.220.525.825 OR hstnt OR hs-tnt OR hsctnt OR hs-ctnt OR tnt-hs OR tnths OR ctnths OR ctnt-hs OR hstni OR hs-tni OR hsctni OR hs-ctni OR tni-hs OR tnihs OR ctnihs OR ctni-hs OR ctni-ultra)) AND (db:("LILACS")) AND (year_cluster:[2013 TO 2019])	159
Total	159

Science Citation Index – Expanded (Web of Science)

Date range searched: 1988 to 24 September 2019.

Conference Proceedings Citation Index – Science

Date range searched: 1990 to 24 September 2019.

Date of search: 25 September 2019.

Search strategy

1 TS = (Hstnt or hs-tnt or hsctnt or hs-ctnt or tnt-hs or tnths or ctnths or ctnt-hs) (1113)
2 TS = (Hstni or hs-tni or hsctni or hs-ctni or tni-hs or tnihs or ctnihs or ctni-hs or ctni-ultra) (439)
3 TS = ((troponin* or tnt or ctnt or tropt or tni or ctni or tropI or "trop t" or "trop I") NEAR/2 (sensitiv* or hs or early or initial or rapid or present* or ultra or "high performance" or ultrasensitive)) (5176)
4 ((troponin*) NEAR/5 (architect or elecsys or access or unicel or centaur or vidas or vitros or dimension or vista or triagetrue or triage-true or atellica or alinity or advia)) (201)
5 #4 OR #3 OR #2 OR #1 (5334)
6 TS = ((chest or thorax or thoracic) NEAR (pain* or discomfort or tight* or pressure)) (37,887)
7 TS = (acute NEAR/2 coronary NEAR/2 syndrome*) (42,293)
8 TS = (preinfarc* angina* or pre infarc* angina) (1114)
9 TS = unstable angina* (16,970)
10 TS = ((heart* or myocard* or cardiac or coronary) NEAR/2 (preinfarc* or infarc* or attack* or arrest* or occlusion* or isch?emia*)) (308,052)
11 TS = (MI or ACS or STEMI or NSTE-ACS or NSTEACS or nonSTEMI or NSTEMI or AMI or UAP or OMI) (118,099)
12 #6 OR # & or #8 OR #9 OR #10 OR #11 (426,084)
13 #12 AND #5 (1897)

ClinicalTrials.gov (internet)

URL: http://clinicaltrials.gov/ct2/search/advanced

Date of search: 20 September 2019.

Expert search option.

First posted from 1 January 2013 to 31 December 2019.

Search strategy

Search term	Records
troponin AND INFLECT ("01/01/2013" : "12/31/2019") [STUDY-FIRST-POSTED] AND (architect OR elecsys OR access OR unicel OR centaur OR vidas OR vitros OR dimension OR vista OR triagetrue OR triage-true OR atellica OR alinity OR advia)	55
troponin AND INFLECT ("01/01/2013" : "12/31/2019") [STUDY-FIRST-POSTED] AND (sensitive OR hs OR early OR initial OR rapid OR presentation OR ultra OR high performance OR ultrasensitive)	618
Total	673
Total after duplicates removed	629 (44 duplicates removed)

World Health Organization International Clinical Trials Registry Platform (internet)

URL: www.who.int/ictrp/en/

Date of search: 25 September 2019.

Advanced search option: Title and Intervention combined with OR.

Date of registration limited to 1 January 2013 to 25 September 2019.

Search strategy

Title	Condition	Intervention	Records
Troponin OR Troponins			
		Troponin OR Troponins	
Total			139 trials

Health Technology Assessment database

URL: www.crd.york.ac.uk/CRDWeb/

Dates searched: up to March 2018.

Database of Abstracts of Reviews of Effects

URL: www.crd.york.ac.uk/CRDWeb/

Dates searched: up to March 2015.

Date of search: 26 September 2019.

Forty-five records after date restriction.

Search strategy

1. MeSH DESCRIPTOR Troponin EXPLODE 1 IN DARE, HTA (32)
2. (Hstnt or hs-tnt or hsctnt or hs-ctnt or tnt-hs or tnths or ctnths or ctnt-hs) IN DARE, HTA FROM 2013 TO 2019 (0)
3. (Hstni or hs-tni or hsctni or hs-ctni or tni-hs or tnihs or ctnihs or ctni-hs or ctni-ultra) IN DARE, HTA FROM 2013 TO 2019 (0)
4. (troponin t or tnt or ctnt or tropt or trop t) IN DARE, HTA FROM 2013 TO 2019 (8)
5. (troponin I or tni or ctni or tropI or trop I) IN DARE, HTA FROM 2013 TO 2019 (10)
6. (troponin or troponins) IN DARE, HTA FROM 2013 TO 2019 (29)
7. #1 OR #2 OR #3 OR #4 OR #5 OR #6 (45)

PROSPERO (International Prospective Register of Systematic Reviews) (internet)

URL: www.crd.york.ac.uk/prospero/#searchadvanced

Dates searched: up to 20 September 2019.

Date of search: 20 September 2019.

Searched in 'All fields'.

Search strategy

Terms	Records
Troponin*	112
Limited to 2013–2019	

National Institute for Health Research Health Technology Assessment

URL: www.nihr.ac.uk/explore-nihr/funding-programmes/health-technology-assessment.htm

Date of search: 26 September 2019.

One record (URL: www.nihr.ac.uk/documents/case-studies/trapid-ami-impact-case-study/21537www.nihr.ac.uk/documents/case-studies/trapid-ami-impact-case-study/21537).

Conference abstracts

The following conference abstracts were manually searched to compliment those conference abstracts indexed in EMBASE:

- American Association for Clinical Chemistry 2017–19
- AHA Scientific Sessions 2017–19
- ESC 2019.

Additional UK-specific cost searches

EMBASE (Ovid)

Dates searched: 1974 to 9 January 2020.

Date of search: 10 January 2020.

Search strategy

1. "high sensitivity cardiac troponin T"/or high sensitivity troponin t assay/ (88)
2. "high sensitivity cardiac troponin I"/or high sensitivity troponin i assay/ (43)
3. (Hstnt or hs-tnt or hsctnt or hs-ctnt or tnt-hs or tnths or ctnths or ctnt-hs).ti,ab,ot. (3051)
4. (Hstni or hs-tni or hsctni or hs-ctni or tni-hs or tnihs or ctnihs or ctni-hs or ctni-ultra).ti,ab,ot. (1246)
5. ((troponin t or tnt or ctnt or tropt or trop t) adj2 (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive)).ti,ab,ot,hw. (4333)
6. ((troponin I or tni or ctni or tropI or trop I) adj2 (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive)).ti,ab,ot,hw. (2510)
7. (troponin$ adj2 (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive)).ti,ab,ot,hw. (6836)
8. (troponin$ adj5 (architect or elecsys or access or centaur or vidas or vitros or dimension or vista or triagetrue or triage-true or atellica or alinity or advia)).ti,ab,hw,ot. (414)
9. ("dimension exl" or "atellica IM" or atellica-im or "alinity i" or alinity-i or "advia centaur" or "dimension vista").ti,ab,hw,ot. (1318)
10. troponin$.mv,my. (66)
11. (elecsys$ or architect$ or centaur or vidas or vitros or atellica or alinity).dv. (2923)
12. (advia or advia120 or advia1800 or advia2120i or advia2400 or adviacentaur).dv. (1000)
13. or/1-12 (12,496)
14. troponin t/or troponin I/or (60304-72-5 or 77108-40-8).rn. (38,546)
15. (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive).ti,ab,ot,hw. (10,000,737)
16. 14 and 15 (22,046)
17. 13 or 16 (28,399)
18. health-economics/ (32,473)
19. exp economic-evaluation/ (299,466)
20. exp health-care-cost/ (285,436)
21. exp pharmacoeconomics/ (199,679)
22. or/18-21 (634,055)
23. (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (1,023,679)
24. (expenditure$ not energy).ti,ab. (38,862)
25. (value adj2 money).ti,ab. (2361)
26. budget$.ti,ab. (37,347)
27. or/23-26 (1,058,833)

28. 22 or 27 (1,380,813)
29. letter.pt. (1,099,578)
30. editorial.pt. (638,530)
31. note.pt. (785,740)
32. or/29-31 (2,523,848)
33. 28 not 32 (1,262,897)
34. (metabolic adj cost).ti,ab. (1461)
35. ((energy or oxygen) adj cost).ti,ab. (4231)
36. ((energy or oxygen) adj expenditure).ti,ab. (30,901)
37. or/34-36 (35,509)
38. 33 not 37 (1,255,639)
39. exp animal/ (24,976,369)
40. exp animal-experiment/ (2,482,604)
41. nonhuman/ (6,026,401)
42. (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh. (5,603,915)
43. or/39-42 (26,921,217)
44. exp human/ (20,412,882)
45. exp human-experiment/ (480,344)
46. 44 or 45 (20,414,345)
47. 43 not (43 and 46) (6,507,765)
48. 38 not 47 (1,144,073)
49. 17 and 48 (837)
50. limit 49 to yr = "2013 -Current" (475)
51. United Kingdom/ (385,970)
52. (national health service* or nhs*).ti,ab,in,ad. (334,600)
53. (english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) adj5 english)).ti,ab. (41,191)
54. (gb or "g.b." or britain* or (british* not "british columbia") or uk or "u.k." or united kingdom* or (england* not "new england") or northern ireland* or northern irish* or scotland* or scottish* or ((wales or "south wales") not "new south wales") or welsh*).ti,ab,jx,in,ad. (3,091,729)
55. (bath or "bath's" or ((birmingham not alabama*) or ("birmingham's" not alabama*) or bradford or "bradford's" or brighton or "brighton's" or bristol or "bristol's" or carlisle* or "carlisle's" or (cambridge not (massachusetts* or boston* or harvard*)) or ("cambridge's" not (massachusetts* or boston* or harvard*)) or (canterbury not zealand*) or ("canterbury's" not zealand*) or chelmsford or "chelmsford's" or chester or "chester's" or chichester or "chichester's" or coventry or "coventry's" or derby or "derby's" or (durham not (carolina* or nc)) or ("durham's" not (carolina* or nc)) or ely or "ely's" or exeter or "exeter's" or gloucester or "gloucester's" or hereford or "hereford's" or hull or "hull's" or lancaster or "lancaster's" or leeds* or leicester or "leicester's" or (lincoln not nebraska*) or ("lincoln's" not nebraska*) or (liverpool not (new south wales* or nsw)) or ("liverpool's" not (new south wales* or nsw)) or ((london not (ontario* or ont or toronto*)) or ("london's" not (ontario* or ont or toronto*)) or manchester or "manchester's" or (newcastle not (new south wales* or nsw)) or ("newcastle's" not (new south wales* or nsw)) or norwich or "norwich's" or nottingham or "nottingham's" or oxford or "oxford's" or peterborough or "peterborough's" or plymouth or "plymouth's" or portsmouth or "portsmouth's" or preston or "preston's" or ripon or "ripon's" or salford or "salford's" or salisbury or "salisbury's" or sheffield or "sheffield's" or southampton or "southampton's" or st albans or stoke or "stoke's" or sunderland or "sunderland's" or truro or "truro's" or wakefield or "wakefield's" or wells or westminster or "westminster's" or winchester or "winchester's" or wolverhampton or "wolverhampton's" or (worcester not (massachusetts* or boston* or harvard*)) or ("worcester's" not (massachusetts* or boston* or harvard*)) or (york not ("new york*" or ny or ontario* or ont or toronto*)) or ("york's" not ("new york*" or ny or ontario* or ont or toronto*))))).ti,ab,in,ad. (2,372,103)

56. (bangor or "bangor's" or cardiff or "cardiff's" or newport or "newport's" or st asaph or "st asaph's" or st davids or swansea or "swansea's").ti,ab,in,ad. (96,722)
57. (aberdeen or "aberdeen's" or dundee or "dundee's" or edinburgh or "edinburgh's" or glasgow or "glasgow's" or inverness or (perth not australia*) or ("perth's" not australia*) or stirling or "stirling's").ti,ab,in,ad. (327,742)
58. (armagh or "armagh's" or belfast or "belfast's" or lisburn or "lisburn's" or londonderry or "londonderry's" or derry or "derry's" or newry or "newry's").ti,ab,in,ad. (43,867)
59. or/51-58 (3,767,357)
60. (exp "arctic and antarctic"/or exp oceanic regions/or exp western hemisphere/or exp africa/or exp asia/or exp "australia and new zealand"/) not (exp united kingdom/or europe/) (2,999,470)
61. 59 not 60 (3,559,996)
62. 50 and 61 (67)

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

Dates searched: 1946 to 9 January 2020.

Date of search: 10 January 2020.

Search strategy

1. (Hstnt or hs-tnt or hsctnt or hs-ctnt or tnt-hs or tnths or ctnths or ctnt-hs).ti,ab,ot. (1220)
2. (Hstni or hs-tni or hsctni or hs-ctni or tni-hs or tnihs or ctnihs or ctni-hs or ctni-ultra or accutni or accu-tni).ti,ab,ot. (588)
3. ((troponin t or tnt or ctnt or tropt or trop t) adj2 (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive)).ti,ab,ot. (2041)
4. ((troponin I or tni or ctni or tropI or trop I) adj2 (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive)).ti,ab,ot. (1170)
5. (troponin$ adj2 (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive)).ti,ab,ot. (3211)
6. (troponin$ adj5 (architect or elecsys or access or centaur or vidas or vitros or dimension or vista or triagetrue or triage-true or atellica or alinity or advia)).ti,ab,hw,ot. (145)
7. ("dimension exl" or "atellica IM" or atellica-im or "alinity i" or alinity-i or "advia centaur" or "dimension vista").ti,ab,hw,ot. (415)
8. or/1-7 (4401)
9. troponin t/or troponin I/or (60304-72-5 or 77108-40-8).rn. (12,356)
10. (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive).ti,ab,ot. (7,299,032)
11. 9 and 10 (6557)
12. 8 or 11 (8656)
13. economics/(27,118)
14. exp "costs and cost analysis"/ (231,602)
15. economics, dental/ (1909)
16. exp "economics, hospital"/ (24,141)
17. economics, medical/ (9050)
18. economics, nursing/ (3996)
19. economics, pharmaceutical/ (2905)
20. (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (760,923)
21. (expenditure$ not energy).ti,ab. (28,754)
22. (value adj1 money).ti,ab. (33)
23. budget$.ti,ab. (28,351)
24. or/13-23 (910,365)
25. ((energy or oxygen) adj cost).ti,ab. (4005)

26. (metabolic adj cost).ti,ab. (1367)
27. ((energy or oxygen) adj expenditure).ti,ab. (24,380)
28. or/25-27 (28,784)
29. 24 not 28 (903,751)
30. letter.pt. (1,058,044)
31. editorial.pt. (514,173)
32. historical article.pt. (356,143)
33. or/30-32 (1,909,174)
34. 29 not 33 (868,281)
35. 12 and 34 (241)
36. limit 35 to yr = "2013 -Current" (133)
37. exp United Kingdom/ (359,811)
38. (national health service* or nhs*).ti,ab,in. (184,469)
39. (english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) adj5 english)).ti,ab. (93,416)
40. (gb or "g.b." or britain* or (british* not "british columbia") or uk or "u.k." or united kingdom* or (england* not "new england") or northern ireland* or northern irish* or scotland* or scottish* or ((wales or "south wales") not "new south wales") or welsh*).ti,ab,jw,in. (1,999,631)
41. (bath or "bath's" or ((birmingham not alabama*) or ("birmingham's" not alabama*) or bradford or "bradford's" or brighton or "brighton's" or bristol or "bristol's" or carlisle* or "carlisle's" or (cambridge not (massachusetts* or boston* or harvard*)) or ("cambridge's" not (massachusetts* or boston* or harvard*)) or (canterbury not zealand*) or ("canterbury's" not zealand*) or chelmsford or "chelmsford's" or chester or "chester's" or chichester or "chichester's" or coventry or "coventry's" or derby or "derby's" or (durham not (carolina* or nc)) or ("durham's" not (carolina* or nc)) or ely or "ely's" or exeter or "exeter's" or gloucester or "gloucester's" or hereford or "hereford's" or hull or "hull's" or lancaster or "lancaster's" or leeds* or leicester or "leicester's" or (lincoln not nebraska*) or ("lincoln's" not nebraska*) or (liverpool not (new south wales* or nsw)) or ("liverpool's" not (new south wales* or nsw)) or ((london not (ontario* or ont or toronto*)) or ("london's" not (ontario* or ont or toronto*)) or manchester or "manchester's" or (newcastle not (new south wales* or nsw)) or ("newcastle's" not (new south wales* or nsw)) or norwich or "norwich's" or nottingham or "nottingham's" or oxford or "oxford's" or peterborough or "peterborough's" or plymouth or "plymouth's" or portsmouth or "portsmouth's" or preston or "preston's" or ripon or "ripon's" or salford or "salford's" or salisbury or "salisbury's" or sheffield or "sheffield's" or southampton or "southampton's" or st albans or stoke or "stoke's" or sunderland or "sunderland's" or truro or "truro's" or wakefield or "wakefield's" or wells or westminster or "westminster's" or winchester or "winchester's" or wolverhampton or "wolverhampton's" or (worcester not (massachusetts* or boston* or harvard*)) or ("worcester's" not (massachusetts* or boston* or harvard*)) or (york not ("new york*" or ny or ontario* or ont or toronto*)) or ("york's" not ("new york*" or ny or ontario* or ont or toronto*))))).ti,ab,in. (1,349,609)
42. (bangor or "bangor's" or cardiff or "cardiff's" or newport or "newport's" or st asaph or "st asaph's" or st davids or swansea or "swansea's").ti,ab,in. (52,779)
43. (aberdeen or "aberdeen's" or dundee or "dundee's" or edinburgh or "edinburgh's" or glasgow or "glasgow's" or inverness or (perth not australia*) or ("perth's" not australia*) or stirling or "stirling's").ti,ab,in. (201,032)
44. (armagh or "armagh's" or belfast or "belfast's" or lisburn or "lisburn's" or londonderry or "londonderry's" or derry or "derry's" or newry or "newry's").ti,ab,in. (24,860)
45. or/37-44 (2,573,849)
46. (exp africa/or exp americas/or exp antarctic regions/or exp arctic regions/or exp asia/or exp oceania/) not (exp great britain/or europe/) (2,796,611)
47. 45 not 46 (2,431,577)
48. 36 and 47 (27)

Economics filters

Centre for Reviews and Dissemination

NHS EED MEDLINE using OvidSP. York: CRD; 2014. URL: www.crd.york.ac.uk/crdweb/searchstrategies.asp#nhseedmedline (accessed 2 June 2014).

NHS EED EMBASE using OvidSP. York: CRD; 2014. URL: www.crd.york.ac.uk/crdweb/searchstrategies.asp#nhseedembase (accessed 2 June 2014).

UK filter

Ayiku L, Levay P, Hudson T, Craven J, Barrett E, Finnegan A, *et al*. The MEDLINE UK filter: development and validation of a geographic search filter to retrieve research about the UK from OVID MEDLINE. *Health Info Libr J* 2017;**34**:200–16.

Ayiku L, Levay P, Hudson T, Craven J, Finnegan A, Adams R, *et al*. The EMBASE UK filter: validation of a geographic search filter to retrieve research about the UK from OVID EMBASE. *Health Info Libr J* 2019;**36**:121–33.

American Economic Association's electronic bibliography (EBSCO*host*)

Dates searched: 2013 to 9 January 2020.

Date of search: 16 January 2020.

Search modes: Boolean/Phrase.

Search strategy

S1 TX Troponin* (1)

S2 TX Hstnt or hs-tnt or hsctnt or hs-ctnt or tnt-hs or tnths or ctnths or ctnt-hs (0)

S3 TX Hstni or hs-tni or hsctni or hs-ctni or tni-hs or tnihs or ctnihs or ctni-hs or ctni-ultra or accutni or accu-tni (0)

NHS Economic Evaluation Database

URL: www.crd.york.ac.uk/CRDWeb/)

Dates searched: up to March 2015.

Date of search: 16 January 2020.

Search strategy

1. MeSH DESCRIPTOR troponin EXPLODE ALL TREES IN NHSEED (15)
2. * FROM 2013 TO 2020 (25,075)
3. #1 AND #2 (3)
4. (troponin) OR (troponins) IN NHSEED FROM 2013 TO 2020 (3)
5. #3 OR #4 (3)

Appendix 2 Data extraction tables

TABLE 35 Baseline study details

Study	Selection criteria	Participant details	Assay
ADAPT (ACTRN1261100106994) Aldous *et al.* 2014[53] [a]**Boeddinghaus *et al.* 2016**[57] [b]**Cullen *et al.* 2013**[156] [a]**Cullen *et al.* 2014**[68] **Eggers *et al.* 2016**[69] **Greenslade *et al.* 2015**[71] Meller *et al.* 2015[118] Parsonage *et al.* 2013[130] **van der Linden *et al.* 2018**[109] Wildi *et al.* 2017[112] *Country:* Australia and New Zealand *Funding:* The manufacturers (Abbott, Roche and Siemens) provided partial funding *Recruitment:* November 2007 to February 2011 *Number of participants:* 1194	*Inclusion criteria:* Prospectively recruited adults (aged ≥ 18 years) with possible cardiac symptoms in accordance with the AHA case definitions (i.e. acute chest, epigastric, neck, jaw or arm pain; or discomfort or pressure without a clear non-cardiac source) *Exclusion criteria:* Clear cause, other than ACS, for symptoms; staff considered recruitment to be inappropriate (e.g. receiving palliative treatment); transfer from another hospital; pregnancy; STEMI; patients who stated that their first episode of pain commenced > 12 hours before presentation; and patients with missing zero- or 2-hour samples *Patient category:* NSTEMI and 30-day MACE	*Median age (years) (IQR):* 61 (50–73) *Male (%):* 59 *Previous CAD (%):* 21 *Previous AMI (%):* 26 *Previous revascularisation (%):* 24 *Diabetes (%):* 14 *Smoking (%):* 18 *Hypertension (%):* 56 *Dyslipidaemia (%):* 53	Abbott ARCHITECT hs-cTnI; Roche Elecsys hs-cTnT
ADAPT/IMPACT (ACTRN12611001069943/ ACTRN12611000206921) **Nestelberger *et al.* 2019**[171] *Country:* Australia *Funding:* ADAPT was supported by research grants from the Emergency Medicine Foundation (Milton, QLD, Australia) and the Royal Brisbane and Women's Hospital Foundation (Brisbane, QLD, Australia), and Beckman Coulter and investigational reagents were provided by the manufacturers. No information was reported about the funding of IMPACT	*Inclusion criteria:* Adults (aged ≥ 18 years) with at least 5 minutes of symptoms where the attending physician planned to perform serial cTnI tests. The AHA case definitions for possible cardiac symptoms were used (i.e. acute chest, epigastric, neck, jaw or arm pain, or discomfort or pressure without an apparent non cardiac source) *Exclusion criteria:* STEMI; clear cause other than ACS for the symptoms at presentation (e.g. examination findings of pneumonia); inability to provide informed consent; staff considered recruitment to be inappropriate (e.g. receiving palliative treatment); transfer from	*Median age (years) (IQR):* 51 (43–62) *Male (%):* 60.1 *Previous AMI:* 14.3 *Previous CAD (%):* 17.3 *Previous revascularisation (%):* 12.4 *Diabetes (%):* 12.8 *Smoking (%):* 27.7 *Hypertension (%):* 43.6 *Dyslipidaemia (hypercholesterolemia) (%):* 42.3 *Median BMI (kg/m^2) (IQR):* 28.3 (25.0–32.8)	Beckman Coulter ACCESS hs-cTnI

continued

TABLE 35 Baseline study details (*continued*)

Study	Selection criteria	Participant details	Assay
Recruitment: ADAPT November 2007 to February 2011; IMPACT February 2011 to March 2014 *Number of participants:* 1280	another hospital; pregnancy; previous enrolment; and inability to be contacted after discharge *Patient category:* NSTEMI		
[a,b]**Aldous *et al.* 2012**[139] [b]**Aldous *et al.* 2012**[134] [b]Aldous *et al.* 2011[143] *Country:* New Zealand *Funding:* Funded by the National Heart Foundation (Auckland, New Zealand) and assay reagents were provided by the manufacturer (Roche). One author declared personal funding from Abbott *Recruitment:* November 2007 to December 2010 *Number of participants:* 939[139] and 385[134]	*Inclusion criteria:* Adults (aged ≥ 18 years) with symptoms suggestive of cardiac ischemia (i.e. acute chest, epigastric, neck, jaw or arm pain; or discomfort or pressure without an apparent non-cardiac source) *Exclusion criteria:* ST segment elevation on an ECG;[139] unable to provide informed consent; and would not be available to follow-up *Patient category:* NSTEMI[139] and mixed[134]	*Median age (years) (IQR):* 65 (56–76) *Male (%):* 60 *White (%):* 89 *Previous CAD (%):* 52 *Previous revascularisation (%):* 30 *Family history (%):* 60 *Diabetes (%):* 17 *Smoking (%):* 61 *Hypertension (%):* 61 *Dyslipidaemia (%):* 58 *Median BMI (kg/m^2) (IQR):* 28 (25, 31) *Median (IQR) time (hours) to presentation:* 6.3 (3.3–13.3)	Roche Elecsys hs-cTnT
[b]**Aldous 2011**[147] [b]Aldous 2010[155] [b]Aldous 2011[162] *Country:* New Zealand *Funding:* Manufacturers (Roche and Abbott) supplied the assays. The study was funded by a New Zealand National Heart Foundation grant *Recruitment:* November 2006 to April 2007 *Number of participants:* 332	*Inclusion criteria:* Consecutive patients presenting to the ED with chest pain. Participants were eligible for inclusion if the attending clinician had sufficient suspicion of ACS and serial troponins and electrocardiography were considered necessary *Exclusion criteria:* aged < 18 years; samples not stored for both time points (on admission and at 6–24 hours) *Patient category:* Mixed	*Median age (years) (IQR):* 64 (53–74) *Male (%):* 60 *White (%):* 85 *Previous CAD (%):* 54 *Family history (%):* 40 *Diabetes (%):* 16 *Smoking (%):* 45 *Hypertension (%):* 46 *Dyslipidaemia (%):* 38 *Median (IQR) time (hours) to presentation:* 4.0 (2.0–8.6)	Roche Elecsys hs-cTnT
APACE (NCT00470587) Badertscher *et al.* 2018[54] Badertscher *et al.* 2018[55]	*Inclusion criteria:* Consecutive adults (aged > 18 years) presenting to the ED with symptoms suggestive of AMI (e.g. acute chest pain, angina pectoris at rest, other thoracic	*Median age (years) (IQR):* 62 (49–74) *Male (%):* 68	Roche Elecsys hs-cTnT; Abbott ARCHITECT hs-cTnI; Siemens Healthcare ADVIA Centaur

TABLE 35 Baseline study details (*continued*)

Study	Selection criteria	Participant details	Assay
[a]Boeddinghaus *et al.* 2017[58] Boeddinghaus *et al.* 2018[59] Boeddinghaus *et al.* 2019[60] Boeddinghaus *et al.* 2019[123] Boeddinghaus *et al.* 2019[170] [b]Cullen *et al.* 2013[156] [b]Hoeller *et al.* 2013[168] [b]Haaf *et al.* 2012[136] [b]Hochholzer *et al.* 2011[149] [b]Irfan *et al.* 2013[158] Jaeger *et al.* 2016[74] Kaier *et al.* 2017[75] Lindahl *et al.* 2017[132] [b]Potocki *et al.* 2012[140] Reichlin *et al.* 2015[90] Reichlin *et al.* 2015[91] [b]Reiter *et al.* 2011[146] [b]Reiter *et al.* 2012[138] [b]Reichlin *et al.* 2009[167] [b]Reichlin *et al.* 2011[145] Rubini Gimenez *et al.* 2014[70] Rubini Gimenez *et al.* 2015[92] Rubini Gimenez *et al.* 2015[93] Rubini Giménez *et al.* 2016[94] Twerenbold *et al.* 2017[105] Twerenbold *et al.* 2017[103] Twerenbold *et al.* 2017[104] Twerenbold *et al.* 2018[106] Twerenbold *et al.* 2018[107]	sensations) within an onset or peak within the last 12 hours *Exclusion criteria:* Terminal kidney failure requiring dialysis *Patient category:* Mixed	*Previous AMI (%):* 24 *Previous CAD (%):* 33 *Previous revascularisation (%):* 27 *Diabetes (%):* 18 *Smoking (%):* 25 *Hypertension (%):* 61 *Dyslipidaemia (hypercholesterolemia) (%):* 49 *Median BMI (kg/m^2) (IQR):* 27 (24–30)	hs-cTnI; Siemens Healthcare Dimension Vista hs-cTnI

continued

TABLE 35 Baseline study details (*continued*)

Study	Selection criteria	Participant details	Assay
Twerenbold *et al.* 2019[108] Wildi *et al.* 2016[111] Wildi *et al.* 2019[113] *Country:* Czechia, Italy, Poland, Spain and Switzerland *Funding:* Swiss National Science Foundation (Bern Switzerland), Swiss Heart Foundation (Bern Switzerland), Department of Internal Medicine of the University Hospital Basel (Basel, Switzerland), Roche, Siemens, Abbott, Brahms, Nanosphere (Northbrook, IL, USA) and 8sense (Rosenheim, Germany) *Recruitment:* April 2006 to August 2011 *Number of participants:* 2245			
BACC (NCT02355457) [a]**Neumann *et al.* 2016**[84] Neumann *et al.* 2017[85] Neumann *et al.* 2017[86] *Country:* Germany *Funding:* This study was supported by the German Center of Cardiovascular Research (Berlin, Germany) and an unrestricted grant from Abbott *Recruitment:* July 2013 to December 2014 *Number of participants:* 1040	*Inclusion criteria:* Adults (aged > 18 years) presenting to the ED with symptoms suggestive of AMI *Exclusion criteria:* STEMI *Patient category:* NSTEMI	*Median age (years) (IQR):* 65 (52–75) *Male (%):* 64.7 *Previous CAD or revascularisation (%):* 33.6 *Previous AMI (%):* 15.6 *Diabetes (%):* 14.4 *Smoking (%):* 23.2 *Hypertension (%):* 69.1 *Dyslipidaemia (hyperlipoproteinemia) (%):* 43.8 *Median BMI (kg/m^2) (IQR):* 26.0 (23.5–29.4)	Abbott ARCHITECT hs-cTnI
BEST [a]**Body *et al.* 2019**[115] **Body *et al.* 2020**[172] *Country:* UK *Funding:* Manchester University NHS Foundation Trust (Manchester, UK). Singulex, Inc. (Alameda, CA, USA) loaned the Singulex Clarity® System and Roche provided reagents without charge for this study	*Inclusion criteria:* Adults (aged > 18 years) who presented to the ED with pain, discomfort or pressure in the chest, epigastrium, neck, jaw or upper limb without an apparent non-cardiac source, which warranted investigation for possible ACS *Exclusion criteria:* Patients with peak symptoms occurring > 12 hours before enrolment; those with unequivocal ST elevation MI; those with another medical condition requiring hospital admission; and patients	*Mean age (years) (SD):* 56 (15) *Male (%):* 60.8 *Previous AMI (%):* 25.4 *Previous revascularisation (%):* 24.2 *Diabetes (%):* 20.5 *Hypertension (%):* 46.5 *Dyslipidaemia (%):* 37.9	Roche Elecsys hs-cTnT

TABLE 35 Baseline study details (*continued*)

Study	Selection criteria	Participant details	Assay
Recruitment: NR *Number of participants:* 665	lacking the mental capacity to provide written informed consent *Patient category:* NSTEMI		
[b]**Body *et al.* 2011**[161] [b]Body *et al.* 2011[153] [b]Body *et al.* 2010[169] *Country:* UK *Funding:* Central Manchester NHS Trust *Recruitment:* January 2006 to February 2007 *Number of participants:* 703	*Inclusion criteria:* Patients presenting to the ED with chest pain; aged > 25 years and chest pain within previous 24 hours that initial treating physician suspected may be cardiac in nature *Exclusion criteria:* Renal failure requiring dialysis; trauma with suspected myocardial contusion; another medical condition mandating hospital admission; and if the patient did not consent to and provide a blood sample for use by the research team *Patient category:* Mixed	*Mean age (years) (SD):* 59 (14) *Male (%):* 61 *Kidney disease (%):* 1 *Previous AMI (%):* 24 *Previous revascularisation (%):* 20 *Previous family history (%):* 48 *Diabetes (%):* 18 *Smoking (%):* 31 *Dyslipidaemia (%):* 48 *Median time to presentation (hours):* 3.5	Roche Elecsys hs-cTnT
Body *et al.* 2015[56] *Country:* UK *Funding:* UK College of Emergency Medicine. hs-cTn kits were donated to the research team by Roche Diagnostics *Recruitment:* NR *Number of participants:* 463	*Inclusion criteria:* Adult patients presenting to the ED with chest pain suspected to be of cardiac origin *Exclusion criteria:* Patients requiring hospital admission for a concomitant medical condition were excluded, as well as those with renal failure needing dialysis, significant chest trauma with suspected myocardial contusion, or who were pregnant; non-English speakers; prisoners (for ethics reasons); and those in whom all means of follow-up would be impossible *Patient category:* Mixed and 30-day MACE	**Mean (SD):** 64 (16) **Male (%):** 58.3 **Previous AMI (%):** 30 **Family History (%):** 36.9 **Diabetes (%):** 17.3 **Smoking (%):** 20.7 **Hypertension (%):** 42.5 **Dyslipidaemia (%):** 40.2	Roche Elecsys hs-cTnT
Cappellini *et al.* 2019[62] *Country:* Italy *Funding:* Not stated *Recruitment:* November 2011 to October 2015 (derivation cohort) *Number of participants:* 6403 (derivation cohort)	*Inclusion criteria:* Adults (aged ≥ 18 years) with suspect NSTEMI arriving at the ED within a median time of 3.4 hours and with three serial time-point measures of hs-cTnT *Exclusion criteria:* Patients with STEMI or with unclassified AMI (because of rapid transfer to other hospitals or death occurring before AMI classification) *Patient category:* NSTEMI	*Median age (years) (IQR):* 73 (59–82) *Male (%):* 55.4 *White (%):* NR No further participant characteristics were reported	Roche Elecsys hs-cTnT

continued

TABLE 35 Baseline study details (*continued*)

Study	Selection criteria	Participant details	Assay
[b]**Christ *et al.* 2010**[150] *Country:* Germany *Funding:* hs-cTnT test kits were provided by Roche *Recruitment:* 7 September 2009 to 21 September 2009 *Number of participants:* 137	*Inclusion criteria:* Consecutive patients with acute chest pain of possible coronary origin presenting to the ED *Exclusion criteria:* NR *Patient category:* Mixed	*Mean age (years) (SD):* 66 (16) *Male (%):* 64 *Previous AMI (%):* 32 *Previous CAD (%):* 34 *Previous revascularisation (%):* 24 *Family history (%):* 12 *Diabetes (%):* 22 *Smoking (%):* 22 *Hypertension (%):* 66 *Dyslipidaemia (%):* 35 *Mean BMI (kg/m^2) (SD):* 28 (5) *Time to presentation:* 0–2 hours 36%; 2–6 hours 22%; 6–24 hours 33%; > 24 hours 20%	Roche Elecsys hs-cTnT
CORE **Borna *et al.* 2018**[116] Mokhtari *et al.* 2016[119] [a]**Mokhtari *et al.* 2016**[121] **Mokhtari *et al.* 2017**[120] *Country:* Sweden *Funding:* The study was funded by an ALF research grant at Skåne University Hospital (Scania, Sweden) and by a grant from Region Skåne (Kristianstad, Sweden), which are national grants from the Swedish government *Recruitment:* February 2013 to April 2014 *Number of participants:* 1138	*Inclusion criteria:* Adults (aged ≥ 18 years) with a primary symptom of non-traumatic chest pain and for whom hs-cTnT was ordered at presentation (0 hours) were enrolled during weekdays between 09.00 and 21.00 *Exclusion criteria:* Patients with severe communication barriers, (e.g. not speaking Swedish or English, or with dementia); STEMI *Patient category:* 30-day MACE	*Median age (years) (IQR):* 63.2 (49.1–73.7) *Male (%):* 54.6 *Previous AMI (%):* 19.9 *Previous revascularisation (%):* 20.3 *Family history (%):* 22.6 *Diabetes (%):* 13.9 *Smoking (current or previous) (%):* 56.3 *Hypertension (%):* 43.5 *Dyslipidaemia (hypercholesterolemia) (%):* 22.8	Roche Elecsys hs-cTnT
FASTER I and FAST II [b]**Eggers *et al.* 2012**[137] *Country:* Sweden *Funding:* Swedish Society of Medicine (Stockholm, Sweden) and the Selander Foundation (Greenwich, CT, USA)	*Inclusion criteria:* Chest pain with ≥ 15-minute duration within the last 24 hours (FAST II) or the last 8 hours (FASTER I). Analysis restricted to patients with symptom onset < 8 hours *Exclusion criteria:* ST segment elevation on the admission 12-lead ECG leading to immediate reperfusion therapy or its consideration was used as	*Median age (years) (IQR):* 67 (58–76) *Male (%):* 66 *Previous AMI (%):* 38 *Previous revascularisation (%):* 18 *Diabetes (%):* 18	Roche Elecsys hs-cTnT

TABLE 35 Baseline study details (*continued*)

Study	Selection criteria	Participant details	Assay
Recruitment: May 2000 to March 2001 (FAST II); October 2002 to August 2003 (FASTER I) *Number of participants eligible (enrolled):* 495 (360)	exclusion criterion *Patient category:* NSTEMI	*Smoking (%):* 18 *Hypertension (%):* 43 *Dyslipidaemia (%):* 38 *Delay < 4 hours (%):* 40	
[b]**Freund *et al.* 2011**[142] [b]Freund *et al.* 2010[166] *Country:* France *Funding:* Assay kits for the study were provided by the manufacturers (Roche) *Recruitment:* August 2005 to January 2007 *Number of participants:* 317	*Inclusion criteria:* Consecutive adults (aged > 18 years) presenting to the ED with chest pain suggestive of ACS (onset or peak within the previous 6 hours) *Exclusion criteria:* Patients with acute kidney failure requiring dialysis were excluded *Patient category:* Mixed (13 were STEMI and 32 NSTEMI)	*Mean age (years) (SD):* 57 (17) *Male (%):* 65 *Previous CAD (%):* 26 *Family history (%):* 32 *Diabetes (%):* 14 *Smoking (%):* 40 *Dyslipidaemia (%):* 36	Roche Elecsys hs-cTnT
High-STEACS (NCT01852123) [a]**Bularga *et al.* 2019**[61] **Chapman *et al.* 2017**[65] **Chapman *et al.* 2018**[66] **Chapman *et al.* 2019**[67] **Miller-Hodges *et al.* 2018**[79] Shah *et al.* 2015[98] *Country:* UK (Scotland) *Funding:* This trial was funded by the British Heart Foundation (Birmingham, UK) (SP/12/10/29922), with support from a Research Excellence Award (RE/18/5/34216). CJW was supported by NHS Lothian through the Edinburgh Clinical Trials Unit. Abbott Laboratories provided cTn assay reagents, calibrators and controls without charge *Recruitment:* June 2013 to March 2016 *Number of participants:* 32,837	*Inclusion criteria:* All patients presenting to the ED were screened by the attending clinician and prospectively included in the trial if cTn was requested for suspected ACS *Exclusion criteria:* Patients were excluded if they had been admitted previously during the study period, were pregnant or did not live in Scotland. Patients with myocardial injury at presentation, with ≤ 2 hours of symptoms or with STEMI elevation MI were excluded *Patient category:* NSTEMI and 30-day MACE	*Mean age (years) (SD):* 58.4 (17.1) *Male (%):* 53.0 *Previous CAD (%):* 23.0 *Previous AMI (%):* 8.0 *Previous revascularisation (%):* 8.8 *Diabetes (%):* 6.0	Abbott ARCHITECT hs-cTnI; Siemens Healthcare Atellica hs-cTnI
High-US Nowak *et al.* 2019[128]	*Inclusion criteria:* ED patients aged ≥ 22 years with suspected AMI. Patients had to have at least one hs-cTnI concentration	*Mean age (years) (SD):* 57 (13) *Male (%):* 56.0	Siemens Healthcare Atellica hs-cTnI; Siemens Healthcare

continued

TABLE 35 Baseline study details (*continued*)

Study	Selection criteria	Participant details	Assay
Nowak *et al.* 2019[129] [a]**Sandoval *et al.* 2019**[176] *Country:* USA *Funding:* Siemens Healthcare *Recruitment:* April 2015 to April 2016 *Number of participants:* 2212	available at presentation, using both the Atellica and ADVIA Centaur assays *Exclusion criteria:* Patients in whom results were not available for either one or both assays, did not have a valid baseline hs-cTnI result, did not have a 12-lead ECG, in whom post-discharge follow-up was missing or presented with STEMI were excluded from analyses *Patient category:* NSTEMI	*White (%):* 56.0 *Previous CAD (%):* 38.0 *Diabetes (%):* 30.0 *Smoking (%):* 27.0 *Hypertension (%):* 70.0	ADVIA Centaur hs-cTnI
Huang *et al.* 2015[72] Guangquan *et al.* 2016[73] *Country:* China *Funding:* Roche Diagnostics GmbH in Shanghai *Recruitment:* July 2009 to December 2013 *Number of participants:* 2249	*Inclusion criteria:* Patients with a suspected diagnosis of AMI (chest pain onset < 12 hours) presenting at the ED *Exclusion criteria:* Patients requiring renal replacement therapy, who had metal coronary stents implanted or who had transferred from other hospitals were excluded (patients with STEMI were excluded from the NSTEMI analysis) *Patient category:* NSTEMI and mixed	*Mean age (years) (range):* 61 (48–71) *Male (%):* 65 *Previous CAD (%):* 15 *Previous revascularisation (%):* 2 *Diabetes (%):* 12.9 *Smoking (%):* 31 *Hypertension (%):* 26 *Dyslipidaemia (%):* 5.4	Roche Elecsys hs-cTnT
[b]**Keller *et al.* 2011**[141] [b]Keller *et al.* 2011[163] *Country:* Germany *Funding:* Abbott Diagnostics provided study funding *Recruitment:* January 2007 to December 2008 *Number of participants:* 1818	*Inclusion criteria:* Consecutive adults (aged 18–85 years) presenting to three chest pain units with chest pain suggestive of ACS *Exclusion criteria:* Major surgery or trauma within the previous 4 weeks; pregnancy; intravenous drug abuse; and anaemia (haemoglobin < 10 g/dl) *Patient category:* Mixed	*Mean age (years) (SD):* 61 (14) *Male (%):* 66 *Previous CAD (%):* 36 *Family history (%):* 32 *Diabetes (%):* 16 *Smoking (%):* 24 *Hypertension (%):* 74 *Dyslipidaemia (%):* 73 *Mean BMI (kg/m^2) (SD):* 28 (5)	Abbott ARCHITECT hs-cTnI
[b]**Kurz *et al.* 2011**[148] *Country:* Germany *Funding:* Investigators were supported by Roche Diagnostics and assay kits were also provided by the manufacturer *Recruitment:* May 2008 to December 2008 *Number of participants:* 94	*Inclusion criteria:* Consecutive patients admitted to a chest pain unit with symptoms suggestive of ACS *Exclusion criteria:* ST segment elevation; severe kidney dysfunction (eGFR < 60 ml/minute/1.73 m^2); and patients undergoing PCI during follow-up sampling *Patient category:* NSTEMI	*Mean age (years) (SD):* 66 (11) *Male (%):* 71 *Previous AMI (%):* 37 *Previous CAD (%):* 50 *Previous revascularisation (%):* 17 *Family history (%):* 32 *Diabetes (%):* 31	Roche Elecsys hs-cTnT

TABLE 35 Baseline study details (*continued*)

Study	Selection criteria	Participant details	Assay
		Smoking (%): 22 *Hypertension (%):* 78 *Dyslipidaemia (%):* 65 *Median symptom onset (minutes) (IQR):* 358 (152–929) *Mean (SD) BMI (kg/m²):* 28 (4)	
Lin *et al.* 2019[117] *Country:* Singapore *Funding:* This study was funded by the SingHealth Foundation Research grant (SHF/FG403P/2008) and National University of Singapore *Recruitment:* March 2010 to April 2014 *Number of participants:* 2444	*Inclusion criteria:* Adults (aged ≥ 25 years) presenting to the ED, from Monday to Friday, from 08.00 to 21.00 hours, with symptoms suggestive of ACS (e.g. chest pain or angina equivalent) *Exclusion criteria:* STEMI; end-stage renal failure; no cTn obtained as part of standard care; lost to follow-up *Patient category:* 30-day MACE	*Median age (years) (IQR):* 55 (47–64) *Male (%):* 66.9 *Previous CAD (%):* 25.3 *Previous AMI (%):* 10.1 *Previous revascularisation (%):* 21.3 *Family history (%):* 14.7 *Diabetes (%):* 13.3 *Smoking (current and previous) (%):* 26.8 *Hypertension (%):* 70.9 *Dyslipidaemia (%):* 52.7	Roche Elecsys hs-cTnT
[b]**Melki *et al.* 2011**[144] [b]Melki *et al.* 2010[154] *Country:* Sweden *Funding:* Partially supported by a grant from Roche Diagnostics, who also provided reagents. Supported by the Swedish Heart and Lung Foundation (Stockholm, Sweden) and the National Board of Health and Welfare (Stockholm, Sweden) *Recruitment:* August 2006 to January 2008 *Number of participants:* 233	*Inclusion criteria:* Patients admitted to a coronary care unit with chest pain or other symptoms suggestive of ACS within 12 hours of admission *Exclusion criteria:* Patients with persistent ST segment elevation *Patient category:* NSTEMI	*Median age (years) (IQR):* 65 (55–76) *Male (%):* 67 *Previous AMI (%):* 30 *Previous revascularisation (%):* 21 *Diabetes (%):* 23 *Smoking (%):* 17 *Hypertension (%):* 50 Median time (hours) from symptom onset (25th to 75th centile): 5 (3–8)	Roche Elecsys hs-cTnT
[a]**Peacock *et al.* 2018**[89] **Chang *et al.* 2018**[124] *Country:* USA *Funding:* Roche Diagnostics	*Inclusion criteria:* Adults (aged ≥ 21 years) presenting to one of 15 US EDs with suspected ACS, within 24 hours of symptom onset *Exclusion criteria:* AMI in previous 3 months; transfer from another medical facility;	*Median age (years) (IQR):* 55 (47–64) *Male (%):* 51.6 *Previous CAD (%):* 26.5 *Previous AMI (%):* 18.6	Roche Elecsys hs-cTnT STAT

continued

TABLE 35 Baseline study details (*continued*)

Study	Selection criteria	Participant details	Assay
Recruitment: 2011–15 *Number of participants:* 1679	surgery (including percutaneous coronary intervention) or hospitalisation within the last 3 months; recent cardioversion or defibrillation, acute non-cardiac primary illness prior to enrolment (e.g. severe sepsis); cardiogenic shock; and pregnancy *Patient category:* Mixed and MACE	*Previous revascularisation (%):* 22.5 *Diabetes (%):* 26.1 *Smoking (%):* 30.5 *Hypertension (%):* 66.2 *Dyslipidaemia (%):* 50.1 *Median BMI (kg/m^2) (IQR):* 29.9 (25.9–35.4)	
PITAGORAS [b]**Sanchis *et al.* 2012**[135] *Country:* Spain *Funding:* Supported by a grant from Roche Diagnostics *Recruitment:* NR *Number of participants:* 446	*Inclusion criteria:* Patients presenting to the ED with chest pain of possible coronary origin and onset of pain within the previous 24 hours *Exclusion criteria:* Persistent ST segment elevation on an ECG; troponin elevation in any of two serial determinations (at arrival and 6–8 hours later); prior diagnosis of ischemic heart disease by either the finding of significant stenosis in a prior coronary angiogram or previously documented AMI; left bundle branch block or other non-interpretable ECG or inability to perform exercise test; structural heart disease different to ischemic heart disease; concomitant heart failure or significant bradyarrhythmia (< 55 beats/minute) or tachyarrhythmia (> 110 beats/minute) at admission *Patient category:* NSTEMI	*Mean age (years) (SD):* 60 (12) *Male (%):* 59 *Family history (%):* 14 *Diabetes (%):* 20 *Smoking (%):* 25 *Hypertension (%):* 54 *Dyslipidaemia (%):* 46	Roche Elecsys hs-cTnT
QUART (ACTRN12610000053022) [b]Parsonage *et al.* 2013[151] Parsonage *et al.* 2013[131] [a]**Parsonage *et al.* 2014**[88] *Country:* Australia *Funding:* Emergency Medicine Foundation (Milton, QLD, Australia) and Roche Diagnostics *Recruitment:* November 2008 to February 2011 *Number of participants:* 764	*Inclusion criteria:* Consecutive adult patients (aged ≥ 18 years) presenting during office hours to a single, large, metropolitan tertiary hospital ED with symptoms suggestive of cardiac chest pain *Exclusion criteria:* A clear cause of symptoms other than ACS; inability or unwillingness to provide consent or be contacted after discharge; recruitment considered inappropriate by staff (e.g. palliative treatment); interhospital transfer; pregnancy; and previous enrolment *Patient category:* Mixed	*Mean age (years) (SD):* 55.3 (15.1) *Male (%):* 61.3 *Previous AMI (%):* 17.9 *Previous revascularisation (%):* 17.1 *Family history (%):* 50.5 *Diabetes (%):* 14.7 *Smoking (recent or current) (%):* 31.0 *Hypertension (%):* 49.2 *Dyslipidaemia (%):* 50.9 *Median (IQR) time to presentation (hours):* 4.97 (1.63–20.60)	Roche Elecsys hs-cTnT

TABLE 35 Baseline study details (*continued*)

Study	Selection criteria	Participant details	Assay
RATPAC (point-of-care arm) [b]**Collinson 2013**[159] [b]Collinson 2012[164] [b]Collinson 2012[152] *Country:* UK *Funding:* UK HTA programme *Recruitment:* February 2007 to June 2008 *Number of participants:* 850	*Inclusion criteria:* Patients presenting to the ED with chest pain due to suspected, but not proven, AMI *Exclusion criteria:* ECG changes diagnostic for AMI or high-risk ACS (> 1 mm ST deviation or > 3 mm inverted T waves); known CAD with prolonged (> 1 hour) or recurrent typical cardiac-type pain; proven or suspected serious non-cardiac pathology (e.g. PE); comorbidity or social problems requiring hospital admission even if AMI ruled out; obvious non-cardiac cause of chest pain (e.g. pneumothorax or muscular pain); and presentation > 12 hours after most significant episode of pain *Patient category:* NSTEMI	*Median age (years) (IQR):* 54 (44–64) *Male (%):* 60 *Previous AMI (%):* 40 *Previous revascularisation (%):* 1 *Diabetes (%):* 8 *Smoking (%):* 28 *Hypertension (%):* 35 *Dyslipidaemia (%):* 24 *Median (IQR) time to presentation (hours):* 8.25 (5.17–12.30)	Roche Elecsys hs-cTnT
REACTION-US **Nowak *et al.* 2018**[87] Nowak *et al.* 2018[127] *Country:* USA *Funding:* The Henry Ford Health System (Detroit, MI, USA) and Roche Diagnostics *Recruitment:* NR *Number of participants:* 569	*Inclusion criteria:* Convenience sample (patients screened when research co-ordinators were available) of adults (aged > 21 years) presenting to the ED with symptoms suggestive of ACS and for whom a triage ECG was available *Exclusion criteria:* Patients with acute distress requiring immediate life-saving interventions; cardioversion or defibrillation or thrombolytic therapy within the previous 24 hours; STEMI leading to immediate reperfusion therapy; traumatic injuries; transfers from other facilities; and patients who were pregnant or breast feeding *Patient category:* NSTEMI	*Median age (years) (IQR):* 55 (49–63) *Male (%):* 52 *Previous CAD (%):* 35.9 *Previous AMI (%):* 29.5 *Previous revascularisation (%):* 24.6 *Family history (%):* 38.8 *Diabetes (%):* 28.8 *Smoking (%):* 37.3 *Hypertension (%):* 81.5 *Dyslipidaemia (hypercholesterolemia) (%):* 50.3 *Median (IQR) time to presentation (hours):* 8.7 (2.3–41.5)	Roche Elecsys hs-cTnT
ROMI-3 (NCT01994577) Kavasak *et al.* 2017[76] [a]**Shortt *et al.* 2017**[101] *Country:* Canada *Funding:* Canadian Institutes of Health Research (Ottawa, ON, Canada), Abbott Laboratories, Roche Diagnostics, Healthcare Diagnostics, Ortho Clinical	*Inclusion criteria:* Adults (aged ≥ 18 years) presenting to the ED with symptoms of and investigated for ACS (i.e. troponin ordered by an ED physician) *Exclusion criteria:* Patients were excluded if they met any of the following exclusion criteria before troponin I testing: death (all cause); STEMI; and serious ventricular cardiac dysrhythmia. Patients who had any of the	*Mean age (years) (SD):* with MI 73.3 (14.1), without MI 65.8 (16.6) *Male (%):* 47.1 *Family history (%):* 54.2 *Diabetes (%):* 29.3 *Smoking (%):* 25.7 *Hypertension (%):* 70.7	Roche Elecsys hs-cTnT; Abbott ARCHITECT hs-cTnI

continued

TABLE 35 Baseline study details (*continued*)

Study	Selection criteria	Participant details	Assay
Diagnostics, Randox Laboratories, Beckman Coulter and CADTH *Recruitment:* May 2013 to August 2013 *Number of participants:* 1137	following health conditions within the previous 30 days were also excluded: traumatic chest pain, including surgery or cardiac manipulation; STEMI or NSTEMI; diagnosis of pulmonary embolus; known active malignancy; sepsis; patients who were previously enrolled or transferred from another primary care facility *Patient category:* NSTEMI	*Dyslipidaemia (hypercholesterolemia) (%):* 59.5	
[b]**Saenger *et al.* 2010**[165] *Country:* USA *Funding:* Two authors declared individual funding from manufacturers (one from Roche Diagnostics and one from Beckman Coulter and Abbott) *Recruitment:* NR. Conference abstract only Number of participants: 288	*Inclusion criteria:* Patients presenting to the ED with symptoms suggestive of AMI *Exclusion criteria:* None reported *Patient category:* Mixed *Details:* NSTEMI 19% and STEMI 15%	No further participant details reported	Roche Elecsys hs-cTnT
[b]**Sebbane 2013**[157] *Country:* France *Funding:* Study funded by the hospital, with assay reagents supplied by the manufacturers *Recruitment:* December 2009 to November 2011 *Number of participants:* 248	*Inclusion criteria:* Adults presenting to the ED with chest pain–recent (within 12 hours of presentation) *Exclusion criteria:* Traumatic causes of chest pain. STEMI was defined by the persistent elevation of the ST segment of at least 1 mm in two contiguous ECG leads or by the presence of a new left bundle branch block with positive cardiac enzyme results. Patients with STEMI were excluded from the analysis for our review *Patient category:* NSTEMI (data also reported for mixed AMI but not extracted)	*Median age (years) (IQR):* 61 (48–75) *Male (%):* 63	Roche Elecsys hs-cTnT
Shiozaki *et al.* 2017[100] *Country:* Japan and Taiwan *Funding:* This work was supported by Japan Society for the Promotion of Science (Tokyo, Japan) Grants-in-Aid for Scientific Research (grant number JP24591070)	*Inclusion criteria:* Patients presenting with chest pain suggestive of ACS in whom the attending physician planned to perform serial biomarker tests *Exclusion criteria:* STEMI; patients who staff considered recruitment inappropriate for (e.g. terminal illness); and patients with trauma that may have increased troponin levels *Patient category:* NSTEMI	*Median age (years) (IQR):* 72 (59–81) *Male (%):* 60.8 *Previous revascularisation (%):* 24.9 *Diabetes (%):* 26.9 *Smoking (%):* 18.9 *Hypertension (%):* 63.9	Roche Elecsys hs-cTnT

TABLE 35 Baseline study details (*continued*)

Study	Selection criteria	Participant details		Assay
Recruitment: November 2014 to April 2015 *Number of participants:* 413		*Dyslipidaemia (%):* 60.5 *Median BMI (kg/m²) (IQR):* 23.3 (20.6–25.8)		
Slagman *et al.* 2017[102] *Country:* Germany *Funding:* NR *Recruitment:* October 2012 to March 2013, and August 2013 to November 2013 *Number of participants:* 3423	*Inclusion criteria:* All patients with routine point-of-care troponin T measurement at admission, who presented to the ED of a tertiary care hospital *Exclusion criteria:* Patients with a final diagnosis of STEMI and patients with surgical conditions were excluded, as were patients with missing troponin values *Patient category:* NSTEMI	*Median age (years) (IQR):* 61 (45–73) *Male (%):* 57.2 *Family history (%):* 32.0 *Diabetes (%):* 22.8 *Smoking (%):* 34.2 *Hypertension (%):* 18.4 *Dyslipidaemia (hypercholesterolemia) (%):* 9.6 *Median BMI (kg/m²) (IQR):* 27 (24–30)		Roche Elecsys hs-cTnT
TRAPID-AMI Body *et al.* 2015[122] **Body *et al.* 2016**[114] McCord *et al.* 2017[126] [a]**Mueller *et al.* 2016**[80] Mueller-Hennessen *et al.* 2016[81] **Mueller-Hennessen *et al.* 2017**[82] Mueller-Hennessen *et al.* 2019[83] *Country:* Belgium, Germany, Italy, Switzerland, Spain, Sweden, UK, USA and Australia *Funding:* Roche Diagnostics *Recruitment:* April 2011 to June 2013 *Number of participants:* 1282	*Inclusion criteria:* Adults (aged ≥ 18 years) presenting to the ED with symptoms suggestive of AMI (such as acute chest pain and angina pectoris) and with an onset or maximum of discomfort or pain within the previous 6 hours *Exclusion criteria:* Patients with renal failure requiring long-term haemodialysis; those with trauma, cardioversion, defibrillation, or thrombolytic therapy before inclusion; individuals receiving coronary artery bypass grafting within the last month or hospitalised for AMI within the last 3 weeks; and pregnant and breastfeeding women *Patient category:* NSTEMI, mixed and 30-day MACE	*Median age (years) (IQR):* 62 (50–74) *Male (%):* 62.8 *Previous AMI (%):* 24.9 *Previous revascularisation (%):* 30.3 *Diabetes (%):* 21.1 *Smoking (%):* 22.8 *Hypertension (%):* 62.8 *Dyslipidaemia (hypercholesterolemia) (%):* 10.8		Roche Elecsys hs-cTnT
TRUST (ISRCTN 21109279) **Carlton *et al.* 2015**[63] [a]**Carlton *et al.* 2015**[64] *Country:* UK	*Inclusion criteria:* Consecutive patients were screened and recruited 24 hours a day, 7 days a week, during the study period. Patients were included if they were aged ≥ 18 years and had at least 5 minutes of chest pain suggestive of ACS, and for whom the attending physician	Roche hs-cTnT cohort *Mean age (years) (SD):* 58.0 (13.3) *Male (%):* 58.8	Abbott hs-cTnI cohort *Mean age (years) (SD):* 57.9 (13.0) *Male (%):* 59.4	Roche Elecsys hs-cTnT; Abbott ARCHITECT hs-cTnI

continued

TABLE 35 Baseline study details (*continued*)

Study	Selection criteria	Participant details		Assay
Funding: This study was funded by the Royal College of Emergency Medicine (London, UK) and Bournemouth University (Dorset, UK). The lead author received funding from Abbott for related research *Recruitment:* July 2012 to August 2013 *Number of participants:* 963 (959 Roche hs-cTnT; 867 Abbott hs-cTnI)	determined that evaluation with serial troponin testing was required. Possible cardiac symptoms included acute chest, epigastric, neck, jaw, or arm pain, or discomfort or pressure without an apparent non-cardiac source, in accordance with the AHA case definitions *Exclusion criteria:* Patients were excluded if any of the following were present: STEMI or left bundle branch block not known to be old; ECG changes diagnostic of ischemia (ST segment depression ≥ 1 mm or T-wave inversion); arrhythmias (new-onset atrial fibrillation, atrial flutter, sustained supraventricular tachycardia, second-degree or complete heart block, or sustained or recurrent ventricular arrhythmias); aged ≥ 80 years; atypical symptoms in the absence of chest discomfort; a clear non-ACS cause for chest pain at presentation (e.g. pulmonary embolism, pneumonia, aortic dissection); another medical condition requiring hospital admission; refusal or inability to give informed consent; non-English speaking; pregnancy; renal failure requiring dialysis; or inability to be contacted after discharge *Patient category:* NSTEMI	*White (%):* 95.2 *Previous AMI (%):* 21.3 *Previous revascularisation (%):* 24.3 *Family history (%):* 36.8 *Diabetes (%):* 17.1 *Smoking (%):* 24.1 *Hypertension (%):* 55.1 *Dyslipidaemia (%):* 66.1 *Median time to presentation (hours):* 2.4	*White (%):* 95.4 *Previous AMI (%):* 21.9 *Previous revascularisation (%):* 24.1 *Family history (%):* 37.7 *Diabetes (%):* 16.7 *Smoking (%):* 24.2 *Hypertension (%):* 55.0 *Dyslipidaemia (%):* 67.2 *Median time to presentation (hours):* 2.3	
TUSCA [b]**Santaló *et al.* 2013**[133] *Country:* Spain *Funding:* Reagents and logistical support were provided by Roche Diagnostics *Recruitment:* NR *Number of participants:* 358	*Inclusion criteria:* Adult (aged > 18 years) described as presenting with ACSs and symptom duration ≥ 5 minutes. Population included 174 people with a final diagnosis of non-ACSs *Exclusion criteria:* ST segment elevation; new left bundle branch block; pre-admission thrombolytic therapy; defibrillation or cardioversion before sampling; pregnancy; renal failure requiring dialysis; UA within 2 months; and coronary artery bypass graft within 3 months *Patient category:* NSTEMI	*Mean age (years) (range):* 69 (27–93) *Male (%):* 68 *Previous CAD (%):* 35 *Diabetes (%):* 26 *Hypertension (%):* 62 *Presentation within 3 hours:* 46.2%		Roche Elecsys hs-cTnT

TABLE 35 Baseline study details (*continued*)

Study	Selection criteria	Participant details	Assay
UTROPIA (NCT02060760) Dodd *et al.* 2019[125] **Sandoval *et al.* 2017**[95] [a]**Sandoval *et al.* 2017**[96] *Country:* USA *Funding:* Abbott Diagnostics and the Minneapolis Medical Research Foundation (Minneapolis, MN, USA) *Recruitment:* February 2014 to May 2014 *Number of participants:* 1631	*Inclusion criteria:* Consecutive unselected patients in whom initial pre-set serial troponin I measurements at 0, 3, 6 and 9 hours were ordered on clinical indication to rule in and rule out AMI. For inclusion, patients needed a baseline troponin I measurement at presentation and at least one additional troponin I measured within 24 hours of presentation before discharge and at least one 12-lead ECG *Exclusion criteria:* Aged < 18 years; STEMI; pregnancy; trauma; declined to participate on research, as documented on information disclosure; did not present through the ED; or were transferred from an outside hospital *Patient category:* NSTEMI	*Mean age (years) (SD):* 57 (15) *Male (%):* 56 *Previous CAD (%):* 23 *Previous AMI (%):* 12 *Previous revascularisation (%):* 14 *Diabetes (%):* 43 *Smoking (history of tobacco use) (%):* 59 *Hypertension (%):* 66 *Dyslipidaemia (%):* 43	Abbott ARCHITECT hs-cTnI
Venge *et al.* 2017[110] *Country:* Germany, France, Austria and the Netherlands *Funding:* NR *Recruitment:* NR *Number of participants:* 450	*Inclusion criteria:* Adults (aged ≥ 18 years) presenting with symptoms suggestive of MI, presenting for the first time and < 12 hours after symptom onset *Exclusion criteria:* NR *Patient category:* Mixed	*Median age (years) (range):* 62 (18–94) *Male (%):* 58.9 *Previous CAD (%):* 36.2 *Previous AMI (%):* 17.9 *Previous revascularisation (%):* 28.2 *Family history (%):* 28.0 *Diabetes (%):* 22.1 *Smoking (%):* 25.9 *Hypertension (%):* 61.1 *Dyslipidaemia (%):* 42.4 *Median BMI (kg/m^2) (range):* 26.4 (15.9–50.6)	Abbott ARCHITECT hs-cTnI

BACC, Biomarkers in Acute Cardiac Care; BMI, body mass index; CORE, Clinical Objective Rule-out Evaluation; FAST II, Fast Assessment of Thoracic Pain II; FASTER I, Fast Assessment of Thoracic Pain by nEuRal networks I; NR, not reported; PCI, percutaneous coronary intervention; PE, pulmonary embolism; REACTION-US, Rapid Evaluation of Acute Myocardial Infarction in the United States; TUSCA, UltraSensitive Troponin in Acute Coronary syndromes; UTROPIA, Use of TROPonin In Acute coronary syndromes.

a Publication(s) from which participant details have been taken.

b Publication included in the assessment report for DG15.[2]

Note

Publications in bold have provided data for inclusion in this assessment.

TABLE 36 Index test and reference standard details

	High-sensitivity troponin (ng/l)				Reference standard			
Study	Assay(s)	LoD	99th centile	CoV	Target condition(s)	Reference standard	Standard troponin	Observer
ADAPT (ACTRN12611001069943) Aldous *et al.* 2014[53] **Boeddinghaus *et al.* 2016**[57] [a]**Cullen *et al.* 2013**[156] [b]**Cullen *et al.* 2014**[68] Eggers *et al.* 2016[69] **Greenslade *et al.* 2015**[71] Meller *et al.* 2015[118] Parsonage *et al.* 2013[130] **van der Linden *et al.* 2018**[109] Wildi *et al.* 2017[112]	Abbott ARCHITECT hs-cTnI	1.9	26.2	< 5% at 26.2	NSTEMI; MACE	*Third Universal Definition of Myocardial Infarction*[43] The criteria for a MACE included any of the following: death (excluding clearly non-cardiac); cardiac arrest; AMI; emergency revascularisation procedure; cardiogenic shock; ventricular arrhythmia requiring intervention; and a high-degree atrioventricular block requiring intervention, within 30 days after initial presentation	Conventional troponins were measured using Abbott Diagnostics TnI (Abbott Laboratories, Abbott Park, IL, USA) (LoD 10 ng/l, 99th centile 28 ng/l, CoV < 10% at 32 ng/l, decision threshold 30 ng/l) or Beckman Coulter second generation Accutane (Beckman Coulter, Brea, CA, USA) (LoD 10 ng/l, 99th centile 40 ng/l, CoV < 10% at 60 ng/l, decision threshold 40 ng/l) Serial sampling up to at least 6 hours	Adjudication of all cardiac end points was made by two cardiologists, with consultation of a third cardiologist in case of disagreement. Cardiologists had knowledge of the clinical record, ECG, troponin results and objective testing from standard care
	Roche Elecsys hs-cTnT	5	14	10% at 13				
ADAPT/IMPACT (ACTRN12611001069943/ ACTRN12611000206921) **Nestelberger *et al.* 2019**[171]	Beckman Coulter ACCESS hs-cTnI	2.3	18; females 12; males 20	< 10% at 18	NSTEMI	*Third Universal Definition of Myocardial Infarction*[43]	NR	Two independent cardiologists not directly involved in patient care reviewed all available medical records (i.e. history, physical examination, results of laboratory testing, including hs-cTnT concentrations, radiologic testing, electrocardiography, echocardiography, cardiac exercise test,

Study	High-sensitivity troponin (ng/l)				Reference standard			
	Assay(s)	LoD	99th centile	CoV	Target condition(s)	Reference standard	Standard troponin	Observer
								lesion severity and morphology in coronary angiography, discharge summary) pertaining to the patient from the time of ED presentation to 30-day follow-up
[a]**Aldous *et al.* 2012**[139] [a]**Aldous *et al.* 2012**[134] [a]Aldous *et al.* 2011[143]	Roche Elecsys hs-cTnT	5	14	< 10% at 13	NSTEMI	ACC[227]	Conventional troponins were measured using Abbott Diagnostics TnI (LoD 10 ng/l, 99th centile 28 ng/l, CoV < 10% at 32 ng/l, decision threshold 30 ng/l) *Timing:* On presentation and at 2 hours and 6–12 hours	Diagnoses on admission and at follow-up were independently adjudicated by one cardiologist, who was blinded to hs-cTnT results
[a]**Aldous *et al.* 2011**[147] [a]Aldous *et al.* 2010[155] [a]Aldous *et al.* 2011[162]	Roche Elecsys hs-cTnT	5	14	< 10% at 13	AMI	Joint ESC, ACC, AHA and WHF[9]	Conventional troponins were measured using Abbott Diagnostics TnI 2 (LoD 10 ng/l, 99th centile 28 ng/l, CoV < 10% at 32 ng/l) Change (rise or fall) in troponin I 2, or no change but no clear alternative cause of troponin elevation, were considered indicative of AMI *Timing:* On presentation and at follow-up (6–24 hours)	Final diagnoses were adjudicated independently by cardiologists, blinded to patient history and hs-cTnT

continued

TABLE 36 Index test and reference standard details (*continued*)

	High-sensitivity troponin (ng/l)				Reference standard			
Study	Assay(s)	LoD	99th centile	CoV	Target condition(s)	Reference standard	Standard troponin	Observer
APACE (NCT00470587) Badertscher *et al.* 2018[54] Badertscher *et al.* 2018[55] **Boeddinghaus *et al.* 2017**[58] [b]**Boeddinghaus *et al.* 2018**[59] [b]**Boeddinghaus *et al.* 2019**[60] Boeddinghaus *et al.* 2019[123] [b]**Boeddinghaus *et al.* 2019**[170] [a]**Cullen *et al.* 2013**[156] [a]**Hoeller *et al.* 2013**[168] [a]Haaf *et al.* 2012[136] [a]**Hochholzer *et al.* 2011**[149] [a]Irfan *et al.* 2013[158] **Jaeger *et al.* 2016**[74] **Kaier *et al.* 2017**[75] [b]**Lindahl *et al.* 2017**[132]	Roche Elecsys hs-cTnT Abbott ARCHITECT hs-cTnI Beckman Coulter Access hs-cTnI Siemens Healthcare ADVIA Centaur hs-cTnI Siemens Healthcare Dimension Vista hs-cTnI Ortho VITROS hs-cTnI bioMérieux VIDAS hs-cTnI	5 1.9 2.3 2.2 0.5 0.4 1.3–3.2	14 26.2 18 47 9 11 19	10% at 13 < 5% at 1.9 < 5% at 18 < 5% at 47 10% at 3 < 7% at 11 7% at 19	NSTEMI; AMI; MACE	*Third Universal Definition of Myocardial Infarction*[43]	Myocardial necrosis was diagnosed by at least one conventional troponin value above the 99th centile together with a significant rising or falling	Adjudication of the final diagnosis was performed by two independent cardiologists at the core laboratory (University Hospital Basel, Basel, Switzerland), applying the universal definition of AMI by using two sets of data. First, all available medical records obtained during clinical care, including history, physical examination, results of laboratory testing [including serial clinical (hs)-Tn levels], radiological testing, electrocardiography, echocardiography, cardiac exercise test, lesion severity and morphology in coronary angiography, pertaining to the patient from the time of ED presentation to 90-day follow-up. Second, study-specific assessments, including detailed chest pain characteristics using 34 predefined criteria, serial hs-cTnT concentrations and

Study	High-sensitivity troponin (ng/l)				Reference standard			
	Assay(s)	LoD	99th centile	CoV	Target condition(s)	Reference standard	Standard troponin	Observer
[a]**Potocki *et al.* 2012**[140]								clinical follow-up by telephone. In situations of disagreement about the diagnosis, cases were reviewed and adjudicated in conjunction with a third cardiologist
Reichlin *et al.* 2015[90]								
Reichlin *et al.* 2015[91]								
[a]Reiter *et al.* 2011[146]								
[a]Reiter *et al.* 2012[138]								
[a]Reichlin *et al.* 2009[167]								
[a]Reichlin *et al.* 2011[145]								
Rubini Gimenez *et al.* 2014[70]								
Rubini Gimenez *et al.* 2015[92]								
Rubini Gimenez *et al.* 2015[93]								
Rubini Giménez *et al.* 2016[94]								
Twerenbold *et al.* 2017[105]								
Twerenbold *et al.* 2017[103]								
Twerenbold *et al.* 2017[104]								
Twerenbold *et al.* 2018[106]								
Twerenbold *et al.* 2018[107]								
Twerenbold *et al.* 2019[108]								

continued

TABLE 36 Index test and reference standard details (*continued*)

	High-sensitivity troponin (ng/l)				Reference standard			
Study	**Assay(s)**	**LoD**	**99th centile**	**CoV**	**Target condition(s)**	**Reference standard**	**Standard troponin**	**Observer**
Wildi *et al.* 2016[111]								
Wildi *et al.* 2019[113]								
BACC	Abbott ARCHITECT hs-cTnI	1.9	27	10% at 5.2	NSTEMI	ESC[33]	Roche Elecsys hs-cTnT on admission and at 3 hours	The final diagnosis was adjudicated based on all available clinical and imaging results, electrocardiography and standard laboratory testing, including hs-cTnT. The final diagnosis of all patients was made by two cardiologists independently and disagreements were resolved by consultation with a third cardiologist
Neumann *et al.* 2016[84]								
Neumann *et al.* 2017[85]								
Neumann *et al.* 2017[86]								
BEST	Roche Elecsys hs-cTnT	5	14 (16 males, 9 females)	< 10% at 5	NSTEMI	*Third Universal Definition of Myocardial Infarction*[43]	Roche Elecsys hs-cTnT on admission and at 3 hours	Outcomes were adjudicated by two independent investigators based on all available clinical data up to 30 days after presentation
[b]**Body *et al.* 2019**[115]								
[b]**Body *et al.* 2020**[172]	Siemens ADVIA Centaur hs-cTnI	1.6	47	< 10% at 6				
[a]**Body *et al.* 2011**[161]	Roche Elecsys hs-cTnT	5	14	< 10% at 9	AMI	Joint ESC, ACC, AHA and WHF[9]	Rise or fall of cTnT, or both, above the 99th centile (10 ng/l) in the appropriate clinical context. For patients with modest elevations of cTnT (< 0.1 ng/ml) at baseline, an absolute difference of at least 20 ng/l on serial sampling was considered	Two independent investigators who had all clinical, laboratory and imaging data available for review, but who were blinded to hs-cTnT levels
[a]Body *et al.* 2011[153]								
[a]Body *et al.* 2010[169]								

Study	High-sensitivity troponin (ng/l)				Reference standard			
	Assay(s)	LoD	99th centile	CoV	Target condition(s)	Reference standard	Standard troponin	Observer
							to represent a significant rise, fall, or both based on the analytical performance of the cTnT assay *Timing:* At least 12 hours after the onset of the most significant symptoms	
Body *et al.* 2015[56]	Roche Elecsys hs-cTnT	5	14	< 10% at 12	AMI	AMI was diagnosed on the basis of a rise and/or fall of cTnT above the 99th centile, with a minimum change between samples of 0.02 µg/l, in conjunction with the appropriate clinical context, imaging evidence of MI or ischemic ECG changes MACE within 30 days was defined as death, incident AMI or the need for coronary revascularisation, or if the treating cardiologist reported the presence of a coronary stenosis of > 50%	Standard troponin T (cTnT, fourth generation Elecsys, Roche Diagnostics; 99th centile 0.01 µg/l, CoV < 10% at 0.035 µg/l, LoD 0.01 µg/l) at the time of arrival in the ED and 12 hours after symptom onset	The primary outcome of AMI was adjudicated by two independent investigators, with all clinical, laboratory and imaging data (including reference standard 12-hour cTnT concentrations) available for review, but blinded to investigational assay (hs-cTnT) results. Disagreements were resolved by discussion
Cappellini *et al.* 2019[62]	Roche Elecsys hs-cTnT	5	14	NR	NSTEMI	AMI in accordance with the *Third Universal Definition of Myocardial Infarction*[43]	NR	Final diagnoses were made by the attending ED physician if participants were not

continued

TABLE 36 Index test and reference standard details (*continued*)

Study	High-sensitivity troponin (ng/l)				Reference standard			
	Assay(s)	LoD	99th centile	CoV	Target condition(s)	Reference standard	Standard troponin	Observer
								hospitalised and by a physician of the specific medical unit in the case of hospitalisation, with cardiologist consultations when required
[a]**Christ *et al.* 2010**[150]	Roche Elecsys hs-cTnT	3	14	< 10% at 13	AMI	Joint ESC, ACC, AHA and WHF[9]	Myocardial necrosis was diagnosed on the basis of a rising and/or falling cTnT pattern (> 20% or < 20% compared with the cTnT levels admission) with at least one value above the 99th centile and an imprecision of < 10%. Myocardial necrosis not related to AMI was defined as a typical rise and fall of cTnT levels without clinical evidence of CAD, and cardiac pain without necrosis was defined as a typical patient history and clinical signs of cardiac pain without increased levels of cTnT. UA was diagnosed when a patient had normal troponin levels and typical angina at rest or exercise, or a cardiac catheterisation result compatible with the diagnosis. cTnT cut-off level of 0.04 µg/l	Two independent consultants

Study	High-sensitivity troponin (ng/l)				Reference standard			
	Assay(s)	LoD	99th centile	CoV	Target condition(s)	Reference standard	Standard troponin	Observer
							Timing: At presentation and about 6 hours at discretion of physician	
CORE **Borna *et al.* 2018**[116] Mokhtari *et al.* 2016[119] **Mokhtari *et al.* 2016**[121] **Mokhtari *et al.* 2017**[120]	Roche Elecsys hs-cTnT	5	14	< 10% at 14	MACE	MACEs were defined as an adjudicated diagnosis of AMI, UA, cardiac arrest, cardiogenic shock, ventricular arrhythmia requiring intervention, high-degree atrioventricular block requiring intervention, or death from a cardiac or unknown cause AMI was defined in accordance with the universal definition, requiring a significant increase or decrease of hs-cTnT levels, with at least one value above the 99th centile, combined with symptoms or signs of cardiac ischaemia	Roche Elecsys hs-cTnT	MACEs were independently adjudicated by two clinicians (internal medicine and cardiology, and emergency medicine), blinded to each other's assessments and hs-cTnT results. Disagreements were resolved by consultation with two or three cardiologists
FASTER I and FAST II [a]**Eggers *et al.* 2012**[137]	Roche Elecsys hs-cTnT	3	14	< 10% at 13	NSTEMI	Joint ESC, ACC, AHA and WHF[9]	cTnI (Stratus CS, Siemens Healthcare Diagnostics, Deerfield, IL, USA). Non-STEMI defined as cTnI above the 99th centile of 0.07 µg/l at least at one measurement together with a ≥ 20% rise and/or fall and an absolute change ≥ 0.0 µg/l within	NR

continued

TABLE 36 Index test and reference standard details (*continued*)

Study	High-sensitivity troponin (ng/l)				Reference standard			
	Assay(s)	LoD	99th centile	CoV	Target condition(s)	Reference standard	Standard troponin	Observer
							24 hours. To allow for the calculation of relative changes, cTnI was set to 0.02 µg/l (i.e. a concentration below the lowest level of detection) when reported as 0.00 or 0.01 µg/l *Timing:* Eight time points during the first 24 hours following enrolment	
[a]**Freund *et al.* 2011**[142] [a]Freund *et al.* 2010[166]	Roche Elecsys hs-cTnT	3	14	< 10% at 14	AMI	Joint ESC, ACC, AHA and WHF[9]	cTnI (Siemens Healthcare Diagnostica Inc., Newark, NJ, USA or Access analyser Beckman Coulter Inc., Brea, CA, USA) Threshold for Siemens assay 140 ng/l and CoV ≤ 10% Threshold for Beckman assay 60 ng/l, CV 10% *Timing:* On presentation and at 3–9 hours if needed	Two independent ED physicians who were blinded to hs-cTnT results. Disagreements were adjudicated by a third ED physician
High-STEACS **Bularga *et al.* 2019**[61] **Chapman *et al.* 2017**[65] [b]**Chapman *et al.* 2018**[66]	Abbott ARCHITECT hs-cTnI Siemens Healthcare Atellica hs-cTnI	2 1.6	16 (females), 34 (males) 34 (females), 53 (males)	10% at 4.7 NR	NSTEMI; MACE	*Third Universal Definition of Myocardial Infarction*[43]	NR	MI was independently adjudicated by two clinicians, based on all clinical information and serial cTn measurements, in accordance with the third universal definition of MI. MI and death after

Study	High-sensitivity troponin (ng/l)				Reference standard			
	Assay(s)	LoD	99th centile	CoV	Target condition(s)	Reference standard	Standard troponin	Observer
[b]**Chapman *et al.* 2019**[67] **Miller-Hodges *et al.* 2018**[79] Shah *et al.* 2015[98]								discharge were also independently adjudicated by two clinicians. Any disagreements were resolved by consultation with a third clinician
High-US Nowak *et al.* 2019[128] Nowak *et al.* 2019[129] **Sandoval *et al.* 2019**[176]	Siemens Healthcare Atellica hs-cTnI Siemens Healthcare ADVIA Centaur hs-cTnI	NR NR	45 47	20% at 1.6 20% at 2.5	NSTEMI	*Third Universal Definition of Myocardial Infarction*[43] 30-day MACE: AMI or death, including index MI, within 30 days	Local hospital standard cTn results, including both the manufacturers' package and locally established cTn cut-off points where applicable. Assays varied across the participating sites [Abbott ARCHITECT STAT Troponin-I, seven sites; Abbott iSTAT POC Cardiac Troponin I (Abbott Laboratories, Abbott Park, IL, USA), five sites; Siemens ADVIA Centaur TnI-Ultra (Siemens Healthcare, Erlangen, Germany), six sites; Beckman Coulter Accutane (Beckman Coulter, Brea, CA, USA), two sites; Beckman Coulter AccuTnI+3 (Beckman Coulter, Brea, CA, USA), one site; Siemens Dimension Vista® LOCI® CTNI (Siemens Healthcare, Erlangen, Germany), four sites; Siemens	Each case was adjudicated by a unique combination of five adjudicators, with a majority rule applied to determine the final MI classification. The adjudicators were blinded to the investigational Atellica IM and ADVIA Centaur hs-cTnI results and patient diagnosis established by the treating hospital. Each adjudicator independently used their expert opinion to assess whether the requirements of an MI diagnosis were met

continued

TABLE 36 Index test and reference standard details (*continued*)

	High-sensitivity troponin (ng/l)				Reference standard			
Study	Assay(s)	LoD	99th centile	CoV	Target condition(s)	Reference standard	Standard troponin	Observer
							Dimension® EXLTM LOCI® TNI (Siemens Healthcare, Erlangen, Germany), two sites; Ortho Clinical Diagnostics VITROS Troponin I ES (Ortho Clinical Diagnostics, Marlow, UK), three sites; Roche Cardiac Troponin T, Gen 4, 8 series (Roche, Basel, Switzerland); Siemens Stratus® CS High-sensitivity Troponin I (Siemens Healthcare Diagnostics, Deerfield, IL, USA), one site]	
Huang *et al.* 2015[72] Guangquan *et al.* 2016[73]	Roche Elecsys hs-cTnT	3	14	10% at 13	AMI; NSTEMI	AMI in accordance with guidelines by Thygesen *et al.*[43]	Conventional cTnT (fourth generation). Diagnosis of AMI, either NSTEMI or STEMI, required a conventional cTnT above 99th centile together with at least two of the following: symptoms of ischaemia, new ST-T changes or a new Q wave on the ECG and imaging showing new loss of viable myocardium *Timing:* At presentation and repeated after 6 to 9 hours at the discretion of the physician in charge	Final diagnosis was adjudicated by both emergency physician and cardiologist from the time of enrolment to discharge. A third cardiologist refereed in situations of disagreement

Study	High-sensitivity troponin (ng/l)				Reference standard			
	Assay(s)	LoD	99th centile	CoV	Target condition(s)	Reference standard	Standard troponin	Observer
[a]**Keller *et al.* 2011**[141] [a]Keller *et al.* 2011[163]	Abbott ARCHITECT hs-cTnI *STAT*	3.4	24–30 for this study population	10% at 5.2	AMI	Joint ESC, ACC, AHA and WHF[9]	Conventional serial troponin T or I (no further details) *Timing:* On presentation and at 3 and 6 hours	Final diagnosis adjudicated by two independent cardiologists, with disagreements referred to a third cardiologist. All three were blinded to hs-cTnI results
[a]**Kurz *et al.* 2011**[148]	Roche Elecsys hs-cTnT	3	13.5	8% at 10	NSTEMI	Joint ESC, ACC, AHA and WHF[9]	Fourth generation cTnT (Roche Elecsys, Mannheim, Germany): LoD 10 ng/l, diagnostic threshold 30 ng/l Diagnosis of NSTEMI required elevated cTnT concentration in at least one of the consecutive samples collected within 24 hours of the index event *Timing:* On presentation, at 6 hours and at least one sample between presentation and 6 hours	NR
Lin *et al.* 2019[117]	Roche Elecsys hs-cTnT	5	14	< 10% at 13	MACE	MACE was defined as any of the following: cardiac death; ventricular fibrillation; MI; critical stenosis found on coronary angiography (≥ 50% for the left main coronary artery stenosis or ≥ 70% for epicardial vessel	Roche Elecsys hs-cTnT	MACEs were independently adjudicated by an emergency medicine attending physician and an attending cardiologist based on the case records, which included investigation results and data on

continued

TABLE 36 Index test and reference standard details (*continued*)

Study	High-sensitivity troponin (ng/l)				Reference standard			
	Assay(s)	LoD	99th centile	CoV	Target condition(s)	Reference standard	Standard troponin	Observer
						stenosis); and emergency cardiac revascularisation procedures (e.g. coronary artery bypass graft, percutaneous coronary intervention)		troponin collected during the index visit and up to 1 year of follow-up. Disagreements were resolved by consensus
[a]**Melki *et al.* 2011**[144] [a]Melki *et al.* 2010[154]	Roche Elecsys hs-cTnT	2	14	< 10% at 13	NSTEMI	Joint ESC, ACC, AHA and WHF[9]	Conventional troponin Roche fourth generation cTnT (LoD 10 ng/l, 10% CoV at 35 ng/l) or Beckman Coulter Access Accutane (LoD 10 ng/l, 99th centile 40 ng/l, CoV < 10% at 60 ng/l) *Timing:* On presentation and 9–12 hours later	Final diagnosis determined by the individual cardiologist and then adjudicated by two independent evaluators. All three were blinded to hs-cTnT results
Peacock *et al.* 2018[89] **Chang *et al.* 2018**[124]	Roche Elecsys hs-cTnT, STAT	6	19	NR	AMI; MACE	*Third Universal Definition of Myocardial Infarction*[43] MACE included all post-discharge death, AMI or urgent myocardial revascularisation	NR, presentation and at 3 hours, 6–9 hours and 12–24 hours	An independent clinical events committee, made up of two cardiologists and one emergency physician, adjudicated the rule-in AMI diagnosis. The clinical events committee had access to all clinical data (including the local troponin assay results), but was blinded to hs-cTnT results
PITAGORAS [a]**Sanchis *et al.* 2012**[135]	Roche Elecsys hs-cTnT	3	14	< 10% at 14	MACE	MACE	NR	NR

Study	High-sensitivity troponin (ng/l)				Reference standard			
	Assay(s)	LoD	99th centile	CoV	Target condition(s)	Reference standard	Standard troponin	Observer
QUART [a]Parsonage *et al.* 2013[151] Parsonage *et al.* 2013[131] **Parsonage *et al.* 2014**[88]	Roche Elecsys hs-cTnT	5	14	10% at 13	AMI	*Third Universal Definition of Myocardial Infarction*[43]	Local cTnI measurement at presentation and then 6 hours afterwards. The cTnI values, measured with the Access Accu-cTnI assay on a UniCel DxI 800 platform (Beckman Coulter, Brea, CA, USA) were used for adjudication. This assay had an LoD of 10 ng/l and imprecision giving a 10% CoV at 60 ng/l. The 99th centile of a healthy reference population was 40 ng/l	Final diagnoses were adjudicated independently by one of two cardiologists, with all ACS end points and 10% of non-ACS end points re-adjudicated by both cardiologists. Consensus was achieved for all end points
RATPAC (point-of-care arm) [a]**Collinson *et al.* 2013**[159] [a]Collinson *et al.* 2012[164] [a]Collinson *et al.* 2012[152]	Roche Elecsys hs-cTnT	3	14	< 10% at 13	NSTEMI	Joint ESC, ACC, AHA and WHF[9]	Conventional troponins were measured using one of the following methods: Siemens cTnI Ultra (LoD 6 ng/l, 99th centile 40 ng/l, CoV 10% at 30 ng/l); Abbott cTnI (LoD 10 ng/l, 99th centile 12 ng/l, CoV 10% at 32 ng/l); Beckman Accutane (LoD 10 ng/l, 99th centile 40 ng/l, CoV 10% at 60 ng/l) and Roche cTnT (LoD 10 ng/l, 99th centile 10 ng/l, CV 10% at 30 ng/l) *Timing:* On presentation and at 10–12 hours	An initial working diagnosis was recorded by the senior ED clinician and reviewed by two independent clinicians; all were blind to hs-cTnT results

continued

TABLE 36 Index test and reference standard details (*continued*)

	High-sensitivity troponin (ng/l)				Reference standard			
Study	Assay(s)	LoD	99th centile	CoV	Target condition(s)	Reference standard	Standard troponin	Observer
REACTION-US **Nowak *et al.* 2018**[87] Nowak *et al.* 2018[127]	Roche Elecsys hs-cTnT	5	14	< 10% at 13	NSTEMI	*Third Universal Definition of Myocardial Infarction*[43]	Siemens Centaur system TnI Ultra assay on a Centaur XP analyzer (99th centile 40 ng/l)	Adjudication of the final diagnosis of AMI was performed by a board-certified cardiologist and emergency physician working as a team, with additional review by another board-certified cardiologist in the event of disagreement. The adjudicating physicians were blinded to the hs-cTnT results
ROMI-3 Kavasak *et al.* 2017[76]	Roche Elecsys hs-cTnT	5	14	2.3% at 30	NSTEMI	*Third Universal Definition of Myocardial Infarction*[43]	Abbott cTnI (LoD 10 ng/l, 99th centile 30 ng/l)	Outcome adjudication was led by an emergency physician and independently adjudicated by at least two other study authors. All adjudicators were blinded to the hs-cTn results
Shortt *et al.* 2017[101]	Abbott ARCHITECT hs-cTnI	2	26	4.4–7.1% at 20				
[a]**Saenger *et al.* 2010**[165]	Roche Elecsys hs-cTnT	NR	14	NR	AMI	AMI (unclear method)	NR	NR
[a]**Sebbane *et al.* 2013**[157]	Roche Elecsys hs-cTnT	5	14	< 10% at 13	NSTEMI	Joint ESC, ACC, AHA and WHF[9]	cTnI measured using the Access2 analyser (Access Immunosystem, Beckman Instruments, Paris, France). The LoD was <10 ng/l and the decision threshold was 40 ng/l *Timing:* Convention cTn (cTnI) on presentation, 6 hours later and beyond as needed	Two independent ED physicians, blinded to hs-cTnT results

Study	High-sensitivity troponin (ng/l)				Reference standard			
	Assay(s)	LoD	99th centile	CoV	Target condition(s)	Reference standard	Standard troponin	Observer
Shiozaki *et al.* 2017[100]	Roche Elecsys hs-cTnT	5	14	NR	NSTEMI	Joint ESC and ACC guidelines	NR	Two senior cardiologists
Slagman *et al.* 2017[102]	Roche Elecsys hs-cTnT	5	14	3.5% at 16	NSTEMI	The end point (reference standard) of this study was a main hospital diagnosis of NSTEMI. Diagnoses were retrieved from the hospital information system as ICD-10 codes and were coded by treating physicians who had access to all available clinical information	Roche Elecsys hs-cTnT at 3 hours or troponin T at 6 hours	NR
TRAPID-AMI Body *et al.* 2015[122] **Body *et al.* 2016**[114] McCord *et al.* 2017[126] **Mueller *et al.* 2016**[80] Mueller-Hennessen *et al.* 2016[81] **Mueller-Hennessen *et al.* 2017**[82] Mueller-Hennessen *et al.* 2019[83]	Roche Elecsys hs-cTnT	5	14	10% at 13	AMI; NSTEMI; MACE	*Third Universal Definition of Myocardial Infarction*[43] and ESC guidelines	s-cTnI ultra (ADVIA Centaur, 99th centile 40 ng/l) at baseline, 1 hour, 2 hours and 4–14 hours	Each patient was adjudicated by two independent cardiologists. Adjudicators reviewed all available medical records [i.e. patient history; physical examination results; results of laboratory testing, including levels of s-cTnI ultra, local cTn obtained before the first or after the last blood draw for the study if available, creatinine, cystatin C, free haemoglobin (to quantify haemolysis), and NT-proBNP; radiologic imaging; electrocardiography; echocardiography; cardiac stress test; and lesion

continued

TABLE 36 Index test and reference standard details (*continued*)

	High-sensitivity troponin (ng/l)				Reference standard			
Study	Assay(s)	LoD	99th centile	CoV	Target condition(s)	Reference standard	Standard troponin	Observer
								severity and morphology in coronary angiography] pertaining to the patient from ED presentation to 30-day follow-up, blind to hs-cTnT. Discrepancies were solved by discussion with a third cardiologist
TRUST **Carlton *et al.* 2015**[63]	Roche Elecsys hs-cTnT	NR	14	< 10% at 9	NSTEMI	*Third Universal Definition of Myocardial Infarction*[43]	Roche Elecsys hs-cTnT at presentation and after 6 hours	Adjudication of the end point was carried out by two local cardiologists blinded to all risk scores, but who had access to the clinical record, ECG results and serial high-sensitivity troponin T results
	Abbott ARCHITECT hs-cTnI	1.9	26.2	5% at 1.9				
TUSCA [a]**Santaló *et al.* 2013**[133]	Roche Elecsys hs-cTnT	NR	14	10% at 9.3	NSTEMI	National Academy of Clinical Biochemistry and International Federation of Clinical Chemistry Committee[228]	Roche Elecsys hs-cTnT. NSTEMI was defined as cTnT > 10 ng/l and Δ cTnT > 20% *Timing:* 30 minutes after arrival and at 2, 4 and 6–8 hours or until discharge	Final diagnosis was made by an adjudication committee
UTROPIA Dodd *et al.* 2019[125] **Sandoval *et al.* 2017**[95] **Sandoval *et al.* 2017**[96]	Abbott ARCHITECT hs-cTnI	1.9	Female: 16 Male: 34	5.3% at 15	NSTEMI	*Third Universal Definition of Myocardial Infarction*[43]	Abbott ARCHITECT contemporary cTnI	Final diagnosis was adjudicated by two clinicians after review of all available medical records, including 12-lead ECG, echocardiography, angiography, hs-cTnI values and clinical presentation

Study	High-sensitivity troponin (ng/l)				Reference standard			
	Assay(s)	LoD	99th centile	CoV	Target condition(s)	Reference standard	Standard troponin	Observer
Venge *et al.* 2017[110]	Abbott ARCHITECT hs-cTnI	NR	26.2	NR	AMI	*Third Universal Definition of Myocardial Infarction*[43]	Roche Elecsys hs-cTnT, measured at a central laboratory Diagnosis of an MI required at least one troponin T result above the 99th centile upper reference limit *Timing:* Presentation and at 2–4 hours and 6–24 hours	Final diagnosis was adjudicated by two independent cardiologists, with access to electrocardiography, clinical records and hospital standard TnT results. Disagreements were resolved by consultation with a third cardiologist

BACC, Biomarkers in Acute Cardiac Care; CORE, Clinical Objective Rule-out Evaluation; FAST II, Fast Assessment of Thoracic Pain II; FASTER I, Fast Assessment of Thoracic Pain by nEuRal networks I; ICD-10, *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision; REACTION-US, Rapid Evaluation of Acute Myocardial Infarction in the United States; TUSCA, UltraSensitive Troponin in Acute Coronary syndromes; WHF, World Heart Federation; NR, not reported; NT-proBNP, N-terminal pro-brain natriuretic peptide; s-cTnI ultra, sensitive cardiac troponin I ultra; UTROPIA, Use of TROPonin In Acute coronary syndromes.

a Publication included in the assessment report for DG15.[2]

b Publication(s) from which participant details have been taken.

Note

Publications in bold have provided data for inclusion in this assessment.

TABLE 37 Study results

Study	Publication	Assay	Participants	Threshold (ng/l)	Target condition	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
ADAPT	Boeddinghaus *et al.* 2016[57]	Abbott ARCHITECT hs-cTnI	All	(< 6 at 0 hours AND 2 hours) AND Δ < 2 at 0 to 2 hours	NSTEMI	254	325	2	713	99 (97 to 100)	69 (66 to 72)
				< 26.2 at 0 hours AND 2 hours		150	65	12	967	93 (87 to 96)	94 (92 to 95)
		Roche Elecsys hs-cTnT		(< 14 at 0 hours AND 2 hours) AND Δ < 4 at 0 to 2 hours		140	233	5	775	97 (92 to 99)	77 (74 to 79)
	Greenslade *et al.* 2015[71]	Abbott ARCHITECT hs-cTnI		< 2 at 0 hours		182	979	0	251	100 (98 to 100)	20 (18 to 23)
				< 4 at 0 hours		180	530	2	700	99 (96 to 100)	57 (54 to 60)
	Cullen *et al.* 2014[68]			< 26.2 at 0 hours		181	83	23	1284	89 (84 to 93)	94 (93 to 95)
				< 26.2 at 0 hours AND 2 hours		195	103	9	1264	96 (92 to 98)	92 (91 to 94)
				< 26.2 at 2 hours			94		1273		93 (92 to 94)
		Roche Elecsys hs-cTnT		< 14 at 0 hours		185	262	19	1105	91 (86 to 94)	81 (79 to 83)
				< 14 at 2 hours		191	258	13	1109	94 (89 to 97)	81 (79 to 83)
				< 14 at 0 hours AND 2 hours		192	287	12	1080	94 (90 to 97)	79 (77 to 81)
	Eggers *et al.* 2016[69]	Abbott ARCHITECT hs-cTnI		< 15.5 at 0 hours AND 2 hours		221	497	4	902	98 (96 to 100)	64 (62 to 67)
	van der Linden *et al.* 2018[109]	Abbott ARCHITECT hs-cTnI and Roche Elecsys hs-cTnT		< 4 at 0 hours AND < 9 at 0 hours		403	1046	5	1083	99 (97 to 100)	51 (49 to 53)
	Cullen *et al.* 2013[156]	Abbott ARCHITECT hs-cTnI		< 26.2 at 0 hours AND 2 hours	MACE	227	96	20	1292	92 (88 to 95)	93 (92 to 94)

Study	Publication	Assay	Participants	Threshold (ng/l)	Target condition	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
ADAPT/IMPACT	Nestelberger *et al.* 2019[171]	Beckman Coulter ACCESS hs-cTnI		(< 4 at 0 hours AND symptoms > 3 hours) OR (< 5 at 0 hours AND Δ < 5 at 0 to 2 hours)	NSTEMI	86	197	2	995	98 (92 to 100)	83 (81 to 86)
APACE	Kaier *et al.* 2017[75]	Abbott ARCHITECT hs-cTnI		< 2 at 0 hours		224	881	0	199	100 (99 to 100)	18 (16 to 21)
		Roche Elecsys hs-cTnT		< 5 at 0 hours		218	763	1	326	100 (97 to 100)	30 (27 to 33)
	Boeddinghaus *et al.* 2019[60]	Beckman Coulter ACCESS hs-cTnI		ESC 0/1-hour pathway: (symptoms > 3 hours AND < 4 at 0 hours) OR (< 5 at 0 hours AND Δ < 4 at 0 to 1 hours)		95	176		408	99 (94 to 100)	70 (66 to 74)
	Boeddinghaus *et al.* 2107[58]	Abbott ARCHITECT hs-cTnI		< 2 at 0 hours		451	1924	0	453	100 (99 to 100)	19 (17 to 21)
				< 5 at 0 hours		438	874	13	1503	97 (95 to 98)	63 (61 to 65)
				< 5 at 0 hours AND Δ < 2 at 0–1 hour		444	925	7	1452	98 (97 to 99)	61 (59 to 63)
				< 2 at 0 hours OR (< 5 at 0 hours AND Δ < 2 at 0 to 1 hours)			921		1456		61 (59 to 63)
	Boeddinghaus *et al.* 2018[59]			ESC 0/1-hour pathway: (symptoms > 3 hours AND < 2 at 0 hours) OR (< 5 at 0 hours AND Δ < 2 at 0 to 1 hours)		112	195	2	355	98 (94 to 100)	65 (60 to 69)
		Roche Elecsys hs-cTnT		ESC 0/1-hour pathway: (symptoms > 3 hours AND < 5 at 0 hours) OR (< 12 at 0 hours AND Δ < 3 at 0 to 1 hours)		113	169	1	381	99 (95 to 100)	69 (65 to 73)
		Siemens ADVIA Centaur hs-cTnI		ESC 0/1-hour pathway: (symptoms > 3 hours AND < 3 at 0 hours) OR (< 6 at 0 hours AND Δ < 3 at 0 to 1 hours)			243		307		56 (52 to 60)
				< 3 at 0 hours OR (< 8 at 0 hours AND Δ < 7 at 0 to 2 hours)		61	100	0	200	100 (95 to 100)	67 (61 to 72)
	Boeddinghaus *et al.* 2020[173]	Quidel TriageTrue		ESC 0/1-hour pathway: (symptoms > 3 hours AND < 4 at 0 hours) OR (< 5 at 0 hours AND Δ < 3 at 0 to 1 hours)		88	155	0	302	100 (97 to 100)	66 (62 to 70)

continued

TABLE 37 Study results (*continued*)

Study	Publication	Assay	Participants	Threshold (ng/l)	Target condition	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
	Twerenbold *et al.* 2019[108]	Roche Elecsys hs-cTnT		ESC 0/1-hour pathway: (symptoms > 3 hours AND < 5 at 0 hours) OR (< 12 at 0 hours AND Δ < 3 at 0 to 1 hours)	MACE	228	648	3	1417	99 (96 to 100)	69 (67 to 71)
					NSTEMI	224	652	0	1420	100 (99 to 100)	69 (66 to 71)
	Twerenbold *et al.* 2017[104]	Abbott ARCHITECT hs-cTnI		ESC 0/1-hour pathway: (symptoms > 3 hours AND < 2 at 0 hours) OR (< 5 at 0 hours AND Δ < 2 at 0 to 1 hours)		732	1628	8	1982	99 (98 to 100)	55 (53 to 57)
		Roche Elecsys hs-cTnT		ESC 0/1-hour pathway: (symptoms > 3 hours AND < 5 at 0 hours) OR (< 12 at 0 hours AND Δ < 3 at 0 to 1 hours)		741	1136	5	2468		68 (67 to 70)
	Rubini Giménez *et al.* 2016[94]		Female	< 14 at 0 hours		116	156	11	593	91 (85 to 96)	79 (76 to 82)
				< 9 at 0 hours		127	284	2	463	98 (95 to 100)	62 (58 to 65)
			Male	< 14 at 0 hours		313	325	32	1188	91 (87 to 94)	79 (76 to 81)
				< 15.5 at 0 hours		304	276	40	1238	88 (85 to 92)	82 (80 to 84)
	Rubini Gimenez *et al.* 2014[70]	Abbott ARCHITECT hs-cTnI	All	< 26.2 at 0 hours		287	132	112	1695	72 (67 to 76)	93 (91 to 94)
		Roche Elecsys hs-cTnT		< 14 at 0 hours		367	387	32	1440	92 (89 to 94)	79 (77 to 81)
	Reichlin *et al.* 2015[90]			(< 14 at 0 hours AND 2 hours) AND Δ < 4 at 0 to 2 hours		188	277	1	682	99 (97 to 100)	71 (68 to 74)
	Reichlin *et al.* 2015[91]			< 12 at 0 hours AND Δ < 3 at 0 to 1 hours		228	306		785	100 (98 to 100)	72 (69 to 75)
	Rubini Gimenez *et al.* 2015[92]	Abbott ARCHITECT hs-cTnI		< 5 at 0 hours AND Δ < 2 at 0–1 hour		163	285	2	455	99 (96 to 100)	61 (58 to 65)
	Boeddinghaus *et al.* 2019[170]	Ortho VITROS hs-cTnI		ESC 0/1-hour pathway: (symptoms > 3 hours AND < 1 at 0 hours) OR (< 2 at 0 hours AND Δ < 1 at 0 to 1 hours)		61	184	0	275	100 (95 to 100)	60 (55 to 64)
	Cullen *et al.* 2013[156]	Abbott ARCHITECT hs-cTnI		< 26.2 at 0 hours AND 2 hours	MACE	129	62	27	691	83 (76 to 88)	92 (90 to 94)

Study	Publication	Assay	Participants	Threshold (ng/l)	Target condition	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
	Lindahl *et al.* 2017[132]	bioMérieux VIDAS hs-cTnI		< 2 at 0 hours OR (< 6 at 0 hours AND 2 hours)	NSTEMI	85	184	2	321	98 (92 to 100)	64 (59 to 68)
	Reichlin *et al.* 2009[167]	Abbott ARCHITECT hs-cTnI		≤ 10 at 0 hours	AMI	116	77	7	518	94 (89 to 98)	87 (84 to 90)
		Roche Elecsys hs-cTnT		≤ 2 at 0 hours		123	512	0	83	100 (98 to 100)	14 (11 to 17)
	Reiter *et al.* 2011[146]		> 70 years	< 14 at 0 hours		96	157	2	151	98 (93 to 100)	49 (43 to 55)
				< 5 at 0 hours		98	305	0	3	100 (97 to 100)	1 (0 to 3)
			≤ 70 years	< 14 at 0 hours		54	87	7	533	89 (78 to 95)	86 (83 to 89)
	Potocki *et al.* 2012[140]		With pre-existing CAD			73	142	5	213	94 (86 to 98)	60 (55 to 65)
			Without pre-existing CAD			100	114	6	517	94 (88 to 98)	82 (79 to 85)
	Hochholzer 2011[149]		All	< 11 at 0 hours		129	177	3	454	98 (94 to 100)	72 (68 to 75)
					NSTEMI	90				97 (91 to 99)	72 (68 to 75)
	Reichlin *et al.* 2011[145]			Δ 30% at 0–2 hours		43	84	24	439	64 (52 to 76)	84 (81 to 87)
APACE	Twerenbold *et al.* 2018[106]	Abbott ARCHITECT hs-cTnI	Normal renal function	ESC 0/1-hour pathway: (symptoms > 3 hours AND < 2 at 0 hours) OR (< 5 at 0 hours AND Δ < 2 at 0 to 1 hours)		326	730	4	1444	99 (97 to 100)	66 (64 to 68)
			Renal dysfunction (eGFR < 60 ml/minute/1.73 m^2)			141	227	2	75	99 (95 to 100)	25 (20 to 30)
		Roche Elecsys hs-cTnT	Normal renal function	ESC 0/1-hour pathway: (symptoms > 3 hours AND < 5 at 0 hours) OR (< 12 at 0 hours AND Δ < 3 at 0 to 1 hours)		360	528	4	1875	99 (97 to 100)	78 (76 to 80)
			Renal dysfunction (eGFR < 60 ml/minute/1.73 m^2)			150	249	0	88	100 (98 to 100)	26 (22 to 31)
	Jaeger *et al.* 2016[74]	Siemens Dimension Vista hs-cTnI	All	< 5 at 0 hours AND Δ < 2 at 0–1 hour		98	224		428	100 (97 to 100)	66 (62 to 69)
			Female			25	57		152	100 (89 to 100)	73 (66 to 79)
			Male			72	168	4	272	95 (87 to 99)	62 (57 to 66)
	Hoeller *et al.* 2011[168]	Abbott ARCHITECT hs-cTnI	All	< 26.2 at 0 hours	AMI	240	93	71	1163	77 (72 to 82)	93 (91 to 94)
		Roche Elecsys hs-cTnT		< 14 at 0 hours		398	363	46	1265	90 (86 to 92)	78 (76 to 80)

continued

TABLE 37 Study results (*continued*)

Study	Publication	Assay	Participants	Threshold (ng/l)	Target condition	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
BACC	Neumann *et al.* 2016[84]	Abbott ARCHITECT hs-cTnI		≤ 27 at 0 hours AND 3 hours	NSTEMI	161	74	23	725	88 (82 to 92)	91 (89 to 93)
				≤ 6 at 0 hours		170	312	14	487	92 (88 to 96)	61 (57 to 64)
				≤ 6 at 0 hours AND 1 hour		180	373	4	426	98 (95 to 99)	53 (50 to 57)
				≤ 6 at 0 hours AND 3 hours		182	402	2	397	99 (96 to 100)	50 (46 to 53)
				≤ 27 at 0 hours AND 1 hour		143	59	41	740	78 (71 to 84)	93 (91 to 94)
BEST	Body *et al.* 2019[115]	Roche Elecsys hs-cTnT		< 5 at 0 hours		76	313	1	275	99 (93 to 100)	47 (43 to 51)
	Body *et al.* 2020[172]	Siemens ADVIA Centaur hs-cTnI		< 3 at 0 hours		131	580		287	99 (96 to 100)	33 (30 to 36)
Body 2015	Body *et al.* 2015[56]	Roche Elecsys hs-cTnT		< 14 at 0 hours	AMI	75	106	4	278	95 (88 to 99)	72 (68 to 77)
					MACE	88	92	10	272	90 (82 to 95)	75 (70 to 79)
				< 3 at 0 hours	AMI	79	360	0	24	100 (96 to 100)	6 (4 to 9)
					MACE	99	352		13	100 (97 to 100)	4 (2 to 6)
				< 5 at 0 hours	AMI	78	289	1	95	99 (93 to 100)	25 (21 to 29)
					MACE	97	270			99 (94 to 100)	26 (22 to 31)
Cappellini 2019	Cappellini *et al.* 2019[62]			< 14 at 0 hours AND Δ ≤ 4 at 0–3 hours	NSTEMI	473	3178	2	2758	100 (98 to 100)	46 (45 to 48)
			All	< 14 at 0 hours AND Δ ≤ 3 at 0–1 hour		471	3284	4	2652	99 (98 to 100)	45 (43 to 46)
			Female			189	1560	0	1109	100 (98 to 100)	42 (40 to 43)
				< 14 at 0 hours AND Δ ≤ 4 at 0–3 hours			1496		1173		44 (42 to 46)
			Male	< 14 at 0 hours AND Δ ≤ 3 at 0–1 hour		282	1702	4	1565	99 (96 to 100)	48 (46 to 50)
				< 14 at 0 hours AND Δ ≤ 4 at 0–3 hours		285	1714	1	1553	100 (98 to 100)	48 (46 to 49)

Study	Publication	Assay	Participants	Threshold (ng/l)	Target condition	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
CORE	Borna *et al.* 2018[116]		All	≤ 14 at 0 hours AND 2 hours	MACE	78	152	12	509	87 (78 to 93)	77 (74 to 80)
	Mokhtari *et al.* 2017[120]			< 5 at 0 hours OR (< 12 at 0 hours AND Δ < 3 at 0 to 1 hours)		117	471	2	430	98 (94 to 100)	48 (44 to 51)
	Mokhtari *et al.* 2016[121]			< 5 at 0 hours		121	674	4	339	97 (92 to 99)	33 (31 to 36)
				≤ 14 at 0 hours		93	206	32	807	74 (66 to 82)	80 (77 to 82)
				< 12 at 0 hours AND Δ < 3 at 0–1 hour		117	163	2	146	98 (94 to 100)	47 (42 to 53)
High-STEACS	Bularga *et al.* 2019[61]	Abbott ARCHITECT hs-cTnI		< 2 at 0 hours		4289	27,857	24	14,931	99 (99 to 100)	35 (34 to 35)
				< 5 at 0 hours		4215	15,386	98	27,402	98 (97 to 98)	64 (64 to 64)
			Analysis population (excluding patients with cTn > 99th centile at presentation, presenting ≤ 2 hours from symptom onset, with STEMI, with missing presentation hs-cTnI)	< 2 at 0 hours		502	19,619	15	12,701	97 (95 to 98)	39 (39 to 40)
				< 5 at 0 hours		462	9115	55	23,205	89 (86 to 92)	72 (71 to 72)
	Chapman *et al.* 2020[174]	Roche Elecsys hs-cTnT	All	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
	Chapman *et al.* 2019[67]	Siemens Atellica hs-cTnI		ESC 0/1-hour pathway: (symptoms ≥ 3 hours AND < 3 at 0 hours) OR (< 6 at 0 hours AND Δ < 3 at 0 to 1 hours)	NSTEMI	29	115	2	260	94 (79 to 99)	69 (64 to 74)
				ESC 0/3-hour pathway: [symptoms ≥ 6 hours AND ≤ 34 (F) ≥ 53 (M) at 0 hours] OR [≥ 34 (F) ≥ 53 (M) at 3 hours] OR Δ < 50% of 99th centile at 0 to 3 hours		252	420	25	1223	91 (87 to 94)	74 (72 to 77)
				High-STEACS pathway: (symptoms ≥ 2 hours AND < 5 at 0 hours) OR [≤ 34 (F) ≤ 53 (M) at 3 hours AND Δ < 3 at 0 to 3 hours]		272	430	6	1212	98 (95 to 99)	74 (72 to 76)

continued

TABLE 37 Study results (*continued*)

Study	Publication	Assay	Participants	Threshold (ng/l)	Target condition	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
	Chapman *et al.* 2018[66]	Abbott ARCHITECT hs-cTnI		ESC 0/1-hour pathway: (symptoms ≥ 3 hours AND < 3 at 0 hours) OR (< 6 at 0 hours AND Δ < 3 at 0 to 1 hours)		33	83	0	290	100 (91 to 100)	78 (73 to 82)
				ESC 0/3-hour pathway: [symptoms ≥ 6 hours AND ≤ 16 (F) ≤ 34 (M) at 0 hours] OR [≤ 16 (F) ≤ 34 (M) at 3 hours] OR Δ < 50% of 99th centile at 0 to 3 hours	MACE	327	231	49	1279	87 (83 to 90)	85 (83 to 86)
					NSTEMI	244	314	27	1301	90 (86 to 93)	81 (79 to 82)
				High-STEACS pathway: (symptoms ≥ 2 hours AND < 5 at 0 hours) OR [≤ 16 (F) ≤ 34 (M) at 3 hours AND Δ < 3 at 0 to 3 hours]	MACE	378	295	6	1238	98 (97 to 99)	81 (79 to 83)
					NSTEMI	273	400	2	1242	99 (97 to 100)	76 (73 to 78)
	Chapman *et al.* 2017[65]		Age < 65 years	ESC 0/3-hour pathway: [symptoms ≥ 6 hours AND ≤ 16 (F) ≤ 34 (M) at 0 hours] OR [≤ 16 (F) ≤ 34 (M) at 3 hours] OR Δ < 50% of 99th centile at 0 to 3 hours		72	29	7	593	91 (83 to 96)	95 (93 to 97)
				High-STEACS pathway: (symptoms ≥ 2 hours AND < 5 at 0 hours) OR [≤ 16 (F) ≤ 34 (M) at 3 hours AND Δ < 3 at 0 to 3 hours]		78	39	1	583	99 (93 to 100)	94 (92 to 96)
			Age ≥ 65 years	ESC 0/3-hour pathway: [symptoms ≥ 6 hours AND ≤ 16 (F) ≤ 34 (M) at 0 hours] OR [≤ 16 (F) ≤ 34 (M) at 3 hours] OR Δ < 50% of 99th centile at 0 to 3 hours		99	57	13	348	88 (81 to 94)	86 (82 to 89)
				High-STEACS pathway: (symptoms ≥ 2 hours AND < 5 at 0 hours) OR [≤ 16 (F) ≤ 34 (M) at 3 hours AND Δ < 3 at 0 to 3 hours]		109	88	3	317	97 (92 to 99)	78 (74 to 82)

Study	Publication	Assay	Participants	Threshold (ng/l)	Target condition	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
			Female	ESC 0/3-hour pathway: [symptoms ≥ 6 hours AND ≤ 16 (F) ≤ 34 (M) at 0 hours] OR [≤ 16 (F) ≤ 34 (M) at 3 hours] OR Δ < 50% of 99th centile at 0 to 3 hours		61	48	5	362	92 (83 to 97)	88 (85 to 91)
				High-STEACS pathway: (symptoms ≥ 2 hours AND < 5 at 0 hours) OR [≤ 16 (F) ≤ 34 (M) at 3 hours AND Δ < 3 at 0 to 3 hours]		65	54	1	356	98 (92 to 100)	87 (83 to 90)
			Known ischaemic heart disease	ESC 0/3-hour pathway: [symptoms ≥ 6 hours AND ≤ 16 (F) ≤ 34 (M) at 0 hours] OR [≤ 16 (F) ≤ 34 (M) at 3 hours] OR Δ < 50% of 99th centile at 0 to 3 hours		73	52	16	377	82 (72 to 89)	88 (84 to 91)
				High-STEACS pathway: (symptoms ≥ 2 hours AND < 5 at 0 hours) OR [≤ 16 (F) ≤ 34 (M) at 3 hours AND Δ < 3 at 0 to 3 hours]		85	77	4	352	96 (89 to 99)	82 (78 to 86)
			Male	ESC 0/3-hour pathway: [symptoms ≥ 6 hours AND ≤ 16 (F) ≤ 34 (M) at 0 hours] OR [≤ 16 (F) ≤ 34 (M) at 3 hours] OR Δ < 50% of 99th centile at 0 to 3 hours		110	38	15	579	88 (81 to 93)	94 (92 to 96)
				High-STEACS pathway: (symptoms ≥ 2 hours AND < 5 at 0 hours) OR [≤ 16 (F) ≤ 34 (M) at 3 hours AND Δ < 3 at 0 to 3 hours]		122	73	3	544	98 (93 to 100)	88 (85 to 91)
			No known ischaemic heart disease	ESC 0/3-hour pathway: [symptoms ≥ 6 hours AND ≤ 16 (F) ≤ 34 (M) at 0 hours] OR [≤ 16 (F) ≤ 34 (M) at 3 hours] OR Δ < 50% of 99th centile at 0 to 3 hours		95	33	4	548	96 (90 to 99)	94 (92 to 96)
				High-STEACS pathway: (symptoms ≥ 2 hours AND < 5 at 0 hours) OR [≤ 16 (F) ≤ 34 (M) at 3 hours AND Δ < 3 at 0 to 3 hours]		99	48	0	533	100 (97 to 100)	92 (89 to 94)

continued

TABLE 37 Study results (*continued*)

Study	Publication	Assay	Participants	Threshold (ng/l)	Target condition	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
	Miller-Hodges *et al.* 2018[79]		Female patients with an eGFR < 60 ml/minute/1.73 m^2	< 16 at 0 hours		105	121	1	243	99 (95 to 100)	67 (62 to 72)
			Female patients with an eGFR ≥ 60 ml/minute/1.73 m^2			160	156		1269	99 (97 to 100)	89 (87 to 91)
			Male patients with an eGFR < 60 ml/minute/1.73 m^2	< 34 at 0 hours		98	82	2	252	98 (93 to 100)	75 (70 to 80)
			Male patients with an eGFR ≥ 60 ml/minute/1.73 m^2			280	109	4	1843	99 (96 to 100)	94 (93 to 95)
			Patients aged < 65 years with an eGFR < 60 ml/minute/1.73 m^2	< 16 (females), < 34 (males) at 0 hours		23	17	0	76	100 (88 to 100)	82 (72 to 89)
			Patients aged < 65 years with an eGFR ≥ 60 ml/minute/1.73 m^2			197	75	1	1926	99 (97 to 100)	96 (95 to 97)
			Patients aged ≥ 65 years with an eGFR < 60 ml/minute/1.73 m^2			180	186	3	419	98 (95 to 100)	69 (65 to 73)
			Patients aged ≥ 65 years with an eGFR ≥ 60 ml/minute/1.73 m^2			243	190	4	1186	98 (96 to 100)	86 (84 to 88)
			Patients with an eGFR < 60 ml/minute/1.73 m^2	< 1.2 at 0 hours	MACE	224	661	0	19	100 (99 to 100)	3 (2 to 4)
				< 16 (females), < 34 (males) at 0 hours	NSTEMI	203	203	3	495	99 (96 to 100)	71 (67 to 74)
				< 5 at 0 hours	MACE	222	525	2	155	99 (97 to 100)	23 (20 to 26)
			Patients with an eGFR ≥ 60 ml/minute/1.73 m^2	< 1.2 at 0 hours		455	2739	3	625	99 (98 to 100)	19 (17 to 20)
				< 16 (females), < 34 (males) at 0 hours	NSTEMI	440	265	5	3112	99 (97 to 100)	92 (91 to 93)
				< 5 at 0 hours	MACE	451	1227	7	2137	98 (97 to 99)	64 (62 to 65)

Study	Publication	Assay	Participants	Threshold (ng/l)	Target condition	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
High-US	Sandoval *et al.* 2019[176]	Siemens ADVIA Centaur hs-cTnI	All	< 2 at 0 hours		276	1481	1	454	100 (98 to 100)	23 (22 to 25)
					NSTEMI	259	1498	0	455	100 (99 to 100)	23 (21 to 25)
				< 3 at 0 hours	MACE	274	1248	3	687	99 (97 to 100)	36 (33 to 38)
					NSTEMI	257	1265	2	688		35 (33 to 37)
				< 5 at 0 hours	MACE	273	924	4	1011	99 (96 to 100)	52 (50 to 54)
					NSTEMI	257	940	2	1013	99 (97 to 100)	52 (50 to 54)
		Siemens Atellica hs-cTnI		< 2 at 0 hours	MACE	275	1432		503		26 (24 to 28)
					NSTEMI	258	1449	1	504	100 (98 to 100)	26 (24 to 28)
				< 3 at 0 hours	MACE	273	1207	4	728	99 (96 to 100)	38 (35 to 40)
					NSTEMI	256	1224	3	729	99 (97 to 100)	37 (35 to 40)
				< 5 at 0 hours	MACE	274	899	4	1036	99 (96 to 100)	54 (51 to 56)
					NSTEMI	256	916	3	1037	99 (97 to 100)	53 (51 to 55)
Huang *et al.* 2015[72]	Huang *et al.* 2015[72]	Roche Elecsys hs-cTnT		≤ 14 at 0 hours	AMI	1064	331	44	810	96 (95 to 97)	71 (68 to 74)
					NSTEMI	308		13		96 (93 to 98)	71 (68 to 74)
			Patients with an eGFR ≥ 90 ml/minute/1.73 m^2		AMI	363	70	19	367	95 (92 to 97)	84 (80 to 87)
					NSTEMI	59		5	370	92 (83 to 97)	84 (80 to 87)
			Patients with an eGFR of 30–59 ml/minute/1.73 m^2		AMI	197	87	2	75	99 (96 to 100)	46 (38 to 54)
					NSTEMI	78	86	0	77	100 (96 to 100)	47 (39 to 55)
			Patients with an eGFR of 60–89 ml/minute/1.73 m^2		AMI	462	148	19	362	96 (94 to 98)	71 (67 to 75)
					NSTEMI	156	142	7	364	96 (91 to 98)	72 (68 to 76)
			Patients with an eGFR < 30 ml/minute/1.73 m^2		AMI	46	28	0	4	100 (94 to 100)	13 (4 to 29)
					NSTEMI	16				100 (83 to 100)	13 (4 to 29)
Lin *et al.* 2019[117]	Lin *et al.* 2019[117]		All	< 10 at 0 hours	MACE	165	328	108	1843	60 (54 to 66)	85 (83 to 86)
				< 20 at 2 hours		163	161	110	2010		93 (91 to 94)
				< 5 at 0 hours AND 2 hours		185	367	88	1804	68 (62 to 73)	83 (81 to 85)
				Δ < 10 at 0–2 hours		115	63	158	2108	42 (36 to 48)	97 (96 to 98)

continued

TABLE 37 Study results (*continued*)

Study	Publication	Assay	Participants	Threshold (ng/l)	Target condition	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Peacock *et al.* 2018	Chang *et al.* 2018[124]	Roche Elecsys hs-cTnT STAT		< 19 at 0 hours	AMI	125	164	8	1058	94 (88 to 97)	87 (85 to 88)
				Δ ≤ 10% at 0–3 hours AND < 19 at 3 hours		129	549	4	673	97 (92 to 99)	55 (52 to 58)
				Δ ≤ 2 at 0–3 hours AND < 19 at 3 hours		127	263	6	959	95 (90 to 98)	78 (76 to 81)
				Δ ≤ 50% at 0–3 hours AND < 19 at 3 hours		125	187	8	1035	94 (88 to 97)	85 (83 to 87)
				Δ ≤ 8 at 0–3 hours AND < 19 at 3 hours			169		1053		86 (84 to 88)
	Peacock *et al.* 2019[89]			< 19 at 0 hours AND 3 hours			178		1044		85 (83 to 87)
					MACE	8	282	7	967	53 (27 to 79)	77 (75 to 80)
				< 6 at 0 hours AND 3 hours	AMI	131	610	2	612	98 (95 to 100)	50 (47 to 53)
					MACE	11	694	4	555	73 (45 to 92)	44 (42 to 47)
QUART	Parsonage *et al.* 2014[88]	Roche Elecsys hs-cTnT		≤ 14 at 0 hours	AMI	52	113		595	93 (83 to 98)	84 (81 to 87)
				≤ 14 at 2 hours		54	116	2	592	96 (88 to 100)	84 (81 to 86)
				≤ 14 at 0 hours OR 2 hours			123		585		83 (80 to 85)
REACTION-US	Nowak *et al.* 2018[87]			< 6 at 0 hours	NSTEMI	44	361	0	164	100 (93 to 100)	31 (27 to 35)
				< 8 at 0 hours AND Δ < 3 at 0–0.5 hours			274		221		45 (40 to 49)
ROMI-3	Shortt *et al.* 2017[101]	Abbott ARCHITECT hs-cTnI		< 1 at 0 hours		132	920	1	84	99 (96 to 100)	8 (7 to 10)
				< 15 at 0 hours		110	216	23	788	83 (75 to 89)	78 (76 to 81)
				< 2 at 0 hours		132	846	1	158	99 (96 to 100)	16 (14 to 18)
				< 26 at 0 hours		96	105	37	899	72 (64 to 80)	90 (87 to 91)
				< 3 at 0 hours		132	691	1	313	99 (96 to 100)	31 (28 to 34)
				< 4 at 0 hours		131	586	2	418	98 (95 to 100)	42 (39 to 45)
				< 5 at 0 hours		129	504	4	500	97 (92 to 99)	50 (47 to 53)

Study	Publication	Assay	Participants	Threshold (ng/l)	Target condition	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
		Roche Elecsys hs-cTnT		< 12 at 0 hours		126	476	7	528	95 (89 to 98)	53 (49 to 56)
				< 14 at 0 hours		123	417	10	587	92 (87 to 96)	58 (55 to 62)
				< 24 at 0 hours		108	229	25	775	81 (74 to 87)	77 (74 to 80)
				< 3 at 0 hours		132	891	1	113	99 (96 to 100)	11 (9 to 13)
				< 5 at 0 hours			824		180		18 (16 to 20)
				< 8 at 0 hours		129	638	4	366	97 (92 to 99)	36 (33 to 40)
	Shortt *et al.* 2017[101]	Abbott ARCHITECT hs-cTnI		< 7 at 0 hours		126	393	7	611	95 (89 to 98)	61 (58 to 64)
Shiozaki *et al.* 2017[100]	Shiozaki *et al.* 2017[100]	Roche Elecsys hs-cTnT		< 13 at 0 hours		57	246	0	110	100 (95 to 100)	31 (26 to 36)
				< 13 at 0 hours AND Δ < 3 at 0–1 hour			120		236		66 (61 to 71)
Slagman *et al.* 2017[100]	Slagman *et al.* 2017[102]			< 14 at 0 hours		115	1086	9	2213	93 (87 to 97)	67 (65 to 69)
TRAPID-AMI	Body *et al.* 2016[114]				AMI	189	198	24	871	89 (84 to 93)	81 (79 to 84)
				< 3 at 0 hours		210	653	3	416	99 (96 to 100)	39 (36 to 42)
				< 5 at 0 hours		209	513	4	556	98 (95 to 99)	52 (49 to 55)
	Mueller *et al.* 2016[80]			< 12 at 0 hours AND Δ < 3 at 0–1 hour		206	263	7	806	97 (93 to 99)	75 (73 to 78)
					NSTEMI	185				96 (93 to 99)	75 (73 to 78)
	Mueller-Hennessen *et al.* 2017[229]			≤ 14 at 0 hours AND Δ < 9.2 at 0–1 hour	AMI	98	9	115	1060	46 (39 to 53)	99 (98 to 100)
				≤ 14 at 0 hours AND Δ < 9.2 at 0–2 hours		126	13	87	1056	59 (52 to 66)	99 (98 to 99)
				≤ 14 at 0 hours AND Δ < 20% at 0–1 hour		83	28	130	1041	39 (32 to 46)	97 (96 to 98)
				≤ 14 at 0 hours AND Δ < 20% at 0–2 hours		119	46	94	1023	56 (49 to 63)	96 (94 to 97)

continued

TABLE 37 Study results (*continued*)

Study	Publication	Assay	Participants	Threshold (ng/l)	Target condition	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
	Mueller-Hennessen *et al.* 2017[81]		Aged < 65 years	(≤ 14 at 0 hours AND 1 hour) AND Δ < 20% at 0 to 1 hours	MACE	76	23	79	547	49 (41 to 57)	96 (94 to 97)
			Aged ≥ 65 years			123	43	102	289	55 (48 to 61)	87 (83 to 90)
				(≤ 28 at 0 hours AND 1 hour) AND Δ < 20% at 0 to 1 hours		92	10	133	322	41 (34 to 48)	97 (95 to 99)
			Female	(≤ 14 at 0 hours AND 1 hour) AND Δ < 20% at 0 to 1 hours		62	17	37	361	63 (52 to 72)	96 (93 to 97)
				(≤ 9 at 0 hours AND 1 hour) AND Δ < 20% at 0 to 1 hours		71	37	28	341	72 (62 to 80)	90 (87 to 93)
			Male	(≤ 14 at 0 hours AND 1 hour) AND Δ < 20%		137	49	144	475	49 (43 to 55)	91 (88 to 93)
				(≤ 15.5 at 0 hours AND 1 hour) AND Δ < 20% at 0 to 1 hours		129	41	152	483	46 (40 to 52)	92 (90 to 94)
TRUST	Carlton *et al.* 2015[64]	Abbott ARCHITECT hs-cTnI	All	≤ 26.2 at 0 hours	NSTEMI	41	22	25	779	62 (49 to 74)	97 (96 to 98)
		Roche Elecsys hs-cTnT		≤ 14 at 0 hours		66	127	13	753	84 (74 to 91)	86 (83 to 88)
	Carlton *et al.* 2015[63]			< 3 at 0 hours	MACE	94	755	1	72	99 (94 to 100)	9 (7 to 11)
					NSTEMI	78	771	0	73	100 (96 to 100)	9 (7 to 11)
				< 5 at 0 hours	MACE	92	560	3	267	97 (91 to 99)	32 (29 to 36)
					NSTEMI	78	574	0	270	100 (96 to 100)	32 (29 to 35)
UTROPIA	Sandoval *et al.* 2017[96]	Abbott ARCHITECT hs-cTnI		< 1.9 at 0 hours		168	1018	2	443	99 (96 to 100)	30 (28 to 33)
				< 5 at 0 hours		161	657	9	804	95 (90 to 98)	55 (52 to 58)
	Sandoval *et al.* 2017[95]			Males < 34 at 0 hours AND females < 16 at 0 hours		113	191	57	1270	66 (59 to 74)	87 (85 to 89)
				Males < 34 AND females < 16 at 0 AND 3 hours		104	137	5	822	95 (90 to 98)	86 (83 to 88)
Venge *et al.* 2017[110]	Venge *et al.* 2017[110]			< 26.2 at 0 hours	AMI	46	28	18	325	72 (59 to 82)	92 (89 to 95)
				< 26.2 at 2–4 hours		52	27	6	268	90 (79 to 96)	91 (87 to 94)
Aldous *et al.* 2011[147]	Aldous *et al.* 2011[147]	Roche Elecsys hs-cTnT		< 13 at 0 hours		92	38	18	184	84 (75 to 90)	83 (77 to 88)
				< 14 at 0 hours			36		186		84 (78 to 88)
				< 15 at 0 hours		93	29	17	193	85 (76 to 91)	87 (82 to 91)
				< 5 at 0 hours		106	131	4	91	96 (91 to 99)	41 (34 to 48)

Study	Publication	Assay	Participants	Threshold (ng/l)	Target condition	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Aldous *et al.* 2012	Aldous *et al.* 2011[143]			Peak < 14 at 0–2 hours	NSTEMI	189	149	11	590	95 (90 to 97)	80 (77 to 83)
				< 14 at 0–2 hours AND Δ < 20% at 0–2 hours		99	43	101	696	50 (42 to 57)	94 (92 to 96)
				< 14 at 0–2 hours OR Δ < 20% at 0–2 hours		195	260	5	479	98 (94 to 99)	65 (61 to 68)
	Aldous *et al.* 2012[134]			< 14 at 0 hours	AMI	74	54	8	249	90 (82 to 96)	82 (77 to 86)
				< 14 at 0 AND 2 hours		78	74	4	229	95 (88 to 99)	76 (70 to 80)
				< 14 at 0–1 hour		77	63	5	240	94 (86 to 98)	79 (74 to 84)
				< 14 at 0–2 hours		78	67	4	236	95 (88 to 99)	78 (73 to 82)
				< 14 at 0 hours AND Δ < 20% at 0–2 hours		49	81	33	222	60 (48 to 70)	73 (68 to 78)
				< 14 at 0 hours OR Δ < 20% at 0–2 hours		81	131	1	172	99 (93 to 100)	57 (51 to 62)
	Aldous *et al.* 2012[139]			< 14 at 0 hours	NSTEMI	181	134	24	600	88 (83 to 92)	82 (79 to 84)
				< 3 at 0 hours		196	383	9	351	96 (92 to 98)	48 (44 to 52)
				< 5 at 0 hours		192	305	13	429	94 (89 to 97)	58 (55 to 62)
				< 14 at 2 hours		189	149	16	585	92 (88 to 95)	80 (77 to 83)
				< 5 at 2 hours		196	340	9	394	96 (92 to 98)	54 (50 to 57)
				< 3 at 2 hours		201	424	4	310	98 (95 to 99)	42 (39 to 46)
Body *et al.* 2011[161]	Body *et al.* 2011[161]			< 14 at 0 hours	AMI	111	101	199	472	36 (30 to 41)	82 (79 to 85)
				< 3 at 0 hours		130	378	0	195	100 (98 to 100)	34 (30 to 38)
Christ *et al.* 2010[150]	Christ *et al.* 2010[150]			< 14 at 0 hours		19	45	1	72	95 (75 to 100)	62 (52 to 70)
				< 3 at 0 hours		20	92	0	25	100 (86 to 100)	21 (14 to 30)
FASTER I and FAST II	Eggers *et al.* 2012[137]			< 14 at 0 hours	NSTEMI	101	59	27	173	79 (71 to 86)	75 (68 to 80)
				< 45.7 at 0 hours		65	11	63	221	51 (42 to 60)	95 (92 to 98)
Freund *et al.* 2011[142]	Freund *et al.* 2011[142]			< 14 at 0 hours	AMI	42	48	3	224	93 (82 to 99)	82 (77 to 87)
			Low/moderate pre-test probability			20	36	2	200	91 (71 to 99)	85 (80 to 89)
			High pre-test probability			22	12	1	24	96 (78 to 100)	67 (49 to 81)

continued

TABLE 37 Study results (*continued*)

Study	Publication	Assay	Participants	Threshold (ng/l)	Target condition	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Keller *et al.* 2011[141]	Keller *et al.* 2011[141]	Abbott ARCHITECT hs-cTnI	All	< 3.4		282	633	0	345	100 (99 to 100)	35 (32 to 38)
							959		19		2 (1 to 3)
				< 3		232	77	50	901	82 (77 to 87)	92 (90 to 94)
				< 30		277	94	5	884	98 (96 to 99)	90 (88 to 92)
				Δ < 20% at 0–3 hours		218	723	64	255	77 (72 to 82)	26 (23 to 29)
				< 3.4 at 0 hours AND Δ < 20% at 0–3 hours		254	454	54	498	82 (78 to 87)	52 (49 to 56)
				< 30 at 3 hours AND Δ < 20% at 0–3 hours		187	34	110	929	63 (57 to 68)	96 (95 to 98)
				(< 30 at 0 AND 3 hours) AND Δ < 20% at 0 to 3 hours		52	26	4	869	93 (83 to 98)	97 (96 to 98)
Kurz *et al.* 2011[148]	Kurz *et al.* 2011[148]	Roche Elecsys hs-cTnT		< 14 at 0 hours	NSTEMI	16	7	10	24	62 (41 to 80)	77 (59 to 90)
				< 9.5 at 0 hours		38	11	8	37	83 (69 to 92)	77 (63 to 88)
				< 14 at 0 AND 3 hours		26	7	0	23	100 (89 to 100)	77 (58 to 90)
				< 14 at 0 hours AND Δ <20% at 0–3 hours		11	27	15	3	42 (23 to 63)	10 (2 to 27)
Melki *et al.* 2011[144]	Melki *et al.* 2011[144]			< 14 at 0 hours		112	21	2	98	98 (94 to 100)	82 (74 to 89)
				< 14 at 2 hours		114	25	0	94	100 (97 to 100)	79 (71 to 86)
PITAGORAS	Sanchis *et al.* 2012[135]			< 3 at 0 hours	MACE	53	207	9	177	85 (74 to 93)	46 (41 to 51)
RATPAC (point-of-care arm)	Collinson *et al.* 2013[159]			< 14 at 0 hours	NSTEMI		33	14	733	79 (67 to 88)	96 (94 to 97)
				Peak < 14 at 0–1.5 hours		57	43	11	736	84 (73 to 92)	94 (93 to 96)
Saenger *et al.* 2010[165]	Saenger *et al.* 2010[165]			< 14 at 0 hours	AMI	92	38	6	152	94 (87 to 98)	80 (74 to 85)
				Δ < 8 at 0–3 hours		94	9	4	181	96 (90 to 99)	95 (91 to 98)
Sebbane *et al.* 2013[157]	Sebbane *et al.* 2013[157]			< 14 at 0 hours	NSTEMI	19	25	6	142	76 (55 to 91)	85 (79 to 90)
				< 18 at 0 hours			17		150		90 (84 to 94)
TUSCA	Santaló *et al.* 2013[133]			< 14 at 0 hours		71	80	8	199	90 (81 to 96)	71 (66 to 77)

BACC, Biomarkers in Acute Cardiac Care; CORE, Clinical Objective Rule-out Evaluation; FAST II, Fast Assessment of Thoracic Pain II; FASTER I, Fast Assessment of Thoracic Pain by nEuRal networks I; REACTION-US, Rapid Evaluation of Acute Myocardial Infarction in the United States; TUSCA, UltraSensitive Troponin in Acute Coronary syndromes; UTROPIA, Use of TROPonin In Acute coronary syndromes.

Appendix 3 QUADAS-2 assessments

Study: ADAPT/IMPACT, Nestelberger *et al.* 2019[171]

Domain 1: patient selection

A. Risk of bias	
Adults presenting to the ED with possible cardiac symptoms	
Was a consecutive or random sample of patients enrolled?	Yes
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Risk: low
B. Applicability	
Patients with STEMI excluded (target condition NSTEMI)	
Do the included patients match the question?	Concerns: low

Domain 2: index test(s)

A. Risk of bias	
Beckman Coulter ACCESS hs-cTnI, reference standard adjudication occurred after the index test	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Risk: low
B. Applicability	
Are there concerns that the index test, its conduct or interpretation differ from the review question?	Concerns: low

Domain 3: reference standard

A. Risk of bias	
AMI (third universal definition), with access to clinical records, ECG and conventional troponin and hs-cTnT results	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could the reference standard, its conduct or its interpretation have introduced bias?	Risk: low
B. Applicability	
Is there concern that the target condition, as defined by the reference standard, does not match the review question?	Concerns: low

Domain 4: flow and timing

A. Risk of bias	
All patients received the same reference standard	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Risk: low

Study: Aldous *et al.* 2011[147]

Domain 1: patient selection

A. Risk of bias	
Consecutive adults presenting to the ED with chest pain were eligible for inclusion	
Was a consecutive or random sample of patients enrolled?	Yes
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Risk: low
B. Applicability	
Unselected chest pain population AMI diagnoses may have included both NSTEMI and STEMI	
Do the included patients match the question?	Concerns: high

Domain 2: index test(s)

A. Risk of bias	
Roche Elecsys hs-cTnT on admission and after 6 hours. Data reported for admission for four thresholds	
No details of interpretation reported. One threshold was derived from ROC analysis and primary analysis based on 99th centile	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Risk: low
B. Applicability	
Are there concerns that the index test, its conduct or interpretation differ from the review question?	Concerns: low

Domain 3: reference standard

A. Risk of bias	
Reference standard diagnosis of AMI based on joint ESC and ACC criteria, and included serial conventional cTnI (10- to 12-hour time point not specified)	
Determination of diagnosis was made blind to hs-cTnT results	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Risk: low
B. Applicability	
Is there concern that the target condition, as defined by the reference standard, does not match the review question?	Concerns: high

Domain 4: flow and timing

A. Risk of bias	
Participants for whom stored samples were not available at both time points were excluded	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	Risk: high

Study: Aldous *et al.* 2012[139]

Domain 1: patient selection

A. Risk of bias	
Patients presenting to the ED between 05.30 and 20.00 with chest pain	
Was a consecutive or random sample of patients enrolled?	No
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Risk: high
B. Applicability	
Patients with ST segment elevation excluded	
Do the included patients match the question?	Concerns: low

Domain 2: index test(s)

A. Risk of bias	
Roche Elecsys hs-cTnT	
Data reported for multiple thresholds based on predetermined properties of the assay	
Frozen samples used, unclear whether or not interpretation of index test was blind to reference standard	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Risk: low
B. Applicability	
Are there concerns that the index test, its conduct or interpretation differ from the review question?	Concerns: low

Domain 3: reference standard

A. Risk of bias	
Reference standard was final diagnosis of AMI based on ACC criteria and including the results of serial conventional cTnI (10- to 12-hour time point not specified), but blinded to hs-cTnT results	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could the reference standard, its conduct or its interpretation have introduced bias?	Risk: low
B. Applicability	
Is there concern that the target condition, as defined by the reference standard, does not match the review question?	Concerns: high

Domain 4: flow and timing

A. Risk of bias	
All participants appear to have been included in the analyses	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Risk: low

Study: Biomarkers in Acute Cardiac Care (BACC), Neumann *et al.* 2016[84]

Domain 1: patient selection

A. Risk of bias	
Prospective recruitment of adult patients presenting to the ED with acute chest pain. Patients with STEMI (ECG) were excluded from the analysis	
Was a consecutive or random sample of patients enrolled?	Yes
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Risk: low
B. Applicability	
Patients with chest pain, STEMI excluded	
Do the included patients match the question?	Concerns: low

Domain 2: index test(s)

A. Risk of bias	
Abbott ARCHITECT hs-cTnI on admission and at 1 and 3 hours, adjudication of diagnosis made at a later time	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Risk: low
B. Applicability	
Are there concerns that the index test, its conduct or interpretation differ from the review question?	Concerns: low

Domain 3: reference standard

A. Risk of bias	
2015 ESC guidelines and the third universal definition of AMI, including 0- and 3-hour troponins measured using Roche Elecsys TnT. Adjudication made by two independent cardiologists who were unaware of the hs-cTnI results	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could the reference standard, its conduct or its interpretation have introduced bias?	Risk: low
B. Applicability	
Is there concern that the target condition, as defined by the reference standard, does not match the review question?	Concerns: low

Domain 4: flow and timing

A. Risk of bias	
All patients received the same reference standard	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Risk: low

Study: Body *et al.* 2011[161]

Domain 1: patient selection

A. Risk of bias	
Prospective enrolment of patients; unclear if consecutive	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Risk: unclear
B. Applicability	
Mixed chest pain	
Do the included patients match the question?	Concerns: high

Domain 2: index test(s)

A. Risk of bias	
Roche Elecsys hs-cTnT. Threshold: 99th centile cut-off point and LoD. Blinding not reported. Objective test interpreted prior to reference standard and so unlikely to have been influenced by knowledge of reference standard	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Risk: low
B. Applicability	
Are there concerns that the index test, its conduct or interpretation differ from the review question?	Concerns: low

Domain 3: reference standard

A. Risk of bias	
Universal definition of AMI. Time point not specified. Clinicians were blinded to Hs-cTn	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could the reference standard, its conduct or its interpretation have introduced bias?	Risk: low
B. Applicability	
Is there concern that the target condition, as defined by the reference standard, does not match the review question?	Concerns: high

Domain 4: flow and timing

A. Risk of bias	
301 patients were excluded prior to enrolment. All patients enrolled were included in the 2 × 2 table	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Risk: low

Study: Body *et al.* 2015[56]

Domain 1: patient selection

A. Risk of bias	
Consecutive adult patients presenting to the ED with chest pain suspected to be of cardiac origin. Patients requiring hospitalisation for a concomitant medical condition and those with renal failure needing dialysis or chest trauma were excluded	
Was a consecutive or random sample of patients enrolled?	Yes
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Risk: low
B. Applicability	
Target condition was mixed AMI	
Do the included patients match the question?	Concerns: high

Domain 2: index test(s)

A. Risk of bias	
Reference standard determined after the index test	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Risk: low
B. Applicability	
Are there concerns that the index test, its conduct or interpretation differ from the review question?	Concerns: low

Domain 3 reference standard

A. Risk of bias	
AMI diagnosis made based on cTnT (0 and 12 hours), ECG and all clinical and imaging data. Clinicians adjudicating AMI were blind to the hs-cTnT results	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could the reference standard, its conduct or its interpretation have introduced bias?	Risk: low
B. Applicability	
Is there concern that the target condition, as defined by the reference standard, does not match the review question?	Concerns: low

Domain 4: flow and timing

A. Risk of bias	
All patients received the same reference standard	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Risk: low

Study: Cappellini *et al.* 2019[62]

Domain 1: patient selection

A. Risk of bias	
All cases of suspected AMI arriving at the ED	
Was a consecutive or random sample of patients enrolled?	Yes
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Risk: low
B. Applicability	
All cases of suspect AMI in patients arriving at the ED. Patients with STEMI excluded from the analysis (target condition NSTEMI)	
Do the included patients match the question?	Concerns: low

Domain 2: index test(s)

A. Risk of bias	
2 × 2 data were available for the derivation cohort only (i.e. the cohort in which the optimised threshold/algorithm was derived)	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it prespecified?	No
Could the conduct or interpretation of the index test have introduced bias?	Risk: high
B. Applicability	
Are there concerns that the index test, its conduct or interpretation differ from the review question?	Concerns: low

Domain 3: reference standard

A. Risk of bias	
Third universal definition of MI. The hs-cTnT could have been included in the reference standard. Time point not specified	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct or its interpretation have introduced bias?	Risk: unclear
B. Applicability	
Is there concern that the target condition, as defined by the reference standard, does not match the review question?	Concerns: low

Domain 4: flow and timing

A. Risk of bias	
Different physicians made decisions on the AMI depending on whether or not the patient was hospitalised	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Unclear
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Risk: unclear

Study: Christ *et al.* 2010[150]

Domain 1: patient selection

A. Risk of bias	
Retrospective analysis of consecutive patients presenting to ED with chest pain	
Was a consecutive or random sample of patients enrolled?	Yes
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Risk: low
B. Applicability	
Patients with general chest pain symptoms. Includes participants with a final diagnosis of STEMI	
Do the included patients match the question?	Concerns: high

Domain 2: index test(s)

A. Risk of bias	
Roche Elecsys hs-cTnT. Threshold was the 99th centile cut-off point. Blinding not reported. It was retrospective analysis and so disease status may have been known when interpreting results. However, it was an objective test and so unlikely to have been influenced by knowledge of disease state	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Risk: low
B. Applicability	
Are there concerns that the index test, its conduct or interpretation differ from the review question?	Concerns: low

Domain 3: reference standard

A. Risk of bias	
Joint ESC and ACC criteria. Time point not specified. Unclear whether or not clinicians were blinded to hs-cTn. A second consensus diagnosis incorporating hs-cTn was also made and so clinicians may have been aware of the result for the first consensus diagnosis based only on standard troponin	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct or its interpretation have introduced bias?	Risk: unclear
B. Applicability	
Is there concern that the target condition, as defined by the reference standard, does not match the review question?	Concerns: high

Domain 4: flow and timing

A. Risk of bias	
No dropouts reported, all included patients accounted for in flow diagram and numbers suggest that troponin results were available for all	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Risk: low

Study: Clinical Objective Rule-out Evaluation (CORE), Mokhtari *et al.* 2016/17[119,121]

Domain 1: patient selection

A. Risk of bias	
Patients were only enrolled between 09.00 and 21.00 on weekdays. Patients with STEMI or who did not speak Swedish or English were excluded	
Was a consecutive or random sample of patients enrolled?	No
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	No
Could the selection of patients have introduced bias?	Risk: high
B. Applicability	
Patients who present at nights and at weekends may differ from those recruited	
Do the included patients match the question?	Concerns: high

Domain 2: index test(s)

A. Risk of bias	
MACEs were adjudicated after the index test	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Risk: low
B. Applicability	
Are there concerns that the index test, its conduct or interpretation differ from the review question?	Concerns: low

Domain 3: reference standard

A. Risk of bias	
The reference standard was adjudicated independently by multiple clinicians who were blind to hs-cTnT results	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could the reference standard, its conduct or its interpretation have introduced bias?	Risk: low
B. Applicability	
Is there concern that the target condition, as defined by the reference standard, does not match the review question?	Concerns: low

Domain 4: flow and timing

A. Risk of bias	
All patients were assessed for 30-day MACE using the same process	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Risk: low

Study: Fast Assessment of Thoracic Pain by nEuRal networks I (FASTER I) and Fast Assessment of Thoracic Pain II (FAST II), Eggers *et al.* 2012[137]

Domain 1: patient selection

A. Risk of bias	
Unclear whether consecutive or random patients were enrolled	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Risk: unclear
B. Applicability	
Non-STEMI patients with chest pain presenting to coronary care/chest pain unit	
Do the included patients match the question?	Concerns: high

Domain 2: index test(s)

A. Risk of bias	
Roche Elecsys hs-cTnT. A threshold of 99th centile cut-off point and 95% specificity value. Blinding not reported. The objective test interpreted prior to reference standard and so unlikely to have been influenced by knowledge of reference standard	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Risk: low
B. Applicability	
Are there concerns that the index test, its conduct or interpretation differ from the review question?	Concerns: low

Domain 3: reference standard

A. Risk of bias	
Joint ESC and ACC criteria. Time point not specified. Unclear whether or not clinicians were blinded to Hs-cTn. A second consensus diagnosis	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Risk: unclear
B. Applicability	
Is there concern that the target condition, as defined by the reference standard, does not match the review question?	Concerns: high

Domain 4: flow and timing

A. Risk of bias	
Only 360 patients out of 495 who fulfilled inclusion criteria had all biochemical tests performed and were included in the analysis. Reasons for not performing tests were not reported	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	Risk: high

Study: Freund *et al.* 2011[142]

Domain 1: patient selection

A. Risk of bias	
Consecutive adults presenting to the ED with chest pain (onset or peak within previous 6 hours). Patients with acute kidney failure requiring dialysis were excluded	
Was a consecutive or random sample of patients enrolled?	Yes
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Risk: low
B. Applicability	
Unselected ED chest pain population. Includes participants with a final diagnosis of STEMI. Data also presented for subgroups with low–moderate and high pre-test probability	
Do the included patients match the question?	Concerns: high

Domain 2: index test(s)

A. Risk of bias	
Roche Elecsys hs-cTnT on admission and at 3–9 hours, if available. Reference standard (final diagnosis) adjudicated by two independent physicians after acute episode. Threshold was 99th centile	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Risk: low
B. Applicability	
Are there concerns that the index test, its conduct or interpretation differ from the review question?	Concerns: low

Domain 3: reference standard

A. Risk of bias	
Reference standard was final diagnosis based on joint ESC and ACC criteria and included conventional cTnI on admission and at 3–9 hours, if needed (10- to 12-hour time point not specified). Clinicians adjudicating final diagnosis were blind to hs-cTnT results	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could the reference standard, its conduct or its interpretation have introduced bias?	Risk: low
B. Applicability	
Is there concern that the target condition, as defined by the reference standard, does not match the review question?	Concerns: high

Domain 4: flow and timing

A. Risk of bias	
All participants appear to have been included in the analyses	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Risk: low

Study: Huang *et al.* 2015[72]

Domain 1: patient selection

A. Risk of bias	
A consecutive sample of patients with suspected AMI were enrolled. Patients requiring renal replacement therapy who had metal coronary stents implanted or who had transferred from other hospitals were excluded	
Was a consecutive or random sample of patients enrolled?	Yes
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Risk: low
B. Applicability	
A consecutive sample of patients with suspected AMI were enrolled. Results were also reported for NSTEMI (patients with STEMI excluded from the analysis)	
Do the included patients match the question? Yes	Concerns: low

Domain 2: index test(s)

A. Risk of bias	
Roche Elecsys hs-cTnT. Threshold was the 99th centile cut-off point. Blinding not reported. The objective test was interpreted prior to reference standard and so was unlikely to have been influenced by knowledge of reference standard	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Risk: low
B. Applicability	
Are there concerns that the index test, its conduct or interpretation differ from the review question?	Concerns: low

Domain 3: reference standard

A. Risk of bias	
Conventional cTnT (fourth generation). Diagnosis of AMI, either NSTEMI or STEMI required a conventional cTnT above the 99th centile together with at least two of the following: symptoms of ischaemia, new ST-T changes or a new Q wave on the ECG and imaging showing new loss of viable myocardium. Attending physicians were blinded to the hs-cTnT results	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could the reference standard, its conduct or its interpretation have introduced bias?	Risk: low
B. Applicability	
Is there concern that the target condition, as defined by the reference standard, does not match the review question?	Concerns: low

Domain 4: flow and timing

A. Risk of bias	
Final diagnosis was adjudicated by both an emergency physician and a cardiologist from the time of enrolment to discharge. A third cardiologist refereed in situations of disagreement. All patients appear to be included in the analysis	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Risk: low

Study: Keller *et al.* 2011[141]

Domain 1: patient selection

A. Risk of bias	
Consecutive patients presenting to chest pain units	
Was a consecutive or random sample of patients enrolled?	Yes
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Risk: low
B. Applicability	
General chest pain populations. Some participants had a final diagnosis of STEMI	
Do the included patients match the question?	Concerns: high

Domain 2: index test(s)

A. Risk of bias	
Abbott Architect STAT hs-cTnI on admission and at 3 hours. Reference standard (final diagnosis) was adjudicated after hs-cTnI testing. Thresholds based on test properties appeared to be prespecified	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Risk: low
B. Applicability	
Are there concerns that the index test, its conduct or interpretation differ from the review question?	Concerns: low

Domain 3: reference standard

A. Risk of bias	
Reference standard diagnosis of AMI based on joint ESC and ACC criteria and included serial conventional cTnT (10- to 12-hour time point not specified)	
Determination of diagnosis was made blind to hs-cTnT results	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could the reference standard, its conduct or its interpretation have introduced bias?	Risk: low
B. Applicability	
Is there concern that the target condition, as defined by the reference standard, does not match the review question?	Concerns: high

Domain 4: flow and timing

A. Risk of bias	
None of the analyses included all study participants (558 or 867 participants missing)	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	Risk: high

Study: Kurz *et al.* 2011[148]

Domain 1: patient selection

A. Risk of bias	
Consecutive patients admitted to a chest pain unit. 206 patients not included because of 'technical reasons' (not fully defined, e.g. venepuncture not possible)	
Was a consecutive or random sample of patients enrolled?	Yes
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	Risk: unclear
B. Applicability	
Appears to be an unselected chest pain population, STEMI excluded. Second publication[230] is for a retrospectively selected subgroup of participants with a diagnosis of NSTEMI or UA. Patients were admitted to chest pain units	
Do the included patients match the question?	Concerns: high

Domain 2: index test(s)

A. Risk of bias	
Roche Elecsys hs-cTnT. Data reported for admission, 3- and 6-hour samples (6-hour data not extracted)	
Reference standard troponin testing occurred after hs-cTnT. Threshold was prespecified for data extracted from Giannitsis *et al.*,[230] but not from Kurz *et al.*[148] (low risk of bias for Giannitsis *et al.*[230] data)	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Risk: low
B. Applicability	
Are there concerns that the index test, its conduct or interpretation differ from the review question?	Concerns: low

Domain 3: reference standard

A. Risk of bias	
Reference standard diagnosis of AMI based on joint ESC and ACC criteria and included serial conventional cTnT (10- to 12-hour time point not specified)	
Unclear whether or not determination of diagnosis was made blind to hs-cTnT results	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Risk: unclear
B. Applicability	
Is there concern that the target condition, as defined by the reference standard, does not match the review question?	Concerns: high

Domain 4: flow and timing

A. Risk of bias	
All participants appear to have been included in the analyses	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Risk: low

Study: Lin *et al.* 2019[117]

Domain 1: patient selection

A. Risk of bias	
Convenience sample of patients presenting Monday to Friday, from 08.00 to 21.00, with suspected ACS. Patients who did not have any data on cTn obtained as part of standard care, as well as those lost to follow-up and patients with STEMI were excluded	
Was a consecutive or random sample of patients enrolled?	No
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	No
Could the selection of patients have introduced bias?	Risk: high
B. Applicability	
Patients presenting at night and weekends may differ from those recruited	
Do the included patients match the question?	Concerns: high

Domain 2: index test(s)

A. Risk of bias	
MACEs were adjudicated after the index test. Optimised thresholds were derived from ROC analyses conducted as part of the study	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it prespecified?	No
Could the conduct or interpretation of the index test have introduced bias?	Risk: high
B. Applicability	
Are there concerns that the index test, its conduct or interpretation differ from the review question?	Concerns: low

Domain 3: reference standard

A. Risk of bias	
hs-cTnT results were known to clinicians who adjudicated MACEs	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	No
Could the reference standard, its conduct or its interpretation have introduced bias?	Risk: high
B. Applicability	
Is there concern that the target condition, as defined by the reference standard, does not match the review question?	Concerns: low

Domain 4: flow and timing

A. Risk of bias	
All study participants appear to have been assessed for 30-day MACEs using the same procedure	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Risk: low

Study: Melki *et al.* 2011[144]

Domain 1: patient selection

A. Risk of bias	
Recruitment described as 'consecutive except for temporary interruptions of the study due to high work load in the coronary care unit'	
Was a consecutive or random sample of patients enrolled?	No
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Risk: high
B. Applicability	
Chest pain patients admitted to chest pain unit, excluding ST segment elevation	
Do the included patients match the question?	Concerns: high

Domain 2: index test(s)

A. Risk of bias	
Roche Elecsys hs-cTnT on admission and at 2 hours. Reference standard (final diagnosis) determined after hs-cTnT testing. Threshold based on assay characteristics and appears predetermined	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Risk: low
B. Applicability	
Are there concerns that the index test, its conduct or interpretation differ from the review question?	Concerns: low

Domain 3: reference standard

A. Risk of bias	
Reference standard diagnosis of AMI based on joint ESC and ACC criteria and included serial conventional cTnT or cTnI (9- to 12-hour time point specified)	
Determination of diagnosis was made blind to hs-cTnT results	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could the reference standard, its conduct or its interpretation have introduced bias?	Risk: low
B. Applicability	
Is there concern that the target condition, as defined by the reference standard, does not match the review question?	Concerns: low

Domain 4: flow and timing

A. Risk of bias	
All participants appear to have been included in the analyses	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Risk: low

Study: Peacock *et al.* 2018[89]

Domain 1: patient selection

A. Risk of bias	
Patients with suspected ACS presenting to 1 of 15 US EDs within 24 hours of symptom onset. Exclusion criteria were AMI within the last 3 months, transfer from another medical facility, surgery (including percutaneous coronary intervention) or hospitalisation within the last 3 months, recent cardioversion or defibrillation, acute non-cardiac primary illness prior to enrolment (e.g. severe sepsis), cardiogenic shock and pregnancy	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Risk: unclear
B. Applicability	
Target condition mixed AMI	
Do the included patients match the question?	Concerns: high

Domain 2: index test(s)

A. Risk of bias	
Reference standard adjudicated after index test	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Risk: low
B. Applicability	
Are there concerns that the index test, its conduct or interpretation differ from the review question?	Concerns: low

Domain 3: reference standard

A. Risk of bias	
Third universal definition of AMI. Reference standard adjudicated blind to hs-cTnT results	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could the reference standard, its conduct or its interpretation have introduced bias?	Risk: low
B. Applicability	
Is there concern that the target condition, as defined by the reference standard, does not match the review question?	Concerns: low

Domain 4: flow and timing

A. Risk of bias	
All patients received the same reference standard	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Risk: low

Study: PITGORAS, Sanchis *et al.* 2012[135]

Domain 1: patient selection

A. Risk of bias	
Patients excluded because of troponin elevation in any of two serial determinations (at arrival and 6–8 hours later) and prior diagnosis of ischemic heart disease. No details on how patients were selected for the study	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	No
Could the selection of patients have introduced bias?	Risk: high
B. Applicability	
Selected low-risk population	
Do the included patients match the question?	Concerns: high

Domain 2: index test(s)

A. Risk of bias	
Roche Elecsys hs-cTnT on admission and at 6–8 hours (data reported for admission and peak values). Reference standard (30-day composite) occurred after testing. Thresholds were reported as prespecified	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Risk: low
B. Applicability	
Are there concerns that the index test, its conduct or interpretation differ from the review question?	Concerns: low

Domain 3: reference standard

A. Risk of bias	
Composite 30-day end point of AMI, death and revascularisation	
Not clear whether or not those adjudicating AMI were aware of hs-cTnT results	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct or its interpretation have introduced bias?	Risk: unclear
B. Applicability	
Is there concern that the target condition, as defined by the reference standard, does not match the review question?	Concerns: low

Domain 4: flow and timing

A. Risk of bias	
All participants appeared to have been included in the analyses	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Risk: low

Study: QUART, Parsonage *et al.* 2014[88]

Domain 1: patient selection

A. Risk of bias	
Consecutive adult patients presenting to the ED during office hours with symptoms suggestive of cardiac chest pain. Exclusion criteria were reported and were appropriate	
Was a consecutive or random sample of patients enrolled?	No
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Risk: high
B. Applicability	
Target condition mixed (any AMI)	
Do the included patients match the question?	Concerns: high

Domain 2: index test(s)

A. Risk of bias	
Index test conducted before reference standard adjudication	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Risk: low
B. Applicability	
Are there concerns that the index test, its conduct or interpretation differ from the review question?	Concerns: low

Domain 3: reference standard

A. Risk of bias	
Third universal definition of AMI. Results of the investigational hs-cTnT assay were not available at the time of adjudication	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could the reference standard, its conduct or its interpretation have introduced bias?	Risk: low
B. Applicability	
Is there concern that the target condition, as defined by the reference standard, does not match the review question?	Concerns: low

Domain 4: flow and timing

A. Risk of bias	
All patients received the same reference standard	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Risk: low

Study: RATPAC (point-of-care arm), Collinson *et al.* 2013[159]

Domain 1: patient selection

A. Risk of bias	
Participants with chest pain and suspected AMI. Study uses a subgroup of one arm of a RCT. Patients at high risk of NSTEMI were excluded	
Was a consecutive or random sample of patients enrolled?	Yes
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Risk: low
B. Applicability	
Chest pain patients, excluding those with diagnostic ECG changes	
Do the included patients match the question?	Concerns: high

Domain 2: index test(s)

A. Risk of bias	
Roche Elecsys hs-cTnT on admission and at 90 minutes. Reference standard (final diagnosis) determined after hs-cTnT. Threshold based on assay characteristics, including the 99th centile	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Risk: low
B. Applicability	
Are there concerns that the index test, its conduct or interpretation differ from the review question?	Concerns: low

Domain 3: reference standard

A. Risk of bias	
Reference standard diagnosis of AMI based on joint ESC and ACC criteria and included serial conventional cTnT or cTnI (10- to 12-hour time point specified). Determination of diagnosis was made blind to hs-cTnT results	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could the reference standard, its conduct or its interpretation have introduced bias?	Risk: low
B. Applicability	
Is there concern that the target condition, as defined by the reference standard, does not match the review question?	Concerns: low

Domain 4: flow and timing

A. Risk of bias	
1125 patients enrolled: 25 no samples collected and 250 samples taken but study samples not collected	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	Risk: high

Study: Rapid Evaluation of Acute Myocardial Infarction in the United States (REACTION-US), Nowak *et al.* 2018[87]

Domain 1: patient selection

A. Risk of bias	
Convenience sample (patients screened when research co-ordinators were available). Patients with STEMI, acute distress requiring life-saving interventions in the previous 24 hours, or who were transferred from another hospital or were pregnant were excluded. The results section indicates that some patients who did not meet the limited exclusion criteria were excluded	
Was a consecutive or random sample of patients enrolled?	No
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	No
Could the selection of patients have introduced bias?	Risk: high
B. Applicability	
Target condition was NSTEMI, but patients screened may not be representative of all patients presenting with suspected ACS	
Do the included patients match the question?	Concerns: high

Domain 2: index test(s)

A. Risk of bias	
The reference standard was adjudicated after the index test	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Risk: low
B. Applicability	
Are there concerns that the index test, its conduct or interpretation differ from the review question?	Concerns: low

Domain 3: reference standard

A. Risk of bias	
Third universal definition of AMI, adjudicated by a panel of clinicians who were blinded to the hs-TnT result	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could the reference standard, its conduct or its interpretation have introduced bias?	Risk: low
B. Applicability	
Is there concern that the target condition, as defined by the reference standard, does not match the review question?	Concerns: low

Domain 4: flow and timing

A. Risk of bias	
All patients received the same reference standard. Thirty (5%) patients were not included in the 30-minute Δ analysis	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	Risk: low

Study: Saenger *et al.* 2010[165]

Domain 1: patient selection

A. Risk of bias	
No details on how patients were selected. No exclusion criteria reported	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	Risk: unclear
B. Applicability	
No exclusion criteria reported. The reference standard was AMI (diagnosis method not specified). Diagnoses included STEMI	
Do the included patients match the question?	Concerns: high

Domain 2: index test(s)

A. Risk of bias	
Roche Elecsys hs-cTnT on admission and after 3 hours. Data reported for admission and Δ 0–3 hours. No details of interpretation reported. Threshold for Δ value derived from ROC analysis. The 99th centile was also used	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Risk: low
B. Applicability	
Are there concerns that the index test, its conduct or interpretation differ from the review question?	Concerns: low

Domain 3: reference standard

A. Risk of bias	
Reference standard diagnosis of AMI (no details reported)	
Is the reference standard likely to correctly classify the target condition?	Unclear
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct or its interpretation have introduced bias?	Risk: unclear
B. Applicability	
Is there concern that the target condition, as defined by the reference standard, does not match the review question?	Concerns: high

Domain 4: flow and timing

A. Risk of bias	
No withdrawals reported	
Did all patients receive a reference standard?	Unclear
Did patients receive the same reference standard?	Unclear
Were all patients included in the analysis?	Unclear
Could the patient flow have introduced bias?	Risk: unclear

Study: Sebbane *et al.* 2013[157]

Domain 1: patient selection

A. Risk of bias	
No details on how patients were selected for inclusion	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Risk: unclear
B. Applicability	
Unselected cohort of adult patients presenting with chest pain of recent onset (within 12 hours)	
Do the included patients match the question?	Concerns: low

Domain 2: index test(s)

A. Risk of bias	
Roche Elecsys hs-cTnT on admission or from sample taken during pre-hospital management. Final diagnosis adjudicated 1 month after acute episode. Optimal diagnostic thresholds were determined using within-study ROC analyses. The 99th centile was also reported	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Risk: low
B. Applicability	
Are there concerns that the index test, its conduct or interpretation differ from the review question?	Concerns: low

Domain 3: reference standard

A. Risk of bias	
Diagnosis determined by two independent ED physicians, based on joint ESC and ACC criteria. Reference standard included cTnI taken on admission, at 6 hours and beyond, as needed (10- to 12-hour time point not specified). Physicians had access to serial cTnI results, but were blinded to hs-cTnT results	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could the reference standard, its conduct or its interpretation have introduced bias?	Risk: low
B. Applicability	
Is there concern that the target condition, as defined by the reference standard, does not match the review question?	Concerns: high

Domain 4: flow and timing

A. Risk of bias	
Fifty-four patients were excluded from the analyses because of missing data, including lack of copeptin, hs-cTnT and cTnI measurements	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	Risk: high

Study: Shiozaki *et al.* 2017[100]

Domain 1: patient selection

A. Risk of bias	
Patients with chest pain suggestive of ACS, STEMI or trauma that could elevate troponins were excluded. Thirty patients aged > 90 years and 16 with a poor prognosis were excluded (the reasons were not specified in the methods). An additional 21 patients were excluded for additional unspecified reasons	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	No
Could the selection of patients have introduced bias?	Risk: high
B. Applicability	
Target condition was NSTEMI, but exclusions may mean that the study is not representative of the population presenting with suspected ACS	
Do the included patients match the question?	Concerns: high

Domain 2: index test(s)

A. Risk of bias	
The reference standard diagnosis was adjudicated after the index test	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Risk: low
B. Applicability	
Are there concerns that the index test, its conduct or interpretation differ from the review question?	Concerns: low

Domain 3: reference standard

A. Risk of bias	
Adjudicated by two cardiologists based on ESC/ACC guidelines. Unclear whether or not this was carried out with knowledge of the hs-TnT results	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct or its interpretation have introduced bias?	Risk: unclear
B. Applicability	
Is there concern that the target condition, as defined by the reference standard, does not match the review question?	Concerns: low

Domain 4: flow and timing

A. Risk of bias	
All patients received the same reference standard	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Risk: low

Study: Slagman *et al.* 2017[102]

Domain 1: patient selection

A. Risk of bias	
All patients with a routine point-of-care troponin T measurement at admission (presenting symptoms unclear). Patients with a final diagnosis of STEMI and patients with surgical conditions were excluded, as were patients with missing troponin values	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	Risk: unclear
B. Applicability	
Target condition was NSTEMI, but presenting symptoms unclear	
Do the included patients match the question?	Concerns: unclear

Domain 2: index test(s)

A. Risk of bias	
Reference standard diagnosis adjudicated after index test	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Risk: low
B. Applicability	
Are there concerns that the index test, its conduct or interpretation differ from the review question?	Concerns: low

Domain 3: reference standard

A. Risk of bias	
Clinicians adjudicating the reference standard diagnosis had access to all clinical information, including hs-cTnT results. Reference standard diagnosis was retrieved for *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision codes in hospital records	
Is the reference standard likely to correctly classify the target condition?	Unclear
Were the reference standard results interpreted without knowledge of the results of the index test?	No
Could the reference standard, its conduct or its interpretation have introduced bias?	Risk: high
B. Applicability	
Is there concern that the target condition, as defined by the reference standard, does not match the review question?	Concerns: unclear

Domain 4: flow and timing

A. Risk of bias	
All patients appear to have been included in the analysis	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Unclear
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Risk: unclear

Study: TRAPID-AMI, Mueller *et al.* 2016[80]

Domain 1: patient selection

A. Risk of bias	
Adults presenting to the ED with symptoms suggestive of AMI within the previous 6 hours. Exclusion criteria were listed and were appropriate	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Risk: unclear
B. Applicability	
Primary target condition was mixed (any AMI). A subgroup analysis excluding patients with STEMI (target condition NSTEMI) was reported	
Do the included patients match the question?	Concerns: low

Domain 2: index test(s)

A. Risk of bias	
The index test was conducted before reference standard adjudication	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Risk: low
B. Applicability	
Are there concerns that the index test, its conduct or interpretation differ from the review question?	Concerns: low

Domain 3: reference standard

A. Risk of bias	
Third universal definition of AMI and ESC guidelines. Information available to clinical adjudicators was listed and did not include hs-cTnT results	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could the reference standard, its conduct or its interpretation have introduced bias?	Risk: low
B. Applicability	
Is there concern that the target condition, as defined by the reference standard, does not match the review question?	Concerns: low

Domain 4: flow and timing

A. Risk of bias	
All patients received the same reference standard	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Risk: low

Study: UltraSensitive Troponin in Acute Coronary syndromes (TUSCA), Santalo *et al.* 2013[133]

Domain 1: patient selection

A. Risk of bias	
Consecutive adult patients presenting to the ED	
Was a consecutive or random sample of patients enrolled?	Yes
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Risk: low
B. Applicability	
Appears to be an unselected ED chest pain population	
Do the included patients match the question?	Concerns: low

Domain 2: index test(s)

A. Risk of bias	
Roche Elecsys hs-cTnT on admission and at 2, 4 and 6–8 hours or until discharge (data reported for admission and Δ values). Unclear whether or not hs-cTnT was interpreted blind to cTnT	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Risk: low
B. Applicability	
Are there concerns that the index test, its conduct or interpretation differ from the review question?	Concerns: low

Domain 3: reference standard

A. Risk of bias	
Final diagnosis adjudicated by a committee, based on Roche cTnT at admission and 2, 4 and 6–8 hours or until discharge (10- to 12-hour time point not specified). NSTEMI defined as cTnT > 10 ng/l and Δ cTnT > 20%, also 99th centile. Unclear whether or not adjudicators were blinded to hs-cTnT	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct or its interpretation have introduced bias?	Risk: unclear
B. Applicability	
Is there concern that the target condition, as defined by the reference standard, does not match the review question?	Concerns: unclear

Domain 4: flow and timing

A. Risk of bias	
All participants appear to have been included in the analyses	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Risk: low

Study: Use of TROPonin In Acute coronary syndromes (UTROPIA), Sandoval *et al.* 2017[96]

Domain 1: patient selection

A. Risk of bias	
Consecutive, unselected patients with suspected AMI	
Was a consecutive or random sample of patients enrolled?	Yes
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Risk: low
B. Applicability	
Patients with STEMI excluded (target condition was NSTEMI)	
Do the included patients match the question?	Concerns: low

Domain 2: index test(s)

A. Risk of bias	
Final diagnosis adjudicated after the index test. Prespecified thresholds (LoD and High-STEACS) used	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Risk: low
B. Applicability	
Are there concerns that the index test, its conduct or interpretation differ from the review question?	Concerns: low

Domain 3: reference standard

A. Risk of bias	
Final diagnosis made with knowledge of hs-cTnI results	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	No
Could the reference standard, its conduct or its interpretation have introduced bias?	Risk: high
B. Applicability	
Is there concern that the target condition, as defined by the reference standard, does not match the review question?	Concerns: low

Domain 4: flow and timing

A. Risk of bias	
All patients were included in the analyses and the final diagnosis was reached using the same process in all cases	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Risk: low

Study: Venge *et al.* 2017[110]

Domain 1: patient selection

A. Risk of bias	
Prospective enrolment of adult patients with suspected MI. No exclusion criteria listed	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	Risk: unclear
B. Applicability	
Setting is inconsistently described ('Ed' or 'ED' and 'coronary care/chest pain units'). Target condition was mixed AMI	
Do the included patients match the question?	Concerns: high

Domain 2: index test(s)

A. Risk of bias	
Reference standard troponin T was assessed at a central laboratory (after index test)	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Risk: low
B. Applicability	
Are there concerns that the index test, its conduct or interpretation differ from the review question?	Concerns: low

Domain 3: reference standard

A. Risk of bias	
Reference standard included troponin T results at 2–4 and 6–24 hours, as well as clinical information and MI, and was adjudicated by a panel of cardiologists. Not clear if cardiologists adjudicating final diagnosis had access to hs-cTnI results	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct or its interpretation have introduced bias?	Risk: unclear
B. Applicability	
Is there concern that the target condition, as defined by the reference standard, does not match the review question?	Concerns: low

Domain 4: flow and timing

A. Risk of bias	
All patients received the same reference standard. The study compared Abbott ARCHITECT hs-cTnI with a conventional cTnI assay and a point-of-care assay (these assays are not included in the scope of this review). Patients who did not have data for all three assays were excluded from the analyses.	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	Risk: high

Appendix 4 QUADAS-2C assessments

Study: ADAPT, Cullen *et al.* 2014[68]

Domain: patient selection			
Single test accuracy (QUADAS-2)		**Answers for the Abbott ARCHITECT hs-cTnI**	**Answers for the Roche Elecsys hs-cTnT**
Signalling questions	1.1 Was a consecutive or random sample of patients enrolled?	Yes	Yes
	1.2 Was a case–control design avoided?	Yes	Yes
	1.3 Did the study avoid inappropriate exclusions?	Yes	Yes
Risk of bias	1.4 Could the selection of patients have introduced bias?	Low	Low
Concerns regarding applicability	1.5 Are there concerns that the included patients do not match the review question?	Low	Low
Comparative accuracy (QUADAS-2C)		**Answers for the comparison of the ARCHITECT hs-cTnI with the Roche Elecsys hs-cTnT**	
Signalling questions	1.6 Was risk of bias for this domain judged 'low' for all index tests?	Yes	
	1.7 Was the intention for patients either to receive all index tests or to be randomly allocated to index tests?	Yes	
	1.8 If patients were randomised, was the allocation sequence random?	NA	
	1.9 If patients were randomised, was the allocation sequence concealed until patients were enrolled and assigned to index tests?	NA	
Risk of bias	1.10 Could the selection of patients have introduced bias in the comparison?	Low	
Domain: index tests			
Single test accuracy (QUADAS-2)		**Answers for the Abbott ARCHITECT hs-cTnI**	**Answers for the Roche Elecsys hs-cTnT**
Signalling questions	2.1 Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear	Unclear
	2.2 If a threshold was used, was it prespecified?	Yes	Yes
Risk of bias	2.3 Could the conduct or interpretation of the index test have introduced bias?	Unclear	Unclear
Concerns regarding applicability	2.4 Are there concerns that the index test, its conduct or its interpretation differ from the review question?	Low	Low

Comparative accuracy (QUADAS-2C)		Answers for the comparison of the ARCHITECT hs-cTnI with the Roche Elecsys hs-cTnT
Signalling questions	2.5 Was risk of bias for this domain judged 'low' for all index tests?	Unclear
	2.6 If patients received multiple index tests, were test results interpreted without knowledge of the results of the other index test(s)?	Unclear
	2.7 If patients received multiple index tests, is undergoing one index test unlikely to affect the performance of the other index test(s)?	Yes
	2.8 Were differences in the conduct or interpretation between the index tests unlikely to advantage one of the tests?	Yes
Risk of bias	2.9 Could the conduct or interpretation of the index tests have introduced bias in the comparison?	Unclear

Domain: reference standard			
Single test accuracy (QUADAS-2)		**Answers for the Abbott ARCHITECT hs-cTnI**	**Answers for the Roche Elecsys hs-cTnT**
Signalling questions	3.1 Is the reference standard likely to correctly classify the target condition?	Yes	Yes
	3.2 Were the reference standard results interpreted without knowledge of the results of the index test?	Yes	Yes
Risk of bias	3.3 Could the reference standard, its conduct or its interpretation have introduced bias?	Low	Low
Concerns regarding applicability	3.4 Are there concerns that the target condition, as defined by the reference standard, does not match the review question?	Low	Low

Comparative accuracy (QUADAS-2C)		Answers for the comparison of the ARCHITECT hs-cTnI with the Roche Elecsys hs-cTnT
Signalling questions	3.5 Was risk of bias for this domain judged 'low' for all index tests?	Yes
	3.6 Did the reference standard avoid incorporating any of the index tests?	Yes
Risk of bias	3.7 Could the reference standard, its conduct or its interpretation have introduced bias in the comparison?	Low

Domain: flow and timing			
Single test accuracy (QUADAS-2)		**Answers for the Abbott ARCHITECT hs-cTnI**	**Answers for the Roche Elecsys hs-cTnT**
Signalling questions	4.1 Was there an appropriate interval between index tests and reference standard?	Yes	Yes
	4.2 Did all patients receive a reference standard?	Yes	Yes
	4.3 Did all patients receive the same reference standard?	Yes	Yes
	4.4 Were all patients included in the analysis?	Yes	Yes
Risk of bias	4.5 Could the patient flow have introduced bias?	Low	Low

Comparative accuracy (QUADAS-2C)		Answers for the comparison of the ARCHITECT hs-cTnI with the Roche Elecsys hs-cTnT
Signalling questions	4.6 Was risk of bias for this domain judged 'low' for all index tests?	Yes
	4.7 Was there an appropriate interval between the index tests?	Yes
	4.8 Was the same reference standard used for all index tests?	Yes
	4.9 Are the proportions and reasons for missing data similar across index tests?	Yes
Risk of bias	4.10 Could the patient flow have introduced bias in the comparison?	Low

NA, not applicable.

Study: APACE, Boeddinghaus *et al.* 2018/19,[59,170,178] (comparison of assays using ESC 0/1-hour pathway or equivalent)

Domain: patient selection							
Single test accuracy (QUADAS-2)		Answers for the Abbott ARCHITECT hs-cTnI	Answers for the Beckman Coulter ACCESS hs-cTnI	Answers for the Ortho VITROS hs-cTnI	Answers for the Quidel TriageTrue hs-cTnI	Answers for the Roche Elecsys hs-cTnT	Answers for the Siemens ADVIA Centaur hs-cTnI
Signalling questions	1.1 Was a consecutive or random sample of patients enrolled?	Yes	Yes	Yes	Yes	Yes	Yes
	1.2 Was a case–control design avoided?	Yes	Yes	Yes	Yes	Yes	Yes
	1.3 Did the study avoid inappropriate exclusions?	Yes	Yes	Yes	Yes	Yes	Yes
Risk of bias	1.4 Could the selection of patients have introduced bias?	Low	Low	Low	Low	Low	Low
Concerns regarding applicability	1.5 Are there concerns that the included patients do not match the review question?	Low	Low	Low	Low	Low	Low

Comparative accuracy (QUADAS-2C)		Answers for the comparison of all tests
Signalling questions	1.6 Was risk of bias for this domain judged 'low' for all index tests?	Yes
	1.7 Was the intention for patients either to receive all index tests or to be randomly allocated to index tests?	Unclear
	1.8 If patients were randomised, was the allocation sequence random?	NA
	1.9 If patients were randomised, was the allocation sequence concealed until patients were enrolled and assigned to index tests?	NA
Risk of bias	1.10 Could the selection of patients have introduced bias in the comparison?	Unclear

Domain: index tests							
Single test accuracy (QUADAS-2)		Answers for the Abbott ARCHITECT hs-cTnI	Answers for the Beckman Coulter ACCESS hs-cTnI	Answers for the Ortho VITROS hs-cTnI	Answers for the Quidel TriageTrue hs-TnI	Answers for the Roche Elecsys hs-cTnT	Answers for the Siemens ADVIA Centaur hs-cTnI
Signalling questions	2.1 Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	Yes	Yes	Yes	Yes	Yes
	2.2 If a threshold was used, was it prespecified?	Yes	Yes	Yes	Yes	Yes	Yes
Risk of bias	2.3 Could the conduct or interpretation of the index test have introduced bias?	Low	Low	Low	Low	Low	Low
Concerns regarding applicability	2.4 Are there concerns that the index test, its conduct or its interpretation differ from the review question?	Low	Low	Low	Low	Low	Low
Comparative accuracy (QUADAS-2C)		**Answers for the comparison of all tests**					
Signalling questions	2.5 Was risk of bias for this domain judged 'low' for all index tests?	Yes					
	2.6 If patients received multiple index tests, were test results interpreted without knowledge of the results of the other index test(s)?	Unclear					
	2.7 If patients received multiple index tests, is undergoing one index test unlikely to affect the performance of the other index test(s)?	Yes					
	2.8 Were differences in the conduct or interpretation between the index tests unlikely to advantage one of the tests?	Yes					
Risk of bias	2.9 Could the conduct or interpretation of the index tests have introduced bias in the comparison?	Unclear					
Domain: reference standard							
Single test accuracy (QUADAS-2)		Answers for the Abbott ARCHITECT hs-cTnI	Answers for the Beckman Coulter ACCESS hs-cTnI	Answers for the Ortho VITROS hs-cTnI	Answers for the Quidel TriageTrue hs-TnI	Answers for the Roche Elecsys hs-cTnT	Answers for the Siemens ADVIA Centaur hs-cTnI
Signalling questions	3.1 Is the reference standard likely to correctly classify the target condition?	Yes	Yes	Yes	Yes	Yes	Yes
	3.2 Were the reference standard results interpreted without knowledge of the results of the index test?	No	No	No	No	No	No
Risk of bias	3.3 Could the reference standard, its conduct or its interpretation have introduced bias?	High	High	High	High	High	High
Concerns regarding applicability	3.4 Are there concerns that the target condition as defined by the reference standard does not match the review question?	Low	Low	Low	Low	Low	Low

Comparative accuracy (QUADAS-2C)		Answers for the comparison of all tests
Signalling questions	3.5 Was risk of bias for this domain judged 'low' for all index tests?	No
	3.6 Did the reference standard avoid incorporating any of the index tests?	No
Risk of bias	3.7 Could the reference standard, its conduct or its interpretation have introduced bias in the comparison?	High

Domain: flow and timing							
Single test accuracy (QUADAS-2)		Answers for the Abbott ARCHITECT hs-cTnI	Answers for the Beckman Coulter ACCESS hs-cTnI	Answers for the Ortho VITROS hs-cTnI	Answers for the Quidel TriageTrue hs-cTnI	Answers for the Roche Elecsys hs-cTnT	Answers for the Siemens ADVIA Centaur hs-cTnI
Signalling questions	4.1 Was there an appropriate interval between index tests and reference standard?	Yes	Yes	Yes	Yes	Yes	Yes
	4.2 Did all patients receive a reference standard?	Yes	Yes	Yes	Yes	Yes	Yes
	4.3 Did all patients receive the same reference standard?	Yes	Yes	Yes	Yes	Yes	Yes
	4.4 Were all patients included in the analysis?	Yes	Yes	Yes	Yes	Yes	Yes
Risk of bias	4.5 Could the patient flow have introduced bias?	Low	Low	Low	Low	Low	Low

Comparative accuracy (QUADAS-2C)		Answers for the comparison of all tests
Signalling questions	4.6 Was risk of bias for this domain judged 'low' for all index tests?	Yes
	4.7 Was there an appropriate interval between the index tests?	Yes
	4.8 Was the same reference standard used for all index tests?	Yes
	4.9 Are the proportions and reasons for missing data similar across index tests?	No. (Yes for comparison of Abbott ARCHITECT hs-cTnI, Roche Elecsys hs-cTnT and Siemens ADVIA Centaur hs-cTnI)
Risk of bias	4.10 Could the patient flow have introduced bias in the comparison?	High. (Low for comparison of Abbott ARCHITECT hs-cTnI, Roche Elecsys hs-cTnT and Siemens ADVIA Centaur hs-cTnI)

NA, not applicable.

Study: BEST, Body *et al.* 2019/20[115,172]

Domain: patient selection			
Single test accuracy (QUADAS-2)		**Answers for the Roche Elecsys hs-cTnT**	**Answers for the Siemens ADVIA Centaur hs-cTnI**
Signalling questions	1.1 Was a consecutive or random sample of patients enrolled?	Yes	Yes
	1.2 Was a case–control design avoided?	Yes	Yes
	1.3 Did the study avoid inappropriate exclusions?	Yes	Yes
Risk of bias	1.4 Could the selection of patients have introduced bias?	Low	Low
Concerns regarding applicability	1.5 Are there concerns that the included patients do not match the review question?	Low	Low
Comparative accuracy (QUADAS-2C)		**Answers for the comparison of the Roche Elecsys hs-cTnT with the Siemens ADVIA Centaur hs-cTnI**	
Signalling questions	1.6 Was risk of bias for this domain judged 'low' for all index tests?	Yes	
	1.7 Was the intention for patients either to receive all index tests or to be randomly allocated to index tests?	No	
	1.8 If patients were randomised, was the allocation sequence random?	NA	
	1.9 If patients were randomised, was the allocation sequence concealed until patients were enrolled and assigned to index tests?	NA	
Risk of bias	1.10 Could the selection of patients have introduced bias in the comparison?	High	
Domain: index tests			
Single test accuracy (QUADAS-2)		**Answers for the Roche Elecsys hs-cTnT**	**Answers for the Siemens ADVIA Centaur hs-cTnI**
Signalling questions	2.1 Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	Yes
	2.2 If a threshold was used, was it prespecified?	Yes	Yes
Risk of bias	2.3 Could the conduct or interpretation of the index test have introduced bias?	Low	Low
Concerns regarding applicability	2.4 Are there concerns that the index test, its conduct or its interpretation differ from the review question?	Low	Low

Comparative accuracy (QUADAS-2C)		Answers for the comparison of the Roche Elecsys hs-cTnT with the Siemens ADVIA Centaur hs-cTnI
Signalling questions	2.5 Was risk of bias for this domain judged 'low' for all index tests?	Yes
	2.6 If patients received multiple index tests, were test results interpreted without knowledge of the results of the other index test(s)?	Unclear
	2.7 If patients received multiple index tests, is undergoing one index test unlikely to affect the performance of the other index test(s)?	Yes
	2.8 Were differences in the conduct or interpretation between the index tests unlikely to advantage one of the tests?	Yes
Risk of bias	2.9 Could the conduct or interpretation of the index tests have introduced bias in the comparison?	Unclear

Domain: reference standard			
Single test accuracy (QUADAS-2)		**Answers for the Roche Elecsys hs-cTnT**	**Answers for the Siemens ADVIA Centaur hs-cTnI**
Signalling questions	3.1 Is the reference standard likely to correctly classify the target condition?	Yes	Yes
	3.2 Were the reference standard results interpreted without knowledge of the results of the index test?	No	Yes
Risk of bias	3.3 Could the reference standard, its conduct or its interpretation have introduced bias?	High	Low
Concerns regarding applicability	3.4 Are there concerns that the target condition as defined by the reference standard does not match the review question?	Low	Low

Comparative accuracy (QUADAS-2C)		Answers for the comparison of the Roche Elecsys hs-cTnT with the Siemens ADVIA Centaur hs-cTnI
Signalling questions	3.5 Was risk of bias for this domain judged 'low' for all index tests?	No
	3.6 Did the reference standard avoid incorporating any of the index tests?	No
Risk of bias	3.7 Could the reference standard, its conduct or its interpretation have introduced bias in the comparison?	High

Domain: flow and timing			
Single test accuracy (QUADAS-2)		**Answers for the Roche Elecsys hs-cTnT**	**Answers for the Siemens ADVIA Centaur hs-cTnI**
Signalling questions	4.1 Was there an appropriate interval between index tests and reference standard?	Yes	Yes
	4.2 Did all patients receive a reference standard?	Yes	Yes
	4.3 Did all patients receive the same reference standard?	Yes	Yes
	4.4 Were all patients included in the analysis?	Yes	Yes
Risk of bias	4.5 Could the patient flow have introduced bias?	Low	Low
Comparative accuracy (QUADAS-2C)		**Answers for the comparison of the Roche Elecsys hs-cTnT with the Siemens ADVIA Centaur hs-cTnI**	
Signalling questions	4.6 Was risk of bias for this domain judged 'low' for all index tests?	Yes	
	4.7 Was there an appropriate interval between the index tests?	Yes	
	4.8 Was the same reference standard used for all index tests?	Yes	
	4.9 Are the proportions and reasons for missing data similar across index tests?	No	
Risk of bias	4.10 Could the patient flow have introduced bias in the comparison?	High	

NA, not applicable.

Study: High-STEACS, Chapman *et al.* 2018/19[66,67]

Domain: patient selection			
Single test accuracy (QUADAS-2)		**Answers for the Abbott ARCHITECT hs-cTnI**	**Answers for the Siemens Atellica hs-cTnI**
Signalling questions	1.1 Was a consecutive or random sample of patients enrolled?	Yes	Yes
	1.2 Was a case–control design avoided?	Yes	Yes
	1.3 Did the study avoid inappropriate exclusions?	Yes	Yes
Risk of bias	1.4 Could the selection of patients have introduced bias?	Low	Low
Concerns regarding applicability	1.5 Are there concerns that the included patients do not match the review question?	Low	Low

Comparative accuracy (QUADAS-2C)		Answers for the comparison of the ARCHITECT hs-cTnI with the Siemens Atellica hs-cTnI
Signalling questions	1.6 Was risk of bias for this domain judged 'low' for all index tests?	Yes
	1.7 Was the intention for patients either to receive all index tests or to be randomly allocated to index tests?	Unclear
	1.8 If patients were randomised, was the allocation sequence random?	NA
	1.9 If patients were randomised, was the allocation sequence concealed until patients were enrolled and assigned to index tests?	NA
Risk of bias	1.10 Could the selection of patients have introduced bias in the comparison?	Unclear

Domain: Index tests			
Single test accuracy (QUADAS-2)		**Answers for the ARCHITECT hs-cTnI**	**Answers for the Siemens Atellica hs-cTnI**
Signalling questions	2.1 Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	Yes
	2.2 If a threshold was used, was it prespecified?	Yes	Yes
Risk of bias	2.3 Could the conduct or interpretation of the index test have introduced bias?	Low	Low
Concerns regarding applicability	2.4 Are there concerns that the index test, its conduct or its interpretation differ from the review question?	Low	Low

Comparative accuracy (QUADAS-2C)		Answers for the comparison of the ARCHITECT hs-cTnI with the Siemens Atellica hs-cTnI
Signalling questions	2.5 Was risk of bias for this domain judged 'low' for all index tests?	Yes
	2.6 If patients received multiple index tests, were test results interpreted without knowledge of the results of the other index test(s)?	Unclear
	2.7 If patients received multiple index tests, is undergoing one index test unlikely to affect the performance of the other index test(s)?	Yes
	2.8 Were differences in the conduct or interpretation between the index tests unlikely to advantage one of the tests?	Yes
Risk of bias	2.9 Could the conduct or interpretation of the index tests have introduced bias in the comparison?	Unclear

Domain: reference standard			
Single test accuracy (QUADAS-2)		**Answers for the ARCHITECT hs-cTnI**	**Answers for the Siemens Atellica hs-cTnI**
Signalling questions	3.1 Is the reference standard likely to correctly classify the target condition?	Yes	Yes
	3.2 Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear	Unclear
Risk of bias	3.3 Could the reference standard, its conduct or its interpretation have introduced bias?	Unclear	Unclear
Concerns regarding applicability	3.4 Are there concerns that the target condition as defined by the reference standard does not match the review question?	Low	Low
Comparative accuracy (QUADAS-2C)		**Answers for the comparison of the ARCHITECT hs-cTnI with the Siemens Atellica hs-cTnI**	
Signalling questions	3.5 Was risk of bias for this domain judged 'low' for all index tests?	Unclear	
	3.6 Did the reference standard avoid incorporating any of the index tests?	Unclear	
Risk of bias	3.7 Could the reference standard, its conduct or its interpretation have introduced bias in the comparison?	Unclear	
Domain: flow and timing			
Single test accuracy (QUADAS-2)		**Answers for the ARCHITECT hs-cTnI**	**Answers for the Siemens Atellica hs-cTnI**
Signalling questions	4.1 Was there an appropriate interval between index tests and reference standard?	Yes	Yes
	4.2 Did all patients receive a reference standard?	Yes	Yes
	4.3 Did all patients receive the same reference standard?	Yes	Yes
	4.4 Were all patients included in the analysis?	Yes	Yes
Risk of bias	4.5 Could the patient flow have introduced bias?	Low	Low
Comparative accuracy (QUADAS-2C)		**Answers for the comparison of the ARCHITECT hs-cTnI with the Siemens Atellica hs-cTnI**	
Signalling questions	4.6 Was risk of bias for this domain judged 'low' for all index tests?	Yes	
	4.7 Was there an appropriate interval between the index tests?	Yes	
	4.8 Was the same reference standard used for all index tests?	Yes	
	4.9 Are the proportions and reasons for missing data similar across index tests?	No	
Risk of bias	4.10 Could the patient flow have introduced bias in the comparison?	High	

NA, not applicable.

Study: High-Sensitivity Cardiac Troponin I Assays in the United States (High-US), Sandoval *et al.* 2019[176]

Domain: patient selection			
Single test accuracy (QUADAS-2)		**Answers for the Siemens Atellica hs-cTnI**	**Answers for the Siemens ADVIA Centaur hs-cTnI**
Signalling questions	1.1 Was a consecutive or random sample of patients enrolled?	Yes	Yes
	1.2 Was a case–control design avoided?	Yes	Yes
	1.3 Did the study avoid inappropriate exclusions?	Yes	Yes
Risk of bias	1.4 Could the selection of patients have introduced bias?	Low	Low
Concerns regarding applicability	1.5 Are there concerns that the included patients do not match the review question?	Low	Low
Comparative accuracy (QUADAS-2C)		**Answers for the comparison of the Siemens Atellica hs-cTnI with the Siemens ADVIA Centaur hs-cTnI**	
Signalling questions	1.6 Was risk of bias for this domain judged 'low' for all index tests?	Yes	
	1.7 Was the intention for patients either to receive all index tests or to be randomly allocated to index tests?	Yes	
	1.8 If patients were randomised, was the allocation sequence random?	NA	
	1.9 If patients were randomised, was the allocation sequence concealed until patients were enrolled and assigned to index tests?	NA	
Risk of bias	1.10 Could the selection of patients have introduced bias in the comparison?	Low	
Domain: index tests			
Single test accuracy (QUADAS-2)		**Answers for the Siemens Atellica hs-cTnI**	**Answers for the Siemens ADVIA Centaur hs-cTnI**
Signalling questions	2.1 Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	Yes
	2.2 If a threshold was used, was it prespecified?	Yes	Yes
Risk of bias	2.3 Could the conduct or interpretation of the index test have introduced bias?	Low	Low
Concerns regarding applicability	2.4 Are there concerns that the index test, its conduct or its interpretation differ from the review question?	Low	Low

Comparative accuracy (QUADAS-2C)		Answers for the comparison of the Siemens Atellica hs-cTnI with the Siemens ADVIA Centaur hs-cTnI
Signalling questions	2.5 Was risk of bias for this domain judged 'low' for all index tests?	Yes
	2.6 If patients received multiple index tests, were test results interpreted without knowledge of the results of the other index test(s)?	Unclear
	2.7 If patients received multiple index tests, is undergoing one index test unlikely to affect the performance of the other index test(s)?	Yes
	2.8 Were differences in the conduct or interpretation between the index tests unlikely to advantage one of the tests?	Yes
Risk of bias	2.9 Could the conduct or interpretation of the index tests have introduced bias in the comparison?	Unclear

Domain: reference standard			
Single test accuracy (QUADAS-2)		**Answers for the Siemens Atellica hs-cTnI**	**Answers for the Siemens ADVIA Centaur hs-cTnI**
Signalling questions	3.1 Is the reference standard likely to correctly classify the target condition?	Yes	Yes
	3.2 Were the reference standard results interpreted without knowledge of the results of the index test?	Yes	Yes
Risk of bias	3.3 Could the reference standard, its conduct or its interpretation have introduced bias?	Low	Low
Concerns regarding applicability	3.4 Are there concerns that the target condition as defined by the reference standard does not match the review question?	Low	Low
Comparative accuracy (QUADAS-2C)		**Answers for the comparison of the Siemens Atellica hs-cTnI with the Siemens ADVIA Centaur hs-cTnI**	
Signalling questions	3.5 Was risk of bias for this domain judged 'low' for all index tests?	Yes	
	3.6 Did the reference standard avoid incorporating any of the index tests?	Yes	
Risk of bias	3.7 Could the reference standard, its conduct or its interpretation have introduced bias in the comparison?	Low	

Domain: flow and timing			
Single test accuracy (QUADAS-2)		**Answers for the Siemens Atellica hs-cTnI**	**Answers for the Siemens ADVIA Centaur hs-cTnI**
Signalling questions	4.1 Was there an appropriate interval between index tests and reference standard?	Yes	Yes
	4.2 Did all patients receive a reference standard?	Yes	Yes
	4.3 Did all patients receive the same reference standard?	Yes	Yes
	4.4 Were all patients included in the analysis?	Yes	Yes
Risk of bias	4.5 Could the patient flow have introduced bias?	Low	Low
Comparative accuracy (QUADAS-2C)		**Answers for the comparison of the Siemens Atellica hs-cTnI with the Siemens ADVIA Centaur hs-cTnI**	
Signalling questions	4.6 Was risk of bias for this domain judged 'low' for all index tests?	Yes	
	4.7 Was there an appropriate interval between the index tests?	Yes	
	4.8 Was the same reference standard used for all index tests?	Yes	
	4.9 Are the proportions and reasons for missing data similar across index tests?	Yes	
Risk of bias	4.10 Could the patient flow have introduced bias in the comparison?	Low	

NA, not applicable.

Study: ROMI-3, Shortt *et al.* 2017[101]

Domain: patient selection			
Single test accuracy (QUADAS-2)		**Answers for the Abbott ARCHITECT hs-cTnI**	**Answers for the Roche Elecsys hs-cTnT**
Signalling questions	1.1 Was a consecutive or random sample of patients enrolled?	Yes	Yes
	1.2 Was a case–control design avoided?	Yes	Yes
	1.3 Did the study avoid inappropriate exclusions?	Yes	Yes
Risk of bias	1.4 Could the selection of patients have introduced bias?	Low	Low
Concerns regarding applicability	1.5 Are there concerns that the included patients do not match the review question?	Low	Low

Comparative accuracy (QUADAS-2C)		Answers for the comparison of the Abbott ARCHITECT hs-cTnI with the Roche Elecsys hs-cTnT
Signalling questions	1.6 Was risk of bias for this domain judged 'low' for all index tests?	Yes
	1.7 Was the intention for patients either to receive all index tests or to be randomly allocated to index tests?	Yes
	1.8 If patients were randomised, was the allocation sequence random?	NA
	1.9 If patients were randomised, was the allocation sequence concealed until patients were enrolled and assigned to index tests?	NA
Risk of bias	1.10 Could the selection of patients have introduced bias in the comparison?	Low

Domain: index tests			
Single test accuracy (QUADAS-2)		**Answers for the Abbott ARCHITECT hs-cTnI**	**Answers for the Roche Elecsys hs-cTnT**
Signalling questions	2.1 Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	Yes
	2.2 If a threshold was used, was it prespecified?	Yes	Yes
Risk of bias	2.3 Could the conduct or interpretation of the index test have introduced bias?	Low	Low
Concerns regarding applicability	2.4 Are there concerns that the index test, its conduct or its interpretation differ from the review question?	Low	Low
Comparative accuracy (QUADAS-2C)		**Answers for the comparison of the Abbott ARCHITECT hs-cTnI with the Roche Elecsys hs-cTnT**	
Signalling questions	2.5 Was risk of bias for this domain judged 'low' for all index tests?	Yes	
	2.6 If patients received multiple index tests, were test results interpreted without knowledge of the results of the other index test(s)?	Unclear	
	2.7 If patients received multiple index tests, is undergoing one index test unlikely to affect the performance of the other index test(s)?	Yes	
	2.8 Were differences in the conduct or interpretation between the index tests unlikely to advantage one of the tests?	Yes	
Risk of bias	2.9 Could the conduct or interpretation of the index tests have introduced bias in the comparison?	Unclear	

Domain: reference standard			
Single test accuracy (QUADAS-2)		**Answers for the Abbott ARCHITECT hs-cTnI**	**Answers for the Roche Elecsys hs-cTnT**
Signalling questions	3.1 Is the reference standard likely to correctly classify the target condition?	Yes	Yes
	3.2 Were the reference standard results interpreted without knowledge of the results of the index test?	Yes	Yes
Risk of bias	3.3 Could the reference standard, its conduct or its interpretation have introduced bias?	Low	Low
Concerns regarding applicability	3.4 Are there concerns that the target condition as defined by the reference standard does not match the review question?	Low	Low
Comparative accuracy (QUADAS-2C)		**Answers for the comparison of the Abbott ARCHITECT hs-cTnI with the Roche Elecsys hs-cTnT**	
Signalling questions	3.5 Was risk of bias for this domain judged 'low' for all index tests?	Yes	
	3.6 Did the reference standard avoid incorporating any of the index tests?	Yes	
Risk of bias	3.7 Could the reference standard, its conduct or its interpretation have introduced bias in the comparison?	Low	
Domain: flow and timing			
Single test accuracy (QUADAS-2)		**Answers for the Abbott ARCHITECT hs-cTnI**	**Answers for the Roche Elecsys hs-cTnT**
Signalling questions	4.1 Was there an appropriate interval between index tests and reference standard?	Yes	Yes
	4.2 Did all patients receive a reference standard?	Yes	Yes
	4.3 Did all patients receive the same reference standard?	Yes	Yes
	4.4 Were all patients included in the analysis?	Yes	Yes
Risk of bias	4.5 Could the patient flow have introduced bias?	Low	Low
Comparative accuracy (QUADAS-2C)		**Answers for the comparison of the Abbott ARCHITECT hs-cTnI with the Roche Elecsys hs-cTnT**	
Signalling questions	4.6 Was risk of bias for this domain judged 'low' for all index tests?	Yes	
	4.7 Was there an appropriate interval between the index tests?	Yes	
	4.8 Was the same reference standard used for all index tests?	Yes	
	4.9 Are the proportions and reasons for missing data similar across index tests?	Yes	
Risk of bias	4.10 Could the patient flow have introduced bias in the comparison?	Low	

NA, not applicable.

Study: TRUST, Carlton *et al.* 2015[64]

Domain: patient selection			
Single test accuracy (QUADAS-2)		**Answers for the Abbott ARCHITECT hs-cTnI**	**Answers for the Roche Elecsys hs-cTnT**
Signalling questions	1.1 Was a consecutive or random sample of patients enrolled?	Yes	Yes
	1.2 Was a case–control design avoided?	Yes	Yes
	1.3 Did the study avoid inappropriate exclusions?	Yes	Yes
Risk of bias	1.4 Could the selection of patients have introduced bias?	Low	Low
Concerns regarding applicability	1.5 Are there concerns that the included patients do not match the review question?	Low	Low
Comparative accuracy (QUADAS-2C)		**Answers for the comparison of the Abbott ARCHITECT hs-cTnI with the Roche Elecsys hs-cTnT**	
Signalling questions	1.6 Was risk of bias for this domain judged 'low' for all index tests?	Yes	
	1.7 Was the intention for patients either to receive all index tests or to be randomly allocated to index tests?	Yes	
	1.8 If patients were randomised, was the allocation sequence random?	NA	
	1.9 If patients were randomised, was the allocation sequence concealed until patients were enrolled and assigned to index tests?	NA	
Risk of bias	1.10 Could the selection of patients have introduced bias in the comparison?	Low	
Domain: index tests			
Single test accuracy (QUADAS-2)		**Answers for the Abbott ARCHITECT hs-cTnI**	**Answers for the Roche Elecsys hs-cTnT**
Signalling questions	2.1 Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	Yes
	2.2 If a threshold was used, was it prespecified?	Yes	Yes
Risk of bias	2.3 Could the conduct or interpretation of the index test have introduced bias?	Low	Low
Concerns regarding applicability	2.4 Are there concerns that the index test, its conduct or its interpretation differ from the review question?	Low	Low

Comparative accuracy (QUADAS-2C)		Answers for the comparison of the Abbott ARCHITECT hs-cTnI with the Roche Elecsys hs-cTnT
Signalling questions	2.5 Was risk of bias for this domain judged 'low' for all index tests?	Yes
	2.6 If patients received multiple index tests, were test results interpreted without knowledge of the results of the other index test(s)?	Yes
	2.7 If patients received multiple index tests, is undergoing one index test unlikely to affect the performance of the other index test(s)?	Yes
	2.8 Were differences in the conduct or interpretation between the index tests unlikely to advantage one of the tests?	Yes
Risk of bias	2.9 Could the conduct or interpretation of the index tests have introduced bias in the comparison?	Low

Domain: reference standard			
Single test accuracy (QUADAS-2)		**Answers for the Abbott ARCHITECT hs-cTnI**	**Answers for the Roche Elecsys hs-cTnT**
Signalling questions	3.1 Is the reference standard likely to correctly classify the target condition?	Yes	Yes
	3.2 Were the reference standard results interpreted without knowledge of the results of the index test?	No	No
Risk of bias	3.3 Could the reference standard, its conduct or its interpretation have introduced bias?	High	High
Concerns regarding applicability	3.4 Are there concerns that the target condition as defined by the reference standard does not match the review question?	Low	Low

Comparative accuracy (QUADAS-2C)		Answers for the comparison of the Abbott ARCHITECT hs-cTnI with the Roche Elecsys hs-cTnT
Signalling questions	3.5 Was risk of bias for this domain judged 'low' for all index tests?	No
	3.6 Did the reference standard avoid incorporating any of the index tests?	No
Risk of bias	3.7 Could the reference standard, its conduct or its interpretation have introduced bias in the comparison?	High

Domain: flow and timing			
Single test accuracy (QUADAS-2)		**Answers for the Abbott ARCHITECT hs-cTnI**	**Answers for the Roche Elecsys hs-cTnT**
Signalling questions	4.1 Was there an appropriate interval between index tests and reference standard?	Yes	Yes
	4.2 Did all patients receive a reference standard?	Yes	Yes
	4.3 Did all patients receive the same reference standard?	Yes	Yes
	4.4 Were all patients included in the analysis?	No (10% missing)	No (< 1% missing)
Risk of bias	4.5 Could the patient flow have introduced bias?	High	Low
Comparative accuracy (QUADAS-2C)		**Answers for the comparison of the Abbott ARCHITECT hs-cTnI with the Roche Elecsys hs-cTnT**	
Signalling questions	4.6 Was risk of bias for this domain judged 'low' for all index tests?	No	
	4.7 Was there an appropriate interval between the index tests?	Yes	
	4.8 Was the same reference standard used for all index tests?	Yes	
	4.9 Are the proportions and reasons for missing data similar across index tests?	No	
Risk of bias	4.10 Could the patient flow have introduced bias in the comparison?	High	

NA, not applicable.

Appendix 5 Details of excluded studies with rationale

To be included in the review studies had to fulfil the criteria below.

- Population: adults (aged ≥ 18 years) presenting with acute pain, discomfort or pressure in the chest, epigastrium, neck, jaw or upper limb without an apparent non-cardiac source due to a suspected, but not proven, AMI.
- Setting: secondary or tertiary care.
- Index test: the Abbott ARCHITECT hs-cTnI; the Abbott Alinity hs-cTnI; the Beckman Coulter Access hs-cTnI; the bioMérieux VIDAS hs-cTnI; the Ortho VITROS hs-cTnI; the Quidel Triage True hs-cTnI Roche Elecsys (cTnT-hs or cTnT-hs STAT); the Siemens Atellica hs-cTnI; the Siemens Dimension EXL hs-cTnI; the Siemens Dimension Vista hs-cTnI; and the Siemens ADVIA Centaur hs-cTnI. Results were to be available within 3 hours.
- Reference standard: the third or fourth universal definition of AMI,[43] including measurement of troponin T or I (using any method) on presentation and 3–6 hours later, or occurrence of a MACE (any definition used in identified studies) during the 30-day follow-up.
- Outcome: sufficient data to construct a 2 × 2 table of test performance.

Table 38 summarises studies that were screened for inclusion based on full-text publication, but did not fulfil one or more of the above criteria. Studies were assessed sequentially against criteria (as soon as a study had failed based on one of the criteria it was not assessed against subsequent criteria). *Table 38* shows which of the criteria each study fulfilled ('yes') and on which criterion it failed ('no') or was unclear.

TABLE 38 Studies excluded at full-text screening

Study	Study design	Setting	Population	Index test	Reference standard	Outcome
Aguirre *et al.* 2014[231]	Yes	Yes	Yes	Yes	Yes	No
Ambavane *et al.* 2017[192]	Yes	Yes	Yes	Yes	Unclear	No
Badertscher *et al.* 2018[232]	Yes	Yes	Unclear	Unclear	Unclear	Yes
Bandstein *et al.* 2014[233]	Yes	Yes	Yes	Unclear	Yes	No
Biener *et al.* 2013[234]	Yes	Yes	Yes	No		
Borna *et al.* 2014[235]	Yes	No				
Burgio and Marino 2018[236]					No	
Burgio *et al.* 2018[237]	Yes	Yes	Yes	No		
Canadian Institutes of Health Research McMaster University, 2017[238]	No					
Chew *et al.* 2019[215]	Yes	Yes	Yes	Yes	Yes	No
Cortes *et al.* 2018[239]	Yes	Yes	Yes	Yes	Yes	No
Costabel *et al.* 2014[240]	Yes	Yes	Yes	Yes	No	
Costabel 2019[241]	Yes	Yes	Yes	Unclear		
Croce *et al.* 2017[242]	Yes	Yes	No			

continued

TABLE 38 Studies excluded at full-text screening (*continued*)

Study	Study design	Setting	Population	Index test	Reference standard	Outcome
Cullen *et al.* 2013[243]	Yes	Yes	Yes	No		
Cullen *et al.* 2013[244]	Yes	Yes	Yes	Unclear	Unclear	No
Cullen *et al.* 2014[245]	Yes	Yes	Yes	No		
Cullen *et al.* 2014[246]	Yes	Yes	Yes	Yes	Yes	No
Dadkhah *et al.* 2017[247]	Yes	Yes	Yes	No		
Druey *et al.* 2015[248]	Yes	Yes	Yes	No		
Ferencik *et al.* 2017[249]	Yes	Yes	Yes	Yes	Unclear	Unclear
Gandolfo *et al.* 2017[250]	Yes	Yes	Yes	Unclear	Yes	
Gandolfo *et al.* 2017[251]	Unclear	Yes	Unclear	Yes	Unclear	No
Goorden *et al.* 2016[252]	Yes	Yes	Yes	Yes	Unclear	Yes
Greenslade *et al.* 2017[253]	No					
Greenslade *et al.* 2018[254]	No					
Gunsolus *et al.* 2018[255]	Yes	Yes	Unclear	Unclear	Unclear	No
Hoeller *et al.* 2013[168]	Yes[a]	Yes	Yes	Yes	Yes	Yes
Ichise *et al.* 2017[256]	Yes	Yes	Yes	Yes	Unclear	No
Invernizzi *et al.* 2013[257]	Yes	Yes	Yes	Unclear	No	
Isiksacan *et al.* 2017[258]	Yes	Yes	Yes	Yes	No	
Isiksacan *et al.* 2019[259]	Yes	Yes	Yes	Yes	No	
Poole Hospital NHS Foundation Trust, 2013[260]	Yes[b]	Yes	Yes	Yes	Yes	Yes
Kavsak *et al.* 2018[261]	No					
Kavsak *et al.* 2018[262]	Yes	Unclear	Yes	Yes	Yes	No
Kavsak *et al.* 2018[263]	Yes	Yes	Yes	Yes	Yes	No
Kaysak *et al.* 2017[264]	Unclear	No				
Kellens *et al.* 2016[265]	Yes	Yes	Unclear	Yes	Yes	Unclear
Kitamura *et al.* 2013[77]	Yes	Yes	No			
Korley *et al.* 2014[266]	Yes	Yes	Yes	Yes	No	
Kovács *et al.* 2015[267]	Yes	Yes	Yes	Yes	Yes	No
Lin *et al.* 2018[268]	Yes	Yes	Yes	Yes	Yes	No
Ljung *et al.* 2019[269]	No					
Mahler *et al.* 2017[78]	Yes	Yes	Yes	Yes	Yes	No
McCord *et al.* 2017[270]	Yes	Yes	Yes	Yes	Yes	No
McRae *et al.* 2017[271]	No					
McRae *et al.* 2017[272]	No					
McRae *et al.* 2019[273]	No					
Mohsen and Shawky 2016[274]	Yes	Yes	Yes	No		
Mueller *et al.* 2018[275]	No					
Nacke *et al.* 2014[276]	Yes	Yes	Yes	No		

TABLE 38 Studies excluded at full-text screening (*continued*)

Study	Study design	Setting	Population	Index test	Reference standard	Outcome
Nasuruddin *et al.* 2017[277]	Yes	Yes	Yes	Yes	Unclear	No
Nejatian *et al.* 2017[278]	Yes	Yes	No	Unclear		
Nestelberger *et al.* 2016[279]	Yes	Yes	Yes	Yes	Yes	No
Nestelberger *et al.* 2019[280]	Yes	Yes	Yes	No		
Neumann *et al.* 2019[214]	No					
Neumann *et al.* 2019[281]	Yes	Yes	Yes	No		
Nowak *et al.* 2017[282]	Yes	Yes	Yes	Yes	Yes	No
Papendick *et al.* 2017[283]	Yes	Yes	Yes	No		
Peitsmeyer *et al.* 2013[284]	Yes	Yes	Yes	Yes	No	
Peitsmeyer *et al.* 2013[285]	Yes	Yes	Yes	No		
Pettersson *et al.* 2018[286]	Yes	Yes	Yes	Yes	No	
Pickering *et al.* 2015[287]	Yes	Yes	Yes	Yes	Yes	No
Pickering *et al.* 2016[288]	No					
Pickering *et al.* 2016[289]	No					
Pickering *et al.* 2018[290]	Yes	Yes	Yes	No		
Reddy *et al.* 2016[291]	Yes	Yes	Yes	Yes	No	
Reichlin *et al.* 2013[292]	Yes	Yes	Yes	Yes	No	
Renstroum *et al.* 2018[293]	Yes	Yes	Unclear	Unclear	Unclear	No
Riedlinger *et al.* 2018[294]	No					
Sandoval *et al.* 2017[295]	Yes	Yes	Yes	Yes	No	Unclear
Santi *et al.* 2017[296]	Yes	Yes	Yes	Yes	Yes	No
Schoenenberger *et al.* 2016[297]	No					
Schofer *et al.* 2017[298]	Yes	Yes	Yes	No		
Schønemann-Lund *et al.* 2015[299]	Yes	No				
Shah *et al.* 2015[300]	Yes	Yes	Yes	Yes	No	
Shortt *et al.* 2015[301]	Yes	Yes	Yes	No		
Stallone *et al.* 2016[302]	No					
Stoyanov *et al.* 2019[303]	No					
Su *et al.* 2015[304]	Yes	Yes	Yes	Yes	Unclear	No
Suh *et al.* 2018[305]	Yes	No				
Teggert and Twerenbold 2015[306]	Yes	Yes	Yes	No		
Than *et al.* 2014[307]	Yes	Yes	Yes	No		
Than *et al.* 2016[308]	Yes	Yes	Yes	No		
Thelin *et al.* 2013[309]	Yes	Yes	Yes	Yes	No	
Thet *et al.* 2019[310]	Yes	Yes	No			
Twerenbold *et al.* 2013[311]	Yes	Yes	Yes	No		
Twerenbold *et al.* 2013[312]	Yes	Yes	Yes	Yes	Unclear	Yes

continued

TABLE 38 Studies excluded at full-text screening (*continued*)

Study	Study design	Setting	Population	Index test	Reference standard	Outcome
Twerenbold *et al.* 2018[313]	No					
Vigen *et al.* 2018[314]	Yes	Yes	Yes	Unclear	Yes	Yes
Wang *et al.* 2019[315]	No					
Wildi *et al.* 2018[316]	Yes	Yes	No			
Yip *et al.* 2014[317]	No					
Yokoyama *et al.* 2018[318]	Yes	Yes	Yes	Yes	No	

a Duplicate.
b Trial registry entry for TRUST, listed publications already included.

Appendix 6 Selection of test strategies for cost-effectiveness modelling: responses of specialist committee members

The following responses were received from specialist committee members, regarding setting a minimum clinically acceptable sensitivity for hs-cTn-based rule-out strategies.

Response 1

Priority is minimising false negatives and the suggestion of including only strategies that provide NPV [negative predictive value] > 99% or sensitivity > 97% is sensible if only to limit the number of strategies to model.

Gold standard should be a high-sensitivity assay using the 99th centile this time around but could be flexible about when this is measured.

For cost-effectiveness it might make sense to compare one test and two test strategies.

Need to consider whether strategies that use a single test with a risk tool [HEART, TMACs (Troponin-only Manchester Acute Coronary Syndromes), EDACS (Emergency Department Assessment of Chest Pain Score)] should be considered separately – no additional cost, but differences in terms of effectiveness and safety.

We should also consider whether to update our recommendations on the use of the 99th centile, and in particular whether we recommend sex-specific thresholds or not.

Response 2

Most of the rule out strategies are modelled at 99% NPV [negative predictive value]. Modelling including a 99% sensitivity is probably desirable but may be not feasible. I am not sure troponin testing alone will achieve > 99% sensitivity. But would be delighted to be proved wrong.

Choice of assay in the lab is not determined by analytical performance of the cTn assay but by a range of factors as it is one of approximately 200 assays considered as part of a lab automation package.

The choice of pathway is between the ESC approach and High-STEACS. All use admission measurement then a follow up measurement, a decision limit and a delta. Pragmatically, although retest at 1 h [hour] is suggested this is unlikely to be achieved in practice so a 1- to 2-hour second sample is more realistic.

If faced between waiting 1 hour for an answer or 4 hours I know what ED patients will choose. I know I would.

So while I understand the desire to be inclusive it is also desirable to be pragmatic. Current evidence favours admission sampling for rule out then repeat sampling for rule in/rule out/further testing. Troponin testing is NOT a standalone and there are 1–3 time points for decisions all with the same choice. Do I send the patient home (God takes care of him) admit him to the cardiologists or medics (smart doc takes over) or hang on to do more tests. This occurs at presentation and at the retest time(s).

Response 3

I'd say the very minimum should be 95%. However, we could even push that further and go to 97%. Even though clinicians will generally say that they wouldn't accept sensitivities less than 99%, I'd probably err against going much further than 97%, to be honest. Otherwise, we will essentially just be picking the strategy with highest specificity, without balancing the two based on the economic modelling. Risk aversion may ultimately not be the best strategy overall because it, too, has an important cost and risk associated with it.

I'd also stratify the analysis by assay and timing. Running a lifetime model is likely to find that more conservative serial sampling strategies will dominate the faster strategies. For example, if you test troponin on arrival and at 4 hours, it is likely to have slightly higher sensitivity than testing on arrival and at 3 hours (assuming you optimise the cut-offs at each time point with equal rigor).

Running a lifetime economic model would always therefore tend to lead us to issuing conservative recommendations – e.g. 4-hour testing over 3-hour testing. The traditional lifetime model doesn't capture the granular costs of ED visits and certainly doesn't capture the risks of waiting on a trolley in an ED corridor because so many patients are waiting for inpatient tests.

We need to account for that, and we also need to account for the fact that serial testing strategies could be run together, e.g.:

- *if initial troponin is below a certain cut-off, rule out. If not . . .*
- *re-test at 1 hour. If rule-out criteria met, no further tests. If not . . .*
- *re-test at 3 hours. If rule-out criteria met, no further tests. If not . . .*
- *re-test at 6 hours. (That's as far as we'll go because it's likely to be the reference standard.)*

I would suggest collating the evidence we have for each assay. Then, we could perhaps consider using network met-analysis (or similar) to construct the optimal serial testing strategy for each assay.

Alternatively, putting it more simply, we could directly compare the cost-effectiveness of single-test strategies; then (separately) 0/1-hour strategies; then 0/2-hour strategies [and each would be compared against the reference standard to ensure that it isn't dominated]. That would help avoid the potential bias towards making conservative recommendations.

Response 4

A few thoughts on sensitivity. False-negative results, are clearly more dangerous for patients with suspected ACS than false-positive results, particularly if they result in patients being discharged from A&E [accident and emergency] departments with reassurance. On that basis we should probably only consider test strategies that deliver a high level of sensitivity – say > 85% or 90%.

Appendix 7 Scenario analyses

TABLE 39 Scenario 1 conditional on the base case, MI treatment costs for FPs

Strategy	Cost (£)	QALY	Compared with standard troponin			Full incremental ICER: Δ costs/Δ QALYs
			Δ Costs (£)	Δ QALYs	Δ Costs/Δ QALYs (£)	
18. Beckman Coulter ACCESS hs-cTnI: [(symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 5 ng/l at 0 to 2 hours)]	38,724	12.0763	−152	−0.0011	136,383	Cheapest
5. Roche Elecsys hs-cTnT: (< 12 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours)	38,764	12.0765	−112	−0.0009	118,636	Extendedly dominated
17. Beckman Coulter ACCESS hs-cTnI: ESC pathway	38,781	12.0768	−95	−0.0006	170,370	Extendedly dominated
9. Abbott ARCHITECT hs-cTnI: High-STEACS pathway	38,787	12.0768	−89	−0.0006	159,271	Extendedly dominated
1. Roche Elecsys hs-cTnT: 99th centile	38,788	12.0774	−88	0.0000	157,505,897	£57,659
3. Roche Elecsys hs-cTnT: ESC pathway	38,793	12.0768	−83	−0.0006	149,485	Dominated
16. Siemens Atellica hs-cTnI: High-STEACS pathway	38,794	12.0763	−82	−0.0011	73,814	Dominated
6. Siemens Dimension Vista hs-cTnI: (< 5 ng/l at 0 hours AND Δ < 2 ng/l at 0 to 1 hours)	38,809	12.0774	−66	0.0000	119,216,717	Dominated
12. Siemens ADVIA Centaur hs-cTnI: [< 3 ng/l at 0 hours OR (< 8 ng/l at 0 hours AND Δ < 7 ng/l at 0 to 2 hours)]	38,822	12.0774	−54	0.0000	96,913,928	Dominated
20. bioMérieux VIDAS hs-cTnI: [< 2 ng/l at 0 hours OR (< 6 ng/l at 0 AND 2 hours)]	38,828	12.0763	−47	−0.0011	42,608	Dominated
21. Quidel TriageTrue hs-cTnI: ESC pathway	38,843	12.0774	−33	0.0000	58,544,594	Dominated
19. Ortho VITROS hs-cTnI: ESC pathway	38,843	12.0774	−32	0.0000	58,315,678	Dominated
8. Abbott ARCHITECT hs-cTnI: ESC pathway	38,855	12.0768	−21	−0.0006	36,935	Dominated
13. Siemens ADVIA Centaur hs-cTnI: ESC pathway	38,862	12.0768	−14	−0.0006	24,942	Dominated
14. Siemens ADVIA Centaur hs-cTnI: < 5 ng/l at 0 hours	38,867	12.0768	−9	−0.0006	15,429	Dominated
Standard troponin (at presentation and after 10–12 hours)	38,876	12.0774	0	0.0000	NA	£157,505,897
10. Abbott ARCHITECT hs-cTnI: < 4 ng/l at 0 hours	38,878	12.0767	2	−0.0007	−2607	Dominated
4. Roche Elecsys hs-cTnT: (< 8 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 0.5 hours)	38,923	12.0774	47	0.0000	−84,642,503	Dominated
2. Roche Elecsys hs-cTnT: LoD	38,969	12.0769	93	−0.0005	−185,857	Dominated
15. Siemens Atellica hs-cTnI: < 2 ng/l at 0 hours	39,027	12.0774	151	0.0000	−271,257,977	Dominated
11. Siemens ADVIA Centaur hs-cTnI: < 2 ng/l at 0 hours	39,047	12.0774	171	0.0000	−307,122,945	Dominated
7. Abbott ARCHITECT hs-cTnI: LoD	39,055	12.0772	179	−0.0002	−1,073,915	Dominated

NA, not applicable.

TABLE 40 Scenario 1 conditional on secondary analysis, MI treatment costs for FPs

Strategy	Cost (£)	QALY	Compared with standard troponin			Full incremental ICER: Δ costs/Δ QALYs
			Δ Costs (£)	Δ QALYs	Δ Costs/Δ QALYs (£)	
Standard troponin (at presentation and after 10–12 hours)	37,503	11.3230	0	0.0000	NA	Cheapest
18. Beckman Coulter ACCESS hs-cTnI: [(symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 5 ng/l at 0 to 2 hours)]	38,151	11.4610	648	0.1380	4698	£4698
5. Roche Elecsys hs-cTnT: (< 12 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours)	38,158	11.4510	655	0.1280	5117	Dominated
17. Beckman Coulter ACCESS hs-cTnI: ESC pathway	38,167	11.4488	664	0.1259	5277	Dominated
3. Roche Elecsys hs-cTnT: ESC pathway	38,172	11.4469	670	0.1239	5403	Dominated
6. Siemens Dimension Vista hs-cTnI: (< 5 ng/l at 0 hours AND Δ < 2 ng/l at 0 to 1 hours)	38,183	11.4455	680	0.1225	5551	Dominated
9. Abbott ARCHITECT hs-cTnI: High-STEACS pathway	38,192	11.4547	689	0.1317	5233	Dominated
16. Siemens Atellica hs-cTnI: High-STEACS pathway	38,192	11.4522	690	0.1292	5336	Dominated
20. bioMérieux VIDAS hs-cTnI: [< 2 ng/l at 0 hours OR (< 6 ng/l at 0 AND 2 hours)]	38,196	11.4424	693	0.1195	5799	Dominated
1. Roche Elecsys hs-cTnT: 99th centile	38,196	11.4562	694	0.1333	5204	Dominated
14. Siemens ADVIA Centaur hs-cTnI: < 5 ng/l at 0 hours	38,196	11.4313	694	0.1083	6405	Dominated
19. Ortho VITROS hs-cTnI: ESC pathway	38,198	11.4396	695	0.1167	5958	Dominated
12. Siemens ADVIA Centaur hs-cTnI: [< 3 ng/l at 0 hours OR (< 8 ng/l at 0 hours AND Δ < 7 ng/l at 0 to 2 hours)]	38,198	11.4465	696	0.1235	5633	Dominated
8. Abbott ARCHITECT hs-cTnI: ESC pathway	38,200	11.4361	698	0.1132	6162	Dominated
10. Abbott ARCHITECT hs-cTnI: < 4 ng/l at 0 hours	38,201	11.4291	698	0.1062	6572	Dominated
13. Siemens ADVIA Centaur hs-cTnI: ESC pathway	38,204	11.4352	701	0.1122	6247	Dominated
21. Quidel TriageTrue hs-cTnI: ESC pathway	38,217	11.4455	714	0.1225	5826	Dominated
4. Roche Elecsys hs-cTnT: (< 8 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 0.5 hours)	38,230	11.4250	727	0.1020	7129	Dominated
2. Roche Elecsys hs-cTnT: LoD	38,244	11.4147	742	0.0918	8083	Dominated
15. Siemens Atellica hs-cTnI: < 2 ng/l at 0 hours	38,274	11.4064	771	0.0835	9239	Dominated
11. Siemens ADVIA Centaur hs-cTnI: < 2 ng/l at 0 hours	38,284	11.4035	782	0.0805	9705	Dominated
7. Abbott ARCHITECT hs-cTnI: LoD	38,286	11.4014	784	0.0784	9994	Dominated

NA, not applicable.

TABLE 41 Scenario 2 conditional on the base case, lifetime relative risk for mortality and reinfarction for FNs

Strategy	Cost (£)	QALY	Compared with standard troponin			Full incremental ICER: Δ costs/Δ QALYs
			Δ Costs (£)	Δ QALYs	Δ Costs/Δ QALYs (£)	
18. Beckman Coulter ACCESS hs-cTnI: [(symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 5 ng/l at 0 to 2 hours)]	38,654	12.0721	−222	−0.0053	42,267	Cheapest
5. Roche Elecsys hs-cTnT: (< 12 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours)	38,659	12.0729	−216	−0.0045	48,464	Extendedly dominated
17. Beckman Coulter ACCESS hs-cTnI: ESC pathway	38,672	12.0748	−204	−0.0026	77,572	£6962
3. Roche Elecsys hs-cTnT: ESC pathway	38,677	12.0748	−199	−0.0026	75,761	Dominated
16. Siemens Atellica hs-cTnI: High-STEACS pathway	38,692	12.0721	−183	−0.0053	34,891	Dominated
6. Siemens Dimension Vista hs-cTnI: (< 5 ng/l at 0 hours AND Δ < 2 ng/l at 0 to 1 hours)	38,693	12.0774	−183	0.0000	69,706,183	£7874
20. bioMérieux VIDAS hs-cTnI: [< 2 ng/l at 0 hours OR (< 6 ng/l at 0 AND 2 hours)]	38,693	12.0721	−183	−0.0053	34,815	Dominated
14. Siemens ADVIA Centaur hs-cTnI: < 5 ng/l at 0 hours	38,696	12.0748	−179	−0.0026	68,270	Dominated
10. Abbott ARCHITECT hs-cTnI: < 4 ng/l at 0 hours	38,698	12.0740	−177	−0.0034	51,980	Dominated
9. Abbott ARCHITECT hs-cTnI: High-STEACS pathway	38,699	12.0748	−177	−0.0026	67,378	Dominated
8. Abbott ARCHITECT hs-cTnI: ESC pathway	38,702	12.0748	−174	−0.0026	66,291	Dominated
13. Siemens ADVIA Centaur hs-cTnI: ESC pathway	38,705	12.0748	−171	−0.0026	65,057	Dominated
19. Ortho VITROS hs-cTnI: ESC pathway	38,706	12.0774	−170	0.0000	64,644,677	Dominated
12. Siemens ADVIA Centaur hs-cTnI: [< 3 ng/l at 0 hours OR (< 8 ng/l at 0 hours AND Δ < 7 ng/l at 0 to 2 hours)]	38,709	12.0774	−167	0.0000	63,673,276	Dominated
1. Roche Elecsys hs-cTnT: 99th centile	38,709	12.0774	−167	0.0000	63,440,707	Dominated
21. Quidel TriageTrue hs-cTnI: ESC pathway	38,726	12.0774	−149	0.0000	56,850,305	Dominated
4. Roche Elecsys hs-cTnT: (< 8 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 0.5 hours)	38,734	12.0774	−142	0.0000	53,960,316	Extendedly dominated
2. Roche Elecsys hs-cTnT: LoD	38,740	12.0750	−135	−0.0024	57,282	Dominated
15. Siemens Atellica hs-cTnI: < 2 ng/l at 0 hours	38,773	12.0774	−103	0.0000	39,253,952	Dominated
7. Abbott ARCHITECT hs-cTnI: LoD	38,782	12.0766	−94	−0.0008	118,920	Dominated
11. Siemens ADVIA Centaur hs-cTnI: < 2 ng/l at 0 hours	38,782	12.0774	−93	0.0000	35,575,926	Dominated
Standard troponin (at presentation and after 10–12 hours)	38,876	12.0774	0	0.0000	NA	£69,706,183

NA, not applicable.

TABLE 42 Scenario 2 conditional on secondary analysis, lifetime relative risk for mortality and reinfarction for FNs

Strategy	Cost (£)	QALY	Compared with standard troponin			Full incremental ICER: Δ costs/Δ QALYs
			Δ Costs (£)	Δ QALYs	Δ Costs/Δ QALYs (£)	
Standard troponin (at presentation and after 10–12 hours)	36,496	10.9853	0	0.0000	NA	Cheapest
7. Abbott ARCHITECT hs-cTnI: LoD	38,015	11.4007	1519	0.4155	3656	Extendedly dominated
2. Roche Elecsys hs-cTnT: LoD	38,017	11.4128	1521	0.4276	3558	Extendedly dominated
15. Siemens Atellica hs-cTnI: < 2 ng/l at 0 hours	38,022	11.4064	1525	0.4211	3622	Dominated
11. Siemens ADVIA Centaur hs-cTnI: < 2 ng/l at 0 hours	38,022	11.4035	1526	0.4182	3648	Dominated
10. Abbott ARCHITECT hs-cTnI: < 4 ng/l at 0 hours	38,022	11.4265	1526	0.4412	3460	Extendedly dominated
14. Siemens ADVIA Centaur hs-cTnI: < 5 ng/l at 0 hours	38,027	11.4292	1531	0.4439	3448	Extendedly dominated
4. Roche Elecsys hs-cTnT: (< 8 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 0.5 hours)	38,042	11.4250	1546	0.4397	3517	Dominated
8. Abbott ARCHITECT hs-cTnI: ESC pathway	38,048	11.4341	1552	0.4488	3457	Extendedly dominated
13. Siemens ADVIA Centaur hs-cTnI: ESC pathway	38,048	11.4331	1552	0.4478	3465	Dominated
5. Roche Elecsys hs-cTnT: (< 12 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours)	38,054	11.4475	1558	0.4622	3371	Extendedly dominated
3. Roche Elecsys hs-cTnT: ESC pathway	38,057	11.4448	1561	0.4595	3397	Dominated
17. Beckman Coulter ACCESS hs-cTnI: ESC pathway	38,059	11.4468	1563	0.4615	3386	Dominated
20. bioMérieux VIDAS hs-cTnI: [< 2 ng/l at 0 hours OR (< 6 ng/l at 0 AND 2 hours)]	38,061	11.4383	1565	0.4530	3454	Dominated
19. Ortho VITROS hs-cTnI: ESC pathway	38,061	11.4396	1565	0.4544	3445	Dominated
6. Siemens Dimension Vista hs-cTnI: (< 5 ng/l at 0 hours AND Δ < 2 ng/l at 0 to 1 hours)	38,067	11.4455	1571	0.4602	3413	Dominated
18. Beckman Coulter ACCESS hs-cTnI: hsTnI [(symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 5 ng/l at 0 to 2 hours)]	38,081	11.4568	1585	0.4716	3362	£3362
12. Siemens ADVIA Centaur hs-cTnI: [< 3 ng/l at 0 hours OR (< 8 ng/l at 0 hours AND Δ < 7 ng/l at 0 to 2 hours)]	38,086	11.4465	1590	0.4612	3447	Dominated
16. Siemens Atellica hs-cTnI: High-STEACS pathway	38,092	11.4481	1596	0.4628	3448	Dominated
21. Quidel TriageTrue hs-cTnI: ESC pathway	38,101	11.4455	1605	0.4602	3487	Dominated
9. Abbott ARCHITECT hs-cTnI: High-STEACS pathway	38,104	11.4526	1608	0.4674	3441	Dominated
1. Roche Elecsys hs-cTnT: 99th centile	38,118	11.4562	1622	0.4710	3444	Dominated

NA, not applicable.

TABLE 43 Scenario 3 conditional on the base case, differential test costs

Strategy	Cost (£)	QALY	Compared with standard troponin			Full incremental ICER: Δ costs/Δ QALYs
			Δ Costs (£)	Δ QALYs	Δ Costs/Δ QALYs (£)	
18. Beckman Coulter ACCESS hs-cTnI: [(symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 5 ng/l at 0 to 2 hours)]	38,666	12.0763	−210	−0.0011	188,442	Cheapest
5. Roche Elecsys hs-cTnT: (< 12 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours)	38,677	12.0765	−199	−0.0009	210,557	Extendedly dominated
17. Beckman Coulter ACCESS hs-cTnI: ESC pathway	38,678	12.0768	−197	−0.0006	354,684	£22,200
3. Roche Elecsys hs-cTnT: ESC pathway	38,689	12.0768	−187	−0.0006	335,724	Dominated
6. Siemens Dimension Vista hs-cTnI: (< 5 ng/l at 0 hours AND Δ < 2 ng/l at 0 to 1 hours)	38,692	12.0774	−184	0.0000	330,758,895	£23,949
14. Siemens ADVIA Centaur hs-cTnI: < 5 ng/l at 0 hours	38,702	12.0768	−174	−0.0006	312,438	Dominated
16. Siemens Atellica hs-cTnI: High-STEACS pathway	38,704	12.0763	−172	−0.0011	154,774	Dominated
19. Ortho VITROS hs-cTnI: ESC pathway	38,705	12.0774	−171	0.0000	307,200,566	Dominated
9. Abbott ARCHITECT hs-cTnI: High-STEACS pathway	38,707	12.0768	−169	−0.0006	303,093	Dominated
12. Siemens ADVIA Centaur hs-cTnI: [< 3 ng/l at 0 hours OR (< 8 ng/l at 0 hours AND Δ < 7 ng/l at 0 to 2 hours)]	38,708	12.0774	−168	0.0000	302,143,335	Dominated
10. Abbott ARCHITECT hs-cTnI: < 4 ng/l at 0 hours	38,708	12.0767	−168	−0.0007	232,351	Dominated
13. Siemens ADVIA Centaur hs-cTnI: ESC pathway	38,710	12.0768	−166	−0.0006	298,174	Dominated
8. Abbott ARCHITECT hs-cTnI: ESC pathway	38,710	12.0768	−165	−0.0006	297,336	Dominated
20. bioMérieux VIDAS hs-cTnI: [< 2 ng/l at 0 hours OR (< 6 ng/l at 0 AND 2 hours)]	38,711	12.0763	−165	−0.0011	148,321	Dominated
1. Roche Elecsys hs-cTnT: 99th centile	38,716	12.0774	−159	0.0000	286,628,255	Dominated
21. Quidel TriageTrue hs-cTnI: ESC pathway	38,726	12.0774	−149	0.0000	268,289,079	Dominated
4. Roche Elecsys hs-cTnT: (< 8 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 0.5 hours)	38,741	12.0774	−135	0.0000	241,886,429	Dominated
2. Roche Elecsys hs-cTnT: LoD	38,749	12.0769	−126	−0.0005	252,587	Dominated
15. Siemens Atellica hs-cTnI: < 2 ng/l at 0 hours	38,772	12.0774	−104	0.0000	186,143,573	Dominated
11. Siemens ADVIA Centaur hs-cTnI: < 2 ng/l at 0 hours	38,781	12.0774	−94	0.0000	169,540,501	Dominated
7. Abbott ARCHITECT hs-cTnI: LoD	38,785	12.0772	−90	−0.0002	540,570	Dominated
Standard troponin (at presentation and after 10–12 hours)	38,876	12.0774	0	0.0000	NA	£330,758,895

NA, not applicable.

TABLE 44 Scenario 3 conditional on secondary analysis, differential test costs

Strategy	Cost (£)	QALY	Compared with standard troponin			Full incremental ICER: Δ costs/Δ QALYs
			Δ Costs (£)	Δ QALYs	Δ Costs/Δ QALYs (£)	
Standard troponin (at presentation and after 10–12 hours)	37,503	11.3230	0	0.0000	NA	Cheapest
7. Abbott ARCHITECT hs-cTnI: LoD	38,019	11.4014	516	0.0784	6580	Extendedly dominated
11. Siemens ADVIA Centaur hs-cTnI: < 2 ng/l at 0 hours	38,021	11.4035	518	0.0805	6434	Extendedly dominated
15. Siemens Atellica hs-cTnI: < 2 ng/l at 0 hours	38,021	11.4064	518	0.0835	6210	Extendedly dominated
2. Roche Elecsys hs-cTnT: LoD	38,026	11.4147	524	0.0918	5706	Extendedly dominated
10. Abbott ARCHITECT hs-cTnI: < 4 ng/l at 0 hours	38,032	11.4291	529	0.1062	4982	Extendedly dominated
14. Siemens ADVIA Centaur hs-cTnI: < 5 ng/l at 0 hours	38,032	11.4313	530	0.1083	4889	Extendedly dominated
4. Roche Elecsys hs-cTnT: (< 8 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 0.5 hours)	38,050	11.4250	547	0.1020	5360	Dominated
13. Siemens ADVIA Centaur hs-cTnI: ESC pathway	38,053	11.4352	550	0.1122	4901	Extendedly dominated
8. Abbott ARCHITECT hs-cTnI: ESC pathway	38,056	11.4361	554	0.1132	4891	Extendedly dominated
19. Ortho VITROS hs-cTnI: ESC pathway	38,060	11.4396	558	0.1167	4778	Extendedly dominated
17. Beckman Coulter ACCESS hs-cTnI: ESC pathway	38,065	11.4488	562	0.1259	4468	Extendedly dominated
6. Siemens Dimension Vista hs-cTnI: (< 5 ng/l at 0 hours AND Δ < 2 ng/l at 0 to 1 hours)	38,066	11.4455	563	0.1225	4596	Dominated
3. Roche Elecsys hs-cTnT: ESC pathway	38,069	11.4469	567	0.1239	4573	Dominated
5. Roche Elecsys hs-cTnT: (< 12 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours)	38,072	11.4510	569	0.1280	4442	Extendedly dominated
20. bioMérieux VIDAS hs-cTnI: [< 2 ng/l at 0 hours OR (< 6 ng/l at 0 AND 2 hours)]	38,079	11.4424	576	0.1195	4821	Dominated
12. Siemens ADVIA Centaur hs-cTnI: [< 3 ng/l at 0 hours OR (< 8 ng/l at 0 hours AND Δ < 7 ng/l at 0 to 2 hours)]	38,085	11.4465	582	0.1235	4714	Dominated
18. Beckman Coulter ACCESS hs-cTnI: [(symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 5 ng/l at 0 to 2 hours)]	38,094	11.4610	591	0.1380	4281	£4281
21. Quidel TriageTrue hs-cTnI: ESC pathway	38,101	11.4455	598	0.1225	4880	Dominated
16. Siemens Atellica hs-cTnI: High-STEACS pathway	38,103	11.4522	600	0.1292	4643	Dominated
9. Abbott ARCHITECT hs-cTnI: High-STEACS pathway	38,113	11.4547	610	0.1317	4630	Dominated
1. Roche Elecsys hs-cTnT: 99th centile	38,125	11.4562	622	0.1333	4669	Dominated

NA, not applicable.

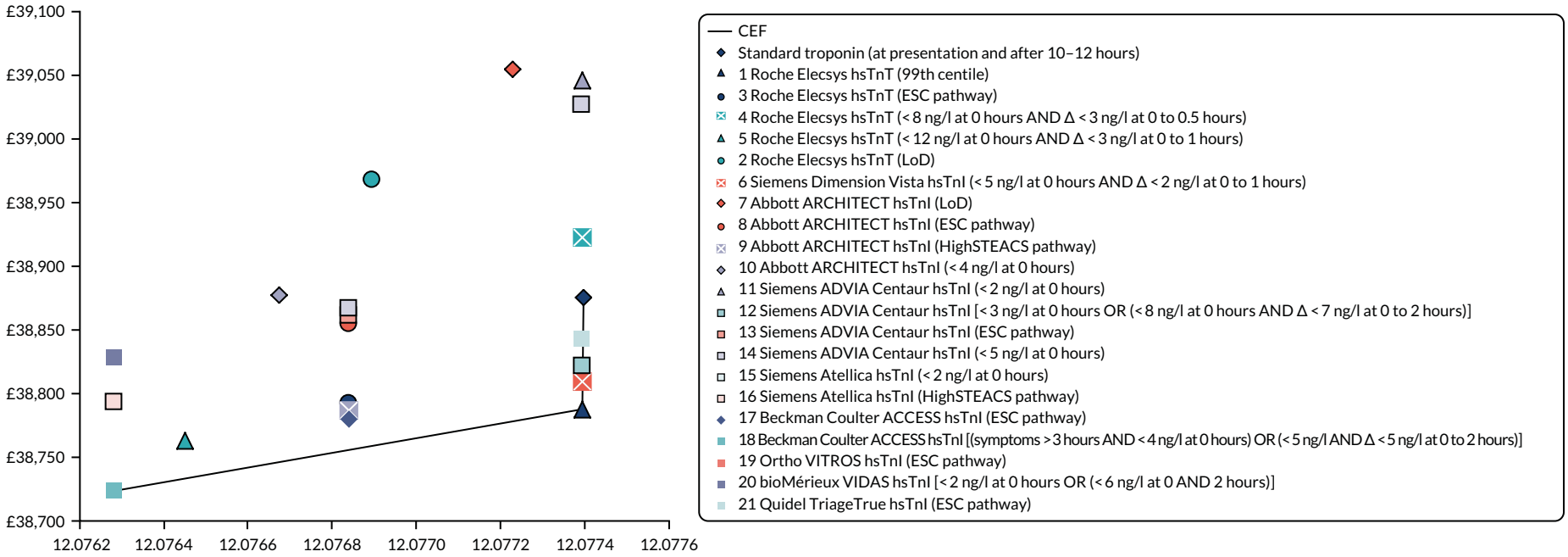

FIGURE 17 Scenario 1 conditional on the base-case cost-effectiveness frontier. CEF, cost-effectiveness frontier.

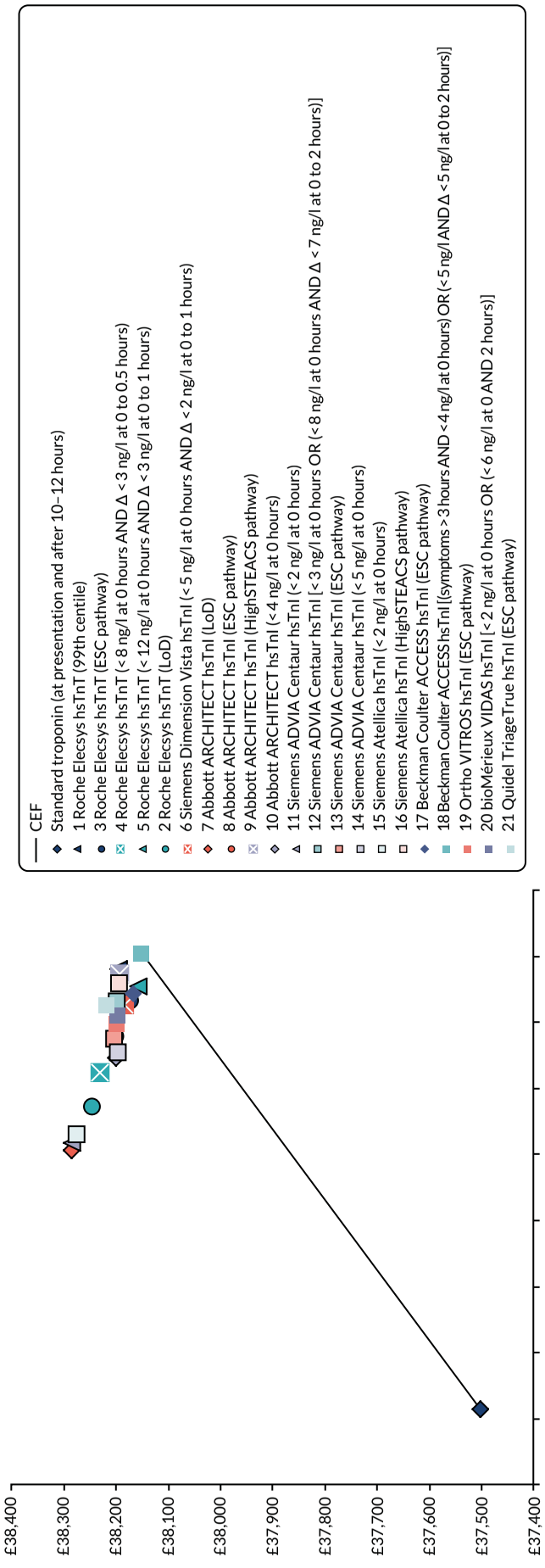

FIGURE 18 Scenario 1 conditional on the secondary analysis cost-effectiveness frontier. CEF, cost-effectiveness frontier.

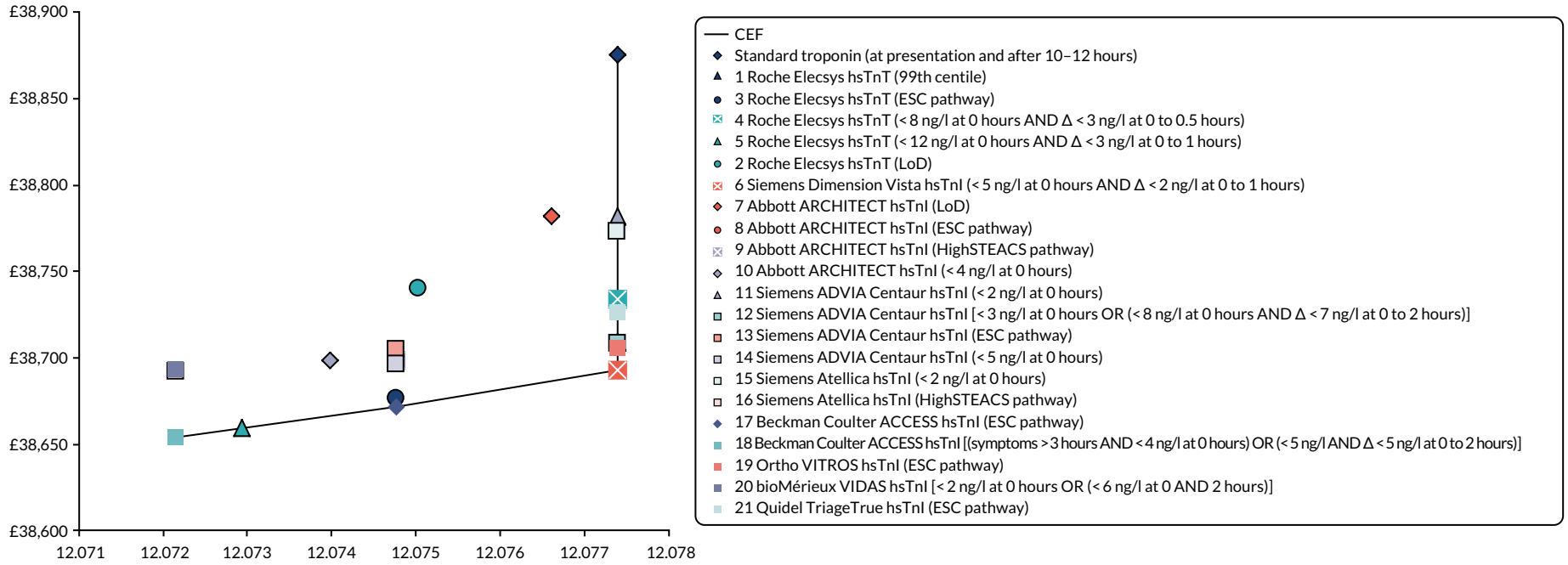

FIGURE 19 Scenario 2 conditional on the base-case cost-effectiveness frontier. Cost-effectiveness frontier.

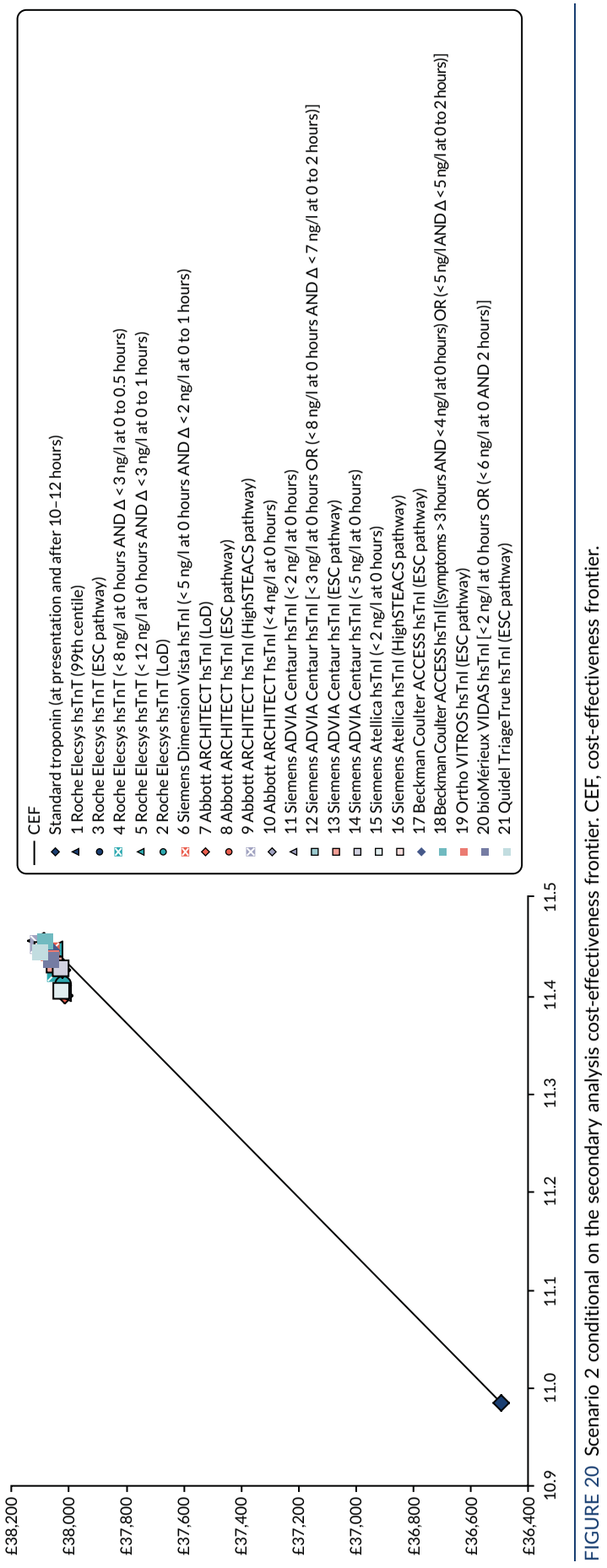

FIGURE 20 Scenario 2 conditional on the secondary analysis cost-effectiveness frontier. CEF, cost-effectiveness frontier.

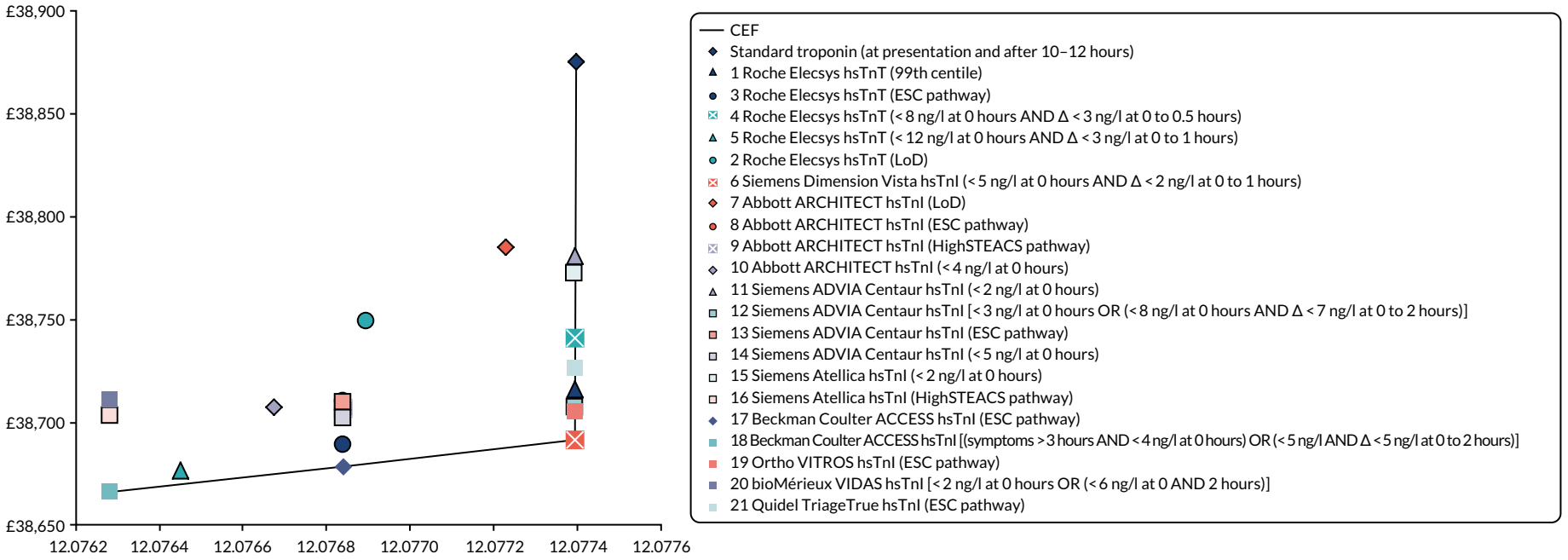

FIGURE 21 Scenario 3 conditional on the base-case cost-effectiveness frontier. CEF, cost-effectiveness frontier.

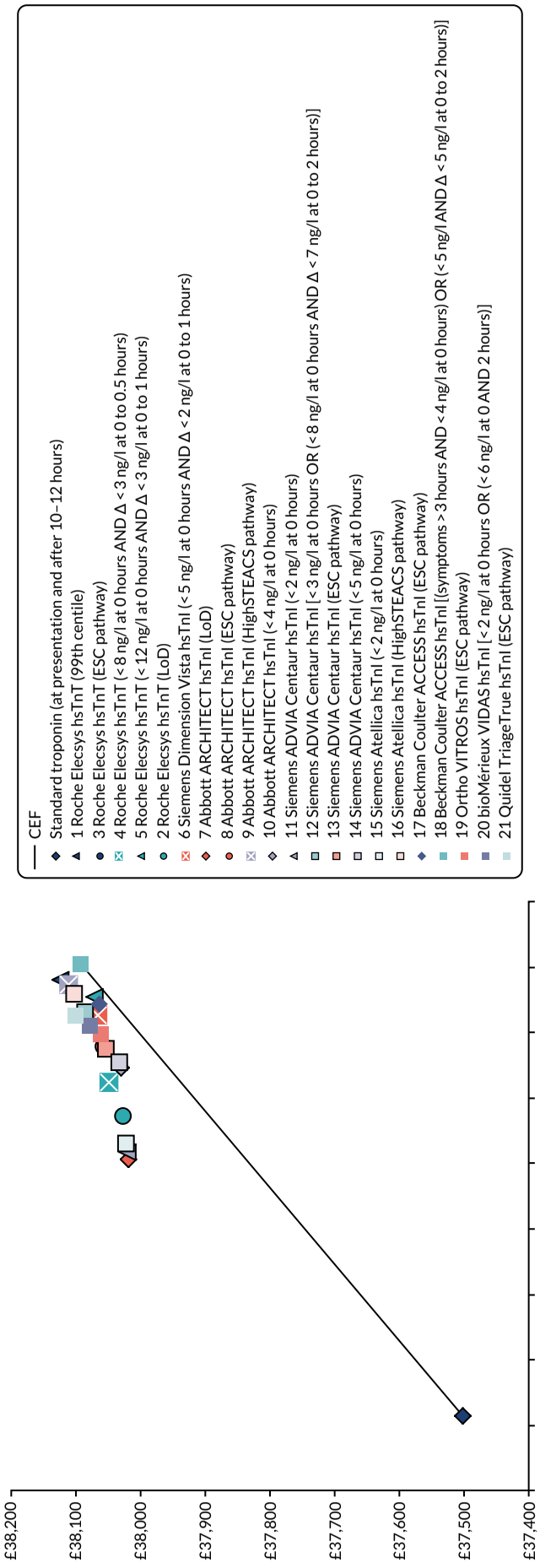

FIGURE 22 Scenario 3 conditional on the secondary analysis cost-effectiveness frontier. CEF, cost-effectiveness frontier.

Appendix 8 Deterministic one-way sensitivity analyses

Deterministic one-way sensitivity analyses for the base case (based on incremental net benefit)

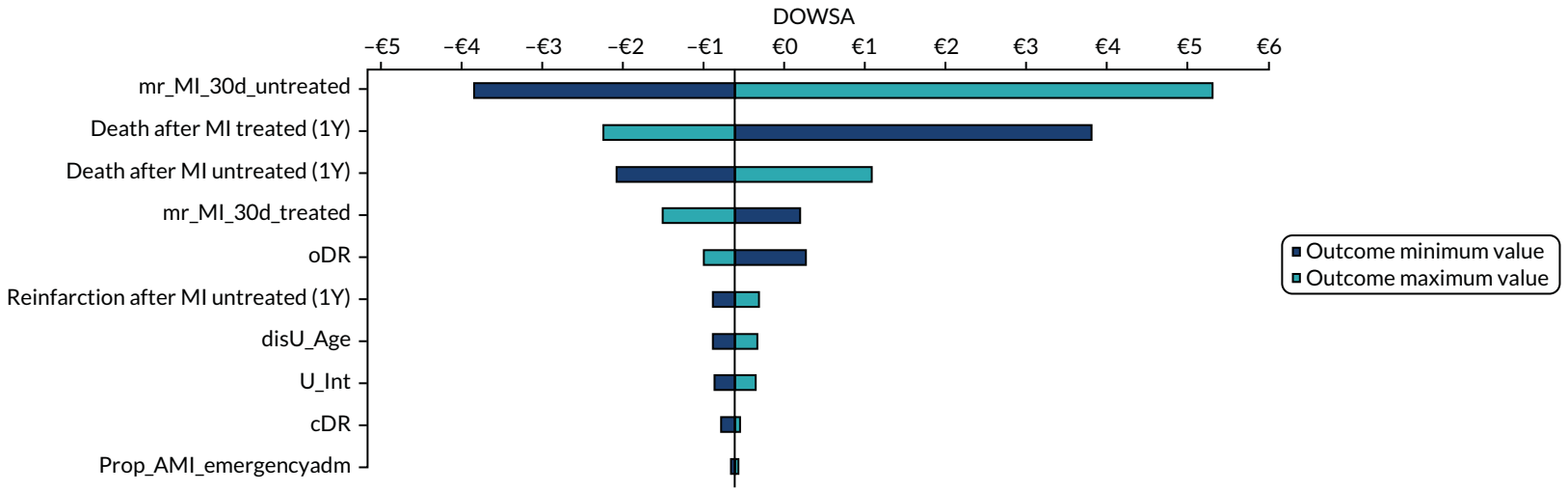

FIGURE 23 Tornado diagram for the comparison of the Roche Elecsys hs-cTnT [ESC 0/1-hour pathway: (symptoms > 3 hours AND < 5 ng/l at 0 hours) OR (< 12 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours)] with the Beckman Coulter ACCESS hs-cTnI [(symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 5 ng/l at 0 to 2 hours)].

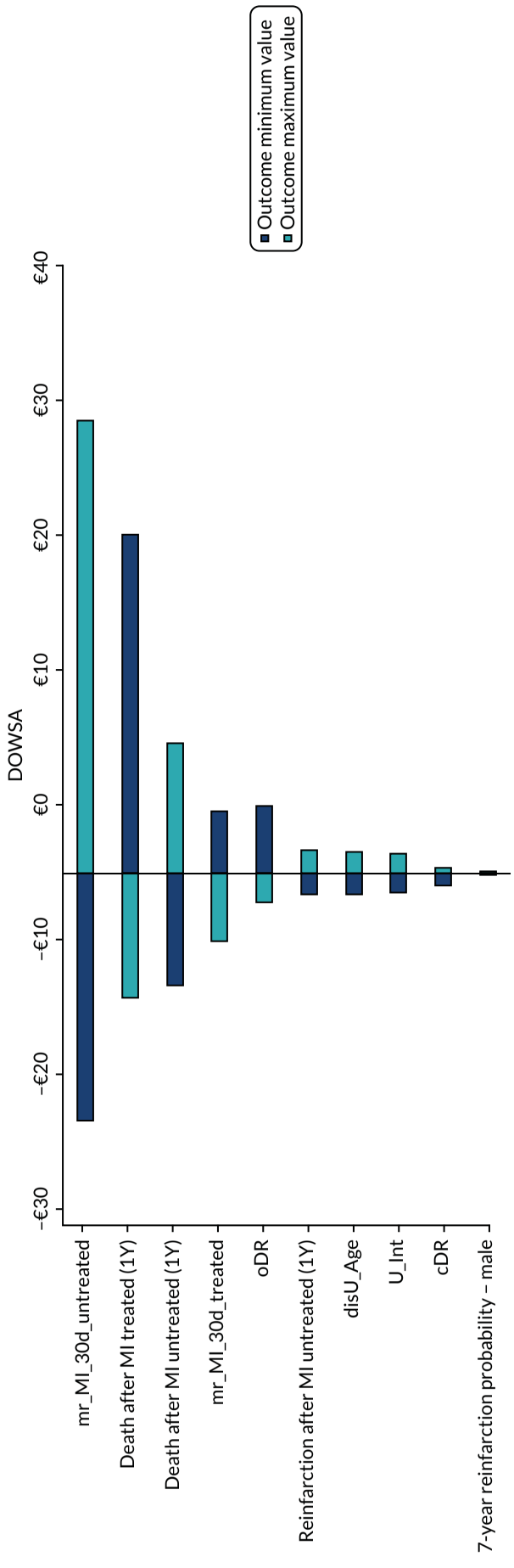

FIGURE 24 Tornado diagram for the comparison of the Siemens Dimension Vista hs-cTnI (< 5 ng/l at 0 hours AND Δ < 2 ng/l at 0 to 1 hours) with the Roche Elecsys hs-cTnT [ESC 0/1-hour pathway: (symptoms > 3 hours AND < 5 ng/l at 0 hours) OR (< 12 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours)]. DOWSA, deterministic one-way sensitivity analysis.

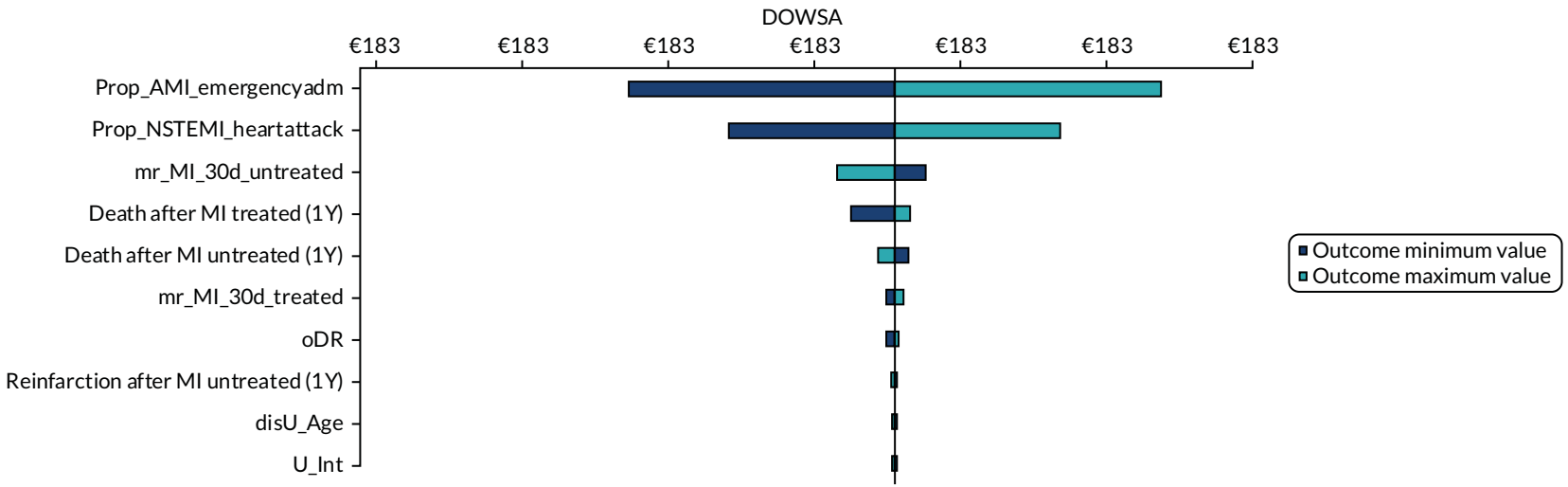

FIGURE 25 Tornado diagram for comparison of standard troponin (at presentation and after 10–12 hours) with the Siemens Dimension Vista hsTnI (< 5 ng/l at 0 hours AND Δ < 2 ng/l at 0 to 1 hours). DOWSA, deterministic one-way sensitivity analysis.

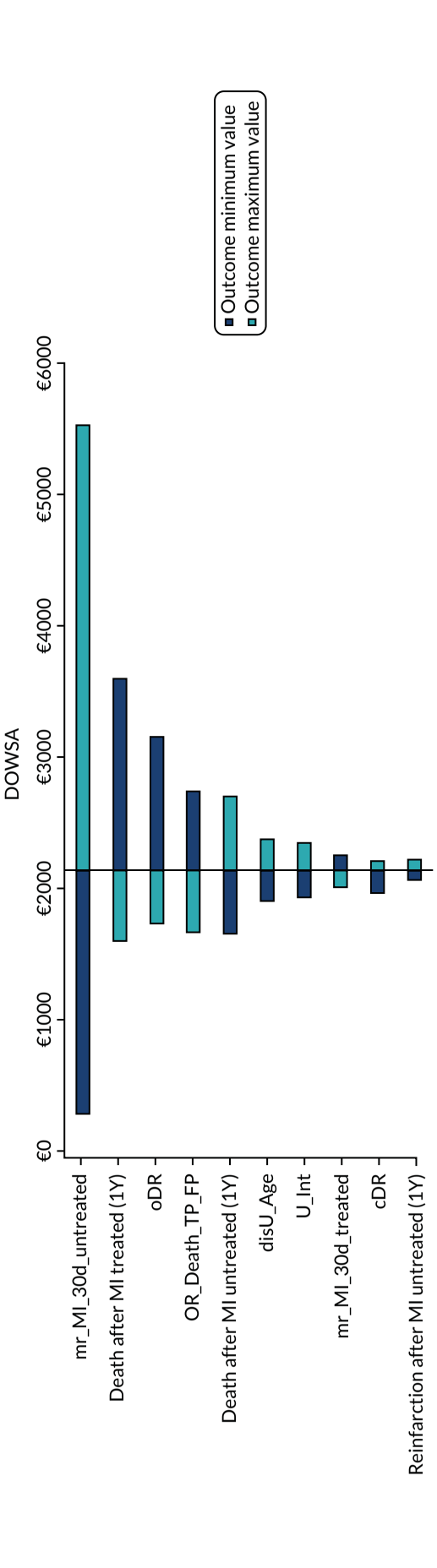

FIGURE 26 Tornado diagram for comparison of the Beckman Coulter ACCESS hsTnI [(symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 5 ng/l at 0 to 2 hours)] with standard troponin (at presentation and after 10–12 hours). DOWSA, deterministic one-way sensitivity analysis.

Appendix 9 NICE guidance relevant to the management of suspected acute coronary syndrome

Myocardial Infarction: Cardiac Rehabilitation and Prevention of Further Cardiovascular Disease. NICE CG172. URL: www.nice.org.uk/guidance/cg172 (accessed 29 January 2020).

Chest Pain of Recent Onset: Assessment and Diagnosis Of Recent Onset Chest Pain or Discomfort of Suspected Cardiac Origin. NICE CG95. URL: www.nice.org.uk/guidance/cg95 (accessed 29 January 2020).

Unstable Angina and NSTEMI: Early Management. NICE CG94. URL: http://guidance.nice.org.uk/CG94/NICEGuidance/pdf/English (accessed 29 January 2020).

Myocardial Infarction with ST-Segment Elevation: The Acute Management of Myocardial Infarction with ST-Segment Elevation. NICE CG167. URL: www.nice.org.uk/guidance/cg167 (accessed 20 February 2020).

Myocardial Infarction (Acute): Early Rule Out Using High-Sensitivity Troponin Tests (*Elecsys Troponin Thigh-sensitive, ARCHITECT STAT High Sensitive Troponin-I and AccuTnI+3 Assays*). *Diagnostics Guidance [DG15]*. URL: www.nice.org.uk/guidance/dg15 (accessed 29 January 2020).

CG94, CG172 and CG167 are currently under revision to become a single guideline. Expected publication date is November 2020 (GID-NG10085).

Appendix 10 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist

Section/topic	#	Checklist item	Reported on page number
Title			
Title	1	Identify the report as a systematic review, meta-analysis or both	Page 1
Abstract			
Structured summary	2	Provide a structured summary, including (as applicable) background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; and systematic review registration number	Pages 14–16
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	Objective, page 27
Objectives	4	Provide an explicit statement of questions being addressed with reference to PICOS	Objective and definition of decision problem, pages 27–41
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address) and, if available, provide registration information including registration number	PROSPERO registration, page 2
Eligibility criteria	6	Specify study characteristics (e.g. PICOS, length of follow-up) and report characteristics (e.g. years considered, language, publication status) used as criteria for eligibility, giving rationale	Systematic review methods, inclusion and exclusion criteria, page 43 and *Table 2*
Information sources	7	Describe all information sources (e.g. databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	Systematic review methods, search strategy, pages 42 and 43
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	*Appendix 1*
Study selection	9	State the process for selecting studies (i.e. screening, eligibility, included in systematic review and, if applicable, included in the meta-analysis)	Systematic review methods, inclusion screening and data extraction, page 46
Data collection process	10	Describe method of data extraction from reports (e.g. piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	Systematic review methods, inclusion screening and data extraction, page 46
Data items	11	List and define all variables for which data were sought (e.g. PICOS, funding sources) and any assumptions and simplifications made	Systematic review methods, inclusion screening and data extraction, page 46

Section/topic	#	Checklist item	Reported on page number
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether or not this was done at the study or outcome level) and how this information is to be used in any data synthesis	Systematic review methods, quality assessment, pages 46 and 47
Summary measures	13	State the principal summary measures (e.g. risk ratio, difference in means)	Systematic review methods, methods of analysis/synthesis, page 47
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g. I^2) for each meta-analysis	Systematic review methods, methods of analysis/synthesis, page 47
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g. publication bias, selective reporting within studies)	NA
Additional analyses	16	Describe methods of additional analyses (e.g. sensitivity or subgroup analyses, meta-regression), if done, indicating which were prespecified	NA
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	Results of the assessment of clinical effectiveness, overview of included studies, pages 47–9 and *Figure 1*
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g. study size, PICOS, follow-up period) and provide the citations	Results of the assessment of clinical effectiveness, pages 62–93, *Table 3* and *Appendix 2*
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12)	Results of the assessment of clinical effectiveness, study quality, pages 57–62 and *Appendix 3*
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study (a) a simple summary data for each intervention group (b) effect estimates and CIs, ideally with a forest plot	Results of the assessment of clinical effectiveness, pages 62–93 and *Appendix 2*
Synthesis of results	21	Present results of each meta-analysis done, including CIs and measures of consistency	Results of the assessment of clinical effectiveness, pages 65–81
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15)	NA
Additional analysis	23	Give results of additional analyses, if done [e.g. sensitivity or subgroup analyses, meta-regression (see item 16)]	NA
Discussion			
Summary of evidence	24	Summarise the main findings, including the strength of evidence for each main outcome, and consider their relevance to key groups (e.g. health-care providers, users and policy-makers)	Discussion, pages 146–51
Limitations	25	Discuss limitations at study and outcome level (e.g. risk of bias) and at review level (e.g. incomplete retrieval of identified research, reporting bias)	Discussion, pages 152–9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence and implications for future research	Conclusions, pages 161 and 162

Section/topic	#	Checklist item	Reported on page number
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g. supply of data) and the role of funders for the systematic review	Page 2

NA, not applicable; PICOS, participants, interventions, comparisons, outcomes, and study design.

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