High sensitivity troponin assays for the early rule-out of acute myocardial infarction in people with acute chest pain: a systematic review and cost-effectiveness analysis

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Contributions of authors

Marie Westwood, Debra Fayter and Gill Worthy planned and performed the systematic review and interpretation of evidence. Bram Ramaekers and Sabine Grimm planned and performed the cost-effectiveness analyses and interpreted results. Nigel Armstrong and Titas Buksnys contributed to planning and interpretation of cost-effectiveness analyses, acquisition of input data and conducted model peer review. Janine Ross devised and performed the literature searches and provided information support to the project. Jos Kleijnen and Manuela Joore provided senior advice and

support to the systematic review and cost-effectiveness analyses, respectively. All parties were involved in drafting and/or commenting on the report.

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LIST OF ABBREVIATIONS

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader.

AACC	American Association for Clinical Chemistry
ACC	American College of Cardiology
ACE	angiotensin converting enzyme
ACS	acute coronary syndrome
AHA	American Health Association
AiC	Academic in confidence
AMI	acute myocardial infarction
ARIF	aggressive Research Intelligence Facility
CAD	coronary artery disease
CADTH	Canadian Agency for Drugs and Technologies in Health
CCT	controlled clinical trial
CDSR	Cochrane Database of Systematic Reviews
CEAC	cost-effectiveness acceptability curve
CEAF	cost-effectiveness acceptability frontier
CENTRAL	Cochrane Central Register of Controlled Trials
CHD	coronary heart disease
CI	confidence interval
CRD	Centre for Reviews and Dissemination
CTCA	computed tomography coronary angiography
cTnI	cardiac troponin I
cTnT	cardiac troponin T
CV	coefficient of variation
DAR	Diagnostic Assessment Report
DARE	Database of Abstracts of Reviews of Effects
DTA	diagnostic test accuracy
ECG	electrocardiography/electrocardiogram
ECLIA	electrochemiluminescence immunoassay
ED	emergency department
EDACS	Emergency Department Assessment of Chest Pain Score
EDTA	ethylenediaminetetraacetic acid
EED	Economic Evaluations Database
eGFR	estimated glomerular filtration rate
ESC	European Society of Cardiology
FN	false negative
FP	false positive
GRACE	Global Registry of Acute Coronary Events
HES	Hospital Episode Statistics
HF	heart failure
HEART	the History ECG Age Risk factors Troponins
HES	hospital episode statistics
HR	hazard ratio

HRQoL	Health-Related Quality of Life
hs-cTn	high sensitivity cardiac troponin
hs-cTnI	high sensitivity cardiac troponin I
hs-cTnT	high sensitivity cardiac troponin T
HSROC	hierarchical summary receiver operating characteristic
HTA	Health technology Assessment
ICER	incremental cost-effectiveness ratio
INAHTA	International Network of Agencies for Health Technology Assessment
IQR	interquartile range
IRR	incidence rate ratio
LILACS	Latin American and Caribbean Health Sciences Literature
LoB	limit of blank
LoD	limit of detection
LR+	Positive likelihood ratio
LR-	Negative likelihood ratio
LY	life year
MACE	major adverse cardiac event
MI	myocardial infarction
MINAP	Myocardial Ischemia National Audit Project
NA	not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
NIHR	National Institute for Health Research
NPV	negative predictive value
NR	not reported
NSTE-ACS	non-ST-segment-elevation ACS
NSTEMI	non-ST segment elevation myocardial infarction
ONS	Office for National Statistics
OR	odds ratio
PoC	point of care
PSA	probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
QALY	Quality-Adjusted Life Year
RCT	randomised controlled trial
ROC	receiver operating characteristic
SCI	Science Citation Index
SD	standard deviation
SIGN	Scottish Intercollegiate Guidelines Network
SROC	summary receiver operating characteristic
STEMI	ST segment elevation myocardial infarction
TIMI	Thrombolysis In Myocardial Infarction
Tn	troponin
TN	true negative
TP	true positive

UA	unstable angina
WHF	World Heart Federation

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 healthcare interventions.
False negative	Incorrect negative test result – number of diseased persons with a negative test result.
False positive	Incorrect positive test result – number of non-diseased persons with a positive test result.
Incremental cost-effectiveness ratio (ICER)	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 whose performance is being evaluated.
Likelihood Ratio (LR)	Likelihood ratios describe 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 of life	An individual's emotional, social and physical well-being and their ability to perform the ordinary tasks of living.
Quality-adjusted life year (QALY)	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.
Receiver Operating Characteristic (ROC) curve	A graph which illustrates the trade-offs between sensitivity and specificity which 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	Proportion of people with the target disorder who have a positive test result.
Specificity	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	Correct negative test result – number of non-diseases persons with a negative test result.
True positive	Correct positive test result – number of diseased persons with a positive test

	result.

EXECUTIVE SUMMARY (2820 WORDS)

Background

Coronary artery disease and myocardial infarction (MI) are a significant health burden in the UK. Many people attend hospital with chest pain and suspected MI; 2017-2018 statistics showed that it accounted for approximately 5% of all emergency admissions. It is important to diagnose people who are suspected of having an MI as early as possible in order to ensure quick and effective treatment. However, only around 20% of emergency admissions for chest pain will actually have an MI and there are many other possible causes of chest pain. Tests which can quickly tell which patients do not have MI could therefore avoid unnecessary hospital admissions, waiting time and anxiety for many people.

Cardiac troponins (Tn) I and T are used as markers of acute myocardial infarction (AMI). They are intended for use in conjunction with clinical history taking and electrocardiography (ECG) monitoring. ST segment elevation myocardial infarction (STEMI) can usually be diagnosed on presentation by electrocardiogram, hence the main diagnostic challenge is the detection or rule-out of non- ST segment elevation myocardial infarction (NSTEMI). High-sensitivity cTn (hs-cTn) assays are now available, which are able to detect lower levels of troponin in the blood than conventional assays and may enable NSTEMI to be ruled out at an earlier time after the onset of acute chest pain. NICE guidance currently recommends the use of some high-sensitivity cardiac troponin (hs-cTn) assays (Elecsys Troponin T high-sensitive assay and ARCHITECT STAT High Sensitive Troponin-I assay) as options for the early rule-out of NSTEMI in people presenting to an emergency department with chest pain and suspected ACS.

This update assessment is being undertaken in order to ensure that guidance is based on current evidence (including new hs-cTn assays developed and marketed since the publication of NICE guidance) 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).

Objectives

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

Methods

Assessment of clinical effectiveness

Sixteen databases, including MEDLINE and 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 text inclusion assessment, 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 (RoB 2.0). The methodological quality of included diagnostic test accuracy (DTA) studies, which evaluated a single hs-cTn assay, was assessed using QUADAS-2. Studies which provided data for two or more hs-cTn assays were assessed using QUADAS-2C, a version of the QUADAS tool which has been developed specifically for the assessment of comparative DTA studies; this tool is currently undergoing piloting and is not yet published.

The hierarchical summary receiver operating characteristic (HSROC) model was used to estimate summary sensitivity and specificity with 95% confidence intervals (CIs) and prediction regions around the summary points, and to derive HSROC 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 hs-cTn assay. Analyses were stratified according to target condition (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.

Assessment of cost-effectiveness

We considered the long-term costs and quality adjusted life years (QALYs) associated with different troponin testing methods, to diagnose or rule-out NSTEMI, for patients presenting at the emergency department (ED) with suspected non-ST-segment-elevation acute coronary syndrome (NSTE-ACS). 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 QALYs were estimated using a state-transition cohort model with a lifetime time horizon (60 years). For the economic analyses, based on expert opinion, only high sensitivity troponin tests that had a sensitivity of 97% or above were selected. The following strategies were included in the main economic analysis:

- Standard troponin at presentation and at 10-12 hours (reference standard)
- Roche Elecsys hsTnT (99th centile threshold (<14 ng/L at 0 h AND 3 h))
- Roche Elecsys hsTnT (LoD (<5ng/L) at 0 h)

- Roche Elecsys hsTnT (ESC 0/1 hour pathway: (symptoms >3 hours AND <5 ng/L at 0 h) OR (<12 ng/L at 0 h AND Δ <3 ng/L at 0 to 1 h))
- Roche Elecsys hsTnT (<8 ng/L at 0 h AND Δ <3 ng/L at 0 to 0.5 h)
- Roche Elecsys hsTnT (<12 ng/L at 0 h AND Δ <3 ng/L at 0 to 1 h)
- Siemens Dimension Vista hsTnI (<5 ng/L at 0 h AND Δ <2 ng/L at 0 to 1 h)
- Abbott ARCHITECT hsTnI (LoD (<2ng/L) at 0 h)
- Abbott ARCHITECT hsTnI (ESC 0/1 hour pathway: (symptoms >3 hours AND <2 ng/L at 0 h) OR (<5 ng/L at 0 h AND Δ <2 ng/L at 0 to 1 h))
- Abbott ARCHITECT hsTnI (HighSTEACS pathway: (symptoms ≥2 h AND <5 at 0 h) OR (≤16 (F) ≤34 (M) at 3 h AND Δ <3))
- Abbott ARCHITECT hsTnI (<4 ng/L at 0 h)
- Siemens ADVIA Centaur hsTnI (<2 ng/L at 0 h)
- Siemens ADVIA Centaur hsTnI (<3 ng/L at 0 h OR (<8 ng/L at 0 h AND Δ <7 ng/L at 0 to 2 h))
- Siemens ADVIA Centaur hsTnI (ESC 0/1 hour pathway: (symptoms >3 h AND <3 ng/L at 0 h) OR (<6 ng/L at 0 h AND Δ <3 at 0 to 1 h))
- Siemens ADVIA Centaur hsTnI (<5 ng/L at 0 h)
- Siemens Atellica hsTnI (<2 ng/L at 0 h)
- Siemens Atellica hsTnI (HighSTEACS pathway: (symptoms ≥2 h AND <5 at 0 h) OR (≤34 (F) ≤53 (M) at 3 h AND Δ <3))
- Beckman Coulter ACCESS hsTnI (ESC 0/1 hour pathway: (symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <4 at 0 to 1 h))
- Beckman Coulter ACCESS hsTnI ((symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h))
- Ortho VITROS hsTnI (ESC 0/1 hour pathway: (symptoms >3 h AND <1 ng/L at 0 h) OR (<2 ng/L at 0 h AND Δ <1 at 0 to 1 h))
- bioMérieux VIDAS hsTnI (<2 ng/L at 0 h OR (<6 ng/l at 0 AND 2 h))
- Quidel TriageTrue hsTnI (ESC 0/1 hour pathway: (symptoms >3 h AND <4 ng/L at 0 h) OR (<5 ng/L at 0 h AND Δ <3 at 0 to 1 h))

In the base case, it was assumed that standard troponin testing had perfect sensitivity and specificity (reference case) for diagnosing AMI and that only patients testing positive with the reference standard (standard troponin), were at increased risk for adverse events (MI and mortality) and would benefit from immediate treatment. In a secondary analysis, a proportion of patients testing positive only with a hs-cTn test and not with standard troponin, i.e. false positives, were assumed to

be at increased risk of MI and mortality. These patients were assumed to be treated for the hs-cTn 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 hs-cTn assay, nine studies reported accuracy data for the Abbott ARCHITECT hs-cTnI assay, two studies reported accuracy data for Siemens Healthineers Atellica hs-cTnI, three studies reported accuracy data for Siemens Healthineers ADVIA Centaur hs-cTnI, two studies reported accuracy data for Beckman Coulter ACCESS hs-cTnI and one study each reported accuracy data for Siemens Healthineers Dimension Vista hs-cTnI, Ortho VITROS hs-cTnI, bioMérieux VIDAS hs-cTnI and Quidel Cardiovascular TriageTrue hs-cTnI. Seven studies reported accuracy data for more than one assay. We did not identify any studies of Abbott Alinity hs-cTnI, or Siemens Healthineers Dimension EXL hs-cTnI, which met the inclusion criteria for this review.

The hs-cTn test strategies evaluated by included studies are defined by the combination of four factors (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 (LoD) 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 NSTEMI, using the Roche Elecsys hs-cTnT assay (5 ng/L) were 99% (95% CI: 97 to 100%) and 35% (95% CI: 25 to 46%), six studies. The summary sensitivity and specificity estimates for the Abbott ARCHITECT hs-cTnI asssay (2 ng/L) were 100% (95% CI: 99 to 100%) and 21% (95% CI: 16 to 26%), 4 studies. Of the remaining hs-cTn assays, only the Siemens Atellica and Siemens ADVIA Centaur hs-cTnI assays 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. 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%) for the Siemens ADVIA Centaur hs-cTnI assay and 100% (95% CI: 98 to 100%) and 26% (95% CI: 24 to 28%) for the Siemens Atellica hs-cTnI assay.

The majority of the multiple test strategies meeting the minimum clinically acceptable sensitivity 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 Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation, from the European Society of Cardiology included a 0/1 hour algorithm, which incorporates a rule-out pathway following this structure. Versions of the ESC 0/1 hour rule-out pathway have been evaluated using the following assays: Roche Elecsys hs-cTnT, sensitivity 99% (95% CI: 98 to 100%) and specificity 68% (95% CI: 67 to 70%); Abbott ARCHITECT hs-cTnI, sensitivity 99% (95% CI: 98 to 100%) and specificity 57% (95% CI: 56 to 59%), summary estimate from 2 studies; Beckman Coulter Access hs-cTnI, sensitivity 99% (95% CI: 94 to 100%) and specificity 70% (95% CI: 66 to74%); Ortho VITROS hs-cTnI, sensitivity 100% (95% CI: 95 to 100%) and specificity 60% (95% CI: 55 to 64%) Quidel TriageTrue hs-cTnI, sensitivity 100% (95% CI: 97 to 100%) and specificity 66% (95% CI: 62 to 70%); Siemens ADVIA Centaur hs-cTnI, sensitivity 99% (95% CI: 95 to 100%) and specificity 67% (95% CI: 61 to 72%). The 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 NSTEMI 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%) using the Abbott ARCHITECT hs-cTnI assay, and 98% (95% CI: 95 to 100% and 74% (95% CI: 72 to 76%) using Siemens Atellica hs-cTnI assay.

Two randomised trials were included in the review. High-STEACS evaluated implementation of an early rule-out pathway in hospitals in Scotland, which 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 using conventional cTnI results. The HiSTORIC trial (un-published report provided AiC), 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). In High-STEACS the Median length of stay was 7 hours (IQR = 3 to 24) in the implementation phase as compared to 4 hours (IQR 3 to 20) in the validation phase. In HiSTORIC [redacted] Both studies reported that the implementation of an early rule-out pathway was not associated with any increase in MI or cardiac death after discharge, at 30 days or one year.

Assessment of cost-effectiveness

Base case analysis

In the base case analysis, 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 effective, resulting in the same LY and QALY gain in up to four decimal places. Comparisons based on the next best alternative showed that for willingness to pay values below £8,455 per QALY, the Beckman Coulter ACCESS hsTnI ((symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h)) would be cost-effective. For thresholds between £8,455 and £20,190 per QALY, the Roche Elecsys hsTnT (<12 ng/L at 0 h AND Δ <3 ng/L at 0 to 1 h) was cost-effective; above £20,190 per QALY Siemens Dimension Vista hsTnI (<5 ng/L at 0 h AND Δ <2 ng/L at 0 to 1 h) would be cost-effective.

Secondary analysis

In the secondary analysis, which assumed that a proportion of false positives in the hs-cTn testing strategies had an increased risk of adverse events (MI and mortality), 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 hsTnI (ESC 0/1 hour pathway: (symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <4 at 0 to 1 h)) 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 hsTnI (ESC 0/1 hour pathway: (symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <4 at 0 to 1 h)) versus Standard troponin (at presentation and after 10-12 hours) was £4,043 per QALY gained.

Sensitivity and scenario analyses

The following input parameters had a noticeable impact on the estimated cost-effectiveness the parameters with notable impact on the estimated cost-effectiveness were: the 30 day mortality for untreated AMI, the mortality one year after treated and untreated AMI, the discount rate used for outcomes, and the relative mortality for patients tested true positive versus those that tested false positive. Moreover, only scenario analysis one, 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 NSTEMI, in adults presenting with acute chest pain, within the four-hour NHS emergency department 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 whilst maintaining clinically acceptable sensitivity (very low rates of missed NSTEMI).

From a cost-effectiveness perspective the Roche Elecsys hsTnT (<12 ng/L at 0 h AND Δ <3 ng/L at 0 to 1 h) and Siemens Dimension Vista hs-cTnI (<5 ng/L at 0 h AND Δ <2 ng/L at 0 to 1 h) might be cost-effective for thresholds of £20,000 and £30,000 per QALY gained respectively (base-case). For the secondary analysis, Beckman Coulter ACCESS hs-cTnI ((symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h)) 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 QALY 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 true negatives (i.e. 65% or above) involve high sensitivity tests strategies with a second test 2 to 3 hours after the initial test (i.e. Siemens Atellica hs-cTnI (High-STEACS pathway), Abbott ARCHITECT hs-cTnI (High-STEACS pathway), Roche Elecsys hs-cTnT (99th centile) and Beckman Coulter ACCESS hs-cTnI ((symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h))).

PLAIN ENGLISH SUMMARY (225 WORDS)

Heart disease is a leading cause of death in the UK, with myocardial infarction (MI) (heart attack) accounting for approximately 4% of all deaths recorded in 2018. Many people attend hospital with chest pain and suspected MI; 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 2017-2018. It is important to diagnose people who are suspected of having an MI as early as possible in order to ensure quick and effective treatment. However, only around 20% of emergency admissions for chest pain will actually have an MI and there are many other possible causes of chest pain (e.g. gastro-oesophageal disorders, muscle pain, anxiety, or stable ischaemic heart disease). Tests which can quickly tell which patients do not have MI could therefore avoid unnecessary hospital admissions and anxiety for many people.

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

We found that high sensitivity troponin tests can safely rule-out MI within the four-hour NHS emergency department target. Health economic analyses indicated that high sensitivity tests may be cost-effective compared to standard troponin tests, which require repeat testing at 10-12 hours.

1. OBJECTIVE

The overall objective of this project was to provide an update to NICE diagnostics guidance on early rule out of acute myocardial infarction using high-sensitivity troponin tests (DG15), published in October 2014.[1] This update summarises the current evidence on the clinical- and cost-effectiveness of high sensitivity troponin assays (including new assays which have become available to the National Health Service (NHS) since publication of DG15) for the management of adults presenting with acute chest pain, focusing on the early (within four hours of presentation) rule-out of NSTEMI. The following research questions were defined to address the review objectives:

- What is the clinical effectiveness of high sensitivity troponin (hs-cTn) assays (used singly or in series) compared with conventional diagnostic assessment, for achieving early discharge within four hours of presentation, where NSTEMI is excluded 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 (MACE) (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 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?

2. BACKGROUND AND DEFINITION OF THE DECISION PROBLEM(S)

2.1 Population

The primary indication for this assessment is the early rule-out of acute myocardial infarction (AMI) and consequent early discharge in people presenting with acute chest pain and suspected, but not confirmed, non-ST segment elevation myocardial infarction (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: unstable angina, ST segment elevation myocardial infarction (STEMI) and NSTEMI. Coronary artery disease and myocardial infarction are a significant health burden in the UK, with Office of National Statistics (ONS) 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%.[2]

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;[3] Hospital Episode Statistics (HES) for 2017-2018 show 226,393 emergency admissions for chest pain, accounting for approximately 5% of all emergency admissions.[4] 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 on the impact of cardiology guidelines on the diagnostic classification of people with ACS in the UK reported that the majority people admitted to hospital with chest pain have either no ischaemic heart disease or stable ischaemic heart disease.[5] HES for 2017-2018 remain consistent with this observation, showing diagnoses of AMI in 45,163 emergency admissions and unstable angina in 13,056 admissions; this represents approximately 20% and 6% of emergency admissions with chest pain, respectively.[4] 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 where required and to avoid unnecessary hospital admissions.

STEMI can usually be diagnosed on presentation by electrocardiogram, 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 unstable angina (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 Hospital Episode Statistics show that the number of Emergency Department attendances where the first recorded investigation was a cardiac biomarker has risen substantially from the 13,743 in 2010-2011 to 28,379 in 2011-2012,[6] recorded in our previous report for DG15,[7] to 36,907 in 2017-2018.[8] Cardiac troponins I and T (cTnI and cTnT), together with cardiac troponin 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 (ECG) 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, which recommended standard cTnI or cTnT testing at initial hospital assessment and again 10-12 hours after the onset of symptoms.[11, 12] Since 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 high-sensitivity cardiac troponin (hs-cTn) assays (Elecsys Troponin T high-sensitive assay and ARCHITECT STAT High Sensitive Troponin-I assay) as options for the early rule-out of NSTEMI in people presenting to an emergency department with chest pain and suspected ACS.[1] This recommendation was incorporated into the 2016 update to the NICE clinical guideline, "Chest pain of recent onset: assessment and diagnosis,"(CG95).[13] High-sensitivity troponin assays are now also included in Scottish Intercollegiate Guidelines Network (SIGN 148) guidance on the management of ACS.[14] This updated assessment is being undertaken in order 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).

2.2 Intervention technologies

High-sensitivity cTn (hs-cTn) assays are now available, which are able to detect lower levels of troponin in the blood. 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 versus 100 ng/L).[15] Use of these high-sensitivity assays enable the detection of small changes in cTn 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 cTn levels. The recommended definition of an hs-cTn assay uses two criteria:[15, 16]

- The total imprecision, co-efficient of variation (CV), of the assay should be ≤10% at the 99th centile value for the healthy reference population.
- 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 cTnI and cTnT (hs-cTnI and hs-cTnT) assays are currently available for use in the NHS in England and Wales; all are designed for use in clinical laboratory settings.

2.2.1 Abbott ARCHITECT high-sensitivity troponin I assay (Abbott Diagnostics)

The ARCHITECT hs-cTnI STAT assay can be used with the Abbott ARCHITECT i2000SR and i1000SR analysers. The assay is a quantitative, chemiluminescent micro particle immunoassay (CMIA) for serum or plasma samples. Results are available within 16 minutes. The ARCHITECT hs-cTnI STAT assay can detect cTnI in 96% of the reference population, and has a recommended 99th centile cut-off of 26.2ng/L with a CV of 4%.[17] The assay is CE marked and available to the NHS.

2.2.2 Alinity i STAT high-sensitivity troponin I assay (Abbott Diagnostics)

The Alinity i STAT High Sensitive Troponin-I assay can be used with the Alinity i analyser. 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 of 26.2 ng/L with a CV of 4.6%. Sex specific 99th centile cut offs of 15.6 ng/L for females (CV of 5.0%) and 34.2 ng/L for males (CV of 4.5%) are also provided.[18] The assay is CE marked and available to the NHS.

2.2.3 Access high-sensitivity troponin I assay (Beckman-Coulter)

The Access hs-cTnI assay can be used with both the Beckman Coulter Access 2 and DxI/DxC analysers. The assay is a quantitative, paramagnetic particle chemiluminescent immunoassay for serum or plasma samples. The turnaround time of the assay is to be confirmed by the company. The

Access hs-cTnI assay has a recommended 99th centile cut-off of 17.5ng/L for the whole population, 11.6 ng/L for females and 19.8 ng/L for males, with a CV of <10%.[19] The assay is CE marked and available to the NHS.

2.2.4 VIDAS high sensitive Troponin I assay (Biomérieux)

The VIDAS High sensitive Troponin I assay is designed for use in a laboratory setting on the following analysers: VIDAS, MINI VIDAS and VIDAS 3. 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 of 19 ng/L. Sex specific 99th centile cut offs of 11 ng/L for females and 25 ng/L for males are provided.[20] The assay is CE marked and available to the NHS.

2.2.5 VITROS high Sensitivity Troponin I Assay (Ortho Clinical Diagnostics)

The VITROS High Sensitivity Troponin I assay is designed for use in a laboratory setting on the following analysers: VITROS ECi/ECiQ/3600 Immunodiagnostic Systems and the VITROS 5600/XT 7600 Integrated System. 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 of 11 ng/L for both lithium heparin and serum samples. Sex specific 99th centile cut offs 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.[21] The assay can detect troponin I in more than 50% of the reference population. The assay is CE marked and available to the NHS.

2.2.6 TriageTrue high Sensitivity Troponin I Test (Quidel Cardiovascular)

The TriageTrue High Sensitivity Troponin I test can be used in a near patient setting (point-of-care [PoC]) or in a laboratory with the Triage MeterPro analyser. It is a fluorescence immunoassay and is intended for the in-vitro quantitative determination of troponin I in ethylenediaminetetraacetic acid (EDTA) anticoagulated whole blood and plasma samples. Test results are available in less than 20 minutes. It has a recommended 99th centile cut-off of 20.5 ng/L with a CV of less than 10%. Sex specific 99th centile cut offs of 14.4 ng/L for females and 25.7 ng/L for males are provided.[22] The test can detect troponin I in more than 50% of the reference population. The test is CE marked and available to the NHS.

2.2.7 Elecsys high-sensitive troponin T assay (Roche diagnostics)

The Elecsys cTnT-hs and Elecsys cTnT-hs STAT assays can be used on the Roche cobas e411, e601, e602 and e801 analysers. The assay is a quantitative, sandwich electrochemiluminescence immunoassay (ECLIA) 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 of 14ng/L with a CV of <10%.[23-25] Both versions of the assay are CE marked and available to the NHS.

2.2.8 ADVIA Centaur high-sensitivity troponin I assay (Siemens Healthineers)

The ADVIA Centaur high-sensitivity troponin I assay can be used with the Siemens ADVIA Centaur XP and ADVIA Centaur XPT analysers. 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 of 47.34 ng/L for the whole population in lithium heparin samples and of 46.47 ng/l in serum samples.[26] Sex specific cut offs of 36.99 ng/L for females and 57.27 ng/L for males are also recommended.[26] Each 99th centile has a CV of < 10%. The assay can detect cTnI in more than 50% of the reference population. The assay is CE marked and available to the NHS.

2.2.9 Atellica IM high-sensitivity troponin I assay (Siemens Healthineers)

The Atellica IM high-sensitivity troponin I assay can only be used with the Siemens Atellica IM analyser. 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 of 45.2 ng/L for lithium heparin samples and 45.43 ng/L for serum samples. Each 99th centile has a CV of <10%.[27] The assay can detect cTnI in more than 50% of the reference population. The assay is CE marked and available to the NHS.

2.2.10 Dimension EXL high-sensitivity troponin I assay (Siemens Healthineers)

The Dimension EXL high-sensitivity troponin I assay is designed for use in a laboratory setting with the Siemens Dimension EXL analyser. 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 of 60.4 ng/L for lithium heparin and 58.2 ng/L for serum.[28] Sex-specific 99th centile cut offs 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.[28] Each 99th centile has a CV of less than 10%. The assay can detect troponin I in more than 50% of the reference population. The assay is CE marked and available to the NHS.

2.2.11 Dimension Vista high-sensitivity troponin I assay (Siemens Healthineers)

The Dimension Vista high-sensitivity troponin I assay is designed for use in a laboratory setting with the Siemens Dimension Vista analysers. 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 of 58.9 ng/L for lithium heparin samples and 57.9% for serum samples.[29] Sex specific 99th centile cut-offs of 53.77 ng/L for females and 78.5 ng/L for males are also recommended.[29] Each 99th centile has a CV of <10%. The assay can detect cTnI in more than 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 as 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 three hours after the onset of chest pain or up to three hours after presentation (as reported); for serial Tn measurements. Data for both relative and absolute change in Tn levels and peak Tn are presented.

Table 1: Overview of cardiac biomarkers

Manufacturer	System and compatible analysers	Assay	99th centile (ng/L)	CV at 99th centile (%)	Proportion of reference population in which cTn is detected (%)	Turn-around time (mins)	LoD (ng/L)	LoQ (ng/L)
Abbott Diagnostics	ARCHITECT i1000sr and i2000sr	ARCHITECT hs-cTnI [17]	Overall: 26.2 Female: 15.6 Male: 34.2	Overall: 4.0 Female: 5.3 Male: 3.5	96[30]	18*	1.9	4.7 (10% CV) 1.3 (20% CV)
Abbott Diagnostics	Alinity i	Alinity hs-cTnI [18]	Overall: 26.2 Female: 15.6 Male: 34.2	Overall: 4.6 Female: 5.0 Male: 4.5	96[30]	18*	1.6	3.7 (10% CV) 2.1 (20% CV)
Beckman Coulter	Access 2, DxI 9000 Access, DxI 800, DxC 600i/880i /860i/680i/660i	Access hs-cTnI [19]	Lithium heparin: Overall: 17.5 Female: 11.6 Male: 19.8	Lithium heparin Overall: 3.7 Female: 4.2 Male: 3.6	>50	17*	2.0	2.0
			Serum: Overall: 18.2 Female: 11.5 Male: 19.7	Serum: Overall: 6.0 Female: 6.9 Male: 5.5				
Biomérieux	VIDAS, MINI VIDAS, VIDAS 3	VIDAS hs-cTnI *	Overall: 19 Female: 11 Male: 25			20		
Ortho Clinical Diagnostics	VITROS ECi/ECiQ/3600 Immunodiagnostic Systems and the	VITROS hs-cTnI [21]	Lithium heparin: Overall: 11 Female: 9	≤10*	>50	15*	0.39 to 0.86	1.23

Manufacturer	System and compatible analysers	Assay	99th centile (ng/L)	CV at 99th centile (%)	Proportion of reference population in which cTn is detected (%)	Turn-around time (mins)	LoD (ng/L)	LoQ (ng/L)
	VITROS 5600/XT 7600 Integrated System		Male: 13 Serum Overall: 11 Female: 9 Male: 12					
Quidel Cardiovascular	Triage MeterPro	TriageTrue hs-cTnI [22]	Overall: 20.5 Female: 14.4 Male: 25.7	Overall: <10	>50	<20*	Plasma: 1.6	Plasma: 8.4 (10% CV) 3.6 (20% CV)
							Whole blood: 1.9	Whole blood: 6.2 (10% CV) 2.8 (20% CV)
Roche	200 test pack: cobas e411, e601, e602 300 test pack cobas: e801	Elecsys hs-cTnT [23, 24]	Overall: 14 Female: 9 Male: 16.8	<10	57	18	3 (cobas e801) 5 (all others)	13
Roche	100 test pack: cobas e411, e601, e602, 300 test pack: cobas e801	Elecsys hs TnT STAT[25]	Overall: 14 Female: 9 Male: 16.8	<10	57	9	3 (cobas e801) 5 (all others)	13
Siemens Healthineers	Atellica	Atellica IM hs-cTnI [27]	Lithium heparin: Overall: 45.2	<4	75	10	1.6	2.5

Manufacturer	System and compatible analysers	Assay	99th centile (ng/L)	CV at 99th centile (%)	Proportion of reference population in which cTn is detected (%)	Turn-around time (mins)	LoD (ng/L)	LoQ (ng/L)
			Female: 34.11 Male: 53.48 Serum: Overall: 45.43 Female: 38.64 Male: 53.53					
Siemens Healthineers	Dimension EXL	Dimension EXL hs-cTnI [28]	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
Siemens Healthineers	Dimension Vista	Dimension Vista hs-cTnI [29]	Lithium heparin: Overall: 58.9 Female: 53.7 Male: 78.5 Serum: Overall: 57.9 Female: 51.1	<5	>50	10	2.0	3.0

Manufacturer	System and compatible analysers	Assay	99th centile (ng/L)	CV at 99th centile (%)	Proportion of reference population in which cTn is detected (%)	Turn-around time (mins)	LoD (ng/L)	LoQ (ng/L)
			Male: 74.9					
Siemens Healthineers	ADVIA Centaur XP and ADVIA Centaur XPT	ADVIA Centaur hs-cTnI [26]	Lithium heparin: Overall: 47.34 Female: 36.99 Male: 57.27	<4.9	63	18	1.6	2.5 (20% CV)
			Serum: Overall: 46.47 Female: 39.59 Male: 58.05					

* Information supplied to NICE by the manufacturer
LoD: limit of detection
LoQ: limit of quantitation

2.3 Comparator

The comparator for this technology appraisal is serial TnT 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),[7] conducted to support the development of DG15.[31]

2.4 Care pathway

2.4.1 Diagnostic assessment

The assessment of patients with suspected ACS is described in NICE clinical guideline 95 (CG95) "Chest pain of recent onset: assessment and diagnosis". This has been updated since the publication of DG15[31] to include recommendations on the use of high sensitivity troponin assays.[13] 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 ECG, management should follow NICE clinical guideline 167 (CG167) "The acute management of myocardial infarction with ST-segment elevation."[32] People without persistent ST-elevation changes on ECG, i.e. with suspected non-ST-segment-elevation ACS (NSTE-ACS), should receive further investigation using cardiac biomarkers with the aim of distinguishing NSTEMI from unstable angina. NICE CG95 makes the following recommendations on the use of cardiac biomarkers:[13]

- 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 myocardial infarction (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 myocardial infarction (DG15) if the first troponin test at presentation is positive.
    - consider performing a single high-sensitivity troponin test only at presentation to rule out NSTEMI if the first troponin test is below the lower limit of detection (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.

CG95 recommends that a diagnosis of NSTEMI should be made using the universal definition of myocardial infarction, which states that AMI is defined as "The detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99th centile upper reference limit and with at least one of the following: symptoms of ischaemia, new or presumed new significant ST-segment-T wave changes or new left branch bundle block, development of pathological Q waves in the ECG, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, or identification of an intracoronary thrombus by angiography or autopsy." [33]

The Scottish Intercollegiate Guidelines Network guideline 148 (SIGN 148), "Acute coronary syndrome," provides the following recommendations in relation to cardiac troponins:[14]

- In patients with suspected acute coronary syndrome, 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 myocardial infarction.

- In patients with suspected acute coronary syndrome, measurement of cardiac troponin at presentation and at three 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 myocardial infarction.

- Sex-specific thresholds of cardiac troponin should be used for the diagnosis of myocardial infarction in men and women.

Guidelines from the European Society of Cardiology, on the management of ACS in patients presenting without persistent ST-segment elevation, recommend "measurement of cardiac troponins with sensitive or high-sensitivity assays to obtain results within 60 minutes."[34] The guideline also describes 0/1 hour and 0/3 hour rule out algorithms, which incorporate both high-sensitivity troponin assays and clinical risk scores.[34] 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.[34]

Guidelines from the American College of Cardiology/American Heart Association (ACC/AHA), on the management of patients with non-ST-elevation ACS, do not include any specific recommendations about the use of high-sensitivity troponin assays.[35] However, the guideline does state that: "The TIMI risk index is useful in predicting 30-day and 1-year mortality in patients with NSTE-ACS. For patients with a TIMI 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."[35]

The 2017 publication "Asia-Pacific consensus statement on the optimal use of high-sensitivity troponin assays in acute coronary syndromes diagnosis: focus on hs-TnI" makes 9 recommendations:[36]

- Troponin is the preferred cardiac biomarker for diagnostic assessment of ACS and is indicated for patients with symptoms of possible ACS

- Hs-cTn assays are recommended
- Serial testing is required for all patients

- Testing should be performed at presentation and 3 hours later

- Gender-specific cut-off values should be used for hs-cTn I assays
- Hs-cTn I level >10 times the upper limit of normal should be considered to 'rule in' a diagnosis of ACS
- Dynamic change >50% in hs-cTn I level from presentation to 3hour retest identifies patients at high risk for ACS
- Where only point-of-care testing is available, patients with elevated readings should be considered at high risk, while patients with low/undetectable readings should be retested after 6 hours or sent for laboratory testing
- Regular education on the appropriate use of troponin tests is essential

The rapidly expanding evidence base on high-sensitivity cardiac troponins, together with their increasing uptake and inclusion in clinical guidelines, means that an up-date to NICE diagnostics guidance on early rule out of acute myocardial infarction using high-sensitivity troponin tests (DG15), published in October 2014,[31] is now considered necessary.

2.4.2 Management/treatment

NICE clinical guideline 94 (CG94) provides recommendations on the management of people with suspected NSTE-ACS "Unstable angina and NSTEMI: The early management of unstable angina and non-ST-segment-elevation myocardial infarction."[37] The guideline states that initial treatment should include a combination of antiplatelet (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. NICE's guidelines on unstable angina and NSTEMI: early management (CG94),[37] myocardial infarction: cardiac rehabilitation and prevention of further cardiovascular disease (CG172),[38] and myocardial infarction with ST-segment elevation: acute management (CG167)[32] are being combined and updated. The new guideline will be titled "acute coronary syndromes" when published; publication is expected in May 2020.

Longer term follow-up of people who have had an acute myocardial infarction is described in full in NICE Clinical Guideline 48 (CG48) "Secondary prevention in primary and secondary care for patients following a myocardial infarction". This includes recommendations on lifestyle changes, cardiac rehabilitation programmes, drug therapy (including a combination of ACE inhibitors, aspirin, beta-blockers and statins), and further cardiological assessment to determine whether coronary revascularisation is required.[39]

3. ASSESSMENT OF CLINICAL EFFECTIVENESS

Systematic review methods followed the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care,[40] NICE Diagnostics Assessment Programme manual[41] and the Cochrane Handbook for Diagnostic Test Accuracy Reviews.[42] All data for studies included in our previous Diagnostic Assessment Report (DAR),[7] conducted to support the development of DG15,[31] were taken directly from that report.

3.1 Systematic review methods

3.1.1 Search strategy

Search strategies utilised in the original report [7] 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 Centre for Reviews and Dissemination (CRD)'s guidance for undertaking reviews in health care[40] and the Cochrane Handbook for Diagnostic Test Accuracy Reviews.[42]

Search strategies were developed specifically for each database and the keywords associated with high sensitivity troponin T/I adapted according to the configuration of each database. No language restrictions were applied.

The following databases were searched between 20.9.2019 and 26.9.2019 for relevant studies from 2013 to the present:

- MEDLINE ALL (Ovid): 1946 to 2019/09/24
- EMBASE (Ovid): 1974 to 2019/09/25
- 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 Database (HTA) (CRD): up to March 2018
- Science Citation Index (SCI) (Web of Science): 1988 to 2019/09/24
- Conference Proceedings Citation Index- Science (CPCI-S) (web of Science): 1990 to 2019/09/24
- LILACS (Latin American and Caribbean Health Sciences Literature) (Internet): 2013 to 2019/09/20
- NIHR Health Technology Assessment Programme (Internet): up to 2019/09/26

- PROSPERO (International Prospective Register of Systematic Reviews) (Internet): up to 2019/09/20

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

- NIH ClinicalTrials.gov (http://www.clinicaltrials.gov/): First posted from 01/01/2013 to 12/31/2019
- WHO International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/): date of registration 01/01/2013 to 25/09/2019

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

- American Heart Association (AHA) Scientific Sessions
- American Association for Clinical Chemistry (AACC)
- European Society of Cardiology (ESC)

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

- AACC 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 CADTH Peer Review checklist.[43].

3.1.2 Inclusion and exclusion criteria

Inclusion criteria for each of the clinical effectiveness questions are summarised in Table 2. Studies which fulfilled these criteria were eligible for inclusion in the review. Studies which were included in our previous Diagnostic Assessment Report (DAR),[7] conducted to support the development of DG15,[31] were also included in this review.

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 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 (≥18 yrs.) presenting with acute 'pain, discomfort or pressure in the chest, epigastrium, neck, jaw, or upper limb without an apparent non-cardiac source'[35] due to a suspected, but not proven, AMI	
Setting:	Secondary or tertiary care	
Interventions (index test):	Any hs-cTnT or hs-cTnI test*, listed in Table 1, hs-cTn assays (used singly or in series**, such that results were available within 3 hours of presentation)	
Comparators:	Any other hs-cTnT 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:	Third universal definition of AMI,[33] including measurement of troponin T or I (using any method) on presentation and 3-6 hours later **or** occurrence of MACE (any definition used in identified studies) during 30-day follow-up	Not applicable
Outcomes$:	Test accuracy (the numbers of true positive, false negative, false positive and true negative test results)	Early discharge (≤4 hrs after initial presentation) without MACE during follow-up, incidence of MACE during follow-up, re-attendance at or re-admission to hospital during follow-up, time to discharge, patient satisfaction or health-related quality of life (HRQoL) measures
Study design:	Diagnostic cohort studies	Randomised controlled trials (RCTs) (controlled clinical trials (CCTs) will be considered if no RCTs are identified)

* A high sensitivity assay is defined as one which has a CV ≤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

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

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

3.1.3 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 4.

Studies cited in materials provided by the manufacturers of hs-cTn assays were first checked against the project reference database, in Endnote X8; 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 Tn T or I testing, clinical and imaging components of the reference standard, method of adjudication (e.g. two independent clinicians)), incidence of 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). Where studies reported data 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[7] 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.

3.1.4 Quality assessment

The methodological quality of included randomised controlled trials was assessed using the revised Cochrane Risk of Bias tool for Randomised Trials (RoB 2.0).[44] The methodological quality of included diagnostic test accuracy (DTA) studies, which evaluated a single hs-cTn assay, was assessed using QUADAS-2.[45] Studies which provided data for two or more hs-cTn assays were assessed using QUADAS-2C,[46] a version of the QUADAS tool which 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 (Section 3.2.2) and are presented in full, by study, in Appendix 3.

3.1.5 Methods of analysis/synthesis

Sensitivity and specificity were calculated for each set of 2×2 data and plotted in receiver operating characteristic space. The hierarchical summary receiver operating characteristic (HSROC) model was used to estimate summary sensitivity and specificity with 95% confidence intervals (CIs) and prediction regions around the summary points, and to plot HSROC curves. Pooled results were only obtained 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 summary receiver operating characteristic plots and statistically using the variance of logit (sensitivity) and logit (specificity) , where "logit" indicates the logistic function: the smaller these values the less heterogeneity between studies. Analyses were performed in Stata 13 (StataCorp LP, College Station, Texas, 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 (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.

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

3.2 Results of the assessment of clinical effectiveness assessment

The literature searches of bibliographic databases conducted for this up-date identified 9,379 new references. After initial screening of titles and abstracts, 212 were considered to be potentially relevant and 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,[7] 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 un-published (AiC) studies,[174, 175]

were provided by specialist committee members. Figure 1 shows the flow of studies through the review process, and Appendix 4 provides details, with reasons for exclusions, of all publications excluded at the full paper screening stage.

3.2.1 Overview of included studies

Based on the up-date searches and inclusion screening described above and information taken from the assessment report conducted for DG15,[7] 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 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 Healthineers Atellica hs-cTnI,[61, 176] three studies reported accuracy data for Siemens Healthineers ADVIA Centaur hs-cTnI,[58, 115, 176] two studies reported accuracy data for Beckman Coulter ACCESS hs-cTnI [58, 171] and one study each reported accuracy data for Siemens Healthineers 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 Abbott Alinity hs-cTnI, or Siemens Healthineers Dimension EXL hs-cTnI, which met the inclusion criteria for this review. The High-STEACS study,[61] which contributed multiple diagnostic accuracy data sets, was a stepped-wedge, cluster randomised controlled trial, evaluating implementation of an early rule-out pathway in hospitals in Scotland.This ssessed 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 randomised controlled trial, the HiSTORIC trial (un-published 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). Publications reporting new data were identified for three of the studies included in the assessment report conducted for DG15;[7] ADAPT,[68] APACE[58] and QUART.[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] three studies did not report any information on funding.[62, 102, 110]

For diagnostic test accuracy 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 (Tables 35-37).

Figure 1: Flow of studies through the review process

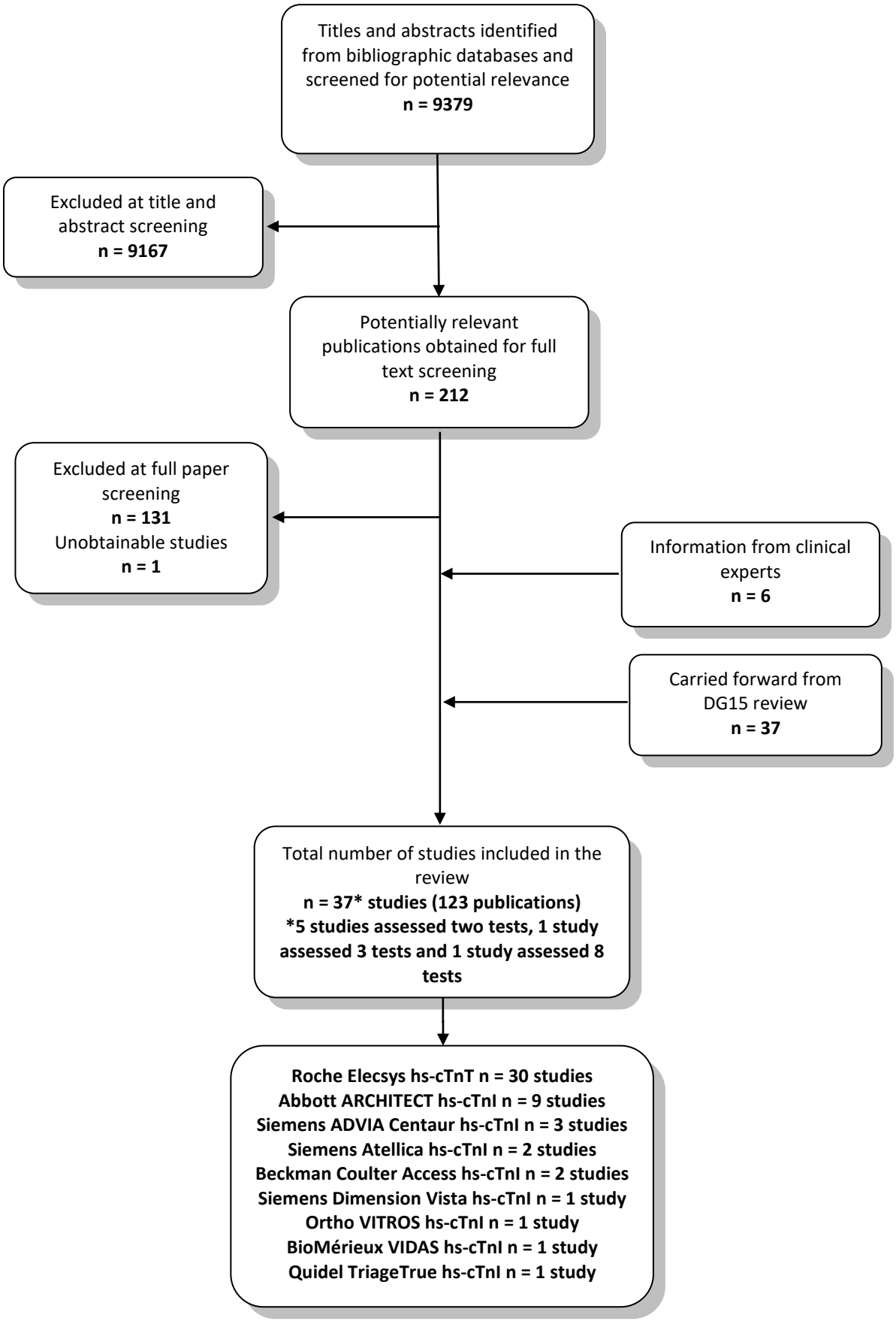


Table 3: Overview of included diagnostic test accuracy studies

Details	Country	N	Target condition(s) reported	Subgroups reported
Abbott ARCHITECT hs-cTnI				
BACC **Neumann 2016[$84]** Neumann 2017[85] Neumann 2017[86]	Germany	1040	NSTEMI	None
Keller 2011[$*141] Keller 2011*[163]	Germany	1818	AMI	None
UTROPIA Dodd 2019[125] **Sandoval 2017[95]** **Sandoval 2017[$96]**	USA	1631	NSTEMI	
Venge 2017[110]	Germany, France Austria and the Netherlands	450	AMI	none
Abbott Alinity hs-cTnI				
No studies identified				
Beckman Coulter ACCESS hs-cTnI				
ADAPT/IMPACT **Nestelberger 2019[171]**	Australia	1280	NSTEMI	None
Siemens Healthineers Dimension EXL hs-cTnI				
No studies identified				
Roche Elecsys hs-cTnT				
Aldous 2012[$*139] **Aldous 2012*[134]** **Aldous 2011*[143]**	New Zealand	939	NSTEMI; AMI	None
Aldous 2011*[147] Aldous 2011*[162] Aldous 2010*[155]	New Zealand	382	AMI	None
Body 2011[$*161]	UK	703	AMI	None

Details	Country	N	Target condition(s) reported	Subgroups reported
Body 2011*[153] Body 2010*[169]				
Body 2015[56]	UK	463	AMI; 30-day MACE	None
Cappellini 2019[62]	Italy	3318	NSTEMI	Gender
Christ 2010*[150]	Germany	137	AMI	None
CORE **Borna 2018[116]** Mokhtari 2016[119] **Mokhtari 2016$[121]** **Mokhtari 2017[120]**	Sweden	1138	30-day MACE	
FASTER I and FAST II **Eggers 2012*[137]**	Sweden	360	NSTEMI	None
Freund 2011$*[142] Freund 2010*[166]	France	317	AMI	Low/moderate vs. high pre-test probability
Huang 2015$[72] Guangquan 2016[73]	China	3458	AMI	Renal function
Kurz 2011*[148]	Germany	94	NSTEMI	None
Lin 2019[117]	Singapore	2444	30-day MACE	None
Melki 2011$*[144] Melki 2010*[154]	Sweden	233	NSTEMI	None
Peacock 2018$[89] **Chang 2018[124]**	USA	1600	AMI	None
PITAGORAS **Sanchis 2012*[135]**	Spain	446	NSTEMI; 30-day MACE	None
QUART Parsonage 2013*[151] Parsonage 2013[131] **Parsonage 2014$[88]**	Australia	764	AMI	None
RATPAC **Collinson 2013$*[159]** Collinson 2012*[164]	UK	850	NSTEMI; 30-day MACE	None

Details	Country	N	Target condition(s) reported	Subgroups reported
Collinson 2012*[152]				
REACTION-US **Nowak 2018[$87]** Nowak 2018[127]	USA	569	NSTEMI	None
Saenger 2010*[165]	USA	288	AMI	None
Sebbane 2013*[157]	France	248	NSTEMI	None
Shiozaki 2017[100]	Japan	413	NSTEMI	None
Slagman 2017[102]	Germany	3423	NSTEMI	None
TRAPID-AMI Body 2015[122] **Body 2016[114]** McCord 2017[126] **Mueller 2016[$80]** Mueller-Hennessen 2016[81] **Mueller-Hennessen 2017[82]** Mueller-Hennessen 2019[83]		1282	NSTEMI; AMI; 30-day MACE	Gender and age (<65 vs. ≥65 years)
TUSCA **Santaló 2013*[133]**	Spain	358	NSTEMI	None
Abbott ARCHITECT hs-cTnI and Roche Elecsys hs-cTnT				
ADAPT Aldous 2014[53] **Boeddinghaus 2016[57]** **Cullen 2013*[156]** **Cullen 2014[$68]** **Eggers 2016[69]** **Greenslade 2015[71]** Meller 2015[118] Parsonage 2013[130] **Van der Linden 2018[109]** Wildi 2017[112]	Australia and New Zealand		NSTEMI; AMI; 30-day MACE	None
ROMI-3	USA	1137	NSTEMI	Renal function

Details	Country	N	Target condition(s) reported	Subgroups reported
Kavasak 2017[76] **Shortt 2017[$101]**				
TRUST **Carlton 2015[$64]** **Carlton 2015[63]**	UK	963 (867 Abbott hs-cTnI, 959 Roche hs-cTnT)	NSTEMI	None
Abbott ARCHITECT hs-cTnI, Siemens Healthineers Atellica hs-cTnI and Roche Elecsys hs-cTnT				
High-STEACS **Bularga 2019[$61]** **Chapman 2017[65]** **Chapman 2018[66]** **Chapman 2019[67]** **Miller-Hodges 2018 [79]** Shah 2015[98] **Chapman 2020[174]**	UK (Scotland)	32837	NSTEMI; 30-day MACE	Gender, age (<65 vs. ≥65 years), history of ischaemic heart disease
Roche Elecsys TnT and Siemens ADVIA Centaur hs-cTnI				
BEST **Body 2019[$115]** **Body 2020[172]**	UK	665	NSTEMI	None
Siemens Healthineers Atellica hs-cTnI and ADVIA Centaur hs-cTnI				
High-US Nowak 2019[128] Nowak 2019[129] **Sandoval 2019[$176]**	USA	2212	NSTEMI; 30-day MACE	None
Abbott ARCHITECT hs-cTnI, Roche Elecsys hs-cTnT, Siemens Healthineers ADVIA Centaur hs-cTnI, Siemens Healthineers Dimension Vista hs-cTnI, Beckman Coulter ACCESS hs-cTnI, Ortho VITROS hs-cTnI, bioMérieux VIDAS hs-cTnI and Quidel Cardiovascular TriageTrue hs-cTn				
APACE Badertscher 2018[54]			NSTEMI; AMI; 30-day MACE	Gender, age (≤70 vs. >70 years), previous CAD, renal function

Details	Country	N	Target condition(s) reported	Subgroups reported
Badertscher 2018[55]				
Boeddinghaus 2017[$58]				
Boeddinghaus 2018[59]				
Boeddinghaus 2019[60]				
Boeddinghaus 2019[123]				
Boeddinghaus 2019[170]				
Boeddinghaus 2020[173]				
Cullen 2013*[156]				
Hoeller 2013*[168]				
Haaf 2012*[136]				
Hochholzer 2011*[149]				
Irfan 2013*[158]				
Jaeger 2016[74]				
Kaier 2017[75]				
Lindahl 2017[132]				
Potocki 2012*[140]				
Reichlin 2015[90]				
Reichlin 2015[91]				
Reiter 2011*[146]				
Reiter 2012*[138]				
Reichlin 2009*[167]				
Reichlin 2011*[145]				
Rubini Gimenez 2014[70]				
Rubini Gimenez 2015[92]				
Rubini Gimenez 2015[93]				
Rubini Gimenez 2016[94]				
Twerenbold 2017[105]				
Twerenbold 2017[103]				
Twerenbold 2017[104]				
Twerenbold 2018[106]				
Twerenbold 2018[107]				
Twerenbold 2019[108]				

Details	Country	N	Target condition(s) reported	Subgroups reported
Wildi 2016[111] Wildi 2019[113]				

* Publication included in the assessment report for DG15[7]

[$]Primary publication for citation

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

3.2.2 Study quality

We conducted a quality assessment of the two randomised controlled trials included in this assessment using the revised Cochrane Risk of Bias tool for Cluster Randomised Trials (RoB 2.0).[44] Results are shown in Table 4.

Table 4: Quality assessment of High-STEACS and **HiSTORIC**

	High-STEACS[99]	**HiSTORIC[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

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

The methodological quality of included diagnostic test accuracy (DTA) studies, which evaluated a single hs-cTn assay, was assessed using QUADAS-2.[45] Studies which provided data for two or more hs-cTn assays were assessed using QUADAS-2C.[46] The main potential sources of bias in the included diagnostic test accuracy 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,[7] but this was not the case for any of the new studies identified for this update. The results of QUADAS-2 and QUADAS-2C assessments are summarised in Tables 5 and 6; full QUADAS-2 or QUADAS-2C assessments for each study are provided in Appendix 3. A summary of the risks of bias and applicability concerns within each QUADAS-2 or QUADAS-2C domain is provided below.

Patient spectrum

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

All studies assessed using QUADAS-2C were rated 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 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 High-STEACS[66, 67] were rated as unclear risk of bias, with respect to the comparison between hs-cTn assays.

As with our previous systematic review, [7] 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, 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 from our previous systematic review were restricted to patients in whom STEMI had been excluded.[133, 137, 139, 144, 148, 157, 159] 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 further study had strict inclusion criteria which resulted in the inclusion of a very low risk population.[159] These four studies were not considered to be representative of the spectrum of patients with chest pain presenting to the emergency department and so were also rated as having high concerns regarding applicability. This assessment includes a further 13 which were restricted to patients in whom STEMI had been excluded.[58, 61, 62, 64, 68, 72, 80, 84, 96, 101, 115, 171, 176]

Index test

All but three[62, 68, 117] of the studies were rated as low risk of bias for the index as they reported data for at least one threshold that was pre-specified. Two studies were rated as high risk of bias on this domain because they reported data for optimised thresholds which were derived in the same population.[62, 117] As the reference standard (diagnosis of AMI or MACE) was generally interpreted after the high sensitivity Tn test blinding was not considered important for these studies. However, all but one[64] of the studies that compared two or more hs-cTn assays were rated as unclear risk of

bias with respect to the comparison, using QUADAS-2C, as no information was provided about whether index tests were interpreted blind to the results of other index tests. Inclusion criteria were very tightly defined in terms of the high sensitivity Tn 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 were rated as unclear risk of bias for reference standard because it was unclear whether the diagnosis of NSTEMI/AMI/MACE was made without knowledge of the high sensitivity Tn results.[61, 62, 100, 110, 133, 135, 137, 150, 165] One study, assessed using QUADAS-2C,[115] was rated as 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 taken from our previous systematic review had high concerns regarding the applicability of the reference standard.[137, 139, 141, 142, 147, 148, 150, 157, 161, 165] All new studies identified for this assessment had low concerns regarding the applicability of the reference standard.

Patient flow

Six of the studies that reported data for a single hs-cTn assay, assessed using QUADAS-2, were considered at high risk of bias for patient flow[110, 137, 141, 147, 157, 159] and a further three were considered at unclear risk of bias.[62, 102, 165] 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 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,[115, 172] High-STEACS[66, 67] and TRUST[64]) were rated as high risk of bias, with respect to at least one between assay comparison; in all cases, this was because the number of patients for whom hs-cTn results were available differed between assays.

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 2019[171]	☺	☺	☺	☺	☺	☺	☺
Aldous(2011)*[147]	☺	☺	☺	☹	☹	☺	☹
Aldous(2012)*[139]	☹	☺	☺	☺	☺	☺	☹
BACC, Neumann 2016[84]	☺	☺	☺	☺	☺	☺	☺
Body(2011)*[161]	?	☺	☺	☺	☹	☺	☹

Study	RISK OF BIAS				APPLICABILITY CONCERNS		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Body 2015[56]	☺	☺	☺	☺	☹	☺	☺
Cappellini 2019[62]	☺	☹	?	?	☺	☺	☺
Christ(2010)*[150]	☺	☺	?	☺	☹	☺	☹
CORE, Mokhtari 2016[119, 121]	☹	☺	☺	☺	☹	☺	☺
FASTER I and FAST II, Eggers(2012)*[137]	?	☺	?	☹	☹	☺	☹
Freund(2011)*[142]	☺	☺	☺	☺	☹	☺	☹
Huang 2015[72]	☺	☺	☺	☺	☺	☺	☺
Keller(2011)*[141]	☺	☺	☺	☹	☹	☺	☹
Kurz(2011)*[148]	?	☺	☺	☺	☹	☺	☹
Lin 2019[117]	☹	☹	☹	☺	☹	☺	☺
Melki(2011)*[144]	☹	☺	☺	☺	☹	☺	☺
Peacock 2018[89]	?	☺	☺	☺	☹	☺	☺
PITGORAS, Sanchis(2012)*[135]	☹	☺	?	☺	☹	☺	☺
QUART, Parsonage(2014)[88]	☹	☺	☺	☺	☹	☺	☺
RATPAC, Collinson(2013)*[159]	☺	☺	☺	☹	☹	☺	☺
REACTION-US, Nowak 2018[87]	☹	☺	☺	☺	☹	☺	☺
Saenger(2010)*[165]	?	☺	?	?	☹	☺	☹
Sebbane(2013)*[157]	?	☺	☺	☹	☺	☺	☹
Shiozaki 2017[100]	☹	☺	?	☺	☹	☺	☺
Slagman 2017[102]	?	☺	☹	?	?	☺	?
TRAPID-AMI, Mueller 2016[80]	?	☺	☺	☺	☺	☺	☺
TUSCA, Santalo(2013)*[133]	☺	☺	?	☺	☺	☺	?
UTROPIA, Sandoval 2017[96]	☺	☺	☹	☺	☺	☺	☺
Venge 2017[110]	?	☺	?	☹	☹	☺	☺

☺Low Risk ☹High Risk ? Unclear Risk

*Information taken from our previous systematic review[7]

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 2014[68]							

Study	RISK OF BIAS				APPLICABILITY CONCERNS		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Abbott ARCHIRECT hs-cTnI	☺	?	☺	☺	☺	☺	☺
Roche Elecsys hs-cTnT	☺	?	☺	☺	☺	☺	☺
Abbott ARCHIRECT hs-cTnI vs. Roche Elecsys hs-cTnT	☺	?	☺	☺			
APACE, Boeddinghaus 2018,[59] Boeddinghaus 2019,[170] Boeddinghaus 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 2019,[115] Body 2020[172]							
Roche Elecsys hs-cTnT	☺	☺	☹	☺	☺	☺	☺
Siemens ADVIA Centaur hs-cTnI	☺	☺	☺	☺	☺	☺	☺
Comparison of Roche Elecsys hs-cTnT vs. Siemens ADVIA Centaur hs-cTnI	☹	?	☹	☹			
High-STEACS, Chapman 2018,[66] Chapman 2019[67] (Comparison of assays using ESC 0/1 hour pathway, ESC 0/3 hour pathway and HghSTEACS 0/3 hour pathway)							
ARCHITECT hs-cTnI	☺	☺	?	☺	☺	☺	☺

Study	RISK OF BIAS				APPLICABILITY CONCERNS		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Siemens Atellica hs-cTnI	☺	☺	?	☺	☺	☺	☺
Comparison of ARCHITECT hs-cTnI vs Siemens Atellica hs-cTnI	?	?	?	☹			
HIGH-US, Sandoval 2019[176]							
Siemens Atellica hs-cTnI	☺	☺	☺	☺	☺	☺	☺
Siemens ADVIA Centaur hs-cTnI	☺	☺	☺	☺	☺	☺	☺
Comparison of Siemens Atellica hs-cTnI vs Siemens ADVIA Centaur hs-cTnI	☺	?	☺	☺			
ROMI-3, Shortt 2017[101]							
Abbott ARCHIRECT hs-cTnI	☺	☺	☺	☺	☺	☺	☺
Roche Elecsys hs-cTnT	☺	☺	☺	☺	☺	☺	☺
Abbott ARCHIRECT hs-cTnI vs. Roche Elecsys hs-cTnT	☺	?	☺	☺			
TRUST, Carlton 2015[64]							
Abbott ARCHIRECT hs-cTnI	☺	☺	☹	☹	☺	☺	☺
Roche Elecsys hs-cTnT	☺	☺	☹	☺	☺	☺	☺
Abbott ARCHIRECT hs-cTnI vs. Roche Elecsys hs-cTnT	☺	☺	☹	☹			

☺Low Risk ☹High Risk ? Unclear Risk

3.2.3 Randomised controlled trials comparing high sensitivity troponin assays to conventional troponin assays

Study details

Two randomised controlled trials (RCTs) were identified.[99, 175] The High-STEACS study, which contributed multiple diagnostic accuracy data sets, was a stepped-wedge, cluster randomised controlled trial, evaluating 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 randomised controlled trial, the HiSTORIC trial (un-

published 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 High-STEACS and HiSTORIC, is provided in Table 7.

Table 7: Summary of study details for included RCTs

	High-STEACS[99]	**HiSTORIC[175]**
No of patients	48282 (47% female)	31492 (45% female)
Location and setting	10 secondary and tertiary care hospitals in Scotland	7 acute hospitals in Scotland
Trial design	Stepped-wedge, cluster randomised controlled trial	
Study dates	June 2013 to March 2016	December 2014 to December 2016
Participant inclusion criteria	Patients presenting with suspected ACS and with paired cardiac troponin 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) CV < 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 (7 sites) and 50 ng/L (3 sites) at 6 and 12 hours	Serial testing at presentation and repeated 6 to 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 (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

ACS = acute coronary syndrome; CoV = coefficient of variation; CV = cardiovascular; ED = emergency department; MI = myocardial infarction; STEMI = ST-segment elevation myocardial infarction; URL = upper reference limit

Both studies 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 High-STEACS was 61

and in HiSTORIC was 59. HiSTORIC excluded patients with STEMI but High-STEACS did not. As both trials were conducted in Scotland, they are likely to be highly relevant to UK practice.

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

Efficacy results

In High-STEACS patients reclassified by the high sensitivity test were older (mean age (standard deviation [SD]) 75 (14)) compared to those identified by a cardiac troponin I assay (mean 70 (15)) 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. In High-STEACS 2586 (5%) had MI or death from cardiovascular causes at one year. Of 1771 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 vs. validation was 1.10: 95% confidence interval (CI) 0.75 to 1.61).[99] In HiSTORIC [redacted]).[175]

In High-STEACS 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 CV causes (cardiac and non-cardiac), hospital admission for heart failure and ischaemic stroke.[99]

In High-STEACS the Median length of stay was 7 hours (IQR 3 to 24) in the implementation phase as compared to 4 hours (IQR 3 to 20) in the validation phase.[99] In HiSTORIC [redacted][175]

The authors of High-STEACS concluded that, although implementation of a high sensitivity cardiac troponin assay resulted in reclassification of 17% of 10360 patients with myocardial injury or infarction, only a third had a diagnosis of type I MI and the incidence of subsequent MI or death from cardiovascular causes within one year was not affected by use of this assay.[99] [redacted] [175]

3.2.4 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,[7] and a further 17 studies,[56, 58, 61, 62, 64, 68, 72, 80, 87-89, 100-102, 115, 117, 121] newly identified or up-dated (new publications since our previous systematic review) provided data on the diagnostic performance of the Roche Elecsys hs-cTnT assay; one of these studies assessed the STAT version of the assay.[89] Twenty-six of the 30 studies in this section assessed the diagnostic performance of the Roche Elecsys hs-cTnT assay for the detection of AMI, and the remaining three studies assessed performance for the prediction of MACE within 30 days of the index presentation;[117, 121, 135] four studies provided data for both AMI and 30-day MACE.[56, 58, 64, 89] Eighteen studies provided data specific to the population of interest for this assessment; participants with STEMI were excluded, i.e. the target condition was NSTEMI rather than any AMI.[58, 62, 64, 68, 72, 80, 87, 100-102, 115, 133, 137, 139, 144, 148, 157, 159]

All but one[62] of the 26 studies which 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 reported data for the 99th centile for the general population,[56, 64, 68, 70, 72, 88, 100-102, 114, 133, 137, 139, 142, 144, 147, 148, 150, 157, 159, 161, 165] and 14 of these studies provided data for the target condition NSTEMI.[64, 68, 70, 72, 100-102, 133, 137, 139, 144, 148, 157, 159] Nine studies assessed the diagnostic performance of a LoD threshold (5 ng/L) in a single sample taken on presentation,[56, 63, 75, 87, 101, 114, 115, 139, 147] and six of these studies provided data for the target condition NSTEMI.[63, 75, 87, 101, 115, 139] Similarly, eight studies assessed the diagnostic performance of a LoB threshold (3 ng/L) in a single sample taken on presentation,[56, 63, 101, 114, 139, 150, 161, 167] and three of these studies provided data for the target condition NSTEMI.[63, 101, 139] 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 (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 which 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 (see Section 3.2.7). Key results used in the cost-effectiveness modelling conducted for this assessment are highlighted in bold. Table 6 also includes diagnostic performance estimates for pre-specified clinical subgroups, taken from single studies. Full results (including numbers of TP, FP, FN and TN test results), for all studies and all datasets, 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 90% (95% CI: 85 to 94%) and 78% (95% CI: 72 to 83%), 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 which excluded participants with STEMI; summary estimates of sensitivity and specificity were 90% (95% CI: 85 to 94%) and 77% (95% CI: 68 to 84%), respectively (SROC curve shown in Figure 3), based on 14 studies.[64, 68, 70, 72, 100-102, 133, 137, 139, 144, 148, 157, 159] 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 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%), based on data from three studies where the target condition was NSTEMI;[68, 139, 144] later sampling appears to be associated with improved rule-out performance at this threshold.

Figure 2: SROC for the Roche Elecsys hs-cTnT assay using the 99th centile threshold and a presentation sample, target condition any AMI (22 studies)

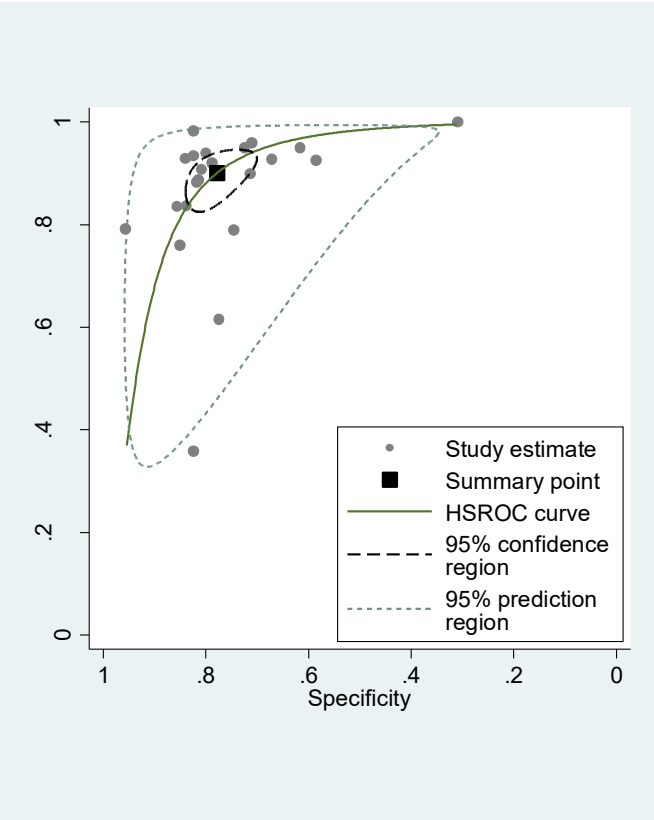


Figure 3: SROC for the Roche Elecsys hs-cTnT assay using the 99th centile threshold and a presentation sample, target condition NSTEMI (14 studies)

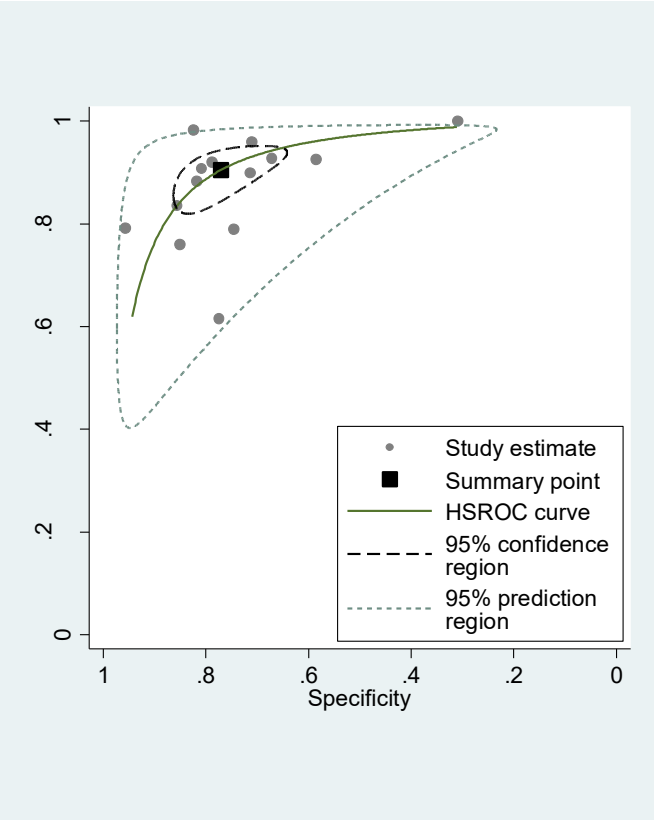


Figure 4: SROC for the Roche Elecsys hs-cTnT assay using the LoD threshold and a presentation sample, target condition any AMI (9 studies)

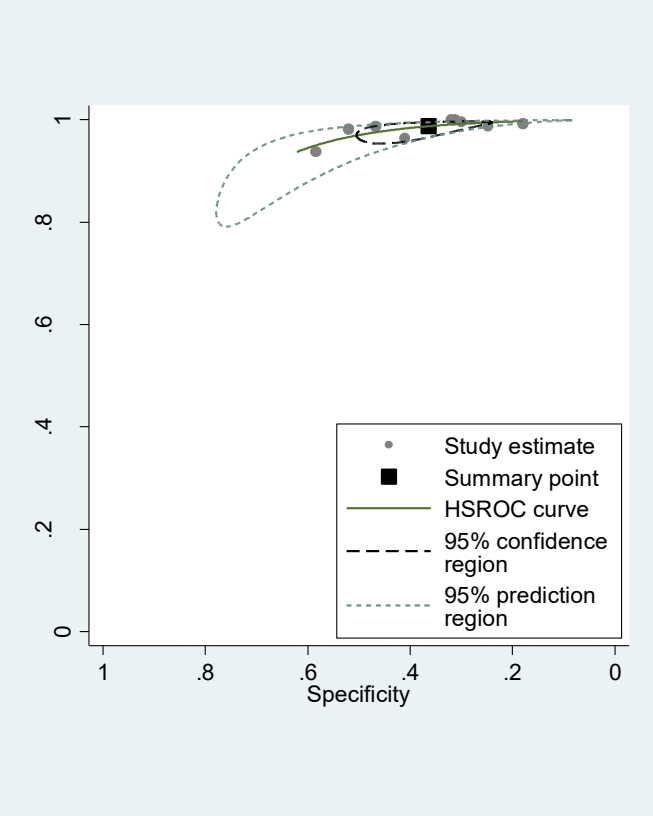


Figure 5: SROC for the Roche Elecsys hs-cTnT assay using the LoD threshold and a presentation sample, target condition any NSTEMI (6 studies)

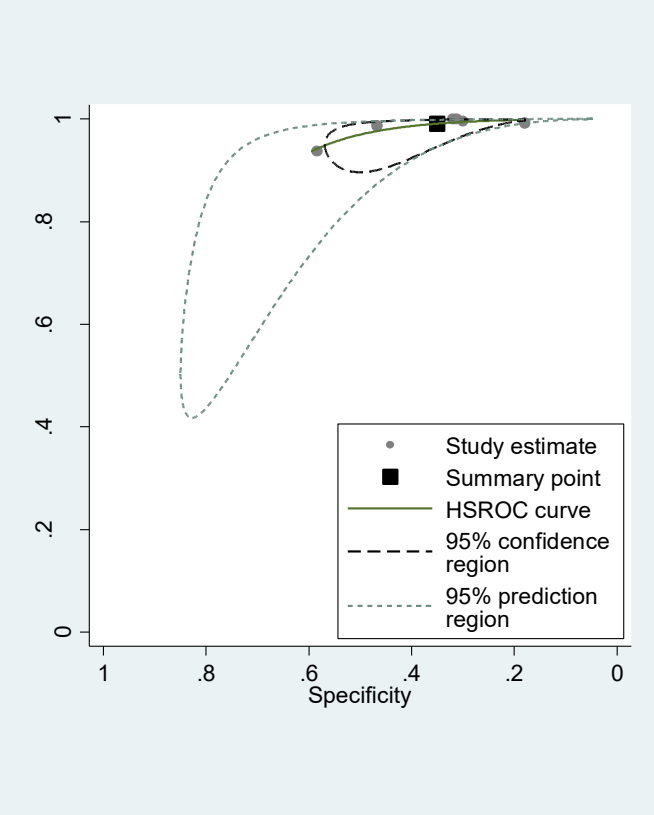
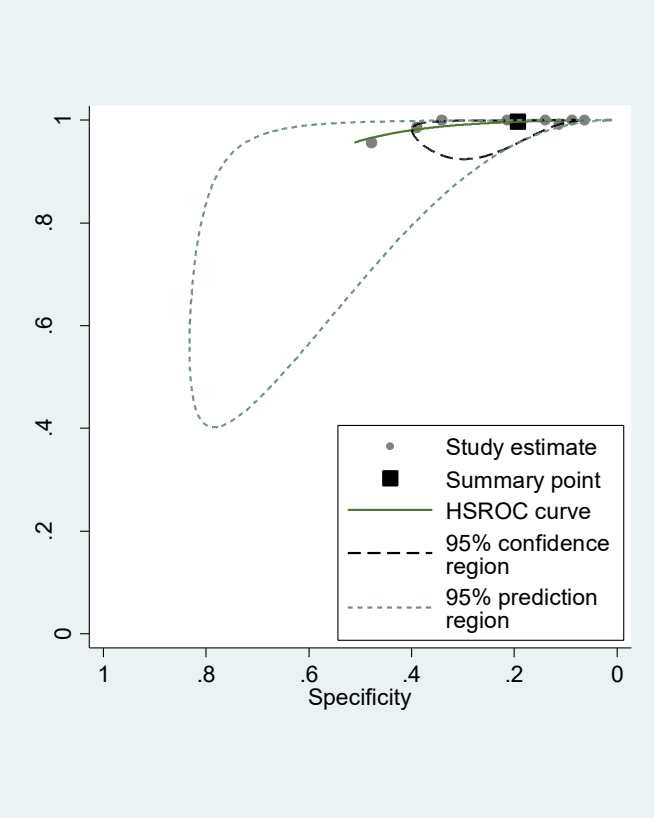


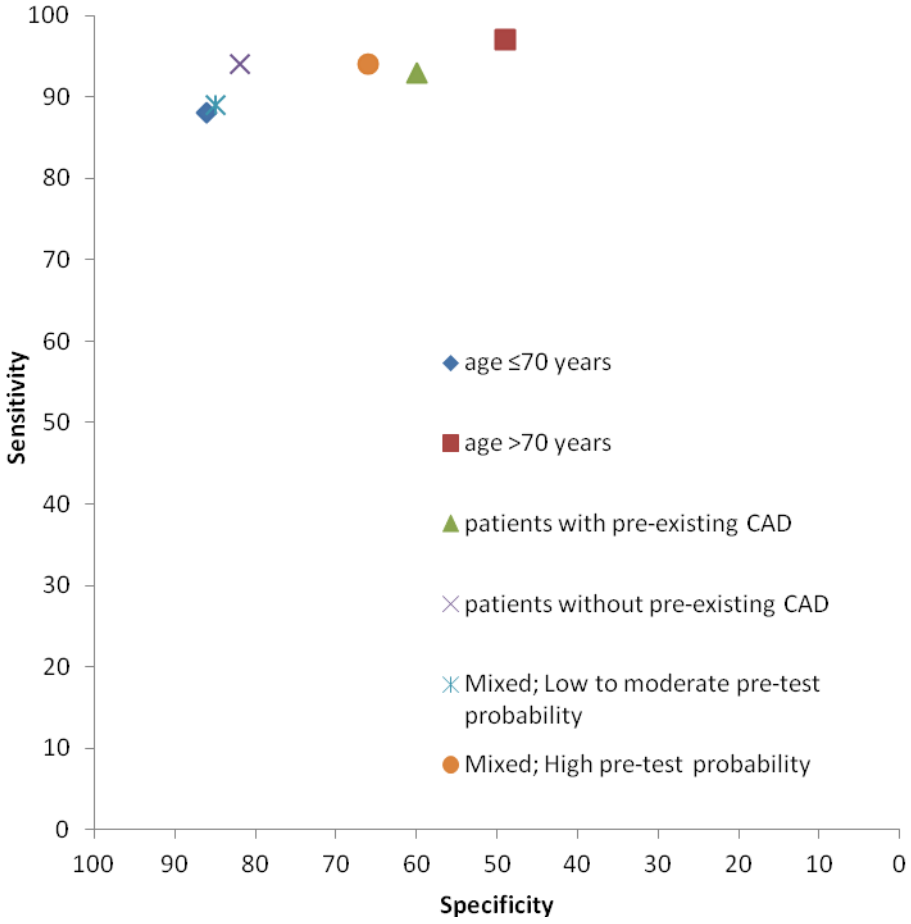
Figure 6: SROC for the Roche Elecsys hs-cTnT assay using the LoB threshold and a presentation sample, target condition any AMI (8 studies)



In our previous systematic review, limited data were identified on additional clinical subgroups (age >70 years versus ≤70 years,[146] without pre-existing CAD versus with pre-existing CAD,[140] and high versus low to moderate pre-test probability (determined by clinical judgement 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 which stratified participants by age,[146] reported a higher estimate of sensitivity (97% (95% CI: 92% to 99%)) in participants >70 years of age than for patients ≤70 years of age (88% (95% CI:78 to 94%); the estimate of sensitivity for people >70 years of age was also higher than the corresponding summary estimates derived from all 22 studies which used the 99th centile diagnostic threshold. A similar pattern was apparent for people with a high pre-test probability compared to those with a low to moderate pre-test probability[142] and for participants without pre-existing CAD compared to 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 22 studies which used the 99th centile diagnostic threshold, for people with a high pre-test probability and for people without pre-existing CAD. Figure 7 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 (older people (≥70 years), those without pre-existing CAD, and people classified by clinical judgement as having a high pre-test probability.

Figure 7: ROC space plot for the Roche Elecsys hs-cTnT assay using the 99th centile threshold and a presentation sample in different clinical subgroups



In addition to these studies, the current assessment identified one further study,[72] which 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, varies with renal function (see Table 8); these data show a marked decrease in specificity as renal function decreases.

Nine studies assessed the diagnostic performance of a LoD threshold (5 ng/L) in a single sample taken on presentation,[56, 63, 75, 87, 101, 114, 115, 139, 147] 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 (SROC curve shown in Figure 4). 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 providing data for the target condition NSTEMI (SROC curve shown in Figure 5).[63, 75, 87, 101, 115, 139] The eight studies that assessed the diagnostic performance of a LoB threshold (3 ng/L) in a

single sample taken on presentation,[56, 63, 101, 114, 139, 150, 161, 167] 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%), (SROC curve shown in Figure 6). 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,[7] and provide some indication that hs-cTnT testing on a single admission sample may be adequate to rule out any AMI or NSTEMI, where 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 which have been evaluated has substantially increased since our previous systematic review.[7] Our previous systematic review[7] included six studies that provided data on the performance of a variety of strategies involving multiple sampling,[133, 139, 143, 145, 151, 158, 165, 168] 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 two or three hours following presentation. The current assessment includes data for a total of 23 distinct multiple sample strategies using the Roche Elecsys hs-cTnT assay (6 for the STAT version of the assay), of which 14 were evaluated in populations which excluded patients with STEMI (target condition NSTEMI). Most strategies were evaluated by a single study; summary sensitivity and specificity estimates for strategies which were evaluated by more than one study are provided in Table 8. 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 (see Section 3.2.7). Key results used in the cost-effectiveness modelling conducted for this assessment are highlighted in bold. 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 to 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, 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 5/746 (0.67%) of 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, whilst the ESC 0/1 hour rule-out pathway did not miss any participants with NSTEMI at the index admission, 3/1420 (0.21%) of participants who met the rule-out criteria experienced MACE during 30-day 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 2 studies). 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 3 studies); 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, whilst the additional very early rule-out step (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 assessed the performance of one or more testing strategies, using the Roche Elecsys hs-cTnT assay, for the prediction of MACE within 30 days of the index presentation.[56, 63, 81, 89, 108, 117, 121, 135, 174] 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 which were assessed by more than one study. The sensitivity estimates for single sample strategies and the target condition MACE were generally slightly lower than those for the target conditions any AMI or MACE and specificity estimates were similar or lower, whilst 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).

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

Test strategy	Population	Target condition	Number of studies	Sensitivity (%)	Specificity (%)
Single sample strategies					
99th centile threshold (14 ng/L) at 0 h	All	Any AMI	22	90 (85,94)	78 (72, 83)
	All	NSTEMI	14	90 (85, 94)	77 (68, 84)
	All	MACE	2	81 (75, 86)	78 (76, 81)
	age ≤70 years	Any AMI	1[146]	88 (78, 94)	86 (83, 89)
	age >70 years	Any AMI	1[146]	97 (92, 99)	49 (44, 55)
	patients with pre-existing CAD	Any AMI	1[140]	93 (85, 97)	60 (55, 65)
	patients without pre-existing CAD	Any AMI	1[140]	94 (88, 97)	82 (79, 85)
	Mixed; Low to moderate pre-test probability	Any AMI	1[142]	89 (70, 97)	85 (79, 89)
	Mixed; High pre-test probability	Any AMI	1[142]	94 (77, 99)	66 (50, 79)
	Female	NSTEMI	1[94]	91 (85, 96)	79 (76, 82)
	Male	NSTEMI	1[94]	91 (87, 94)	79 (76, 81)
	patients with eGFR <30 mL/min/1.73 m^2	NSTEMI	1[72]	100 (83, 100)	13 (4, 29)
	patients with eGFR 30 to 59 mL/min/1.73 m^2	NSTEMI	1[72]	100 (96, 100)	47 (39, 55)
	patients with eGFR 60 to 89 mL/min/1.73 m^2	NSTEMI	1[72]	96 (91, 98)	72 (68, 76)
	patients with eGFR >90 mL/min/1.73 m^2	NSTEMI	1[72]	92 (83, 97)	84 (80, 87)
LoD (<5ng/L) at 0 h	All	Any AMI	9	99 (97, 99)	36 (28, 45)
	All	**NSTEMI**	**6**	**99 (97, 100)**	**35 (25, 46)**
	All	MACE	3	98 (95, 99)	32 (30, 34)
LoB (<3ng/L) at 0 h	All	Any AMI	8	100 (98, 100)	19 (11, 31)
	All	NSTEMI	3	98 (96, 99)	21 (19, 22)
	All	MACE	3	96 (93, 98)	17 (15, 19)
99th centile threshold (14 ng/L) at 2 h	All	NSTEMI	2	95 (92, 96)	81 (79, 82)
Multiple sample strategies					

Test strategy	Population	Target condition	Number of studies	Sensitivity (%)	Specificity (%)
ESC 0/1 hour pathway: (symptoms >3 hours AND <5 ng/L at 0 h) OR (<12 ng/L at 0 h AND Δ <3 ng/L at 0 to 1 h)	**All**	**NSTEMI**	**1[104]**	**99 (98, 100)**	**68 (67, 70)**
	All	MACE	2	99 (97, 100)	62 (61, 64)
	patients with normal renal function	NSTEMI	1[106]	99 (97, 100)	78 (76, 80)
	patients with impaired renal function (eGFR <60 mL/min/1.73 m^2)	NSTEMI	1[106]	100 (98, 100)	26 (22, 31)
(<14 ng/L at 0 h AND 2h) AND Δ <4 ng/L	All	NSTEMI	2	98 (96, 99)	74 (72, 76)
<12 ng/L at 0 h AND Δ <3 ng/L at 0 to 1 h	**All**	**NSTEMI**	**3**	**98 (97, 99)**	**73 (71, 74)**
<8 ng/L at 0 h AND Δ <3 ng/L at 0 to 0.5 h	**All**	**NSTEMI**	**1[87]**	**100 (93, 100)**	**45 (40, 49)**
99th centile threshold (<14 ng/L at 0 h AND 3 h)	**All**	**NSTEMI**	**1[148]**	**100 (89, 100)**	**77 (58, 90)**

Key results, used in cost-effectiveness modelling are highlighted in bold

AMI: acute myocardial infarction; CAD: coronary artery disease; eGFR: estimated glomerular filtration rate; ESC: European Sociaety of Cardiology; MACE: major adverse cardiac event; NSTEMI: non-ST segment elevation myocardial infarction

3.2.5 Diagnostic accuracy of the Abbott ARCHITECT hs-cTnI assay for the rule-out and diagnosis of AMI

Study details

Nine diagnostic cohort studies provided data on the diagnostic performance of the Abbott ARCHITECT hs-cTnI assay,[58, 61, 64, 68, 84, 96, 101, 110, 141] only one[141] of which was taken directly from our previous systematic review.[7] The remaining studies were newly identified or up-dated (new publications since our previous systematic review). All studies in this section assessed the accuracy of the Abbott ARCHITECT hs-cTnI assay for the detection of AMI and seven studies provided data specific to the population of interest for this assessment; participants with STEMI excluded, i.e. the target condition was NSTEMI.[58, 61, 64, 68, 84, 96, 101] Three studies also assessed the performance of the Abbott ARCHITECT hs-cTnI assay for the prediction of MACE within 30 days of the index presentation.[58, 61, 68]

All nine studies in this section reported data on the diagnostic performance of a single sample taken on presentation, for at least one threshold. Five studies reported data for the 99th centile for the general population,[58, 64, 68, 101, 110] and four of these studies provided data for the target condition NSTEMI.[58, 64, 68, 101] Four studies assessed the diagnostic performance of a LoD threshold (2 ng/L) in a single sample taken on presentation,[58, 68, 96, 101] 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 (any AMI or NSTEMI) reported data for a total of 33 different testing strategies (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 which 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 (see Section 3.2.7). Key results used in the cost-effectiveness modelling conducted for this assessment are highlighted in bold. Table 9 also includes diagnostic performance estimates for pre-specified clinical subgroups, taken from single studies. Full results (including numbers of TP, FP, FN and TN test results), for all studies and all datasets, 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%), based on data from 5 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 which excluded

participants with STEMI; summary estimates of sensitivity and specificity were 75% (95% CI: 64 to 84%) and 94% (95% CI: 90 to 96%), respectively (SROC curve shown in Figure 9), based on 4 studies.[58, 64, 68, 101] 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-offs (see Table 9). Data from this study also indicated that specificity is lower in patients with impaired renal function (eGFR <60 mL/min/1.73 m^2).

Four studies assessed the diagnostic performance of a LoD threshold (2 ng/L) in a single sample taken on presentation,[58, 68, 96, 101] 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 (SROC curve 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, where a lower diagnostic threshold (2 ng/L) is used.

Figure 8: SROC for the Abbott ARCHITECT hs-cTnI assay using the 99th centile threshold and a presentation sample, target condition any AMI (5 studies)

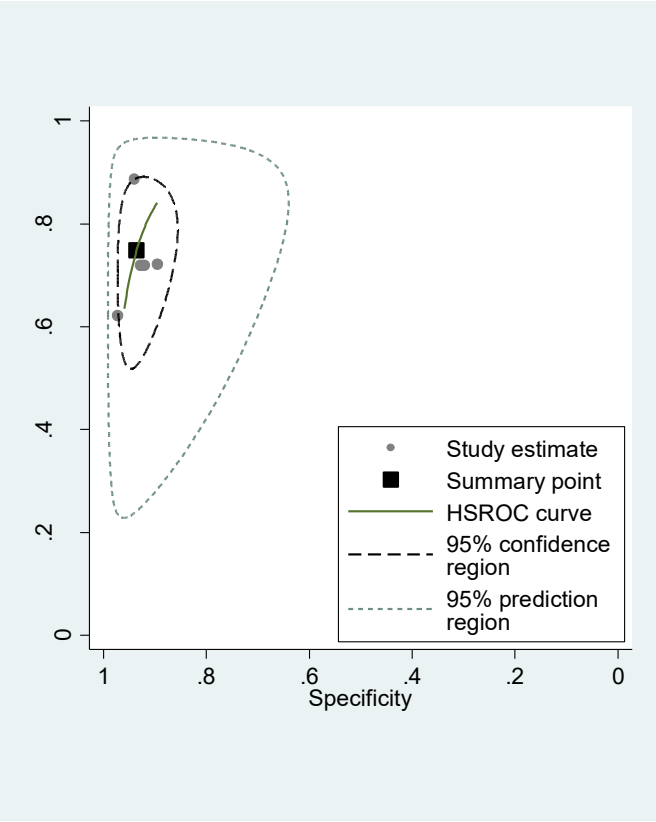


Figure 9: SROC for the Abbott ARCHITECT hs-cTnI assay using the 99th centile threshold and a presentation sample, target condition any NSTEMI (4 studies)

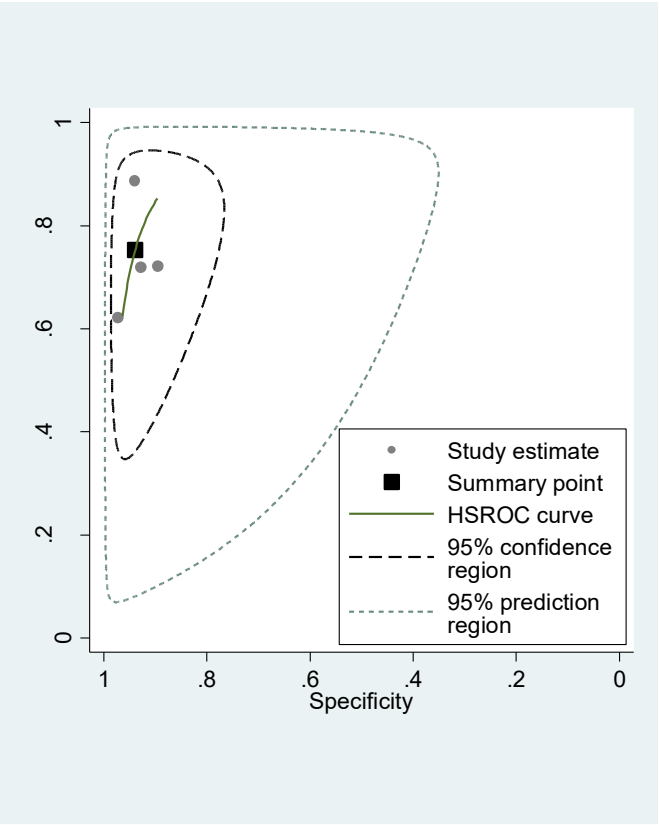
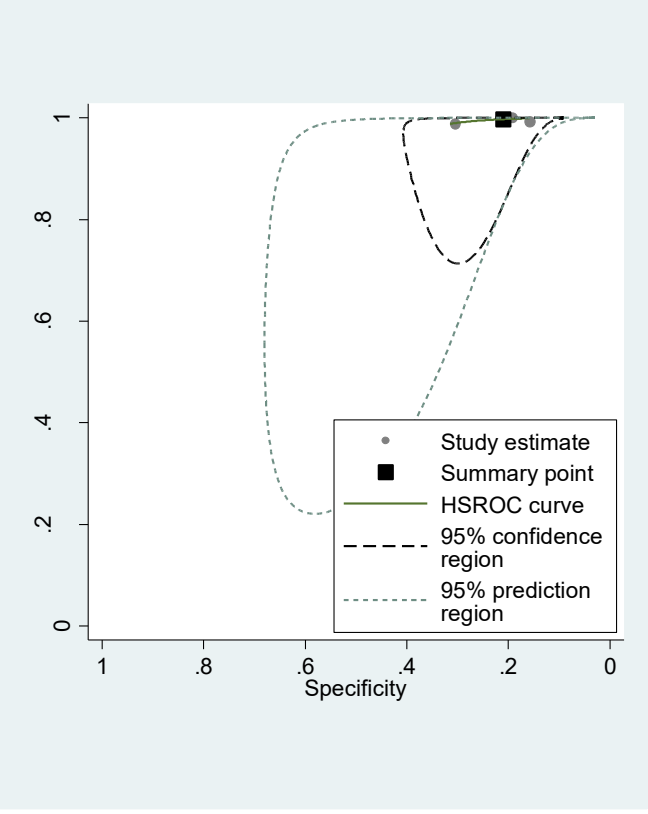


Figure 10: SROC for the Abbott ARCHITECT hs-cTnI assay using the LoD threshold and a presentation sample, target condition any NSTEMI (4 studies)



Multiple sample strategies

The number of multiple sample strategies/rule-out algorithms which have been evaluated has substantially increased since our previous systematic review.[7] Our previous systematic review[7] included only two studies that provided data on the performance of strategies involving multiple sampling.[141, 151] 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 which excluded patients with STEMI (target condition NSTEMI). Most strategies were evaluated by a single study; summary sensitivity and specificity estimates for strategies which were evaluated by more than one study are provided in Table 9. 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 (see Section 3.2.7). Key results used in the cost-effectiveness modelling conducted for this assessment are highlighted in bold. 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 to 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, 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 (2 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] 8/740 (1.08%) of people with NSTEMI were missed, based on the ESC 0/1 hour rule-out criteria. Subgroup analysis indicated a marked reduction in specificity when this strategy was used in people with impaired renal function (eGFR 60 mL/min/1.73 m^2), specificity 25% (95% CI: 20 to 30%).[106] The High-STEACS pathway, which combines 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 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, appears to be offer a further increase in specificity; the sensitivity and specificity estimates for this strategy were 99% (95% CI: 97 to 100%) and 76% (95% CI: 73 to 78%), respectively, for the target condition NSTEMI.[66] The overall rule-out rate for this

pathway was 64.9%, 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 2/275 (0.73%) of patients with NSTEMI. The same publication also provided data for the target condition MACE at 30-day follow-up (including MI at index admission), showing that a further 4 participants, i.e. 4/1244 (0.32%) of those who met the rule-out criteria, experienced MACE during the follow-up period.[66]

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

Prognostic accuracy

Three studies assessed the performance of one or more testing strategies, using the Abbott ARCHITECT hs-cTnI assay, for the prediction of MACE within 30 days of the index presentation. [58, 61, 68] 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, whilst specificity estimates were higher (see Table 7).

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

Test strategy	Population	Target condition	Number of studies	Sensitivity (%)	Specificity (%)
Single sample strategies					
99th centile threshold (26.2 ng/L) at 0 h	All	Any AMI	5	75 (65, 82)	94 (91, 96)
		NSTEMI	4	75 (64, 84)	94 (90, 96)
Sex specific 99th centile threshold (female 16 ng/L, male 34 ng/L at 0 h	patients with eGFR <60 mL/min/1.73 m^2)	NSTEMI	1[79]	99 (96, 100)	71 (67, 74)
	patients with eGFR ≥60 mL/min/1.73 m^2)		1[79]	99 (97, 100)	92 (91, 93)
	patients age ≥65 years with eGFR ≥60 mL/min/1.73 m^2		1[79]	98 (96, 100)	86 (84, 88)
	patients age ≥65 years with eGFR <60 mL/min/1.73 m^2		1[79]	98 (95, 100)	69 (65, 73)
	patients age <65 years with eGFR ≥60 mL/min/1.73 m^2		1[79]	99 (97, 100)	96 (95, 97)
	patients age <65 years with eGFR <60 mL/min/1.73 m^2		1[79]	100 (88, 100)	82 (72,89)
LoD (<2ng/L) at 0 h	**All**	**NSTEMI**	**4**	**100 (99, 100)**	**21 (16, 26)**
	All	MACE	1[61]	97 (95, 98)	39 (39, 40)
<4 ng/L at 0 h	**All**	**NSTEMI**	**2**	**99 (97, 100)**	**50 (48, 52)**
<5 ng/L at 0 h	All	NSTEMI	3	97 (95, 98)	58 (57, 59)
Multiple sample strategies					
ESC 0/1 hour pathway: (symptoms >3 hours AND <2 ng/L at 0 h) OR (<5 ng/L at 0 h AND Δ <2 ng/L at 0 to 1 h)	**All**	**NSTEMI**	**2**	**99 (98, 100)**	**57 (56, 59)**
	Normal renal function	NSTEMI	1[106]	99 (97, 100)	66 (64, 68)
	Impaired renal function (eGFR <60 mL/min/1.73 m^2)	NSTEMI	1[106]	99 (95, 100)	25 (20, 30)

Test strategy	Population	Target condition	Number of studies	Sensitivity (%)	Specificity (%)
High-STEACS pathway: (symptoms ≥2 h AND <5 ng/L at 0 h) OR (≤16 ng/L (F) ≤34 ng/L (M) at 3 h AND Δ <3 ng/L at 0 to 3 hours)	**All**	**NSTEMI**	**1[66]**	**99 (97, 100)**	**76 (73, 78)**
	Male	NSTEMI	1[65]	98 (93, 100)	88 (85, 91)
	Female			98 (92, 100)	87 (83, 90)
	Age <65 years			99 (93, 100)	94 (92, 96)
	Age ≥65 years			97 (92, 99)	78 (74, 82)
	Known ischaemic heart disease			96 (89, 99)	82 (78, 86)
	No known ischaemic heart disease			100 (97, 100)	92 (89, 94)
	All	MACE	1[66]	98 (97, 99)	81 (79, 83)

Key results, used in cost-effectiveness modelling are highlighted in bold

AMI: acute myocardial infarction; eGFR: estimated glomerular filtration rate; ESC: European Society of Cardiology; MACE: major adverse cardiac event; NSTEMI: non-ST segment elevation myocardial infarction

3.2.6 Diagnostic accuracy of the Beckman Coulter Access hs-cTnI assay

Study details

Two studies, the APACE study[58] and ADAPT/IMPACT[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 studies evaluating the Beckman Coulter Access hs-cTnI assay[60, 171] each assessed a different multiple sample strategy. One study reported data for a strategy which 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.[60] 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, 1/96 (1.04%) participants with NSTEMI were missed using the ESC 0/1 hour rule-out criteria.[60] The second study assessed a similar strategy, but with repeat testing at 2 hours.[64] The sensitivity estimates were similar for the two strategies, but the specificity of the 2 hour repeat testing startegy was higher than that of the 1 hour strategy (see Table 10). Full results (including numbers of true positive (TP), false positive (FP), false negative (FN) and true negative (TN) test results) are provided in Appendix 2, Table 37. Both strategies were selected for inclusion in our cost-effectiveness modelling.

3.2.7 Diagnostic accuracy of the Biomérieux VIDAS hs-cTnI assay

Study details

One diagnostic cohort study, which formed part of the APACE study,[58] provided data on the diagnostic performance of the Biomérieux VIDAS hs-cTnI assay.[132] 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 evaluating the Biomérieux VIDAS hs-cTnI assay assessed the performance of a repeat testing strategy, with samples taken on presentation and at two hours (see Table 11).[132] 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 Table11). 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, 2/87 (2.29%) of participants with NSTEMI were missed.[132] Full results (including numbers of true positive (TP), false positive (FP), false negative (FN) and true negative (TN) test results) are provided in Appendix 2, Table 37.

3.2.8 Diagnostic accuracy of the Ortho VITROS hs-cTnI assay

Study details

One diagnostic cohort study, 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 one 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 one hour <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%) (see 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 numbers of true positive (TP), false positive (FP), false negative (FN) and true negative (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.

3.2.9 Diagnostic accuracy of the Quidel TriageTrue hs-cTnI assay

Study details

One diagnostic cohort study, which formed part of the APACE study,[58] provided data on the diagnostic performance of the Quidel TriageTrue hs-cTnI assay.[173] 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 assessed the performance of a Quidel TriageTrue hs-cTnI assay[170] strategy incorporating measurements performed at baseline and at one 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 one hour <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%) (see 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 numbers of true positive (TP), false positive (FP), false negative (FN) and true negative (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.

3.2.10 Diagnostic accuracy of the Siemens ADVIA Centaur hs-cTnI assay

Study details

Three studies, APACE[58] BEST[115] and high-US[176] provided data on the diagnostic performance of the Siemens Healthineers ADVIA Centaur hs-cTnI assay. All three studies reported data for the target condition NSTEMI[59, 172, 176] and one study also assessed the performance of the Siemens ADVIA Centaur hs-cTnI assay for the prediction of MACE within 30 days of the index presentation.[176]

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, and the

high-US study[176] assessed the performace of three different thresholds (2 ng/L, 3 mg/L and 5 ng/L), in a single sample taken at presentation, for both NSTEMI and MACE. 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.

Multiple sample strategies

The APACE evaluated two different multiple sample strategies using the Siemens ADVIA Centaur hs-cTnI assay.[59] 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 1/114 (0.88%) of people with NSTEMI.[59] The second study assessed a similar strategy, but with higher thresholds and repeat testing at 2 hours.[59] The sensitivity estimates were similar for the two strategies, but the specificity of the 2 hour repeat testing startegy 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.

3.2.11 Diagnostic accuracy of the Siemens Atellica hs-cTnI assay

Study details

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

Single sample strategies

The high-US study[176] assessed the performace of three different thresholds (2 ng/L, 3 mg/L and 5 ng/L), in a single sample taken at presentation, for both NSTEMI and MACE. 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 (see Table 15).

Multiple sample strategies

The High-STEACS study assessed the diagnostic performance of three different multiple testing strategies for the target condiction NSTEMI.[67] 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 acceptible sensitivity criterion for inclusion in cost-effectiveness modelling; the sensitivity and specificty 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 (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 6/278 (2.16%) of participants with NSTEMI.[67]

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

Study details

One diagnostic cohort study, which formed part of the APACE study,[58] provided data on the diagnostic performance of the Siemens Healthineers Dimension Vista hs-cTnI assay.[74] This study assessed the accuracy of the Siemens Healthineers Dimension Vista hs-cTnI assay for the detection of AMI.[74] 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 Healthineers Dimension Vista hs-cTnI.[74] assessed the performance of an strategy incorporating measurements performed at baseline and absolute change within one 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 100% (95% CI: 89 to 100%). Specificity for males was 62% (95% CI: 57 to 66%) and for females 73% (95% CI: 66 to 79%). Full results (including numbers of true positive (TP), false positive (FP), false negative (FN) and true negative (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 (%)	Specificity (%)
Multiple sample strategies					
ESC 0/1 hour pathway: (symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <4 ng/L at 0 to 1 h)	**All**	**NSTEMI**	**1[60]**	**99 (94, 100)**	**70 (66, 74)**
(symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 ng/L at 0 to 2 h)			**1[171]**	**98 (92, 100)**	**83 (81, 86)**

Key results, used in cost-effectiveness modelling are highlighted in bold
ESC: European Society of Cardiology; NSTEMI: non-ST segment elevation myocardial infarction

Table 11: Accuracy of the Biomérieux VIDAS hs-cTnI assay: Summary estimates (95% confidence intervals)

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

Key results, used in cost-effectiveness modelling are highlighted in bold
NSTEMI: non-ST segment elevation myocardial infarction

Table 12: Accuracy of the Ortho VITROS hs-cTnI assay: Summary estimates (95% confidence intervals)

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

Key results, used in cost-effectiveness modelling are highlighted in bold
ESC: European Society of Cardiology; NSTEMI: non-ST segment elevation myocardial infarction

Table 13: Accuracy of the Quidel TriageTrue hs-cTnI assay: Summary estimates (95% confidence intervals)

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

Key results, used in cost-effectiveness modelling are highlighted in bold

ESC: European Society of Cardiology; NSTEMI: non-ST segment elevation myocardial infarction

Table 14: Accuracy of the Siemens ADVIA Centaur hs-cTnI assay: Summary estimates (95% confidence intervals)

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

Key results, used in cost-effectiveness modelling are highlighted in bold

ESC: European Society of Cardiology; MACE: major adverse cardiac event; NSTEMI: non-ST segment elevation myocardial infarction

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

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

Key results, used in cost-effectiveness modelling are highlighted in bold
ESC: European Society of Cardiology; MACE: major adverse cardiac event; NSTEMI: non-ST segment elevation myocardial infarction

Table 16: Accuracy of the Siemens Dimension Vista hs-cTnI assay: Summary estimates (95% CI)

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

Key results, used in cost-effectiveness modelling are highlighted in bold
NSTEMI: non-ST segment elevation myocardial infarction

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

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

Four studies, ADAPT,[68] APACE,[58] ROMI-3,[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 or both the 99th centile for the general population or LoD threshold and a single sample at presentation, for the target condition NSTEMI. Since data for these combinations of assay threshold and timing are reported, individually, by a number of additional studies (see Sections 3.2.4 and 3.2.5), it is possible to compare the estimates of relative sensitivity and specificity derived from indirect comparisons of summary estimates to those derived from direct, within study comparisons (see 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 were always ≥99%. The indirect comparison (based on summary estimates, and one of the two direct comparisons[75] 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 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 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 acute coronary syndromes in patients presenting without persistent ST-segment elevation.[34] 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] Orth 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 between Roche Elecsys hs-cTnT, Abbott ARCHITECT hs-cTnI and Siemens ADVIA Centaur hs-cTnI assays has been rated low risk of bias with respect to the flow and timing domain of QUADAS-2C, whilst the all tests comparison was rated high risk of bias (see Table 6, section 3.2.2). 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 which were derived from the particpant subgroup of the APACE study highlighted in bold. Data from the APACE study indicate that the ESC 0/1 hour rule-out pathway performs consistently accross 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] Because results for the two assays were published separately and neither assay was evaluated in all participants in the High-STEACS study, it is not clear that the same group of study participants received both assays. For this reason, the comparison has been rated high risk of bias with respect to the flow and timing domain of QUADAS-2C, whilst the all tests comparison was rated high risk of bias (see Table 6, section 3.2.2). 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 was lower using 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[34] 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 hence 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 (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. 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 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 (sub groups of the BEST study population); for this reason the comparison has been rated high risk of bias with respect to the flow and timing domain of QUADAS-2C (see Table 6, section 3.2.2). 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] whilst 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]

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

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

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

Table 19: Comparison between assays from the High-STEACS study (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 (%)	Specificity (%)
Abbott ARCHITECT hs-cTnI	ESC 0/1 hour: (symptoms >3 hours AND <2 ng/L at 0 h) OR (<5 ng/L at 0 h AND Δ <2 ng/L at 0 to 1 h)	100 (91, 100)	78 (73, 82)
Siemens Atellica hs-cTnI	ESC 0/1 hour: (symptoms ≥3 h AND <3 ng/L at 0 h) OR (<6 ng/L at 0 h AND Δ <3 ng/L at 0 to 1 h)	94 (79, 99)	69 (64, 74)
Abbott ARCHITECT hs-cTnI	ESC 0/3 hour: (symptoms ≥6 hours AND ≤16 ng/L (F) ≤34 ng/L (M) at 0 h) OR (≤16 ng/L (F) ≤34 ng/L (M) at 3 h) OR Δ <50% of 99th centile at 0 to 3 h	91 (87, 94)	74 (72, 77)
Siemens Atellica hs-cTnI	ESC 0/3 hour: (symptoms ≥6 hours AND ≤34 ng/L (F) ≤53 ng/L (M) at 0 h) OR (≤34 ng/L (F) ≤53 ng/L (M) at 3 h) OR Δ <50% of 99th centile at 0 to 3 h	90 (86, 93)	81 (79, 82)
Abbott ARCHITECT hs-cTnI	High-STEACS 0/3 hour: (symptoms ≥2 h AND <5 ng/L at 0 h) OR (≤16 ng/L (F) ≤34 ng/L (M) at 3 h AND Δ <3 ng/L)	99 (97, 100)	76 (73, 78)
Siemens Atellica hs-cTnI	High-STEACS 0/3 hour: (symptoms ≥2 h AND <5 ng/L at 0 h) OR (≤34 ng/L (F) ≤53 ng/L (M) at 3 h AND Δ <3 ng/L at 0 to 3 hours)	98 (95, 99)	74 (72, 76)

ESC: European Society of Cardiology

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 (%)	Specificity (%)
Siemens Atellica hs-cTnI	2 ng/L	100 (98, 100)	26 (24,28)
Siemens ADVIA Centaur hs-cTnI	2 ng/L	100 (99, 100)	23 (21, 25)
Siemens Atellica hs-cTnI	3 ng/L	99 (97, 100)	37 (35, 40)
Siemens ADVIA Centaur hs-cTnI	3 ng/L	99 (97, 100)	35 (33, 37)
Siemens Atellica hs-cTnI	5 ng/L	99 (97, 100)	53 (51, 55)

Siemens ADVIA Centaur hs-cTnI	5 ng/L	99 (97, 100)	52 (50, 54)

3.2.14 Selection of test strategies for inclusion in cost-effectiveness modeling

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

Each test strategy is defined by the combination of four factors: assay, of which there are nine, number (up to two) and timing (between zero and three hours) of tests and threshold concentration, of which there are many. This implies many tens of possible strategies to compare in the 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 QALYs, i.e.

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

According to these criteria, the final number of non-dominated strategies was over 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 there was a minimum acceptable sensitivity (maximum false negative 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:

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

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

4. ASSESSMENT OF COST-EFFECTIVENESS

This chapter explores the cost-effectiveness of hs-cTn assays (used up to four 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.

4.1 Review of economic analyses of hs-cTn assays

4.1.1 Search strategy

The search strategies detailed in section 3.1.1 to identify clinical effectiveness studies were also employed to identify any cost studies since 2013. Details of the databases searched for this update are provided in section 3.1.1, full strategies are available in Appendix 1. Search strategies utilised in the original report [7] 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 Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care[40] and the Cochrane Handbook for Diagnostic Test Accuracy Reviews.[42]

Additional top up searches were run to identify any specific cost studies from the UK utilising 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 between on 10.1.2020 for relevant UK cost studies from 2013 to the present:

- Medline ALL (Ovid): 1946 to 2020/01/09
- EMBASE (Ovid): 1974 to 2020/01/09
- Econlit (EBSCO): 2013-2020/09/01
- NHSEED (https://www.crd.york.ac.uk/CRDWeb/): 2013-March 2015

4.1.2 Inclusion criteria

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

4.1.3 Results

Five studies, identified in our previous assessment report,[7] are described below and summarised in Table 22.

Goodacre (2011)[181] and Fitzgerald (2011)[182]

This study was based on the multicentre pragmatic controlled trial 'Randomised Assessment of Treatment using Panel Assay of Cardiac Markers' (RATPAC).[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 co-morbidity. 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 the trial, with a time horizon of three 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 EQ-5D 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 uncertainty around the effect of the intervention upon the major adverse event rate could influence the potential cost-effectiveness of the intervention. The model used trial data to estimate costs and QALYs up to three months. Beyond this, lifetime cost and QALYs were estimated from a previous study.[183] It was assumed that patients who had died at three months would accrue no further costs or QALYs. Those who had survived non-fatal myocardial infarction (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 less than 1%. The decision-analytic model again resulted in higher costs and less effect for the point-of-care panel assay compared to standard care, also when extrapolated to lifetime survival. The

probability of the point-of-care panel assay being cost-effective for the three 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 was 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 (2012)[184]

This study aimed to assess the cost-effectiveness of an hs-cTnT assay, alone or in combination with the H-FABP assay 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 cost-effectiveness analysis (cost per life year (LY) gained and cost per AMI averted), using a health care perspective and a lifetime time horizon. One way and probabilistic sensitivity analyses were conducted.

The incremental cost-effectiveness ratio (ICER) for hs-cTnT compared to conventional cTnT was €3,748 per QALY gained. For hs-cTnT in combination with H-FABP compared to conventional cTnT the ICER was €5,717 per QALY gained. For LY and AMI averted, no ICERs were reported in the abstract. The probabilistic sensitivity analysis showed the hs-cTnT assay to be the preferable strategy with a probability of over 90%, at a ceiling ratio of €4,800 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 (2013)[185] *and Thokala(2012)*[186]

This study aimed to estimate the cost-effectiveness of using alternative biomarker strategies to diagnose MI, and using biomarkers, computed tomography coronary angiography (CTCA) and exercise ECG to risk-stratify troponin-negative patients. As the second aim was outside the scope of this review, we have only summarised the analysis which compares the biomarker strategies for diagnosing MI, 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, [187] as well as patients' arrival times during the day at the ED. The model assigned each patient a probability of re-infarction 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% coefficient of variation 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 one hour of the test results becoming available. For the 10-12 hours troponin measurement, three different scenarios were tested:

- 'doctor-on-demand' scenario, with medical staff available 24 hours a day to make a disposition decision within one hour of the results being available
- twice-daily ward round scenario, with medical staff only available at twice daily ward rounds to make disposition decisions
- 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 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 false-positives of the hs-cTn testing at presentation will still be discharged home after the 10 to 12-hour troponin test, but false negatives 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 re-infarction and death for patients with MI was based on a study by Mills et al.[188] Life expectancy of patients with MI and MI with re-infarction was estimated from Polanczyk et al,[189] while the utility of patients with MI was based on Ward et al.[190] The utility of patients with re-infarction 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.[190] One-way sensitivity analyses were

performed, as well as a probabilistic sensitivity analysis. 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 £7,487–£17,191 per QALY). The exception was a scenario involving patients without known CAD and doctor available on demand to discharge the patient, where, 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 per 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[191]

This report 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: hs-cTnT, hs-cTnI, and cTnI. As cTnT is no longer available in Canada, it was not taken into account in the analysis. The target population consisted of 65-year old patients 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 which 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 one 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 six 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 a patient had NSTEMI and whether they were treated early, treated late, or untreated (in the case of false negative test results). Those not suffering from NSTEMI were further stratified into unstable angina (UA) or not having acute coronary syndrome (non-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 which 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 six hours later. After the second cTn test, 90% of these false negatives were assumed to become true positives.

Short-term mortality rates and relative risks for treated/non-treated were taken from published clinical studies and one non-referenced study. The relative risk for late versus 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 probabilistic sensitivity analysis.

The base-case results indicated that hs-cTnI was dominated by hs-cTnT, when compared to cTnI, at an ICER of $119,377 per QALY. The probabilistic sensitivity analysis showed that, for willingness-to-pay thresholds up to $124,000, cTnI had the highest probability of being cost-effective. For thresholds over $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 $119,377 or more, otherwise cTnI would be the most cost-effective test. However, there was a lot of uncertainty in results when model assumptions were changed.

Collinson (2013)[159]

This study used the decision tree developed in the related HTA by Goodacre et al[185] to compare the cost-effectiveness of five diagnostic strategies to a hypothetical cohort of patients presenting to hospital with symptoms suggestive of myocardial infarction but with no diagnostic ECG changes, no known history of coronary heart disease and no major co-morbidities requiring inpatient treatment. Essentially, this was a sub-study of the point-of-care arm of the RATPAC trial. All methods and model inputs were identical to the study by Thokala et al [186] and the HTA report by Goodacre et al,[185] but with slightly different strategies applied to the cohort of patients:

- No testing: discharge all patients without treatment (theoretical ‘zero’ option)
- High-sensitivity cTnT at presentation: discharge home if test is negative or admit to hospital for troponin-testing at 10-12 hours if positive
- High-sensitivity 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

- High-sensitivity 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
- Standard troponin testing at 10-12 hours (current standard as per NICE guidelines)

The difference with the other studies is in the addition of H-FABP in the 3rd strategy and in the second high-sensitive troponin test at 90 minutes in the 4th 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 again the reference standard.

At the £20,000 per QALY threshold, 10-hour troponin testing was cost-effective (£12,090 per QALY) in the doctor-on demand scenario, but not in the other scenarios (once-daily ward round and twice-daily ward rounds), when high-sensitivity 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 per QALY), whereas the troponin T and H-FABP measurement at presentation strategy was cost-effective (£14,806 per 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 only in the doctor-on-demand scenario (£24,327 per QALY). The overall conclusion was that 10-hour troponin testing is likely to be cost-effective compared with rapid rule-out strategies only 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. Handsearching identified an additional seven potentially relevant papers but after title and abstract screening these were excluded as these were not full cost-effectiveness studies (n=4),[193-196] or cost-effectiveness studies (n=3),[197-199] not focussed on the UK.

Ambavane (2017)[192]

This UK study used patients (enrolled in the TRAPID-AMI study), who presented to the ED with acute chest pain, to assess the cost-effectiveness of a one-hour rule-out and rule-in algorithm, using hs-cTnT testing, in comparison with standard care. The study reported that the one-hour algorithm had

higher sensitivity (87% vs 69%) but lower specificity (96% vs 97%) than standard care. Total costs were reduced for the one-hour algorithm compared with standard care (£2,480 vs £4,561); 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 have found that the question of whether hs-cTn testing is cost-effective cannot be answered unequivocally. In favour of hs-cTn testing, the abstract by Vaidya et al[184] concluded that hs-cTnT testing is 'very cost effective' and the study by Goodacre[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' (p.xv). 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.

Table 22: Summary of included cost-effectiveness studies

Study details	Goodacre et al (2011)[181] Fitzgerald et al[182]	Vaidya et al[184]	Thokala et al[186] Goodacre et al (2013)[185]	CADTH report[191]	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 ST-segment elevation ECG who require cTn testing for diagnosis of NSTEMI	Patients presenting to hospital with symptoms suggestive of myocardial infarction but with no diagnostic ECG changes (ST deviation >1 mm or T-wave inversion > 3mm), no known history of coronary heart disease and no major comorbidities requiring inpatient treatment
Time horizon	Lifetime	Lifetime	Lifetime	Lifetime	Lifetime
Objective	Estimate the cost-effectiveness of the point-of-care panel in terms of mean costs and QALYs accrued compared with standard care	Assess the cost-effectiveness of a high-sensitive troponin T assay (hs-cTnT), alone or combined with the H-FABP assay in comparison with the conventional cardiac troponin (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 cardiac troponin 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 2013 Goodacre report[185], the RATPAC trial[159] was used for sampling patient characteristics, Mills[188] for risk of re-infarction and death, Polanczyk[200] for life expectancy of patients with MI and re-MI	Sensitivity and specificity from review performed in same report. Proportion 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 re-infarction based on Mills et al[188]. Source for long-term survival and QALYs not specified

Study details	Goodacre et al (2011)[181] Fitzgerald et al[182]	Vaidya et al[184]	Thokala et al[186] Goodacre et al (2013)[185]	CADTH report[191]	Collinson et al[159]
Comparators	Diagnostic assessment using the point-of-care biochemical marker panel Conventional diagnostic assessment without the panel	Conventional cTnT hs-cTnT hs-cTnT combined with H-FABP	No biochemical testing: discharge all patients without treatment (hypothetical) Standard troponin assay measured at presentation using the 10% coefficient of variation 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 10h 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; PSSRU unit costs	No information	Admission and treatment were based on the national tariff. Lifetime costs for MI patients were taken from Ward[190]. The price of a troponin test was taken from the 2011 Goodacre	Costs of hospital admission were based on the Ontario Case Costing Initiative database and the Ontario Schedule of Benefits for Physician	Hospital stay and treatment for MI based on NHS reference cost, biochemical testing based on Goodacre et al[181]

Study details	Goodacre et al (2011)[181] Fitzgerald et al[182]	Vaidya et al[184]	Thokala et al[186] Goodacre et al (2013)[185]	CADTH report[191]	Collinson et al[159]
			report[181]	Services. Costs of ED visits were based on a hospital in Soutwestern Ontario and the Ontario Schedule of Benefits. Unit prices of cTn tests were based on information provided by the manufacturers.	
Measure of benefit	QALY	AMI survivor	QALY	QALY	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 dept 1 hour delay between presentation and start biomarker sampling After short term (test-treatment-outcome), progress only depends on whether or not patient had MI, and whether or not this	No information	10 h troponin testing has perfect sensitivity and specificity (since it is the reference standard) 2 h delay from the time at which sampling could be performed to results available For presentation testing strategies: decision made within 1h of results available For 10h testing strategies: decision made according to scenario applied	Non-NSTEMI patients are further classified into Unstable Angina (UA) or non-ACS, with consequences for costs and outcome There is a small survival benefit (RR 1.01) of treating early compared to treating late (presentation testing vs. standard testing)	10 h Troponin testing has perfect sensitivity and specificity (since it is the reference standard) Presentation blood tests taken in ED and results available and decision made within 2h of sampling For testing at 10-12h delays according to scenario used

Study details	Goodacre et al (2011)[181] Fitzgerald et al[182]	Vaidya et al[184]	Thokala et al[186] Goodacre et al (2013)[185]	CADTH report[191]	Collinson et al[159]
	was treated		Diagnostic strategy only influences outcomes among patients with MI		
Perspective	NHS	Healthcare	NHS	Publicly funded health care system	NHS in England and Wales
Discount rate	Not mentioned	No information	Nothing mentioned	5% discount rate applied to costs and QALYs	Nothing mentioned
Uncertainty around cost-effectiveness ratio expressed	iCE plane, probability of strategy being dominated/cost-effective	Cost-effectiveness acceptability curves (not shown in abstract)	Cost-effectiveness acceptability curves for probabilistic sensitivity analysis (PSA) results, per scenario	As reported in outcomes of one-way sensitivity analyses, and also (for PSA) In cost-effectiveness acceptability curves	Cost-effectiveness acceptability curves
Sensitivity analysis	Probabilistic sensitivity analysis	One way and probabilistic	One-way sensitivity analyses, scenario analyses (doctor on demand, twice-daily ward round, and once daily ward-round), and PSA		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 Lys/QALYs) per comparator	Empirical 3 months PoC £ 1217 QALY 0.158 SC £ 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 Pres standard trop, 10% CV £ 1,560,361 QALY 26,345 Pres standard trop, 99th perc £ 1,609,760 QALY 26,352 Pres hs-trop, 99th perc £ 1,806,910 QALY 26,279 10h troponin £ 2,016,540 QALY 26,286	cTnI $ 2,018 QALY 8.1385 hs-cTnI $ 2,082 QALY 3.1389 hs-cTnT $ 2,186 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 min £ 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

Study details	Goodacre et al (2011)[181] Fitzgerald et al[182]	Vaidya et al[184]	Thokala et al[186] Goodacre et al (2013)[185]	CADTH report[191]	Collinson et al[159]
Summary of incremental analysis	*Empirical 3 months:* Increment PoC vs SC £211 QALY -0.00282 Probability PoC cost-effective at £20,000/QALY = 0.4% *Decision model 3 months:* Increment PoC vs SC £169 QALY -0.002 Probability PoC cost-effective at £20,000/QALY = 22.3% *Decision model lifetime:* Increment PoC vs SC £329 QALY -0.087 Probability PoC cost-effective at £20,000/QALY = 33.6%	Hs-cTnT vs cTnT: incr 111 Euros and 16-17 lives per 1,000 AMI ICER 3,748 Euro/QALY Hs-cTnT + H-FABP vs cTnT: incr 178 Euros ICER 5,717 Euro /QALY	For doctor-on-demand scenario: Pres standard trop. 10% CV vs no testing: £ 5030/QALY Pres standard trop 99th perc vs pres standard trop 10% CV: £ 6518/QALY Pres hs-trop 99th perc vs pres standard trop 99th perc: £ 7487/QALY 10h trop vs pres hs-trop 99th perc: £ 27,546/QALY	cTnI reference hs-cTnI incr costs $64 incr QALYs 0.000352 dominated (by extension) hs-cTnT incr costs $168 incr QALYs 0.001408 ICER $119,377/QALY	No testing – reference strategy hs-cTnT compared to no testing ICER £ 5012/QALY hs-cTnT at presentation and at 90 minutes: dominated hs-cTnT and H-FABP compared to hs-cTnT at presentation: ICER £11,026/QALY (as reported bu t correct number should be 10,871) 10-hour troponin compared to Hs-cTnT and H-FABP: ICER £12,090/QALY Conclusion: if a rapid-rule out strategy with a sensitivity of 95% (and specificity of around 90%) would be available, then a 10-hour troponin strategy does not seem cost-effective

4.2 Model structure and methodology

4.2.1 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 (HF) 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 major adverse cardiac events, particularly cardiac death and re-infarction.

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, using more sensitive troponin tests, for the early rule-out of NSTEMI (within the four-hour NHS emergency department target).[201]

Chapter 3 of this report summarises evidence about the clinical effectiveness of the various hs-cTn test strategies reported in the literature and section 3.2.14 describes the process used to select strategies for inclusion in the economic model. For the economic model, only high sensitivity troponin tests that had a sensitivity of 97% or above 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:

1. Roche Elecsys hs-cTnT (99th centile threshold (<14 ng/L at 0 h AND 3 h))
2. Roche Elecsys hs-cTnT (LoD (<5ng/L) at 0 h)
3. Roche Elecsys hs-cTnT (ESC 0/1 hour pathway: (symptoms >3 hours AND <5 ng/L at 0 h) OR (<12 ng/L at 0 h AND Δ <3 ng/L at 0 to 1 h))
4. Roche Elecsys hs-cTnT (<8 ng/L at 0 h AND Δ <3 ng/L at 0 to 0.5 h)
5. Roche Elecsys hs-cTnT (<12 ng/L at 0 h AND Δ <3 ng/L at 0 to 1 h)
6. Siemens Dimension Vista hs-cTnI (<5 ng/L at 0 h AND Δ <2 ng/L at 0 to 1 h)
7. Abbott ARCHITECT hs-cTnI (LoD (<2ng/L) at 0 h)
8. Abbott ARCHITECT hs-cTnI (ESC 0/1 hour pathway: (symptoms >3 hours AND <2 ng/L at 0 h) OR (<5 ng/L at 0 h AND Δ <2 ng/L at 0 to 1 h))

9. Abbott ARCHITECT hs-cTnI (High-STEACS pathway: (symptoms ≥2 h AND <5 at 0 h) OR (≤16 (F) ≤34 (M) at 3 h AND Δ <3))
10. Abbott ARCHITECT hs-cTnI (<4 ng/L at 0 h)
11. Siemens ADVIA Centaur hs-cTnI (<2 ng/L at 0 h)
12. Siemens ADVIA Centaur hs-cTnI (<3 ng/L at 0 h OR (<8 ng/L at 0 h AND Δ <7 ng/L at 0 to 2 h))
13. Siemens ADVIA Centaur hs-cTnI (ESC 0/1 hour pathway: (symptoms >3 h AND <3 ng/L at 0 h) OR (<6 ng/L at 0 h AND Δ <3 at 0 to 1 h))
14. Siemens ADVIA Centaur hs-cTnI (<5 ng/L at 0 h)
15. Siemens Atellica hs-cTnI (<2 ng/L at 0 h)
16. Siemens Atellica hs-cTnI (High-STEACS pathway: (symptoms ≥2 h AND <5 at 0 h) OR (≤34 (F) ≤53 (M) at 3 h AND Δ <3))
17. Beckman Coulter ACCESS hs-cTnI (ESC 0/1 hour pathway: (symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <4 at 0 to 1 h))
18. Beckman Coulter ACCESS hs-cTnI ((symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h))
19. Ortho VITROS hs-cTnI (ESC 0/1 hour pathway: (symptoms >3 h AND <1 ng/L at 0 h) OR (<2 ng/L at 0 h AND Δ <1 at 0 to 1 h))
20. bioMérieux VIDAS hs-cTnI (<2 ng/L at 0 h OR (<6 ng/l at 0 AND 2 h))
21. Quidel TriageTrue hs-cTnI (ESC 0/1 hour pathway: (symptoms >3 h AND <4 ng/L at 0 h) OR (<5 ng/L at 0 h AND Δ <3 at 0 to 1 h))

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 an hs-cTn test but negative on the standard troponin would be classified as false positives. 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, but 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.[202] A secondary analysis was therefore performed, which attributed a higher risk of adverse events (MI and mortality) to a proportion of patients testing false positive with the hs-cTn test.

Based on the available evidence, two analyses were performed:

- Base case analysis

- Secondary analysis, assuming that false positives in the hs-cTn testing strategies do not have the same risk for adverse events as true negatives. 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 with positive hs-cTn but a negative standard troponin is higher than the patients testing negative on both the hs-cTn test and the standard troponin, but lower than risk of adverse events in patients diagnosed with NSTEMI (i.e. both positive hs-cTn and standard troponin).

4.2.2 Model structure

An identical model structure as reported in the initial diagnostic assessment report[7] 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 and quality adjusted life years (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 emergency department with suspected NSTE-ACS, including patients with NSTEMI and patients without NSTEMI, who are further subdivided into 'no ACS, no unstable angina (UA)' and 'UA'. For this purpose, a decision tree and a state-transtition 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 14.

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

- No acute coronary syndrome and no unstable angina (no ACS, no UA)
- Unstable angina
- Post AMI (treated and untreated)
- Post AMI with re-infarction
- Death

In short, patients presenting at the ED with suspected NSTE-ACS were classified as either true positive, false positive, false negative or true negative. True positive patients were considered to be correctly treated for AMI whilst true negatives were considered not to be treated for AMI (true negative patients can be with or without UA). False positive patients were considered to be those who have no AMI, but who did not meet early rule-out criteria. It was assumed that false positive patients would remain in the hospital longer (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 false positive patients was, in the base case analysis, equal to the life expectancy, quality of life and costs of true negative patients. Finally, false negative patients were assumed to have untreated AMI with consequently increased re-infarction and mortality probabilities for one year.

Figure 11: Decision tree structure

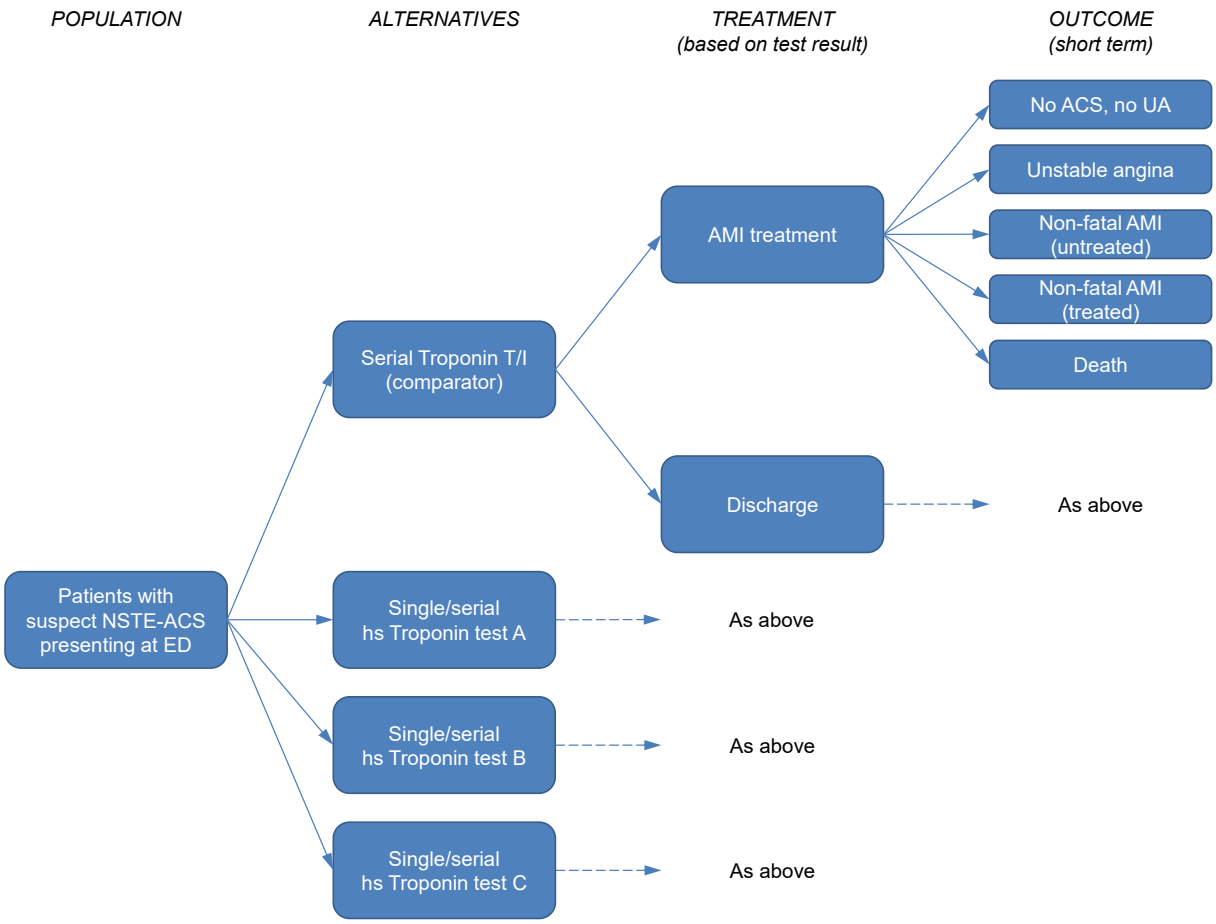
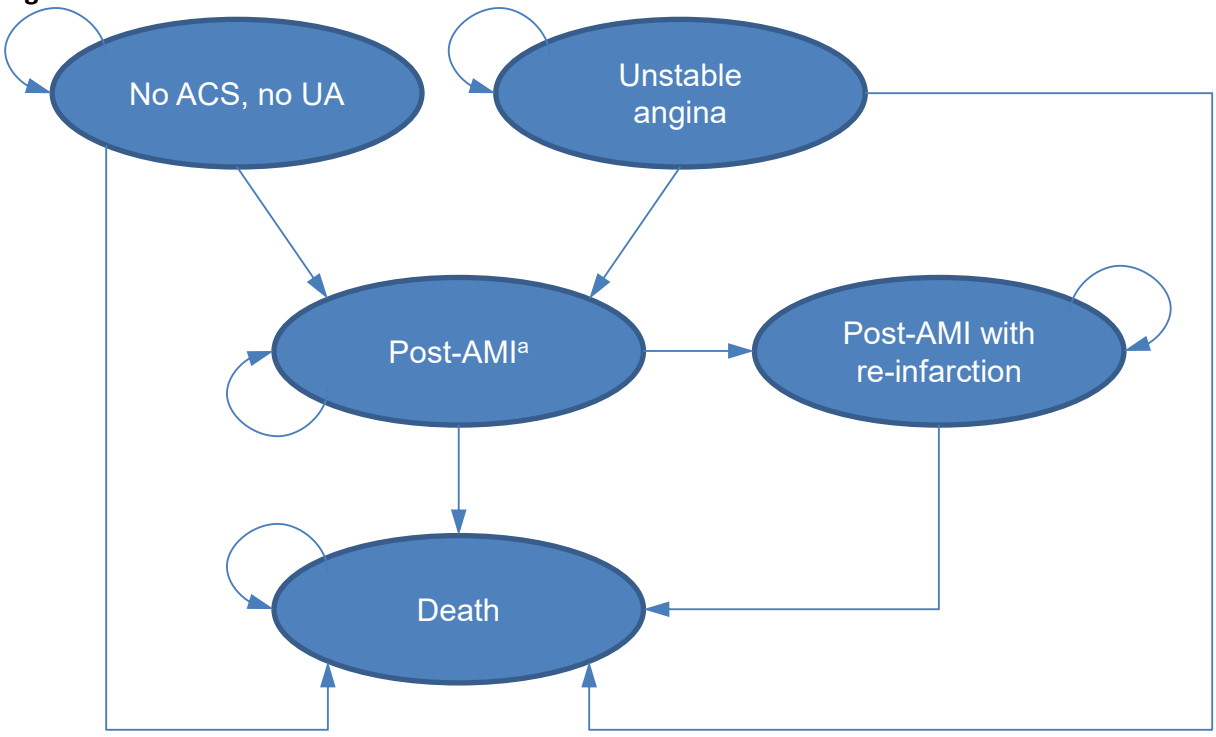


Figure 12: State-transition model structure



[a] During the first year post-AMI a distinction is made between treated and untreated AMI.

4.2.3 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

	Estimate	Se / 95% CI	Distribution	Source
Decision tree (short term)				
Proportion of AMI of all chest pain emergency admissions	0.199	0.001	Beta	Hospital Episode Statistics [4]
Proportion of NSTEMIs of all confirmed cases of heart attack	0.613	0.002	Beta	Healthcare Quality Improvement Programme[203]
NSTEMI prevalence[a]	0.122			Calculated
Proportion of UA (of all non-NSTEMI patients)	0.160	0.038	Beta	CADTH (2013)[191]
Decision tree (30-day) probabilities				
Mortality (30-day) treated AMI	0.097	0.012	Beta	Pope (2000)[204]
Mortality (30-day) untreated AMI	0.105	0.069	Beta	Pope (2000)[204]
Mortality (30-day) treated UA	0.021	0.005	Beta	Pope (2000) [204]
Mortality (30-day) no ACS	[b]	-	Fixed	ONS[205]
State-transition model (long term)				
AMI incidence	[c]	-	Fixed	British Heart Foundation[206]
Annual re-infarction (treated)[d]	0.023	0.001	Beta	Smolina (2012)[207]
RR re-infarction (untreated versus treated)[e]	2.568	1.366 - 5.604	LogNormal	Mills (2011)[188]
Annual mortality no ACS	[b]	-	Fixed	ONS[205]
Annual mortality post-MI[d]	0.066	0.000	Beta	Smolina (2012) [207]
Annual mortality post re-infarction[d]	0.142	0.002	Beta	Smolina (2012)[207]
HR mortality (UA versus NSTEMI)	0.781	0.581 - 1.053	LogNormal	Allen (2006)[208]
RR mortality (untreated versus treated)[d]	1.877	0.951 - 4.239	LogNormal	Mills (2011)[188]
Secondary analysis (adjusted relative risk for patients tested false positive)				
OR AMI[f]	1.210	0.830 – 1.760	LogNormal	Liplinski (2015)[202]
OR Death[f]	1.600	1.140 – 2.240	LogNormal	Liplinski (2015)[202]
Proportion of AMI[g]	0.109	0.011	Beta	Liplinski (2015)[202]

Proportion of Death[g]	0.110	0.011	Beta	Liplinski (2015)[202]
RR AMI[f, h]	0.842		Calculated	Liplinski (2015)[202]
RR Death[f, h]	0.652		Calculated	Liplinski (2015)[202]

ACS: acute coronary syndrome; AMI: acute myocardial infarction; HR: hazard ratio; NSTEMI: non-ST segment elevation myocardial infarction; OR: odds ratio; RR: relative risk; UA: unstable angina

[a] Prevalence was used to calculate the proportions of true/false positives/negatives 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 re-infarction and mortality risk for untreated (versus treated) was assumed for the 1st year after presentation at ED, after which no increased risk was assumed (RR = 1.0).

[f] For patients with both positive high sensitivity and standard troponin tests versus patients with positive high sensitivity and negative standard troponin tests.

[g] Proportion for patients with both positive high sensitivity and standard troponin tests. This proportion is only used to convert odds ratios to relative risks.

[h] ORs were converted to RRs using the method described by Zhang and Yu.[209]

Decision tree

The proportions of patients testing positive or negative (and thus 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%; Table 23). The proportion of true positives (TP), false positives (FP), false negatives (FN) and true negatives (TN) 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

	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	Chapter 3
2 Roche Elecsys hs-cTnT (LoD)	0.99 (0.01)	0.35 (0.05)	Multivariate normal	Chapter 3
3 Roche Elecsys hs-cTnT (ESC pathway)	0.99 (0.01)	0.68 (0.01)	Multivariate normal	Chapter 3
4 Roche Elecsys hs-cTnT (<8 ng/L at 0 h AND Δ <3 ng/L at 0 to 0.5 h)	1.00 (0.02)	0.45 (0.02)	Multivariate normal	Chapter 3
5 Roche Elecsys hs-cTnT (<12 ng/L at 0 h AND Δ <3 ng/L at 0 to 1 h)	0.98 (0.01)	0.73 (0.01)	Multivariate normal	Chapter 3
6 Siemens Dimension Vista hs-cTnI (<5 ng/L at 0 h AND	1.00 (0.02)	0.66 (0.02)	Multivariate normal	Chapter 3

Δ <2 ng/L at 0 to 1 h)				
7 Abbott ARCHITECT hs-cTnI (LoD)	1.00 (0.00)	0.21 (0.03)	Multivariate normal	Chapter 3
8 Abbott ARCHITECT hs-cTnI (ESC pathway)	0.99 (0.00)	0.57 (0.01)	Multivariate normal	Chapter 3
9 Abbott ARCHITECT hs-cTnI (High-STEACS pathway)	0.99 (0.01)	0.76 (0.01)	Multivariate normal	Chapter 3
10 Abbott ARCHITECT hs-cTnI (<4 ng/L at 0 h)	0.99 (0.01)	0.50 (0.01)	Multivariate normal	Chapter 3
11 Siemens ADVIA Centaur hs-cTnI (<2 ng/L at 0 h)	1.00 (0.00)	0.23 (0.01)	Multivariate normal	Chapter 3
12 Siemens ADVIA Centaur hs-cTnI (<3 ng/L at 0 h OR (<8 ng/L at 0 h AND Δ <7 ng/L at 0 to 2 h))	1.00 (0.01)	0.67 (0.03)	Multivariate normal	Chapter 3
13 Siemens ADVIA Centaur hs-cTnI (ESC pathway)	0.99 (0.01)	0.56 (0.02)	Multivariate normal	Chapter 3
14 Siemens ADVIA Centaur hs-cTnI (<5 ng/L at 0 h)	0.99 (0.01)	0.52 (0.01)	Multivariate normal	Chapter 3
15 Siemens Atellica hs-cTnI (<2 ng/L at 0 h)	1.00 (0.01)	0.26 (0.01)	Multivariate normal	Chapter 3
16 Siemens Atellica hs-cTnI (High-STEACS pathway)	0.98 (0.01)	0.74 (0.01)	Multivariate normal	Chapter 3
17 Beckman Coulter ACCESS hs-cTnI (ESC pathway)	0.99 (0.02)	0.70 (0.02)	Multivariate normal	Chapter 3
18 Beckman Coulter ACCESS hs-cTnI ((symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h))	0.98 (0.02)	0.83 (0.01)	Multivariate normal	Chapter 3
19 Ortho VITROS hs-cTnI (ESC pathway)	1.00 (0.01)	0.60 (0.02)	Multivariate normal	Chapter 3
20 bioMérieux VIDAS hs-cTnI (<2 ng/L at 0 h OR (<6 ng/l at 0 AND 2 h))	0.98 (0.02)	0.64 (0.02)	Multivariate normal	Chapter 3
21 Quidel TriageTrue hs-cTnI (ESC pathway)	1.00 (0.01)	0.66 (0.02)	Multivariate normal	Chapter 3

[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 h AND Δ <3 ng/L at 0 to 0.5 h)	0.12	0.48	0.00	0.40	0.20	1.00
5 Roche Elecsys hs-cTnT (<12 ng/L at 0 h AND Δ <3 ng/L at 0 to 1 h)	0.12	0.24	0.00	0.64	0.33	1.00
6 Siemens Dimension Vista hs-cTnI (<5	0.12	0.30	0.00	0.58	0.29	1.00

ng/L at 0 h AND Δ <2 ng/L at 0 to 1 h)						
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 h)	0.12	0.44	0.00	0.44	0.22	1.00
11 Siemens ADVIA Centaur hs-cTnI (<2 ng/L at 0 h)	0.12	0.68	0.00	0.20	0.15	1.00
12 Siemens ADVIA Centaur hs-cTnI (<3 ng/L at 0 h OR (<8 ng/L at 0 h AND Δ <7 ng/L at 0 to 2 h))	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 h)	0.12	0.42	0.00	0.46	0.22	1.00
15 Siemens Atellica hs-cTnI (<2 ng/L at 0 h)	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	0.00	1.00
18 Beckman Coulter ACCESS hs-cTnI ((symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h))	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 h OR (<6 ng/l at 0 AND 2 h))	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

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; 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 FN's, reported in Table 25, can be considered as the proportions 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 (Table 23). It was assumed that UA was always correctly diagnosed, hence the mortality probability for treated UA was used.

State-transition model

The age-dependent AMI incidence in the UK[206] 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 thus received treatment. For patients in the 'Post-MI' health state, the probability of re-infarction after treated AMI was retrieved from a UK record linkage study,

(n=387,452) which assessed long-term survival and recurrence after AMI.[207] 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 re-infarction probability for the 'Post-MI with re-infarction' health state is equal to the re-infarction probability for the 'Post-MI' health state. The re-infarction RR for people with untreated versus treated AMI was calculated from a study by Mills et al.[188] based on patients with a troponin concentration of 5 to 19 ng/L. This RR was assumed only for the first year after presentation at ED, after which no increased risk was assumed (i.e. RR = 1.0 for untreated versus treated AMI after year 1).

Age-dependent mortality from the general population was used for patients in the 'no ACS, no UA' health state.[205] For the 'Post-MI' and 'Post-MI with re-infarction' health states, mortality was extracted from the record linkage study.[207] Again the study by Mills et al.[188] was used to calculate the mortality RR for untreated versus treated AMI for the first year, after which an RR of 1.0 was used. Finally, a multivariate adjusted mortality hazard ratio for UA versus NSTEMI was retrieved from a study by Allen et al.[208] 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.[190] These age-dependent utility scores from the general population, were combined with age-dependent disutilities for AMI[191] to calculate utilities for the 'Post-MI' health states (with or without re-infarction). Utility scores for the 'UA' health state were calculated based on Post-MI utility scores and a utility increment of 0.010[190] (Table 26).

Table 26: Utility scores

	Estimate	Se	Distribution	Source
No ACS, no UA				
Intercept	1.060	0.029	Normal	Ward 2007[190]
Disutility for age	0.004	0.001	Normal	Ward 2007[190]
Post-MI *(disutility compared to no ACS by age)*				
Age = 45	0.060	0.001	Normal	Ward 2007[190]
Age = 55	0.051	0.001	Normal	Ward 2007[190]
Age = 65	0.025	0.001	Normal	Ward 2007[190]
Age = 75	0.007	0.001	Normal	Ward 2007[190]
UA				
Utility increment compared to AMI	0.010	0.042	Normal	Ward 2007[190]

ACS: acute coronary syndrome; AMI: acute myocardial infarction; UA: unstable angina

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 (see 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 27: Resource use (test specific)

	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 h AND Δ <3 ng/L at 0 to 0.5 h)	2.00	-	Fixed	Assumption
5 Roche Elecsys hs-cTnT (<12 ng/L at 0 h AND Δ <3 ng/L at 0 to 1 h)	2.00	-	Fixed	Assumption
6 Siemens Dimension Vista hs-cTnI (<5 ng/L at 0 h AND Δ <2 ng/L at 0 to 1 h)	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 h)	1.00	-	Fixed	Assumption
11 Siemens ADVIA Centaur hs-cTnI (<2 ng/L at 0 h)	1.84	-	Fixed	Assumption
12 Siemens ADVIA Centaur hs-cTnI (<3 ng/L at 0 h OR (<8 ng/L at 0 h AND Δ <7 ng/L at 0 to 2 h))	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 h)	1.00	-	Fixed	Assumption
15 Siemens Atellica hs-cTnI (<2 ng/L at 0 h)	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 h) OR (<5 ng/L and Δ <5 at 0 to 2 h))	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 h OR (<6 ng/l at 0 AND 2 h))	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 h AND Δ <3 ng/L at 0 to 0.5 h)	3.5	-	Fixed	Assumption
5 Roche Elecsys hs-cTnT (<12 ng/L at 0 h AND Δ <3 ng/L at 0 to 1 h)	4	-	Fixed	Assumption
6 Siemens Dimension Vista hs-cTnI (<5 ng/L at 0 h AND Δ <2 ng/L at 0 to 1 h)	4	-	Fixed	Assumption
7 Abbott ARCHITECT hs-cTnI (LoD)	3	-	Fixed	Assumption
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 h)	3	-	Fixed	Assumption
11 Siemens ADVIA Centaur hs-cTnI (<2 ng/L at 0 h)	3	-	Fixed	Assumption
12 Siemens ADVIA Centaur hs-cTnI (<3 ng/L at 0 h OR (<8 ng/L at 0 h AND Δ <7 ng/L at 0 to 2 h))	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 h)	3	-	Fixed	Assumption
15 Siemens Atellica hs-cTnI (<2 ng/L at 0 h)	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 h) OR (<5 ng/L and Δ <5 at 0 to 2 h))	5	-	Fixed	Assumption
19 Ortho VITROS hs-cTnI (ESC pathway)	4	-	Fixed	Assumption
20 bioMérieux VIDAS hs-cTnI (<2 ng/L at 0 h OR (<6 ng/l at 0 AND 2 h))	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.,[210] which was a retrospective cohort study using Clinical Practice Research Datalink records to identify UK individuals that had their first CV event between 2006 and 2012. Direct medical costs were estimated for 24,093 patients.

Additionally, costs of fatal events were accumulated for all fatal AMI's. For this purpose, it was assumed that all 30-day deaths after 'true' NSTEMI 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 (short stays) were retrieved from the Personal Social Services Research Unit (PSSRU) and divided by 24 (to get 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 due to time between arrival at the emergency department and start of first sampling (one hour) and the time between sampling and the results being available (two hours). In the case of multiple testing, the one-hour delay between arrival at the emergency department and start of sampling was only applied to the first test, however, this also affected the timing of the second test if applicable. The two-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 test (i.e. £2.50; which is consistent with the test cost information submitted by the manufacturers) except for point-of-care tests (i.e. Quidel). For this test we assumed £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 to incorporate costs related to the analyser (i.e. 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 2018-2019 price level (Table 28).

Table 28: Health state costs, event costs and unit prices

	Estimate (£)	Se / range (£)	Distribution	Source
Health state costs				
No ACS, no UA first year	2,403.70	175.36	Gamma	Danese (2016)[210]
No ACS, no UA subsequent year	2,403.70	175.36	Gamma	Danese (2016)[210]
UA first year	4,427.02	74.54	Gamma	Danese (2016)[210]
UA subsequent year	2,208.02	69.16	Gamma	Danese (2016)[210]
Post MI first year	6,865.23	151.42	Gamma	Danese (2016)[210]
Post MI subsequent years	2,493.13	176.95	Gamma	Danese (2016)[210]
Post re-MI first year	8,197.80	611.91	Gamma	Danese (2016)[210]
Post re-MI subsequent years	4,123.37	968.43	Gamma	Danese (2016)[210]

Event costs				
AMI treatment costs	2,496.48	-	Fixed	NHS reference costs (2018) [211]
Costs of fatal AMI	1,539.75	10.56	Gamma	Walker (2016)[212]
Unit prices				
Hospital stay costs (per hour)[c]	26.08	-	Fixed	PSSRU (2018)[213]
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	

4.2.4 Overview of main model assumptions

The main assumptions in the health economic analyses were:

- Serial troponin testing (comparator) has perfect accuracy (sensitivity = 1.0 and specificity = 1.0).
- The life expectancy and quality of life for false positive patients is, in the base case analysis, equal to the life expectancy, quality of life and costs of true negative 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 re-infarction) occurring in the state-transition model are diagnosed correctly and thus treated.
- UA is always correctly diagnosed and thus treated.
- The re-infarction probability for the 'Post-MI with re-infarction' health state is equal to the re-infarction probability for the 'Post-MI' health state.
- The increased Post-MI re-infarction and mortality probabilities for untreated AMI were assumed to last one year: afterwards a RR of 1.0 was applied (for untreated versus treated AMI).
- There is no additional benefit of starting treatment early, so treatment effect for high-sensitive strategies is equal to treatment effect for standard troponin strategy.
- All 30-day deaths (after presentation at the emergency department) are due to fatal AMI events and will receive the associated costs.

4.3 Model analyses

Expected costs, life years (LYs) 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 versus standard troponin and versus the next best alternative were calculated. The ICER was then calculated by dividing the incremental costs by the incremental QALYs. Probabilistic sensitivity analyses (10,000 simulations) were performed, and cost-effectiveness acceptability curves (CEACs) were constructed.

4.3.1 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 true negative patients. This assumption is, however, debatable. A meta-analysis by Liplinski et al.,[202] showed that patients with a negative standard troponin test and positive hs-cTn test have an increased risk of (re-)infarction and mortality compared to those who test negative on both 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 false positive (Table 23). It was assumed that for this proportion of patients, the relative treatment benefit would be equal to that for true positive 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, Table 25). This 'higher risk subgroup' was assumed to be treated for all hs-cTn tests (since they tested positive with these tests) and untreated for the standard troponin test (since they tested negative with this test), thus affecting the probability of adverse outcomes (according to relative risk of re-infarction and mortality, Table 23) and treatment costs (Table 28). In addition, the post-MI utility and health state costs were used for this 'higher risk subgroup'.

4.3.2 Sensitivity and scenario analysis

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

1. AMI treatment costs (£2,496 based on NHS reference costs) are applied for patients who tested false positive rather than using no treatment costs, as assumed in the base case analysis.
2. The assumption that the increased post AMI re-infarction and mortality probabilities for untreated AMI only lasts for one year was replaced by the assumption that these probabilities would remain elevated for a lifetime.

3. 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 hsTnT: £6.05
    - Abbott ARCHITECT hsTnI: £4.17
    - Siemens ADVIA Centaur hsTnI: £2.00
    - Siemens Atellica hsTnI: £2.00
    - Siemens Dimension Vista hsTnI: £2.00
    - Beckman Coulter ACCESS hsTnI: £2.75
    - Ortho VITROS hsTnI £1.85
    - BioMérieux VIDAS hsTnI: £6.05
    - Quidel TriageTrue hsTnI (point-of-care): £25.00

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

4.4 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 presented in tabulated form in Appendices 6 and 7.

4.4.1 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 LY and QALY gain in up to four decimal places. These were (starting with the cheapest): Siemens Dimension Vista hs-cTnI (<5 ng/L at 0 h AND Δ <2 ng/L at 0 to 1 h); Ortho VITROS hs-cTnI (ESC 0/1 hour pathway: (symptoms >3 h AND <1 ng/L at 0 h) OR (<2 ng/L at 0 h AND Δ <1 at 0 to 1 h)); Siemens ADVIA Centaur hs-cTnI (<3 ng/L at 0 h OR (<8 ng/L at 0 h AND Δ <7 ng/L at 0 to 2 h)); Roche Elecsys hs-cTnT (99th centile threshold (<14 ng/L at 0 h AND 3 h)); Quidel TriageTrue hs-cTnI (ESC 0/1 hour pathway: (symptoms >3 h AND <4 ng/L at 0 h) OR (<5 ng/L at 0 h AND Δ <3 at 0 to 1 h)); Roche Elecsys hs-cTnT (<8 ng/L at 0 h AND Δ <3 ng/L at 0 to 0.5 h); Siemens Atellica hs-cTnI (<2 ng/L at 0 h); and Siemens ADVIA Centaur hs-cTnI (<2 ng/L at 0 h). Because of the little differences in

outcomes between these strategies, some of these appear to be on the cost effectiveness frontier, even when they are not.

Beckmann Coulter ACCESS hs-cTnI (symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h), the test strategy with the highest specificity (of 83; CI 81, 86), was the cheapest (probabilistic analysis: £38,625), but it was also amongst the least effective (15.5254 LYs and 12.0768 QALYs), owing to a sensitivity of 98 (CI 92, 100). Compared to 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 below £8,455 per QALY, the Beckman Coulter ACCESS hsTnI ((symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h)) would be cost-effective. For thresholds between £8,455 and £20,190 per QALY, the Roche Elecsys hsTnT (<12 ng/L at 0 h AND Δ <3 ng/L at 0 to 1 h) was cost-effective; above £20,190 per QALY Siemens Dimension Vista hsTnI (<5 ng/L at 0 h AND Δ <2 ng/L at 0 to 1 h) would be cost-effective (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 h) OR (<5 ng/L and Δ <4 at 0 to 1 h)) 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 h AND Δ <2 ng/L at 0 to 1 h) had a probability of being cost-effective of 13% and 22% respectively.

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

Strategy			Compared to Standard troponin			Full incremental ICER
	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts / ΔQALYs	ΔCosts / ΔQALYs
18 Beckman Coulter ACCESS hs-cTnI ((symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h))	£38,666	12.0763	-£210	-0.0011	£188,819	Cheapest
5 Roche Elecsys hs-cTnT (<12 ng/L at 0 h AND Δ <3 ng/L at 0 to 1 h)	£38,669	12.0765	-£206	-0.0009	£218,065	ext 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 h AND Δ <2 ng/L at 0 to 1 h)	£38,693	12.0774	-£183	0.0000	£328,961,202	£26,504
14 Siemens ADVIA Centaur hs-cTnI (<5 ng/L at 0 h)	£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 h OR (<6 ng/l at 0 AND 2 h))	£38,705	12.0763	-£171	-0.0011	£153,650	Dominated
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 h)	£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 h OR (<8 ng/L at 0 h AND Δ <7 ng/L at 0 to 2 h))	£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 h AND Δ <3 ng/L at 0 to 0.5 h)	£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 h)	£38,773	12.0774	-£103	0.0000	£185,244,726	Dominated
11 Siemens ADVIA Centaur hs-cTnI (<2 ng/L at 0 h)	£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			Compared to Standard troponin			Full incremental ICER
	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts / ΔQALYs	ΔCosts / ΔQALYs
18 Beckman Coulter ACCESS hs-cTnI ((symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h))	£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	ext dominated
3 Roche Elecsys hs-cTnT (ESC pathway)	£38,662	12.0798	-£209	-0.0027	£77,589	ext dominated
20 bioMérieux VIDAS hs-cTnI (<2 ng/L at 0 h OR (<6 ng/l at 0 AND 2 h))	£38,662	12.0764	-£209	-0.0061	£34,307	Dominated
5 Roche Elecsys hs-cTnT (<12 ng/L at 0 h AND Δ <3 ng/L at 0 to 1 h)	£38,663	12.0813	-£208	-0.0012	£169,682	£8,455
14 Siemens ADVIA Centaur hs-cTnI (<5 ng/L at 0 h)	£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 h AND Δ <2 ng/L at 0 to 1 h)	£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 h)	£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 h OR (<8 ng/L at 0 h AND Δ <7 ng/L at 0 to 2 h))	£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 h AND Δ <3 ng/L at 0 to 0.5 h)	£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 h)	£38,768	12.0825	-£103	0.0000	£21,210,686	ext dominated

11 Siemens ADVIA Centaur hs-cTnI (<2 ng/L at 0 h)	£38,777	12.0825	-£94	0.0000	£31,584,800	ext 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

Figure 13: The cost effectiveness frontier for base case analysis (based on probabilistic sensitivity analysis)

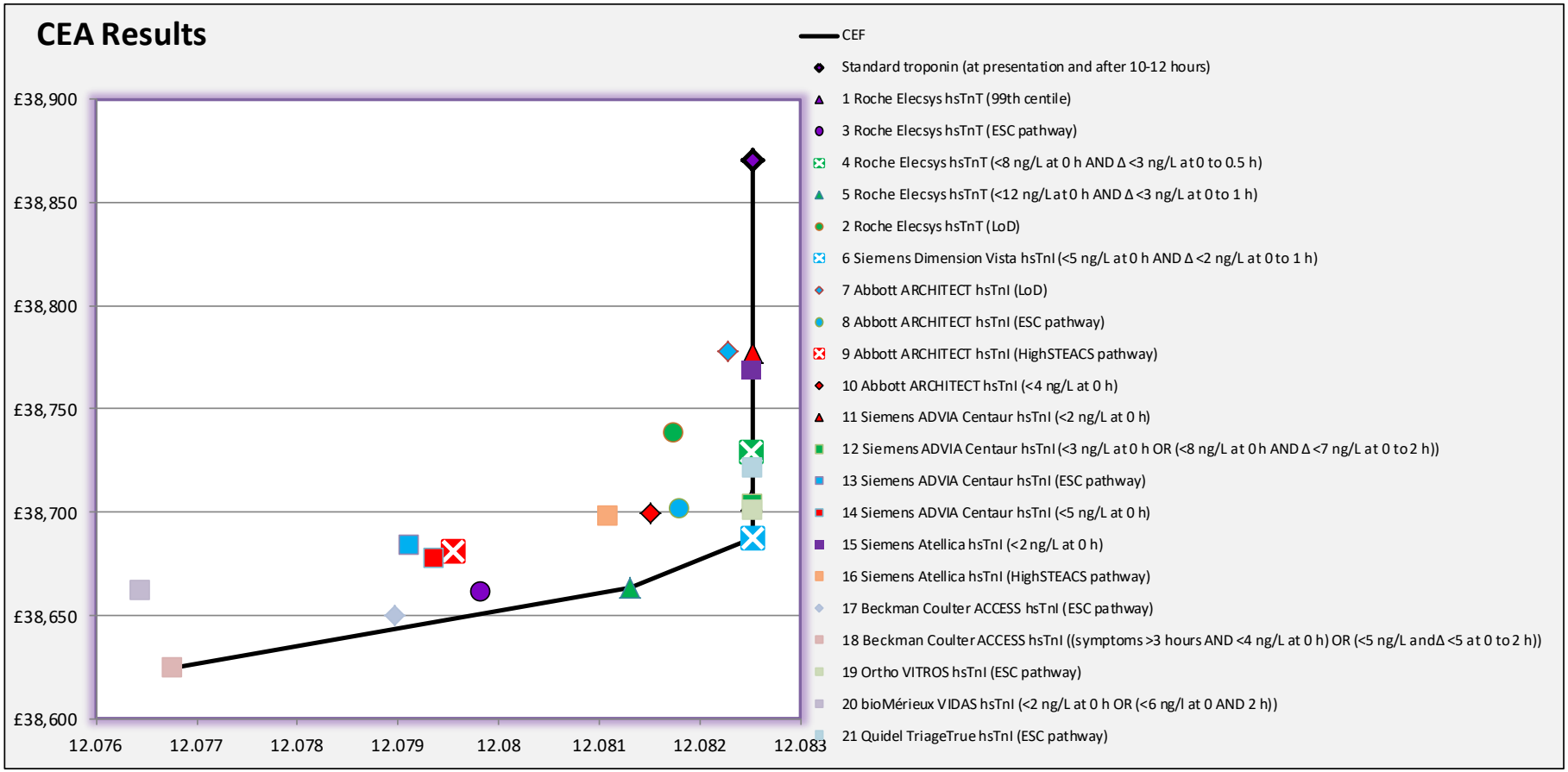
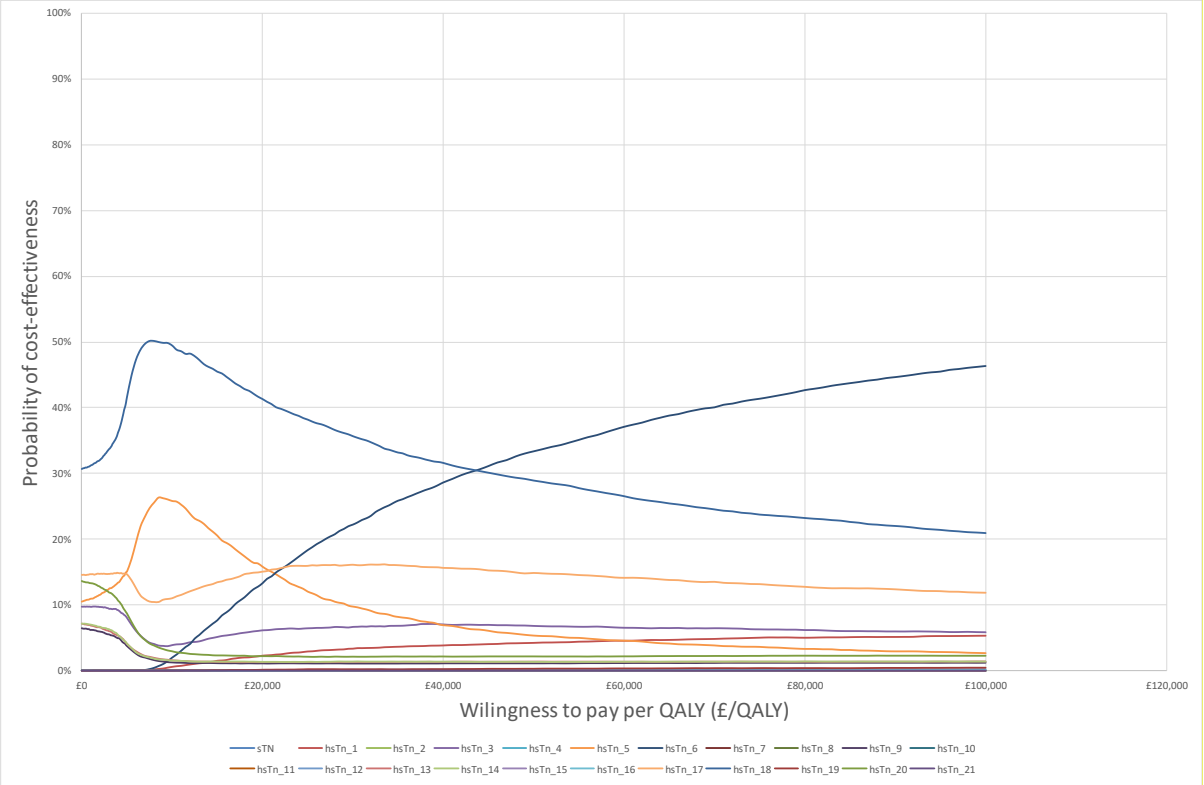


Figure 14: Cost-effectiveness acceptability curve for base case analysis



4.4.2 Secondary analysis

The secondary analysis includes the same test strategies. This analysis assumed that in a proportion of patients with a false positive 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 (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 h) OR (<5 ng/L and Δ <4 at 0 to 1 h)) 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 h) OR (<5 ng/L and Δ <4 at 0 to 1 h)) versus Standard troponin (at presentation and after 10-12 hours) was £4,043 per QALY gained.

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 h) OR (<5 ng/L and Δ <4 at 0 to 1 h)) had a probability of being cost-effective of 67% and 64% respectively (see Figure 15).

Table 31: Deterministic results for secondary analysis: costs and QALYs

Strategy			Compared to Standard troponin			Full incremental ICER
	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts / ΔQALYs	ΔCosts / ΔQALYs
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	£6,559	ext dominated
15 Siemens Atellica hs-cTnI (<2 ng/L at 0 h)	£38,022	11.4064	£519	0.0835	£6,216	ext dominated
11 Siemens ADVIA Centaur hs-cTnI (<2 ng/L at 0 h)	£38,022	11.4035	£519	0.0805	£6,445	dominated
2 Roche Elecsys hs-cTnT (LoD)	£38,023	11.4147	£520	0.0918	£5,668	ext dominated
10 Abbott ARCHITECT hs-cTnI (<4 ng/L at 0 h)	£38,030	11.4291	£527	0.1062	£4,967	ext dominated
14 Siemens ADVIA Centaur hs-cTnI (<5 ng/L at 0 h)	£38,033	11.4313	£530	0.1083	£4,894	ext dominated
4 Roche Elecsys hs-cTnT (<8 ng/L at 0 h AND Δ <3 ng/L at 0 to 0.5 h)	£38,042	11.4250	£540	0.1020	£5,290	dominated
8 Abbott ARCHITECT hs-cTnI (ESC pathway)	£38,054	11.4361	£551	0.1132	£4,867	ext dominated
13 Siemens ADVIA Centaur hs-cTnI (ESC pathway)	£38,054	11.4352	£551	0.1122	£4,910	dominated
19 Ortho VITROS hs-cTnI (ESC pathway)	£38,061	11.4396	£559	0.1167	£4,789	ext dominated
3 Roche Elecsys hs-cTnT (ESC pathway)	£38,063	11.4469	£561	0.1239	£4,523	ext dominated
5 Roche Elecsys hs-cTnT (<12 ng/L at 0 h AND Δ <3 ng/L at 0 to 1 h)	£38,064	11.4510	£562	0.1280	£4,387	ext dominated
17 Beckman Coulter ACCESS hs-cTnI (ESC pathway)	£38,065	11.4488	£562	0.1259	£4,465	dominated
6 Siemens Dimension Vista hs-cTnI (<5 ng/L at 0 h AND Δ <2 ng/L at 0 to 1 h)	£38,067	11.4455	£564	0.1225	£4,605	dominated
20 bioMérieux VIDAS hs-cTnI (<2 ng/L at 0 h OR (<6 ng/l at 0 AND 2 h))	£38,073	11.4424	£570	0.1195	£4,771	dominated
12 Siemens ADVIA Centaur hs-cTnI (<3 ng/L at 0 h OR (<8 ng/L at 0 h AND Δ <7 ng/L at 0 to 2 h))	£38,086	11.4465	£583	0.1235	£4,722	dominated
18 Beckman Coulter ACCESS hs-cTnI ((symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h))	£38,093	11.4610	£590	0.1380	£4,278	£4,278
21 Quidel TriageTrue hs-cTnI (ESC pathway)	£38,101	11.4455	£598	0.1225	£4,880	dominated
16 Siemens Atellica hs-cTnI (High-STEACS pathway)	£38,104	11.4522	£601	0.1292	£4,650	dominated
9 Abbott ARCHITECT hs-cTnI (High-STEACS pathway)	£38,110	11.4547	£608	0.1317	£4,612	dominated

1 Roche Elecsys hs-cTnT (99th centile)	£38,118	11.4562	£615	0.1333	£4,615	dominated

Table 32: Probabilistic results for secondary analysis: costs and QALYs

Strategy			Compared to Standard troponin			Full incremental ICER
	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts / ΔQALYs	ΔCosts / ΔQALYs
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 h)	£38,039	11.4463	£522	0.1123	£4,648	ext dominated
7 Abbott ARCHITECT hs-cTnI (LoD)	£38,046	11.4201	£529	0.0861	£6,148	dominated
2 Roche Elecsys hs-cTnT (LoD)	£38,050	11.4328	£532	0.0988	£5,389	dominated
15 Siemens Atellica hs-cTnI (<2 ng/L at 0 h)	£38,051	11.4249	£534	0.0909	£5,868	dominated
11 Siemens ADVIA Centaur hs-cTnI (<2 ng/L at 0 h)	£38,051	11.4221	£534	0.0881	£6,064	dominated
10 Abbott ARCHITECT hs-cTnI (<4 ng/L at 0 h)	£38,055	11.4466	£538	0.1126	£4,778	ext dominated
13 Siemens ADVIA Centaur hs-cTnI (ESC pathway)	£38,057	11.4497	£540	0.1157	£4,662	ext dominated
20 bioMérieux VIDAS hs-cTnI (<2 ng/L at 0 h OR (<6 ng/l at 0 AND 2 h))	£38,060	11.4547	£543	0.1207	£4,500	ext dominated
17 Beckman Coulter ACCESS hs-cTnI (ESC pathway)	£38,066	11.4628	£548	0.1288	£4,258	ext dominated
4 Roche Elecsys hs-cTnT (<8 ng/L at 0 h AND Δ <3 ng/L at 0 to 0.5 h)	£38,070	11.4430	£553	0.1089	£5,072	dominated
3 Roche Elecsys hs-cTnT (ESC pathway)	£38,072	11.4619	£555	0.1279	£4,337	dominated
18 Beckman Coulter ACCESS hs-cTnI ((symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h))	£38,077	11.4725	£560	0.1385	£4,043	£4,043
8 Abbott ARCHITECT hs-cTnI (ESC pathway)	£38,079	11.4535	£562	0.1195	£4,699	dominated
19 Ortho VITROS hs-cTnI (ESC pathway)	£38,087	11.4571	£570	0.1231	£4,630	dominated
5 Roche Elecsys hs-cTnT (<12 ng/L at 0 h AND Δ <3 ng/L at 0 to 1 h)	£38,088	11.4678	£570	0.1338	£4,263	dominated
6 Siemens Dimension Vista hs-cTnI (<5 ng/L at 0 h AND Δ <2 ng/L at 0 to 1 h)	£38,092	11.4627	£575	0.1287	£4,467	dominated
12 Siemens ADVIA Centaur hs-cTnI (<3 ng/L at 0 h OR (<8 ng/L at 0 h AND Δ <7 ng/L at 0 to 2 h))	£38,111	11.4636	£594	0.1296	£4,580	dominated
9 Abbott ARCHITECT hs-cTnI (High-STEACS pathway)	£38,115	11.4691	£598	0.1351	£4,425	dominated

21 Quidel TriageTrue hs-cTnI (ESC pathway)	£38,126	11.4627	£609	0.1287	£4,729	dominated
16 Siemens Atellica hs-cTnI (High-STEACS pathway)	£38,126	11.4689	£609	0.1349	£4,517	dominated
1 Roche Elecsys hs-cTnT (99th centile)	£38,139	11.4718	£622	0.1378	£4,514	dominated

Figure 15: The cost effectiveness frontier for secondary analysis (based on probabilistic sensitivity analysis)

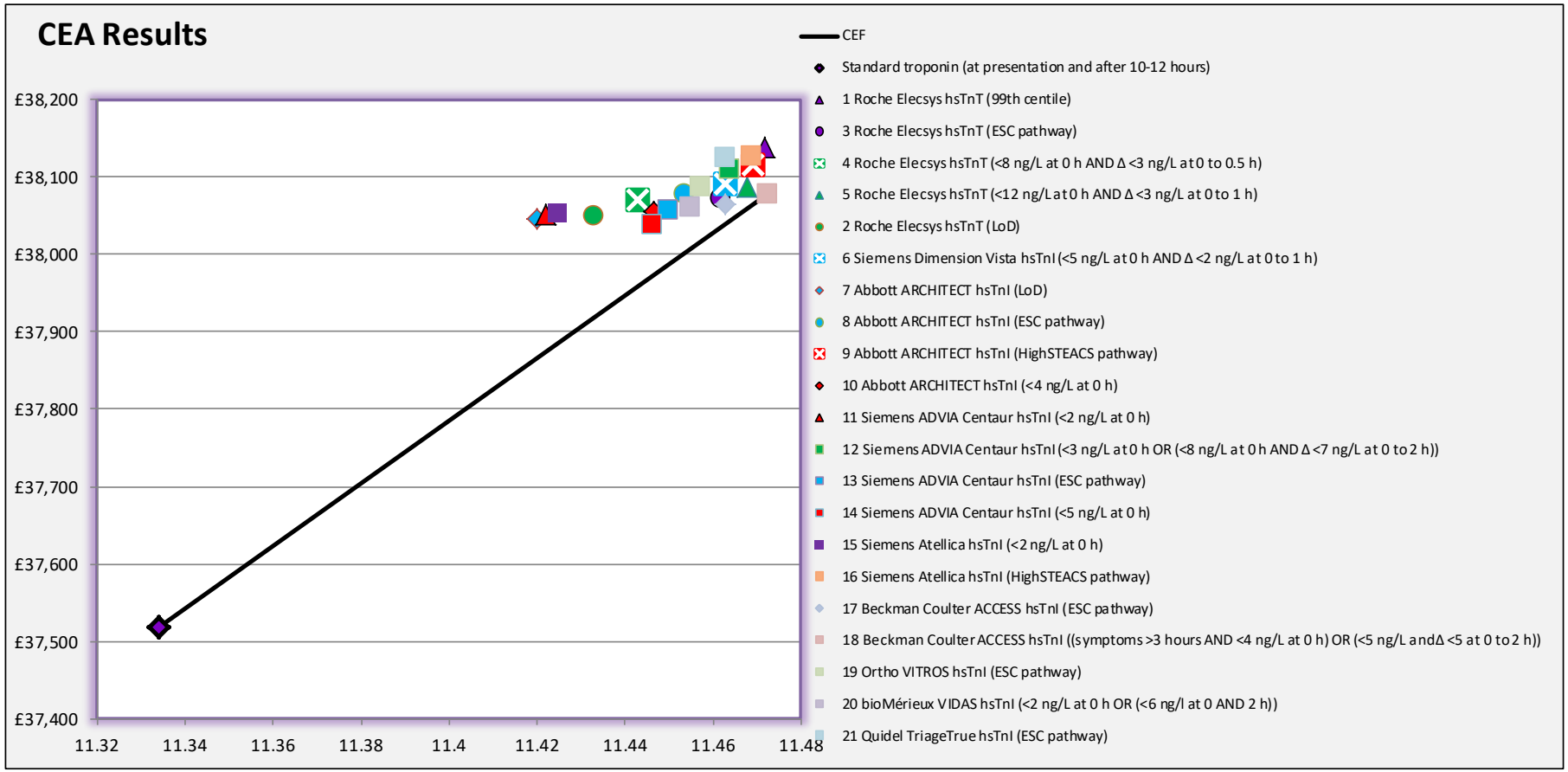
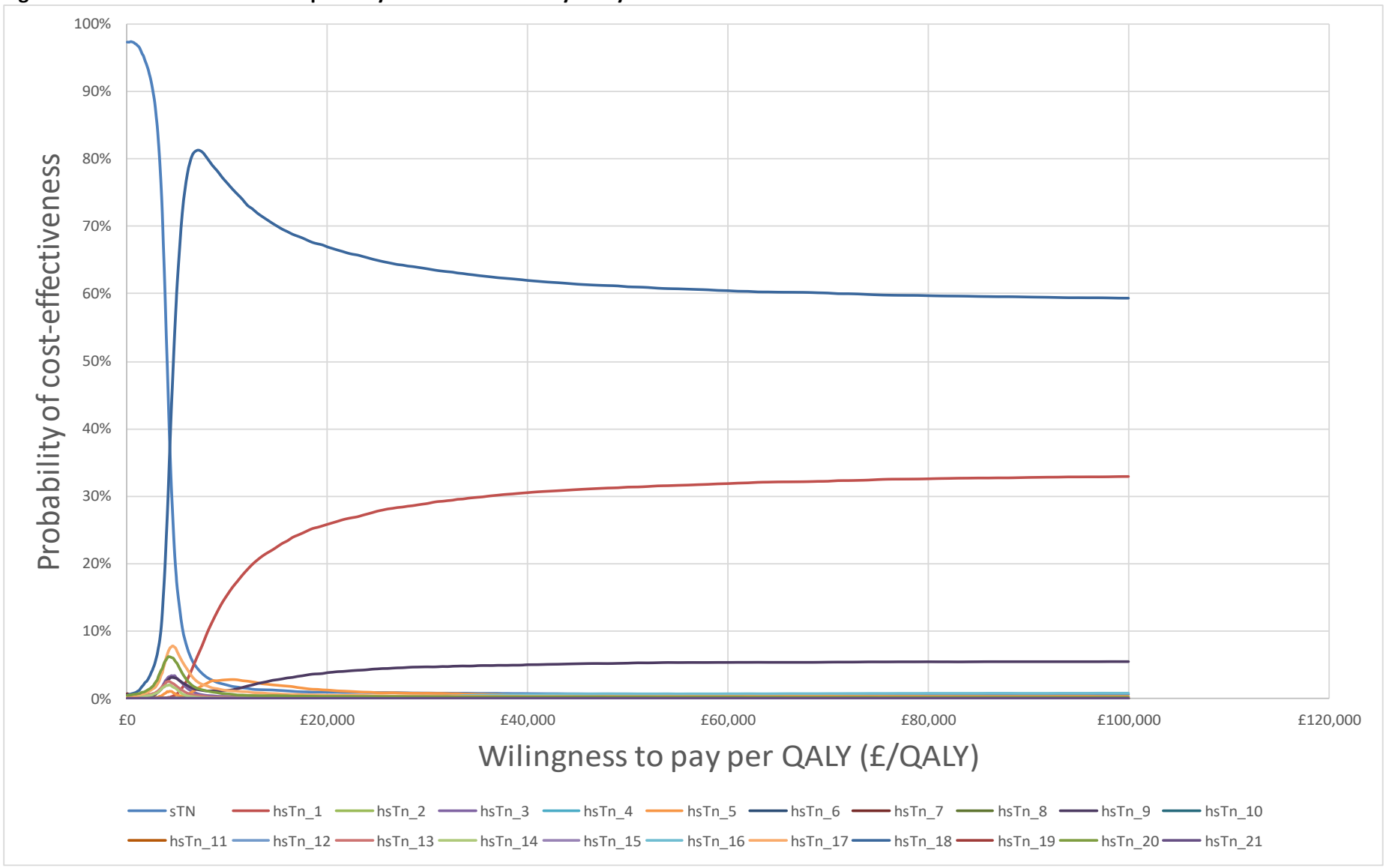


Figure 16: Cost-effectiveness acceptability curve for secondary analysis



4.4.3 Scenario analyses

Three scenario analyses were performed deterministically and conditional on both the base-case and the secondary analysis. Results are shown in Appendix 6. Scenario 1 assumed that patients who tested false positive would receive treatment and a treatment cost would be incurred for these patients. In this scenario conditional on the base-case, Beckmann Coulter ACCESS hs-cTnI (symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h), the test strategy with the highest specificity (of 83; CI 81, 86), was the cheapest. Roche Elecsys hs-cTnT (99th centile threshold (<14 ng/L at 0 h AND 3 h)) was cost-effective for thresholds over £57,659 per QALY gained and Standard troponin (at presentation and after 10-12 hours) would be cost-effective at thresholds over £157,505,897 per QALY gained.

Scenario 1 conditional on the secondary analysis resulted in Standard troponin (at presentation and after 10-12 hours) being the cheapest strategy. Beckmann Coulter ACCESS hs-cTnI (symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h) was cost-effective at and above a threshold of £4,869 per QALY gained and all other test strategies were more costly and not more effective.

Scenario 2 assumed a lifetime relative risk of higher mortality and reinfarction rate for those that tested false negative (instead of only an increased one-year risk). Conditional on the base-case, Beckmann Coulter ACCESS hs-cTnI (symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h), remained the cheapest, and Beckman Coulter ACCESS hs-cTnI (ESC 0/1 hour pathway: (symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <4 at 0 to 1 h)) and Siemens Dimension Vista hs-cTnI (<5 ng/L at 0 h AND Δ <2 ng/L at 0 to 1 h) were cost-effective at thresholds above £6,962 and £7,874 per QALY gained respectively. Standard troponin (at presentation and after 10-12 hours) would be cost-effective thereafter, only over thresholds of almost £70 million.

Scenario 2 conditional on the secondary analysis resulted in Standard troponin (at presentation and after 10-12 hours) testing being the cheapest strategy. Beckmann Coulter ACCESS hs-cTnI (symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h) was cost-effective above a threshold of £3,362 per QALY gained and all other test strategies were less effective and therefore dominated or extendedly dominated.

Scenario 3 assumed differential test costs for all tests, based on information provided by the manufacturers. Conditional on the base-case, Beckmann Coulter ACCESS hs-cTnI (symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h), remained the cheapest, and Beckman Coulter ACCESS hs-cTnI (ESC 0/1 hour pathway: (symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L

and Δ <4 at 0 to 1 h)) and Siemens Dimension Vista hs-cTnI (<5 ng/L at 0 h AND Δ <2 ng/L at 0 to 1 h) were cost-effective over thresholds of £22,200 and £23,949 per QALY gained. Standard troponin (at presentation and after 10-12 hours) would only be cost-effective thereafter, above thresholds of approximately £330 million.

In scenario 3 conditional on the secondary analysis, Standard troponin (at presentation and after 10-12 hours) testing remained the cheapest strategy. Beckmann Coulter ACCESS hs-cTnI (symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h) was cost-effective up to a threshold of £4,281 per QALY gained and all other test strategies were less effective and therefore dominated or extendedly dominated.

4.4.4 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 one 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 Siemens Dimension Vista hs-cTnI (<5 ng/L at 0 h AND Δ <2 ng/L at 0 to 1 h), Roche Elecsys hs-cTnT (ESC 0/1 hour pathway: (symptoms >3 hours AND <5 ng/L at 0 h) OR (<12 ng/L at 0 h AND Δ <3 ng/L at 0 to 1 h)) and Beckman Coulter ACCESS hs-cTnI ((symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h)). In the comparison between Siemens Dimension Vista hs-cTnI (<5 ng/L at 0 h AND Δ <2 ng/L at 0 to 1 h) and Standard troponin (at presentation and after 10-12 hours), in addition to parameters in the other comparisons, parameters with the most impact on results were the proportions of AMI in emergency admissions and of NSTEMI with patients with heart attack (Appendix 7).

In the secondary analysis, the parameters with notable impact on the estimated cost-effectiveness were: the 30 day mortality for untreated AMI, the mortality one year after treated and untreated AMI, the discount rate used for outcomes, and the relative mortality for patients tested true positive versus those that tested false positive (comparison of Beckman Coulter ACCESS hs-cTnI (ESC 0/1 hour pathway: (symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <4 at 0 to 1 h)) versus Standard troponin (at presentation and after 10-12 hours) testing) (Appendix 7).

4.4.5 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 gain the following test strategies would be the most cost-effective use of the

particular assays: Roche Elecsys hs-cTnT (<12 ng/L at 0 h AND Δ <3 ng/L at 0 to 1 h), Abbott ARCHITECT hs-cTnI (ESC pathway), Siemens ADVIA Centaur hs-cTnI (<3 ng/L at 0 h OR (<8 ng/L at 0 h AND Δ <7 ng/L at 0 to 2 h)), Siemens Atellica hs-cTnI (High-STEACS pathway), Beckman Coulter ACCESS hs-cTnI (ESC pathway).

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

Strategy	Costs	QALYs	ICERs
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 h AND Δ <3 ng/L at 0 to 1 h)	£38,663	12.0813	£1,040
1 Roche Elecsys hs-cTnT (99th centile)	£38,706	12.0825	£35,140
4 Roche Elecsys hs-cTnT (<8 ng/L at 0 h AND Δ <3 ng/L at 0 to 0.5 h)	£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 h)	£38,699	12.0815	ext 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 h)	£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 h OR (<8 ng/L at 0 h AND Δ <7 ng/L at 0 to 2 h))	£38,704	12.0825	£8,213
11 Siemens ADVIA Centaur hs-cTnI (<2 ng/L at 0 h)	£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 h)	£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 h) OR (<5 ng/L and Δ <5 at 0 to 2 h))	£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 gain 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 h OR (<8 ng/L at 0 h AND Δ <7 ng/L at 0 to 2 h)), Siemens Atellica hs-cTnI (High-STEACS pathway), Beckman Coulter ACCESS hs-cTnI ((symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h)).

Table 34: Probabilistic results for secondary analysis: per assay

Strategy	Costs	QALYs	ICERs
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 h AND Δ <3 ng/L at 0 to 0.5 h)	£38,070	11.4430	ext dominated
3 Roche Elecsys hs-cTnT (ESC pathway)	£38,072	11.4619	£769
5 Roche Elecsys hs-cTnT (<12 ng/L at 0 h AND Δ <3 ng/L at 0 to 1 h)	£38,088	11.4678	£2,658
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 h)	£38,055	11.4466	£326
8 Abbott ARCHITECT hs-cTnI (ESC pathway)	£38,079	11.4535	ext dominated
9 Abbott ARCHITECT hs-cTnI (High-STEACS pathway)	£38,115	11.4691	£2,666
Siemens ADVIA Centaur hs-cTnI assay			
14 Siemens ADVIA Centaur hs-cTnI (<5 ng/L at 0 h)	£38,039	11.4463	cheapest
11 Siemens ADVIA Centaur hs-cTnI (<2 ng/L at 0 h)	£38,051	11.4221	dominated
13 Siemens ADVIA Centaur hs-cTnI (ESC pathway)	£38,057	11.4497	ext dominated
12 Siemens ADVIA Centaur hs-cTnI (<3 ng/L at 0 h OR (<8 ng/L at 0 h AND Δ <7 ng/L at 0 to 2 h))	£38,111	11.4636	£4,140
Siemens Atellica hs-cTnI assay			
15 Siemens Atellica hs-cTnI (<2 ng/L at 0 h)	£38,051	11.4249	cheapest
16 Siemens Atellica hs-cTnI (High-STEACS pathway)	£38,126	11.4689	£1,719
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 h) OR (<5 ng/L and Δ <5 at 0 to 2 h))	£38,077	11.4725	£1,197

5. DISCUSSION

5.1 Statement of principal findings

5.1.1 Clinical effectiveness

The evidence base relating to the use of high sensitivity cardiac troponin assays for the early rule-out of acute myocardial infarction in people presenting with chest pain has expanded rapidly since the publication of our previous systematic review,[7] which was conducted to support the development of DG15.[31] Up-date searches of bibliographic databases (from 2013 to October 2019), conducted for this assessment, identified a total of 9379 unique references, compared to the total of 6766 unique references identified for the nine-year period (2005 to October 2013) covered by the searches conducted for our previous systematic review. This current assessment includes a total of 123 publications relating to 37 studies, as compared to the 37 publications relating to 18 studies included in our previous systematic review.[7]

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, (Abbott Alinity hs-cTnI, Beckman Coulter Access hs-cTnI, Biomérieux VIDAS hs-cTnI, Ortho Clinical Diagnostics VITROS hs-cTnI, Quidel Cardiovascular TriageTrue hs-cTnI, Siemens Healthineers Atellica hs-cTnI, Siemens Healthineers Dimension EXL hs-cTnI, Siemens Healthineers Dimension Vista hs-cTnI, and Siemens Healthineers ADVIA Centaur hs-cTnI), which were not included in the scope for DG15.[31] One assay that was included in DG15, the Beckman Coulter AccuTnI+3 hs-cTnI assay, is no longer available and hence is not included in this current assessment. As was the case in our previous systematic review,[7] 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, 9 provided data on the Abbott ARCHITECT hs-cTnI assay, 3 provided data on the Siemens ADVIA Centaur hs-cTnI assay, 2 studies 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 (see Section 3.2.1). We did not identify any studies which 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[7] 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, relating to the APACE study,[54, 55, 58-60, 70, 74, 75, 90-94, 103-108, 111, 113, 123, 132, 170, 173] which have been published since our previous systematic review. Of particular significance is the fact that eight different hs-cTn assays (Roche Elecsys hs-cTnT, Abbott ARCHITECT hs-cTnI, Beckman Coulter Access hs-cTnI, bioMérieux VIDAS hs-cTnI, Ortho VITROS hs-cTnI, Quidel TriageTrue hs-cTnI, Siemens ADVIA Centaur hs-cTnI and Siemens Dimension Vista hs-cTnI) have now been evaluated in subgroups of the APACE study population. Five further studies, included in this assessment (ADAPT,[68] BEST,[115] High-US,[176] ROMI-2,[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, proving two potential oportunities to rule-out NSTEMI and hence to discharge patients within the four hour window specified in the scope. Our estimates of the 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 (unique combinations of assay, threshold and timing), which are dominated by multiple testing strategies (59 distinct multiple testing strategies). Thus, the construction of theoretical optimised testing strategies has been rendered obsolete, and the problem has become, rather, 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 section 3.2.14.

With respect to single test strategies, the results of our previous systematic review[7] indicated that very low hs-cTn levels (below a threshold which 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 only available for the Roche elecsys hs-cTnT assay (threshold 5 ng/L); one study[141] evaluated an 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 (Table 8, section 3.2.4). The corresponding summary sensitivity and specificity estimates for the Abbott ARCHITECT hs-cTnI asssay, 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 4 studies (Table 9, section 3.2.5). 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%) for the Siemens ADVIA Centaur hs-cTnI assay (Table 14 and section 3.2.10), and 100% (95% CI: 98 to 100%) and 26% (95% CI: 24 to 28%) for the Siemens Atellica hs-cTnI assay (Table 15 and section 3.2.11).[176]

The majority of the multiple test strategies selected for inclusion in our cost-effectiveness modelling (Table 21, section 3.2.14) 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 Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation, from the European Society of Cardiology,[34] included 0/3 hour 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.[34] 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 three 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 -between presentation and a second sample taken after one 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 asay and the Siemens Dimension Vista hs-cTnI assay.[34] 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, included in this assessment were calculated by dichotomising at the rule-out threshold, i.e. study participants in the observe of the rule-in categories were classified as test positive. Unsurprisingly, the addition of a second rule-out step appears to offer consistently higher specificity, compared to rule-out strategies based on very low hs-cTn levels in a single sample taken

on presentation alone; sensitivity estimates remained high. Sensitivity and specificity estimates for the ESC 0/1 hour rule-out pathway, included in this assessment were: 99% (95% CI: 98 to 100%) and 68% (95% CI: 67 to 70%) for the Roche Elecsys hs-cTnT assay, rule-out threshold (symptoms >3 hours AND <5 ng/L at 0 h) OR (<12 ng/L at 0 h AND Δ <3 ng/L at 0 to 1 h);[104] 99% (95% CI: 98 to 100%) and 57% (95% CI: 56 to 59%) for the Abbott ARCHITECT hs-cTnI assay (summary estimate based on 2 studies), rule-out threshold (symptoms >3 hours AND <2 ng/L at 0 h) OR (<5 ng/L at 0 h AND Δ <2 ng/L at 0 to 1 h);[104, 214] 99% (95% CI: 94 to 100%) and 70% (95% CI: 66 to74%) for the Beckman Coulter Access hs-cTnI assay, rule-out threshold (symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <4 ng/L at 0 to 1 h);[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 h AND <1 ng/L at 0 h) OR (<2 ng/L at 0 h AND Δ <1 ng/L at 0 to 1 h);[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 h AND <4 ng/L at 0 h) OR (<5 ng/L at 0 h AND Δ <3 ng/L at 0 to 1 h);[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 h AND <3 ng/L at 0 h) OR (<6 ng/L at 0 h AND Δ <3 ng/L at 0 to 1 h).[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 2017-2018 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 (MINAP) 2019,[203] 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 1 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 h AND <3 ng/L at 0 h) OR (<6 ng/L at 0 h AND Δ <3 ng/L at 0 to 1 h).[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%), and hence 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. Sensitivity and specificity estimates for the High-STEACS pathway, included in this assessment were: 99% (95% CI: 97 to 100% and 76% (95% CI: 73 to 78%) for the Abbott ARCHITECT hs-cTnI assay, rule-out threshold (symptoms ≥2 h AND <5 ng/L at 0 h) OR (≤16 ng/L (females) ≤34 ng/L (males) at 3 h AND Δ <3 ng/L at 0 to 3 hours),[66] and 98% (95% CI: 95 to 100% and 74% (95% CI: 72 to 76%) for the Siemens Atellica hs-cTnI assay, rule-out threshold (symptoms ≥2 h AND <5 ng/L at 0 h) OR (≤34 ng/L (females) ≤53 ng/L (males) at 3 h 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 2 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, 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 infrom the development of a risk assessment tool.[215] this study found that patients at low risk for myocardial infarction 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 myocardial infarction or death from any cause at 30 days.[215]

In addition to the changes in the evidence about diagnostic accuracy described above, two major randomised controlled trials the High-STEACS trial[99] and the un-published HiSTORIC trial[175] are included in this assessment. Both trials were stepped-wedge, cluster randomised controlled trials, evaluating 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, during the validation phase of the trial (6 to 12 months), results of the hs-cTnI assay were concealed from the attending clinician and a contemporary cardiac troponin assay was used to guide care. A high sensitivity test was introduced after the 6 months (early implementation) or 12 months (late implementation).[99] The HiSTORIC trial also had a validation phase where troponin testing was performed at presentation and repeated 6 to 12 hours after the onset of symptoms if indicated.[175] In the validation phase of HiSTORIC the High-STEACS early rule-out pathway was used.[175 99] In the High-STEACS trial, of 1771 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 OR for implementation vs. validation was 1.10: 95% confidence interval (CI) 0.75 to 1.61).[99] In HiSTORIC [redacted]).[175] In High-STEACS the Median length of stay was 7 hours (IQR = 3 to 24) in the implementation phase as compared to 4 hours (IQR 3 to 20) in the validation phase.[99] In HiSTORIC [redacted][175] The authors of High-STEACS concluded that, although implementation of a high sensitivity cardiac

troponin assay resulted in reclassification of 17% of 10360 patients with myocardial injury or infarction, only a third had a diagnosis of type I MI and the incidence of subsequent MI or death from cardiovascular causes within one year was not affected by use of this assay.[99] [redacted] [175] These studies represent direct, real world evidence about the effects of implementing an early rule-out strategy, based on a high sensitivity cardiac troponin assay, obtained in a UK setting.

We identified a further RCT, RAPID-TnT,[216] conducted in Australia, which did not meet the inclusion criteria for this assessment because it did not compare testing with a high sensitivity cardiac troponin assay to a conventional cardiac troponin assay. Participants in the RAPID-TnT trial (n = 3378) were randomised to either 0/1-hour Roche Elecsys hs-cTnT (reported to the limit of detection [<5ng/L]) or masked Roche Elecsys hs-cTnT hs-cTnT reported to ≤29ng/L evaluated at 0/3-hours (standard arm). The 30-day primary endpoint was all-cause death and MI.[216] Participants in the 0/1-hour arm were more likely to be discharged from the ED (45.1% versus 32.3%, in the standard arm) and the median length of ED stay was also shorter in the 0/1-hour arm, 4.6 hours (IQR: 3.4 to 6.4 hours) versus 5.6 hours (IQR: 4.0 to 7.1 hours) in the standard arm.[216] 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 versus 16/1642 (1.0%) in the standard arm, IRR 1.06 (95% CI: 0.53 to 2.11); non-inferiority was an absolute margin of 0.5% determined by poisson regression.[216]

5.1.2 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 false positives versus this reference standard also have an increased mortality and MI probability, a secondary analysis was conducted which assumed an increased risk of adverse events (MI and mortality) for patients with a false positive hs-cTn test result.

In the base case analysis, standard troponin testing was both most effective and most costly. Strategies considered cost-effective depending upon ICER thresholds were Beckman Coulter ACCESS hsTnI ((symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h)) for willingness to pay thresholds below £8,455 per QALY gained, Roche Elecsys hs-cTnT (ESC 0/1 hour pathway: (symptoms >3 hours AND <5 ng/L at 0 h) OR (<12 ng/L at 0 h AND Δ <3 ng/L at 0 to 1 h)) for

thresholds between £8,455 and £20,190 per QALY gained and Siemens Dimension Vista hs-cTnI (<5 ng/L at 0 h AND Δ <2 ng/L at 0 to 1 h) over £20,190 per QALY gained.

The abovementioned results should however be interpreted while noting that the differences between the strategies in both costs and QALY 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 that are correctly ruled out (i.e. true negatives). 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, making hospital resources available for other patients). It is noticeable that, in the base-case analysis, the high sensitivity test strategies with the highest true negative rates (i.e. 65% or above) involve high sensitivity test strategies with a second test 2 to 3 hour after the initial test (i.e. Siemens Atellica hs-cTnI (High-STEACS pathway), Abbott ARCHITECT hs-cTnI (High-STEACS pathway), Roche Elecsys hs-cTnT (99th centile) and Beckman Coulter ACCESS hs-cTnI ((symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h))).

5.2 Strengths and limitations of assessment

5.2.1 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. Because of the known difficulties in identifying test accuracy studies using study design-related search terms,[217] search strategies were developed to maximise sensitivity at the expense of reduced specificity. Thus, 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 which 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 (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 randomised controlled trials 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.[218] Formal assessment of publication bias in systematic reviews of test accuracy studies remains problematic and reliability is limited.[42] We did not undertake a statistical assessment of publication bias in this review. However, our search strategy included a variety of routes to identify un-published 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 https://www.nice.org.uk/guidance/indevelopment/gid-dg10035/documents. The eligibility of studies for inclusion is therefore transparent. In addition, we have provided specific reasons for exclusion for all of the studies which were considered potentially relevant at initial citation screening and were subsequently excluded on assessment of the full publication (Appendix 4). The review process followed recommended methods to minimise the potential for error and/or bias;[40] studies were independently screened for inclusion by two reviewers and data extraction and quality assessment were done 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.[42] QUADAS-2 is structured into four key domains covering participant selection, index test, reference standard, and the flow of patients through the study (including timing of tests). Each domain is rated for risk of bias (low, high, or unclear); the participant selection, index test and reference standard domain are also, separately rated for concerns regarding the applicability of the study to the review question (low, high, or unclear). Studies which 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 which 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 Appendix 3 and are summarised in section 3.2.2. The methodological quality of included randomised controlled trials was assessed using the revised Cochrane Risk of Bias tool for Randomised Trials (RoB 2.0).[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 '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 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 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 that reported data for a single hs-cTn assay, assessed using QUADAS-2, were considered at high risk of bias for patient flow[110, 137, 141, 147, 157, 159] and a further three were considered at unclear risk of bias.[62, 102, 165] 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 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 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, [7] 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. target condition 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 from our previous systematic review were restricted to patients in whom STEMI had been excluded.[133, 137, 139, 144, 148, 157, 159] This assessment includes a further 13 which were restricted to patients in whom STEMI had been excluded.[58, 61, 62, 64, 68, 72, 80, 84, 96, 101, 115, 171, 176]

The most recent systematic review identified during this assessment, Lee et al. 2019, aimed to compare the diagnostic performance of various accelerated algorithms, using hs-cTn assays, for patients with symptoms suggestive of AMI.[219] This review, by Lee et al, reported summary estimates of sensitivity and specificity for '0 h algorithm', 1 h algorithm, 2 h algorithm and 0-1 h 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., [219] 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 four hour time window corresponding to the target for NHS emergency departments, which specifies that 'no one should be waiting more than four hours in the emergency department from arrival to admission, transfer or discharge.'[201]

This assessment represents an advance upon our previous systematic review,[7] conducted to support the development of DG15,[31] 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 in order 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 about the performance of such strategies, our estimates of their effectiveness and cost-effectiveness relied upon 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.[7]

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,[20] 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 which evaluated the History ECG Age Risk factors Troponins (HEART) score[220] for risk stratification of patients presenting to the ED with chest pain,[221, 222] and which included an assessment of the effect of using hs-cTn (versus conventional troponins) in the heart score. Both studies used the low-risk HEART score (0 to 3) to define the rule-out threshold and reported accuracy data using 30-day to 6-week (short-term) MACE as the reference standard. Van Den Verg and Body 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%).[221] None of the studies in this review compared the performance of the HEART score using a hs-cTn assay versus 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 MACE, reported

differing estimates of sensitivity, 93% (95% CI: 84 to 98%) and 100% (95% CI: 98 to 100%). Laureano-Phillips et al. reported summary sensitivity and specificity estimates, for the original HEART score and the target condition short-term MACE, 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%), the number of studies included in this analysis was unclear.[222] 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 (all time-frame MACE).[222] The findings of these two reviews 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 which include a cardiac troponin 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 h AND <5 ng/L at 0 h) OR (≤16 ng/L (F) ≤34 ng/L (M) at 3 h AND Δ <3 ng/L at 0 to 3 hours), alone and in combination validated clinical risk scores, HEART score ≤3,[220] Global Registry of Acute Coronary Events (GRACE) score ≤108,[223] Thrombolysis Myocardial Infarction (TIMI) score 0 or 1,[224] or Emergency Department Assessment of Chest Pain Score (EDACS) <16.[225] The High-STEACS pathway alone classified 1244/1917 (64.9%) of participants as low-risk (rule-out) and missed instances of NSTEMI at index presentation and 1 further instance during 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%, TIMI 44% and EDACS 41%); 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 h) OR (<5 ng/L at 0 h AND Δ <2 ng/L at 0 to 1 h) 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 four hours (ruled-out), without improving safety.

Our assessment was less comprehensive for the the Beckman Coulter Acces hs-cTnI, Biomérieux VIDAS hs-cTnI, Ortho Clinical Diagnostics VITROS hs-cTnI, Quidel Cardiovascular TriageTrue hs-cTnI, Siemens Healthineers Atellica hs-cTnI, Siemens Healthineers Dimension Vista hs-cTnI, and Siemens Healthineers ADVIA Centaur hs-cTnI assays than for the Roche Elecsys hs-cTnT and the Abbott

ARCHITECT hs-cTnI, because available data were limited for these six assays. Furthermore, we were unable to identify any studies of either the Abbott Alinity hs-cTnI or the Siemens Healthineers Dimension EXL hs-cTnI assay.

5.2.2 Cost-effectiveness

Our cost-effectiveness analysis is 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 diagnostic test accuracy.

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 in order 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 as compared to '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 yet. In addition, there may well be adverse effects associated with early treatment (e.g. the risk of bleeding, unnecessary PCIs, etc.). The Canadian HTA report[191] 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.[226] 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 six 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 assess correctly that a patient is not experiencing a NSTEMI, but some patients with negative test results may still benefit from treatment. To take this possibility into account, a secondary analysis was performed, 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 cost-effectiveness analyses. See clinical review (Chapter 3) for an overview of all high sensitivity troponin strategies that were identified in the literature. For the economic model, only high sensitivity troponin tests that had a sensitivity of 97% or above were selected. Although some of the test strategies with lower sensitivity might potentially be cost-effective, it would be questionable whether these strategies would be considered acceptable for clinicians.

5.3 Uncertainties

5.3.1 Clinical effectiveness

A recent systematic review of sex-specific and overall 99th centiles of hs-cTnI and hs-cTnT derived from healthy reference populations[227] found that 14/16 (87.5%) of hs-cTnI studies and 11/18 (61.1%) of 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." 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 (Table 1, section 2.2.11). Despite this, the effectiveness and cost-effectiveness of using sex-specific threshold for hs-cTn assay remains unclear. Whilst 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-effectivenss modelling, only the High-STEACS pathway utilises sex-specific thresholds.[66, 67] It remains unclear whether the use of sex-specific thresholds in the High-STEACS pathway offers any advantage over the use of a single general population threshold, since no equivalent pathway (using a single general population threshold) has been evaluated.

Our previous systematic review[7] identified some data on the diagnostic performance of hs-cTn testing in clinically important subgroups (older people,[146, 168] and people with and without pre-existing CAD).[140, 168] However, these data were very limited and were only available for the Roche Elecsys hs-cTnT assay. 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 ond over versus those under 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 (eGFR <60 mL/min/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 in section 5.1.1, 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 four 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 acceptible threshold for sensitivity (97%) defined from this assessment, when used in people with known ischemic heart disease, 96% (95% CI: 89 to 99%), compared to 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 upon 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 ≥2 h AND <5 ng/L at 0 h) OR (≤16 ng/L (F) ≤34 ng/L (M) at 3 h 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 ≥2 h AND <5 ng/L at 0 h) OR (≤34 ng/L (F) ≤53 ng/L (M) at 3 h 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 being derived from a study of '1,531 apparently healthy individuals in a US population with normal levels of BNP, HbA1c, and estimated GFR values,' but also recommends that 'each laboratory should verify that the 99th centile is transferable to its own population or establish its own 99th centile.'[17] Similary, the product information leaflet for the Siemens Atellica hs-cTnI asay describes the 99th centile as being derived from 'specimens collected from 2007 apparently healthy individuals from the United States who ranged in age from 22–91 years of age' and also recommends that 'each laboratory should establish its own diagnostic cut off value, which reflects criteria for AMI diagnosis at their institution and is representative of specific populations.'[27]

5.3.2 Cost-effectiveness

The main uncertainties for the cost-effectiveness analysis 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 analysis, the precise implication of false negative test results, where patients are discharged without essential treatment or of false positive 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 cost-effectiveness analysis should be interpreted in the context of potential cost and benefits (e.g. of false negative/ positives) that are not captured in the economic model.

6. CONCLUSIONS

6.1 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 four-hour NHS emergency department 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 whilst 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 for this assessment, the Abbott Alinity hs-cTnI assay and the Siemens Dimension EXL hs-cTnI assay.

From a cost-effectiveness perspective the Roche Elecsys hsTnT (<12 ng/L at 0 h AND Δ <3 ng/L at 0 to 1 h) and Siemens Dimension Vista hs-cTnI (<5 ng/L at 0 h AND Δ <2 ng/L at 0 to 1 h) might be cost-effective for thresholds of £20,000 and £30,000 per QALY gained respectively (base-case). For the secondary analysis, Beckman Coulter ACCESS hs-cTnI ((symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h)) 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 QALY 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 true negatives (i.e. 65% or above) involve high sensitivity tests strategies with a second test 2 to 3 hours after the initial test (i.e. Siemens Atellica hs-cTnI (High-STEACS pathway), Abbott ARCHITECT hs-cTnI (High-STEACS pathway), Roche Elecsys hs-cTnT (99th centile) and Beckman Coulter ACCESS hs-cTnI ((symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h))).

6.2 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, 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: 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.

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APPENDIX 1: LITERATURE SEARCH STRATEGIES

Embase (Ovid): 1974 to 2019/09/25
Searched 26.9.19

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 (12098)
14 troponin t/ or troponin I/ or (60304-72-5 or 77108-40-8).rn. (38060)
15 (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive).ti,ab,ot,hw. (9837120)
16 14 and 15 (21639)
17 13 or 16 (27778)
18 thorax pain/ (84161)
19 ((chest or thorax or thoracic) adj2 (pain$ or discomfort or tight$ or pressure)).ti,ab,ot,hw. (110352)
20 acute coronary syndrome/ (54220)
21 (acute adj2 coronary adj2 syndrome$).ti,ab,ot,hw. (67681)
22 exp heart muscle ischemia/ (91534)
23 exp heart infarction/ (365052)
24 exp Unstable-Angina-Pectoris/ (23610)
25 (preinfarc$ Angina$ or pre infarc$ Angina$).ti,ab,ot,hw. (410)
26 Unstable angina$.ti,ab,ot. (19196)
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. (554354)
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. (163966)
29 or/18-28 (719484)
30 17 and 29 (14259)
31 animal/ (1431471)
32 animal experiment/ (2438936)
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. (6574496)
34 or/31-33 (6574496)

35 exp human/ (20203276)
36 human experiment/ (469138)
37 or/35-36 (20204702)
38 34 not (34 and 37) (5073475)
39 30 not 38 (13490)
40 limit 39 to yr="2013 -Current" (8169)

MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily (Ovid): 1946 to 2019/09/24
Searched 26.9.19

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. (12105)
10 (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive).ti,ab,ot. (7169880)
11 9 and 10 (6385)
12 8 or 11 (8437)
13 chest pain/ (12556)
14 ((chest or thorax or thoracic) adj2 (pain$ or discomfort or tight$ or pressure)).ti,ab,ot,hw. (40643)
15 exp myocardial ischemia/ (419151)
16 (acute adj2 coronary adj2 syndrome$).ti,ab,ot. (29162)
17 (preinfarc$ Angina$ or pre infarc$ Angina$).ti,ab,ot. (321)
18 Unstable angina$.ti,ab,ot. (12789)
19 ((heart$ or myocardi$ or cardiac or coronary) adj2 (preinfarc$ or infarc$ or attack$ or arrest$ or occlusion$ or isch?emia$)).ti,ab,ot. (260414)
20 (MI or ACS or STEMI or NSTE-ACS or NSTEACS or nonSTEMI or NSTEMI or AMI or UAP or OMI).ti,ab,ot. (89398)
21 or/13-20 (570108)
22 12 and 21 (4465)
23 animals/ not (animals/ and humans/) (4585749)
24 22 not 23 (4245)
25 limit 24 to yr="2013 -Current" (2104)

Cochrane Database of Systematic Reviews (CDSR) (Wiley). Issue 9/September 2019
Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley). Issue 9/September 2019
Searched 26.09.19

ID Search Hits
#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 401488
#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 26176
#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 41934
#21 (MI or ACS or STEMI or NSTE-ACS or NSTEACS or nonSTEMI or NSTEMI or AMI or UAP or OMI):ti,ab,kw 17551
#22 #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 63623
#23 #13 and #22 with Cochrane Library publication date Between Sep 2013 and Dec 2019 571

CDSR search retrieved 4 references
CENTRAL search retrieved 567 references (436 when trials and pre 2013 records removed)

LILACS (Latin American and Caribbean Health Sciences): 2013-2019/09/20
http://regional.bvsalud.org/php/index.php?lang=en
Searched 20.09.19

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	159

2019])	
Total	**159**

Science Citation Index – Expanded (SCI) (Web of Science): 1988 –24/9/19
Conference Proceedings Citation Index- Science (CPCI-S) –1990 - 24/9/19
Searched: 25.9.19

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 1, 897

Clinicaltrials.gov (Internet)
http://clinicaltrials.gov/ct2/search/advanced
Searched 20.09.19

Expert search option

First posted from 01/01/2013 – 12/31/2019

Search terms	Condition	Intervention	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			**55**

advia)			
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)**

WHO International Clinical Trials Registry Platform (ICTRP) (Internet)
http://www.who.int/ictrp/en/
Searched 25.09.2019

Advanced search option Title and Intervention combined with OR
Date of registration limited to 01/01/2013 – 25/09/2019

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

Health Technology Assessment Database (https://www.crd.york.ac.uk/CRDWeb/): up to March 2018
Database of Abstracts of Reviews of Effects (DARE) (https://www.crd.york.ac.uk/CRDWeb/): up to March 2015

Searched 26.9.19

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

45 records after date restriction

PROSPERO (International Prospective Register of Systematic Reviews) (Internet): up to 2019/09/20
https://www.crd.york.ac.uk/prospero/#searchadvanced
Searched 20.09.19

Searched in 'All fields'

Terms	Records
Troponin*	112
Limited to 2013-2019	

NIHR Health Technology assessment
https://www.nihr.ac.uk/explore-nihr/funding-programmes/health-technology-assessment.htm

Searched 26.9.19

1 record

https://www.nihr.ac.uk/documents/case-studies/trapid-ami-impact-case-study/21537

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

AACC 2017, 2018, 2019

AHA Scientific Sessions 2017-19

ESC 2019

Additional UK specific Cost Searches

Embase (Ovid): 1974 to 2020 January 09
Searched 10.1.20

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 (12496)
14 troponin t/ or troponin I/ or (60304-72-5 or 77108-40-8).rn. (38546)
15 (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive).ti,ab,ot,hw. (10000737)
16 14 and 15 (22046)
17 13 or 16 (28399)
18 health-economics/ (32473)
19 exp economic-evaluation/ (299466)
20 exp health-care-cost/ (285436)
21 exp pharmacoeconomics/ (199679)
22 or/18-21 (634055)
23 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (1023679)
24 (expenditure$ not energy).ti,ab. (38862)
25 (value adj2 money).ti,ab. (2361)
26 budget$.ti,ab. (37347)
27 or/23-26 (1058833)
28 22 or 27 (1380813)
29 letter.pt. (1099578)
30 editorial.pt. (638530)
31 note.pt. (785740)
32 or/29-31 (2523848)
33 28 not 32 (1262897)
34 (metabolic adj cost).ti,ab. (1461)
35 ((energy or oxygen) adj cost).ti,ab. (4231)
36 ((energy or oxygen) adj expenditure).ti,ab. (30901)
37 or/34-36 (35509)
38 33 not 37 (1255639)
39 exp animal/ (24976369)
40 exp animal-experiment/ (2482604)
41 nonhuman/ (6026401)
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. (5603915)
43 or/39-42 (26921217)
44 exp human/ (20412882)
45 exp human-experiment/ (480344)
46 44 or 45 (20414345)
47 43 not (43 and 46) (6507765)
48 38 not 47 (1144073)
49 17 and 48 (837)
50 limit 49 to yr="2013 -Current" (475)
51 United Kingdom/ (385970)
52 (national health service* or nhs*).ti,ab,in,ad. (334600)

53 (english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) adj5 english)).ti,ab. (41191)
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. (3091729)
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. (2372103)
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. (96722)
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. (327742)
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. (43867)
59 or/51-58 (3767357)
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/) (2999470)
61 59 not 60 (3559996)
62 50 and 61 (67)

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily : 1946 to January 09, 2020
Searched 10.1.20

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. (12356)
10 (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive).ti,ab,ot. (7299032)
11 9 and 10 (6557)
12 8 or 11 (8656)
13 economics/ (27118)
14 exp "costs and cost analysis"/ (231602)
15 economics, dental/ (1909)
16 exp "economics, hospital"/ (24141)
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$).ti,ab. (760923)
21 (expenditure$ not energy).ti,ab. (28754)
22 (value adj1 money).ti,ab. (33)
23 budget$.ti,ab. (28351)
24 or/13-23 (910365)
25 ((energy or oxygen) adj cost).ti,ab. (4005)
26 (metabolic adj cost).ti,ab. (1367)
27 ((energy or oxygen) adj expenditure).ti,ab. (24380)
28 or/25-27 (28784)
29 24 not 28 (903751)
30 letter.pt. (1058044)
31 editorial.pt. (514173)
32 historical article.pt. (356143)
33 or/30-32 (1909174)
34 29 not 33 (868281)
35 12 and 34 (241)
36 limit 35 to yr="2013 -Current" (133)
37 exp United Kingdom/ (359811)
38 (national health service* or nhs*).ti,ab,in. (184469)
39 (english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) adj5 english)).ti,ab. (93416)
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. (1999631)
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. (1349609)
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. (52779)
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. (201032)
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. (24860)
45 or/37-44 (2573849)
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/) (2796611)
47 45 not 46 (2431577)
48 36 and 47 (27)

Economics filters

Centre for Reviews and Dissemination. Search strategies: NHS EED MEDLINE using OvidSP (economics filter) [Internet]. York: Centre for Reviews and Dissemination; 2014 [accessed 2.6.14]. Available from: http://www.crd.york.ac.uk/crdweb/searchstrategies.asp#nhseedmedline

Centre for Reviews and Dissemination. Search strategies: NHS EED EMBASE using OvidSP (economics filter) [Internet]. York: Centre for Reviews and Dissemination; 2014 [accessed 2.6.14]. Available from: http://www.crd.york.ac.uk/crdweb/searchstrategies.asp#nhseedembase

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(3):200-216.

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(2):121-133.

EconLit (EBSCO) 2013-2020/09/01
Searched: 16.01.20

Search modes - Boolean/Phrase

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 EED (https://www.crd.york.ac.uk/CRDWeb/): up to March 2015
Searched 16.1.20

1 MeSH DESCRIPTOR troponin EXPLODE ALL TREES IN NHSEED 15

2 * FROM 2013 TO 2020 25075

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 Details	Selection criteria	Participant details	Assay
ADAPT (ACTRN1261100106994) Aldous 2014[53] **Boeddinghaus 2016[$57]** **Cullen 2013*[156]** **Cullen 2014[$68]** **Eggers 2016[69]** **Greenslade 2015[71]** Meller 2015[118] Parsonage 2013[130] **Van der Linden 2018[109]** Wildi 2017[112] **Country:** Australia and New Zealand **Funding:** The manufacturers (Abbott, Roche and Siemens) provided partial funding **Recruitment:** November 2007 - February 2011 **Number of participants:** 1194	**Inclusion criteria:** Prospectively recruited adults (≥18 years) with possible cardiac symptoms in accordance with the American Heart Association case definitions (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 h before presentation; patients with missing 0 h or 2 h samples. **Patient category:** NSTEMI; 30-day MACE	**Median age (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

Study Details	Selection criteria	Participant details	Assay
ADAPT/IMPACT (ACTRN12611001069943/ ACTRN12611000206921) **Nestelberger 2019**[171] **Country:** Australia **Funding:** ADAPT was supported by research grants from the Emergency Medicine Foundation, the Royal Brisbane and Women's Hospital Foundation and Beckman Coulter and investigational reagents were provided by the manufacturers. No information was reported about the funding of IMPACT **Recruitment:** ADAPT November 2007 - February 2011, IMPACT February 2011 – March 2014 **Number of participants:** 1280	**Inclusion criteria:** Adults (≥18 years), with at least five minutes of symptoms where the attending physician planned to perform serial TnI tests. The American Heart Association 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 acute coronary syndrome 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 another hospital; pregnancy; previous enrolment; inability to be contacted after discharge **Patient category:** NSTEMI	**Median age (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 (hypercholesterolaemia) (%):** 42.3 **Median BMI (IQR):** 28.3 (25.0, 32.8)	Beckman Coulter ACCESS hs-cTnI

Study Details	Selection criteria	Participant details	Assay
Aldous 2012$*[139] **Aldous 2012*[134]** Aldous 2011*[143] **Country:** New Zealand **Funding:** Funded by the National Heart Foundation of New Zealand and assay reagents were provided by the manufacturer (Roche). One author declared personal funding from Abbott **Recruitment:** November 2007 - December 2010 **Number of participants:** 939[139] 385[134]	**Inclusion criteria:** Adults (≥18 years) with symptoms suggestive of cardiac ischemia (acute chest, epigastric, neck, jaw or arm pain or discomfort or pressure without an apparent noncardiac source) **Exclusion criteria:** ST-segment elevation on ECG[139]; unable to provide informed consent; would not be available to follow-up **Patient category:** NSTEMI[139] Mixed[134]	**Median age (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 (IQR):** 28(25, 31) **Median (IQR) time to presentation (hours):** 6.3 (3.3, 13.3)	Roche Elecsys hs-cTnT
Aldous 2011*[147] Aldous 2010*[155] Aldous 2011*[162] **Country:** New Zealand **Funding:** Manufacturers (Roche and Abbott) supplied assays. The study was funded by a New Zealand National Heart Foundation grant **Recruitment:** November 2006 - April 2007 **Number of participants:** 332	**Inclusion criteria:** Consecutive patients presenting to the emergency department with chest pain; participants were eligible for inclusion if the attending clinician had sufficient suspicion of ACS that serial troponins and ECGs were considered necessary **Exclusion criteria:** <18 years; samples not stored for both time points (on admission and at 6-24 hours) **Patient category:** Mixed	**Median age (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 to presentation (hours):** 4.0 (2.0 to 8.6)	Roche Elecsys hs-cTnT
APACE (NCT00470587) Badertscher 2018[54] Badertscher 2018[55] **Boeddinghaus 2017$[58]**	**Inclusion criteria:** Consecutive adults (>18 years) presenting to the ED with symptoms suggestive of AMI (e.g. acute chest pain, angina pectoris at rest, other thoracic sensations) within an onset or peak within the last 12 hours	**Median age (IQR):** 62 (49, 74) **Male (%):** 68 **Previous AMI (%):** 24 **Previous CAD (%):** 33	Roche Elecsys hs-cTnT; Abbott ARCHITECT hs-cTnI; Siemens

Study Details	Selection criteria	Participant details	Assay
Boeddinghaus 2018[59] Boeddinghaus 2019[60] Boeddinghaus 2019[123] **Boeddinghaus 2019**[170] Cullen 2013*[156] Hoeller 2013*[168] Haaf* 2012[136] Hochholzer 2011*[149] Irfan 2013*[158] Jaeger 2016[74] **Kaier 2017**[75] **Lindahl 2017**[132] Potocki 2012*[140] **Reichlin 2015**[90] **Reichlin 2015**[91] Reiter 2011*[146] Reiter 2012*[138] Reichlin 2009*[167] Reichlin 2011*[145] **Rubini Gimenez 2014**[70] **Rubini Gimenez 2015**[92] Rubini Gimenez 2015[93] **Rubini Gimenez 2016**[94] Twerenbold 2017[105] Twerenbold 2017[103] **Twerenbold 2017**[104] **Twerenbold 2018**[106] Twerenbold 2018[107] **Twerenbold 2019**[108] Wildi 2016[111] Wildi 2019[113] **Country:** Czechia, Italy, Poland, Spain and Switzerland	**Exclusion criteria:** Terminal kidney failure requiring dialysis **Patient category:** Mixed	**Previous Revascularisation (%):** 27 **Diabetes (%):** 18 **Smoking (%):** 25 **Hypertension (%):** 61 **Dyslipidaemia (hypercholesterolemia) (%):** 49 **Median BMI (IQR):** 27 (24, 30)	Healthineers ADVIA Centaur hs-cTnI; Siemens Healthineers Dimension Vista hs-cTnI

Study Details	Selection criteria	Participant details	Assay
Funding: Swiss National Science Foundation, Swiss Heart Foundation, Department of Internal Medicine of the University Hospital Basel, Roche, Siemens, Abbott, Brahms, nanosphere, and 8sense **Recruitment:** April 2006 - August 2011 **Number of participants:** 2245			
BACC (NCT02355457) **Neumann 2016[$84]** Neumann 2017[85] Neumann 2017[86] **Country:** Germany **Funding:** This study was supported by the German Center of Cardiovascular Research and an unrestricted grant from Abbott Diagnostics. **Recruitment:** July 2013 – December 2014 **Number of participants:** 1040	**Inclusion criteria:** Adults (>18 years) presenting to the ED with symptoms suggestive of AMI **Exclusion criteria:** STEMI **Patient category:** NSTEMI	**Median age (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 (hyperliporoteinemia) (%):** 43.8 **Median BMI (IQR):** 26.0 (23.5, 29.4)	Abbott ARCHITECT hs-cTnI

Study Details	Selection criteria	Participant details	Assay
BEST **Body 2019**[$115] **Body 2020**[172] **Country:** UK **Funding:** Manchester University NHS Foundation Trust. Singulex loaned the Singulex Clarity® System and Roche provided reagents without charge for this study **Recruitment:** NR **Number of participants:** 665	**Inclusion criteria:** Adults (>18 years of age) who presented to the ED with pain, discomfort, or pressure in the chest, epigastrium, neck, jaw, or upper limb without an apparent noncardiac source, which warranted investigation for possible ACS **Exclusion criteria:** Patients with peak symptoms occurring >12 h before enrolment, those with unequivocal ST elevation myocardial infarction, those with another medical condition requiring hospital admission, and patients lacking the mental capacity to provide written informed consent were excluded. **Patient category:** NSTEMI	**Mean age (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
Body 2011*[161] Body 2011*[153] Body 2010*[169] **Country:** UK **Funding:** Central Manchester NHS Trust **Recruitment:** January 2006 - February 2007 **Number of participants:** 703	**Inclusion criteria:** Presenting to ED with chest pain; age >25 years and chest pain within previous 24h that initial treating physician suspected may be cardiac in nature. **Exclusion criteria:** renal failure requiring dialysis, trauma with suspected myocardial contusion, or another medical condition mandating hospital admission or if they did not consent to and provide a blood sample for use by the research team **Patient category:** Mixed	**Mean age (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 hours	Roche Elecsys hs-cTnT

Study Details	Selection criteria	Participant details	Assay
Body 2015[56] **Country:** UK **Funding:** UK College of Emergency Medicine. High-sensitivity cardiac troponin 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 pregnancy; non-English speakers; prisoners (for ethical reasons); and those in whom all means of follow-up would be impossible **Patient category:** Mixed; 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 2019[62] **Country:** Italy **Funding:** Not stated **Recruitment:** November 2011 to October 2015 (derivation cohort) **Number of participants:** 6403 (derivation cohort	**Inclusion criteria:** Adults (≥18 years) with suspect NSTEMI arriving at the ED within a median time of 3.4 hours with 3 serial time point measures of hs-cTnT. **Exclusion criteria:** Patients with STEMI or with unclassified AMI (due to rapid transfer to other hospitals or death occurring before AMI classification). **Patient category:** NSTEMI	**Median age (IQR):** 73 (59, 82) **Male (%):** 55.4 **White (%):**NR **No further participant characteristics were reported**	Roche Elecsys hs-cTnT

Study Details	Selection criteria	Participant details	Assay
Christ 2010*[150] **Country:** Germany **Funding:** hs-cTnT test kits were provided by Roche **Recruitment:** 7/9/2009 - 21/9/2009 **Number of participants:** 137	**Inclusion criteria:** Consecutive patients with acute chest pain of possible coronary origin presenting to the emergency department **Exclusion criteria:** NR **Patient category:** Mixed	**Mean age (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 (SD):** 28(5) **Time to presentation:** 0-2h 36%; 2-6h 22%; 6-24 h 33%; >24h 20%	Roche Elecsys hs-cTnT
CORE **Borna 2018[116]** Mokhtari 2016[119] **Mokhtari 2016$[121]** **Mokhtari 2017[120]** **Country:** Sweden **Funding:** The study was funded by an ALF research grant at Skåne University Hospital and by a grant from Region Skåne, which are national grants from the Swedish government. **Recruitment:** February 2013 to April 2014 **Number of participants:** 1138	**Inclusion criteria:** Adults (≥18 years), with a primary symptom of nontraumatic chest pain, and for whom hs-cTnT was ordered at presentation (0 hours) were enrolled during weekdays between 9 AM and 9 PM. **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 (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

Study Details	Selection criteria	Participant details	Assay
FASTER I and FAST II **Eggers 2012*[137]** **Country:** Sweden **Funding:** Swedish Society of Medicine and the Selander Foundation **Study Name:** FASTER 1-study and FAST II study **Recruitment:** May 2000 (FAST II), October 2002 (FASTER I) - March 2001 (FAST II), August 2003 (FASTER I) **Number of participants eligible (enrolled):** 495(360)	**Inclusion criteria:** Chest pain with ≥15 min duration within the last 24h (FAST II-study), or the last 8 h (FASTER I-study). Analysis restricted to patients with symptom onset <8h. **Exclusion criteria:** ST-segment elevation on the admission 12-lead ECG leading to immediate reperfusion therapy or its consideration was used as exclusion criterion. **Patient category:** NSTEMI	**Median age (IQR):** 67 (58, 76) **Male (%):** 66 **Previous AMI (%):** 38 **Previous Revascularisation (%):** 18 **Diabetes (%):** 18 **Smoking (%):** 18 **Hypertension (%):** 43 **Dyslipidaemia (%):** 38 **Delay <4 hours (%)**: 40	Roche Elecsys hs-cTnT
Freund 2011*[142] Freund 2010*[166] **Country:** France **Funding:** Assay kits for the study were provided by the manufacturers (Roche) **Study Name:** **Recruitment:** August 2005 - January 2007 **Number of participants:** 317	**Inclusion criteria:** Consecutive adults (>18 years) presenting to the emergency department with chest pain suggestive of ACS (onset or peak within the previous 6 hrs) **Exclusion criteria:** Patients with acute kidney failure requiring dialysis were excluded **Patient category:** Mixed (13 were STEMI and 32 NSTEMI)	**Mean (SD):** 57 (17) **Male (%):** 65 **Previous CAD (%):** 26 **Family History (%):** 32 **Diabetes (%):** 14 **Smoking (%):** 40 **Hypertension (%):** **Dyslipidaemia (%):** 36	Roche Elecsys hs-cTnT

Study Details	Selection criteria	Participant details	Assay
High-STEACS (NCT01852123) **Bularga 2019**[$61] **Chapman 2017**[65] **Chapman 2018**[66] **Chapman 2019**[67] **Miller-Hodges 2018** [79] Shah 2015[98] **Country:** UK (Scotland) **Funding:** This trial was funded by the British Heart Foundation (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 cardiac troponin assay reagents, calibrators, and controls without charge. **Recruitment:** June 2013 to March 2016 **Number of participants:** 32837	**Inclusion criteria:** All patients presenting to the ED were screened by the attending clinician and prospectively included in the trial if cardiac troponin was requested for suspected acute coronary syndrome. **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 myocardial infarction were excluded. **Patient category:** NSTEMI; 30-day MACE	**Mean age (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 Healthineers Atellica hs-cTnI

Study Details	Selection criteria	Participant details	Assay
High-US Nowak 2019[128] Nowak 2019[129] **Sandoval 2019[$176]** **Country:** USA **Funding:** Siemens Healthineers **Recruitment:** April 2015 to April 2016 **Number of participants:** 2212	**Inclusion criteria:** ED patients 22 years of age or older with suspected acute MI. Patients to have at least 1 hs-cTnI concentration available at presentation using both the Atellica and ADVIA Centaur assays. **Exclusion criteria:** Patients in whom results were not available for either 1 or both assays, did not have a valid baseline hs-cTnI result, did not have a 12-lead electrocardiogram (ECG), in whom post-discharge follow-up was missing, or presented with STEMI were excluded from analyses. **Patient category:** NSTEMI	**Mean age (SD):** 57 (13) **Male (%):** 56.0 **White (%):** 56.0 **Previous CAD (%):** 38.0 **Diabetes (%):** 30.0 **Smoking (%):** 27.0 **Hypertension (%):** 70.0	Siemens Healthineers Atellica hs-cTnI; Siemens Healthineers ADVIA Centaur hs-cTnI
Huang 2015[72] Guangquan 2016[73] **Country:** China **Funding:** Roche Diagnostics GmbH in Shanghai **Recruitment:** July 2009 to December 2013 **Number of participants:** 2249	**Inclusion criteria:** Suspected diagnosis of AMI (chest pain onset <12h) presenting at the emergency department **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; Mixed	**Mean age (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

Study Details	Selection criteria	Participant details	Assay
Keller 2011*[141] Keller 2011*[163] **Country:** Germany **Funding:** Abbott Diagnostics provided study funding **Recruitment:** January 2007 - December 2008 **Number of participants:** 1818	**Inclusion criteria:** Consecutive adults (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; anaemia (haemoglobin <10 g/dL) **Patient category:** Mixed	**Mean age (sd):** 61(14) **Male (%):** 66 **Previous CAD (%):** 36 **Family History (%):** 32 **Diabetes (%):** 16 **Smoking (%):** 24 **Hypertension (%):** 74 **Dyslipidaemia (%):** 73 **Mean BMI (sd):** 28(5)	Abbott ARCHITECT hs-cTnI
Kurz 2011*[148] **Country:** Germany **Funding:** Investigators were supported by Roche diagnostics and assay kits were also provided by the manufacturer **Recruitment:** May 2008 - 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 (GFR <60 mL/min/1.73 m^2); patients undergoing PCI during follow-up sampling **Patient category:** NSTEMI	**Mean age (sd):** 66(11) **Male (%):** 71 **Previous AMI (%):** 37 **Previous CAD (%):** 50 **Previous Revascularisation (%):** 17 **Family History (%):** 32 **Diabetes (%):** 31 **Smoking (%):** 22 **Hypertension (%):** 78 **Dyslipidaemia (%):** 65 **Median symptom onset (IQR, minutes):** 358 (152, 929) **BMI (95% CI/range/IQR):** 28(4)	Roche Elecsys hs-cTnT

Study Details	Selection criteria	Participant details	Assay
Lin 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 (25 years and over) presenting to the ED, from Monday to Friday, from 0800 to 2100 hours, with symptoms suggestive of ACS (e.g. chest pain or angina equivalent). **Exclusion criteria:** STEMI; end-stage renal failure; on cardiac troponin obtained as part of standard care; lost to follow-up **Patient category:** 30-day MACE	**Median age (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
Melki 2011*[144] Melki 2010*[154] **Country:** Sweden **Funding:** Partially supported by a grant from Roche Diagnostics, who also provided reagents. Also supported by the Swedish Heart and Lung Foundation and National Board of Health and Welfare **Recruitment:** August 2006 - 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 (IQR):** 65 (55, 76) **Male (%):** 67 **Previous AMI (%):** 30 **Previous Revascularisation (%):** 21 **Diabetes (%):** 23 **Smoking (%):** 17 **Hypertension (%):** 50 **Mean symptom onset (95% CI/range/IQR, hours):** 5 (3, 8)	Roche Elecsys hs-cTnT

Study Details	Selection criteria	Participant details	Assay
Peacock 2018[$89] **Chang 2018**[124] **Country:** USA **Funding:** Roche Diagnostics **Recruitment:** 2011 to 2015 **Number of participants:** 1679	**Inclusion criteria:** Adults (21 years or over) 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, surgery (including percutaneous coronary intervention) or hospitalization within the last 3 months, recent cardioversion or defibrillation, acute noncardiac primary illness prior to enrolment (e.g., severe sepsis), cardiogenic shock, and pregnancy. **Patient category:** Mixed; MACE	**Median age (IQR):** 55 (47, 64) **Male (%):** 51.6 **Previous CAD (%):** 26.5 **Previous AMI (%):** 18.6 **Previous Revascularisation (%):** 22.5 **Diabetes (%):** 26.1 **Smoking (%):** 30.5 **Hypertension (%):** 66.2 **Dyslipidaemia (%):** 50.1 **Median BMI (IQR):** 29.9 (25.9, 35.4)	Roche Elecsys hs-cTnT STAT

Study Details	Selection criteria	Participant details	Assay
PITAGORAS **Sanchis 2012*[135]** **Country:** Spain **Funding:** Supported by a grant from Roche Diagnostics **Recruitment:** NR **Number of participants:** 446	**Inclusion criteria:** Patients presenting to the emergency department with chest pain of possible coronary origin and onset of pain within the previous 24 hrs **Exclusion criteria:** Exclusion criteria: persistent ST-segment elevation on ECG; troponin elevation in any of 2 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 performance exercise test; structural heart disease different to ischemic heart disease; concomitant heart failure or significant bradyarrhythmia (<55 beat/min) or tachyarrhythmia (>110 beat/min) at admission. **Patient category:** NSTEMI	**Mean age (sd):** 60(12) **Male (%):** 59 **Family History (%):** 14 **Diabetes (%):** 20 **Smoking (%):** 25 **Hypertension (%):** 54 **Dyslipidaemia (%):** 46	Roche Elecsys hs-cTnT

Study Details	Selection criteria	Participant details	Assay
QUART (ACTRN12610000053022) Parsonage 2013*[151] Parsonage 2013[131] **Parsonage 2014[$88]** **Country:** Australia **Funding:** Queensland Emergency Medicine research Foundation and Roche Diagnostics **Recruitment:** November 2008 to February 2011 **Number of participants:** 764	**Inclusion criteria:** Consecutive, adult (≥18 years) patients presenting during office hours to a single, large, metropolitan tertiary hospital emergency department with symptoms suggestive of cardiac chest pain **Exclusion criteria:** Patients were excluded for any of the following: a clear cause of symptoms other than acute coronary syndrome (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 (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
RATPAC (Point of care arm) **Collinson 2013*[159]** Collinson 2012*[164] Collinson 2012*[152] **Country:** UK **Funding:** UK Health Technology Assessment Programme **Recruitment:** February 2007 - June 2008 **Number of participants:** 850	**Inclusion criteria:** Patients presenting to the emergency department 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 hr) or recurrent typical cardiac-type pain; proven or suspected serious non-cardiac pathology (e.g. PE); co-morbidity or social problems requiring hospital admission even if AMI ruled out; obvious non-cardiac cause of chest pain (e.g. pneumothorax or muscular pain); presentation >12 hrs after most significant episode of pain **Patient category:** NSTEMI	**Median age (IQR):** 54 (44, 64) **Male (%):** 60 **Previous AMI (%):** 40 **Previous Family History (%):** **Previous Revascularisation (%):** 1 **Diabetes (%):** 8 **Smoking (%):** 28 **Hypertension (%):** 35 **Dyslipidaemia (%):** 24 **Median (IQR) time to presentation (hours):** 8.25 (5.17 to 12.30)	Roche Elecsys hs-cTnT

Study Details	Selection criteria	Participant details	Assay
REACTION-US **Nowak 2018**[87] Nowak 2018[127] **Country:** USA **Funding:** The Henry Ford Health System, Detroit, USA and Roche Diagnostics **Recruitment:** NR **Number of participants:** 569	**Inclusion criteria:** Convenience sample (patients screened when research co-ordinators were available) of adults (>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 lifesaving 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 (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 (hypercholesterolaemia) (%):** 50.3 **Median (IQR) time to presentation (hours):** 8.7 (2.3, 41.5)	Roche Elecsys hs-cTnT

Study Details	Selection criteria	Participant details	Assay
ROMI-3 (NCT01994577) Kavasak 2017[76] **Shortt 2017$[101]** **Country:** Canada **Funding:** Canadian Institutes of Health Research, Abbott Laboratories, Roche Diagnostics, Healthcare Diagnostics, Ortho Clinical Diagnostics, Randox Laboratories, and Beckman Coulter and CADTH **Recruitment:** May 2013 to August 2013 **Number of participants:** 1137	**Inclusion criteria:** Adults (≥18 years) presenting to the ED with symptoms of and investigated for ACS (i.e., Tn ordered by an ED physician) **Exclusion criteria:** Patients were excluded if they met any of the following exclusion criteria before TnI testing: death (all-cause); STEMI; and serious ventricular cardiac dysrhythmia. Patients who had any of the 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, or who were previously enrolled or transferred from another primary care facility **Patient category:** NSTEMI	**Mean (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 **Dyslipidaemia (hypercholesterolemia) (%):** 59.5	Roche Elecsys hs-cTnT; Abbott ARCHITECT hs-cTnI
Saenger 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 - NR **Conference abstract only** **Number of participants:** 288	**Inclusion criteria:** Patients presenting to the emergency department with symptoms suggestive of AMI **Exclusion criteria:** None reported **Patient category:** Mixed **Details:** NSTEMI 19%, STEMI 15%	No further participant details reported	Roche Elecsys hs-cTnT

Study Details	Selection criteria	Participant details	Assay
Sebbane 2013*[157] **Country:** France **Funding:** Study funded by the hospital, with assay reagents supplied by the manufacturers **Recruitment:** December 2009 - November 2011 **Number of participants:** 248	**Inclusion criteria:** Adults presenting to the emergency department with chest pain of recent (within 12 hrs 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 2 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 (IQR):** 61 (48, 75) **Male (%):** 63	Roche Elecsys hs-cTnT
Shiozaki 2017[100] **Country:** Japan and Taiwan **Funding:** This work was supported by JSPSKAKENHI grant number JP24591070 **Recruitment:** November 2014 to April 2015 **Number of participants:** 413	**Inclusion criteria:** Patients presenting with chest pain suggestive of ACS in whom the attending physician planned to perform serial biomarker tests **Exclusion criteria:** STEMI, staff considered recruitment inappropriate (e.g. terminal illness), trauma which may have increased troponin levels **Patient category:** NSTEMI	**Median age (IQR):** 72 (59, 81) **Male (%):** 60.8 **Previous Revascularisation (%):** 24.9 **Diabetes (%):** 26.9 **Smoking (%):** 18.9 **Hypertension (%):** 63.9 **Dyslipidaemia (%):** 60.5 **Median BMI (IQR):** 23.3 (20.6, 25.8)	Roche Elecsys hs-cTnT

Study Details	Selection criteria	Participant details	Assay
Slagman 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 POC-TnT 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 (IQR):** 61 (45, 73) **Male (%):** 57.2 **Family History (%):** 32.0 **Diabetes (%):** 22.8 **Smoking (%):** 34.2 **Hypertension (%):** 18.4 **Dyslipidaemia (hypercholesterolaemia) (%):** 9.6 **Median BMI (IQR):** 27 (24, 30)	Roche Elecsys hs-cTnT
TRAPID-AMI Body 2015[122] **Body 2016**[114] McCord 2017[126] **Mueller$ 2016**[80] Mueller-Hennessen 2016[81] **Mueller-Hennessen 2017**[82] Mueller-Hennessen 2019[83] **Country:** Belgium, Germany, Italy, Switzerland, Spain, Sweden, UK, USA, Australia **Funding:** Roche Diagnostics **Recruitment:** April 2011 to June 2013 **Number of participants:** 1282	**Inclusion criteria:** Adults (≥18 years) presenting to the ED with symptoms suggestive of acute myocardial infarction (such as acute chest pain and angina pectoris) 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 hospitalized for acute myocardial infarction within the last 3 weeks; and pregnant and breastfeeding women were excluded. **Patient category:** NSTEMI; mixed; 30-day MACE	**Median age (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 (hypercholesterolaemia) (%):** 10.8	Roche Elecsys hs-cTnT

Study Details	Selection criteria	Participant details		Assay
TRUST (ISRCTN No. 21109279) **Carlton 2015**[63] **Carlton 2015**[$64] **Country:** UK **Funding:** This study was funded by the College of Emergency Medicine of the UK and Bournemouth University, 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)	**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 or older and had at least 5 minutes of chest pain suggestive of acute coronary syndrome, and for whom the attending physician 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 noncardiac source, in accordance with the American Heart Association 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 Twave 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 or older, atypical symptoms in the absence of chest discomfort, a clear non-acute coronary syndrome 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	**Roche hs-cTnT cohort** **Mean age (SD):** 58.0 (13.3) **Male (%):** 58.8 **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 (IQR) time to presentation (hours):** 2.4	**Abbott hs-cTnI cohort** **Mean age (SD):** 57.9 (13.0) **Male (%):** 59.4 **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 (IQR) time to presentation (hours):** 2.3	Roche Elecsys hs-cTnT; Abbott ARCHITECT hs-cTnI

Study Details	Selection criteria	Participant details	Assay
TUSCA **Santaló 2013*[133]** **Country:** Spain **Funding:** Reagents and logistical support were provided by Roche diagnostics **Study Name:** TUSCA study **Recruitment:** NR **Number of participants:** 358	**Inclusion criteria:** Adult (>18 years) described as presenting with acute coronary syndromes and symptom duration ≥5 min; population included 174 people with a final diagnosis of non-acute coronary syndromes. **Exclusion criteria:** Exclusion criteria: ST-segment elevation; new left bundle branch block; pre-admission thrombolytic therapy; defibrillation or cardioversion before sampling; pregnancy; renal failure requiring dialysis; unstable angina within 2 months; CABG within 3 month **Patient category:** NSTEMI	**Mean age (range):** 69 (27, 93) **Male (%):** 68 **Previous CAD (%):** 35 **Diabetes (%):** 26 **Hypertension (%):** 62 **Presentation within 3 hours:** 46.2%	Roche Elecsys hs-cTnT
UTROPIA (NCT02060760) Dodd 2019[125] **Sandoval 2017[95]** **Sandoval 2017[$96]** **Country:** USA **Funding:** Abbott Diagnostics; the Minneapolis Medical Research Foundation **Recruitment:** February 2014 to May 2014 **Number of participants:** 1631	**Inclusion criteria:** Consecutive, unselected patients, in whom initial pre-set serial TnI 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 TnI measurement at presentation and at least one additional TnI measured within 24 hours of presentation before discharge and at least one 12-lead electrocardiogram **Exclusion criteria:** Age <18 years, STEMI, pregnancy, trauma, declined to participate on research as documented on information disclosure, did not present through the emergency department, or were transferred from an outside hospital **Patient category:** NSTEMI	**Mean age (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

Study Details	Selection criteria	Participant details	Assay
Venge 2017[110] **Country:** Germany, France Austria and the Netherlands **Funding:** NR **Recruitment:** NR **Number of participants:** 450	**Inclusion criteria:** Adults (≥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 (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 (range):** 26.4 (15.9, 50.6	Abbott ARCHITECT hs-cTnI

* Publication included in the assessment report for DG15[7]

$ Publication(s) from which participant details have been taken

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

Table36: Index test and reference standard details

Study Details	High sensitivity troponin details (ng/L)				Reference standard details			
	Assay(s)	LoD	99th Centile	Coefficient of variation	Target Condition(s)	Reference standard	Standard troponin	Observer
ADAPT (ACTRN12611001069943) Aldous 2014[53] **Boeddinghaus 2016[57]** **Cullen 2013*[156]** **Cullen 2014$[68]** Eggers 2016[69] **Greenslade 2015[71]** Meller 2015[118] Parsonage 2013[130] **Van der Linden 2018[109]** Wildi 2017[112]	Abbott ARCHITECT hs-cTnI Roche Elecsys hs-cTnT	1.9 5	26.2 14	<5% at 26.2 10% at 13	NSTEMI MACE	Third universal definition of AMI.[33] The criteria for a MACE included any of the following: death (excluding clearly noncardiac), cardiac arrest, AMI, emergency revascularization procedure, cardiogenic shock, ventricular arrhythmia requiring intervention, and high-degree atrioventricular block requiring intervention, within 30 days after initial presentation	Conventional troponins were measured using Abbott Diagnostics TnI (LoD 10 ng/L, 99th centile 28 ng/L, CV <10% at 32 ng/L, decision threshold 30 ng/L) or Beckman Coulter 2nd generation Accutane (LoD 10 ng/L, 99th centile 40 ng/L, CV <10% at 60 ng/L, decision threshold 40 ng/L) Serial sampling up to at least 6 hours	Adjudication of all cardiac endpoints was made by two cardiologists, with consultation of a third cardiologist in case of disagreement. Cardiologists had knowledge of the clinical record, ECG, Tn results and objective testing from standard care.
ADAPT/IMPACT (ACTRN12611001069943/ ACTRN12611000206921) **Nestelberger 2019[171]**	Beckman Coulter ACCESS hs-cTnI	2.3	18; F 12; M 20	<10% at 18	NSTEMI	Third universal definition of AMI[33]	NR	Two independent cardiologists not directly involved in patient care reviewed all available medical records (including patient history, physical examination, results of laboratory testing including hs-cTnT concentrations, radiologic testing, ECG, echocardiography, cardiac exercise test, lesion severity and morphology in coronary angiography, discharge summary) pertaining to the

Study Details	High sensitivity troponin details (ng/L)				Reference standard details			
	Assay(s)	**LoD**	**99th Centile**	**Coefficient of variation**	**Target Condition(s)**	**Reference standard**	**Standard troponin**	**Observer**
								patient from the time of ED presentation to 30-day follow-up.
Aldous 2012*[139] **Aldous 2012*[134]** Aldous 2011*[143]	Roche Elecsys hs-cTnT	5	14	<10% at 13	NSTEMI	ACC[228]	Conventional troponins were measured using Abbott Diagnostics TnI (LoD 10 ng/L, 99th centile 28 ng/L, CV <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
Aldous 2011*[147] Aldous 2010*[155] Aldous 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, CV <10% at 32 ng/L) Change (rise or fall) in TnI 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

Study Details	High sensitivity troponin details (ng/L)				Reference standard details			
	Assay(s)	LoD	99th Centile	Coefficient of variation	Target Condition(s)	Reference standard	Standard troponin	Observer
APACE (NCT00470587)	Roche Elecsys hs-cTnT	5	14	10% at 13	NSTEMI; AMI; MACE	Third universal definition of AMI[33]	Myocardial necrosis was diagnosed by at least one conventional Tn 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) applying the universal definition of AMI by using 2 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, ECG, 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. In situations of disagreement about the diagnosis, cases were reviewed and adjudicated in conjunction with a third cardiologist.
Badertscher 2018[54]	Abbott ARCHITECT hs-cTnI	1.9	26.2	<5% at 1.9				
Badertscher 2018[55]								
Boeddinghaus 2017[58]	Beckman Coulter Access hs-cTnI	2.3	18	<5% at 18				
Boeddinghaus 2018[$59]								
Boeddinghaus 2019[$60]								
Boeddinghaus 2019[123]	Siemens Healthineers ADVIA Centaur hs-cTnI	2.2	47	<5% at 47				
Boeddinghaus 2019[$170]								
Cullen 2013*[156]								
Hoeller 2013*[168]	Siemens Healthineers Dimension Vista hs-cTnI	0.5	9	10% at 3				
Haaf* 2012[136]								
Hochholzer 2011*[149]								
Irfan 2013*[158]								
Jaeger 2016[74]								
Kaier 2017[75]		0.4	11	<7% at 11				
Lindahl 2017[$132]	Ortho VITROS hs-cTnI							
Potocki 2012*[140]								
Reichlin 2015[90]		1.3 to 3.2	19	7% at 19				
Reichlin 2015[91]	bioMérieux VIDAS hs-							
Reiter 2011*[146]								

Study Details	High sensitivity troponin details (ng/L)				Reference standard details			
	Assay(s)	LoD	99th Centile	Coefficient of variation	Target Condition(s)	Reference standard	Standard troponin	Observer
Reiter 2012*[138] Reichlin 2009*[167] Reichlin 2011*[145] **Rubini Gimenez 2014[70]** **Rubini Gimenez 2015[92]** Rubini Gimenez 2015[93] **Rubini Gimenez 2016[94]** Twerenbold 2017[105] Twerenbold 2017[103] **Twerenbold 2017[104]** **Twerenbold 2018[106]** Twerenbold 2018[107] **Twerenbold 2019[108]** Wildi 2016[111] Wildi 2019[113]	cTnI							
BACC **Neumann 2016[84]** Neumann	Abbott ARCHITECT hs-cTnI	1.9	27	10% at 5.2	NSTEMI	ESC[34]	Roche Elecsys hs-cTnT on admission and at 3 hours	The final diagnosis was adjudicated based on all available clinical and imaging results, ECG, standard laboratory testing, including hs-

Study Details	High sensitivity troponin details (ng/L)				Reference standard details			
	Assay(s)	**LoD**	**99th Centile**	**Coefficient of variation**	**Target Condition(s)**	**Reference standard**	**Standard troponin**	**Observer**
2017[85] Neumann 2017[86]								cTnT. The final diagnosis of all patients was made by 2 cardiologists independently and disagreements were resolved by consultation with a third cardiologist.
BEST **Body 2019[$115]** **Body 2020[$172]**	Roche Elecsys hs-cTnT Siemens ADVIA Centaur hs-cTnI	5 1.6	14 (16 in males, 9 in female) 47	<10% at 5 <10% at 6	NSTEMI	Third universal definition of AMI[33]	Roche Elecsys hs-cTnT on admission and at 3 hours	Outcomes were adjudicated by 2 independent investigators based on all available clinical data up to 30 days after presentation
Body 2011*[161] Body 2011*[153] Body 2010*[169]	Roche Elecsys hs-cTnT	5	14	<10% at 9	AMI	Joint ESC, ACC, AHA and World Heart Federation (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 to represent a significant rise, fall, or both based on the analytical performance of the cTnT assay. Timing: at least 12 h after the onset of the most significant	2 independent investigators who had all clinical, laboratory, and imaging data available for review, but who were blinded to hs-cTnT levels.

Study Details	High sensitivity troponin details (ng/L)				Reference standard details			
	Assay(s)	**LoD**	**99th Centile**	**Coefficient of variation**	**Target Condition(s)**	**Reference standard**	**Standard troponin**	**Observer**
							symptoms.	
Body 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 myocardial infarction, or ischemic ECG changes. MACE within 30 days was defined as death, incident AMI, or the need for coronary revascularization 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, CV <10% at 0.035 µg/L, LoD 0.01 µg/L) at the time of arrival in the ED and 12 h after symptom onset.	The primary outcome of AMI was adjudicated by 2 independent investigators with all clinical, laboratory, and imaging data (including reference standard 12-h cTnT concentrations) available for review but blinded to investigational assay (hs-cTnT) results. Disagreements were resolved by discussion.
Cappellini 2019[62]	Roche Elecsys hs-cTnT	5	14	NR	NSTEMI	AMI according to Third Universal definition of Myocardial Infarction[33]	NR	Final diagnoses were made by the attending ED physician if participants were not hospitalised and by a physician of the specific medical unit in the case of hospitalisation with cardiologist consultations when required.
Christ 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 to the cTnT levels admission) with at least	Two independent consultants

Study Details	High sensitivity troponin details (ng/L)				Reference standard details			
	Assay(s)	LoD	99th Centile	Coefficient of variation	Target Condition(s)	Reference standard	Standard troponin	Observer
							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 coronary artery disease, and cardiac pain without necrosis was defined as a typical patient history and clinical signs of cardiac pain without increased levels of cTnT. Unstable angina was diagnosed when a patient had normal troponin levels and typical angina at rest or exercise, or a cardiac catheterization result compatible with the diagnosis. cTnT cut-off level of 0.04 ug/L, *Timing:* At presentation and about 6 hours at discretion of physician	
CORE **Borna 2018**[116] Mokhtari 2016[119] **Mokhtari 2016**[121] **Mokhtari 2017**[120]	Roche Elecsys hs-cTnT	5	14	<10% at 14	MACE	MACE were defined as an adjudicated diagnosis of AMI, unstable angina, cardiac arrest, cardiogenic shock, ventricular arrhythmia requiring intervention, high-degree atrioventricular block requiring intervention, or death from a cardiac or unknown cause.	Roche Elecsys hs-cTnT	MACE was 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 2-3 cardiologists.

Study Details	High sensitivity troponin details (ng/L)				Reference standard details			
	Assay(s)	**LoD**	**99th Centile**	**Coefficient of variation**	**Target Condition(s)**	**Reference standard**	**Standard troponin**	**Observer**
						AMI was defined according to the universal definition, requiring a significant increase or decrease of hs-cTnT levels, with at least 1 value above the 99th centile, combined with symptoms or signs of cardiac ischaemia.		
FASTER I and FAST II **Eggers 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 ≥0.05 µg/L within 24 h. 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 h following enrolment	Not reported
Freund 2011*[142] Freund 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, USA or Access analyser Beckman Coulter Inc., Brea, USA). Threshold for Siemens assay 140 ng/L, CV ≤10% Threshold for Beckman assay 60 ng/L, CV 10%	Two independent emergency department physicians, who were blinded to hs-cTnT results. Disagreements were adjudicated by a third emergency department physician.

Study Details	High sensitivity troponin details (ng/L)				Reference standard details			
	Assay(s)	**LoD**	**99th Centile**	**Coefficient of variation**	**Target Condition(s)**	**Reference standard**	**Standard troponin**	**Observer**
							Timing: On presentation and at 3-9 hours if needed	
High-STEACS Bularga 2019[61] Chapman 2017[65] Chapman 2018[$66] Chapman 2019[$67] Miller-Hodges 2018 [79] Shah 2015[98]	Abbott ARCHITECT hs-cTnI	2	16 (F), 34 (M)	10% at 4.7	NSTEMI; MACE	Third universal definition of AMI[33]	NR	Two physicians from our adjudication panel independently reviewed all clinical information to classify patients with any high-sensitivity cardiac troponin measurement >99th centile on serial testing during the index presentation in accordance with the third universal definition of myocardial infarction. Myocardial infarction following discharge and all death outcomes were also independently adjudicated by two physicians blinded to study phase and any disagreements were resolved by a third physician.
	Siemens Healthineers Atellica hs-cTnI	1.6	34 (F), 53 (M)	NR				
High-US Nowak 2019[128] Nowak 2019[129] **Sandoval 2019[176]**	Siemens Healthineers Atellica hs-cTnI	NR	45	20% at 1.6	NSTEMI	Third universal definition of AMI[33] 30-day MACE: Acute MI or death, including index MI, within 30 days	Local hospital standard cTn results, including both the manufacturers' package and locally established cTn cut-offs where applicable; assays varied across the participating sites (Abbott ARCHITECT STAT Troponin-I, 7 sites; Abbott iSTAT POC Cardiac Troponin I, 5 sites; Siemens ADVIA Centaur® TnI-	Each case was adjudicated by a unique combination of 5 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
	Siemens Healthineers ADVIA Centaur hs-cTnI	NR	47	20% at 2.5				

Study Details	High sensitivity troponin details (ng/L)				Reference standard details			
	Assay(s)	LoD	99th Centile	Coefficient of variation	Target Condition(s)	Reference standard	Standard troponin	Observer
							Ultra, 6 sites; Beckman Coulter® Accutane, 2 sites; Beckman Coulter® AccuTnI+3, 1 site; Siemens Dimension Vista® LOCI® CTNI,4 sites; Siemens Dimension® EXLTM LOCI® TNI, 2 sites; Ortho-Clinical Diagnostics VITROS® Troponin I ES, 3 sites; Roche Cardiac Troponin T, Gen 4, 8 sires; Siemens Stratus® CS High-sensitivity Troponin I, 1 site)	hospital. Each adjudicator independently used their expert opinion to assess whether the requirements of an MI diagnosis were met.
Huang 2015[72] Guangquan 2016[73]	Roche Elecsys hs-cTnT	3	14	10% at 13	AMI; NSTEMI	AMI according to guidelines by Thygesen (2012)[33]	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.
Keller 2011*[141] Keller 2011*[163]	Abbott ARCHITECT hs-cTnI *STAT*	3.4	24-30 for this study popul-ation	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
Kurz 2011*[148]	Roche	3	13.5	8% at 10	NSTEMI	Joint ESC, ACC, AHA and WHF[9]	4th generation cTnT (Roche	NR

Study Details	High sensitivity troponin details (ng/L)				Reference standard details			
	Assay(s)	**LoD**	**99th Centile**	**Coefficient of variation**	**Target Condition(s)**	**Reference standard**	**Standard troponin**	**Observer**
	Elecsys hs-cTnT						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	
Lin 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 stenosis); and emergency cardiac revascularisation procedures (e.g. coronary artery bypass graft, percutaneous coronary intervention).	Roche Elecsys hs-cTnT	MACE was independently adjudicated by an emergency medicine attending physician and an attending cardiologist based on the case records, which included investigation results and data on troponin collected during the index visit and up to one year of follow-up. Disagreements were resolved by consensus.
Melki 2011*[144] Melki 2010*[154]	Roche Elecsys hs-cTnT	2	14	<10% at 13	NSTEMI	Joint ESC, ACC, AHA and WHF[9]	Conventional troponin Roche 4th generation cTnT (LoD 10 ng/L, 10% CV at 35 ng/L), or Beckman Coulter Access Accutane (LoD 10 ng/L, 99th centile 40 ng/L, CV <10% at 60 ng/L	Final diagnosis determined by the individual cardiologist, then adjudicated by two independent evaluators; all three were blinded to hs-cTnT results

Study Details	High sensitivity troponin details (ng/L)				Reference standard details			
	Assay(s)	**LoD**	**99th Centile**	**Coefficient of variation**	**Target Condition(s)**	**Reference standard**	**Standard troponin**	**Observer**
							Timing: On presentation and 9 to 12 hours later	
Peacock 2018[89] Chang 2018[124]	Roche Elecsys hs-cTnT, STAT	6	19	NR	AMI; MACE	Third universal definition of AMI[33] 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 (CEC), made up of 2 cardiologists and 1 emergency physician, adjudicated the rule-in AMI diagnosis. The CEC had access to all clinical data (including the local troponin assay results), but was blinded to hs-cTnT results
PITAGORAS **Sanchis 2012*[135]**	Roche Elecsys hs-cTnT	3	14	<10% at 14	MACE	MACE	NR	NR
QUART Parsonage 2013*[151] Parsonage 2013[131] **Parsonage 2014[88]**	Roche Elecsys hs-cTnT	5	14	10% at 13	AMI	Third universal definition of AMI[33]	local cTnI measurement at presentation and then 6 h afterwards. The cTnI values, measured with the Access Accu-cTnI assay on a UniCel DxI 800 platform (Beckman Coulter), were used for adjudication. This assay had an LoD of 10 ng/L, and imprecision giving a 10% CV 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 readjudicated by both cardiologists. Consensus was achieved for all end points.
RATPAC (Point of care arm)	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	An initial working diagnosis was recorded by the senior emergency department clinician

Study Details	High sensitivity troponin details (ng/L)				Reference standard details			
	Assay(s)	LoD	99th Centile	Coefficient of variation	Target Condition(s)	Reference standard	Standard troponin	Observer
Collinson 2013*[159] Collinson 2012*[164] Collinson 2012*[152]							Ultra (LoD 6 ng/L, 99th centile 40 ng/L, CV 10% at 30 ng/L; Abbott cTnI (LoD 10 ng/L, 99th centile 12 ng/L, CV 10% at 32 ng/L; Beckman Accutane (LoD 10 ng/L, 99th centile 40 ng/L, CV 10% at 60 ng/L; Roche cTnT (LoD 10 ng/L, 99th centile 10 ng/L, CV 10% at 30 ng/L Timing: On presentation and at 10 to 12 hours	and reviewed by two independent clinicians; all were blind to hs-cTnT results
REACTION-US Nowak 2018[87] Nowak 2018[127]	Roche Elecsys hs-cTnT	5	14	<10% at 13	NSTEMI	Third universal definition of AMI[33]	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 2017[76] **Shortt 2017[101]**	Roche Elecsys hs-cTnT	5	14	2.3% at 30	NSTEMI	Third universal definition of AMI[33]	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.
	Abbott ARCHITECT hs-cTnI	2	26	4.4-7.1% at 20				
Saenger	Roche	NR	14	NR	AMI	AMI (unclear method)	NR	NR

Study Details	High sensitivity troponin details (ng/L)				Reference standard details			
	Assay(s)	**LoD**	**99th Centile**	**Coefficient of variation**	**Target Condition(s)**	**Reference standard**	**Standard troponin**	**Observer**
2010*[165]	Elecsys hs-cTnT							
Sebbane 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, France). The LoD was <10 ng/L and the decision threshold was 40 ng/L *Timing:* Convention cardiac troponin (cTnI) on presentation, 6 hrs later and beyond as needed	Two independent emergency department physicians, blinded to hs-cTnT results
Shiozaki 2017[100]	Roche Elecsys hs-cTnT	5	14	NR	NSTEMI	Joint ESC and ACC guidleines	NR	Two senior cardiologists
Slagman 2017[102]	Roche Elecsys hs-cTnT	5	14	3.5% at 16	NSTEMI	The endpoint (reference standard) of this study was a main hospital diagnosis of NSTEMI. Diagnoses were retrieved from the hospital information system (HIS) as ICD Codes (International Classification of Disease, Version 10) and were coded by treating physicians who had access to all available clinical information.	Roche Elecsys hs-cTnT at 3 hours or TnT at 6 hours	NR
TRAPID-AMI Body 2015[122] **Body 2016[114]** McCord 2017[126] **Mueller 2016[80]** Mueller-	Roche Elecsys hs-cTnT	5	14	10% at 13	AMI; NSTEMI; MACE	Third universal definition of AMI[33] and ESC guidelines	Sensitive cardiac troponin I ultra (s-cTnI-ultra) (ADVIA Centaur, Siemens Healthcare, 99th centile 40 ng/L), at baseline, 1 h, 2 h and 4-14 h	Each patient was adjudicated by 2 independent cardiologists. Adjudicators reviewed all available medical records (including patient history; physical examination results;

Study Details	High sensitivity troponin details (ng/L)				Reference standard details			
	Assay(s)	LoD	99th Centile	Coefficient of variation	Target Condition(s)	Reference standard	Standard troponin	Observer
Hennessen 2016[81] **Mueller-Hennessen 2017[82]** Mueller-Hennessen 2019[83]								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 hemoglobin [to quantify hemolysis], and NT-proBNP; radiologic imaging; ECG; echocardiography; cardiac stress test; and lesion 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 2015[63]	Roche Elecsys hs-cTnT	NR	14	<10% at 9	NSTEMI	Third universal definition of AMI[33]	Roche elecsys hs-cTnT at presentation and after 6 hours	Adjudication of the endpoint was carried out by 2 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 Santaló 2013*[133]	Roche Elecsys hs-cTnT	NR	14	10% at 9.3	NSTEMI	National Academy of Clinical Biochemistry and InternationalFederation of Clinical Chemistry Committee[229]	Roche cTnT; NSTEMI was defined as cTnT >10 ng/L and ΔcTnT >20% *Timing:* 30 minutes after arrival and at 2,4 and 6-8 hours or until	Final diagnosis was made by an adjudication committee

Study Details	High sensitivity troponin details (ng/L)				Reference standard details			
	Assay(s)	**LoD**	**99th Centile**	**Coefficient of variation**	**Target Condition(s)**	**Reference standard**	**Standard troponin**	**Observer**
							discharge	
UTROPIA Dodd 2019[125] **Sandoval 2017[95]** **Sandoval 2017[96]**	Abbott ARCHITECT hs-cTnI	1.9	Female: 16 Male: 34	5.3% at 15	NSTEMI	Third Universal Definition of Myocardial Infarction[33]	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.
Venge 2017[110]	Abbott ARCHITECT hs-cTnI	NR	26.2	NR	AMI	Third Universal Definition of Myocardial Infarction[33]	Roche Elecsys hs-cTnT, measured at a central laboratory Diagnosis of an MI required at least one TnT result above the 99th centile upper reference limit *Timing:* Presentation, 2-4 hours and 6-24 hours	Final diagnosis was adjudicated by two independent cardiologists, with access to ECG, clinical records and hospital standard TnT results. Disagreements were resolved by consultation with a third cardiologist.

* Publication included in the assessment report for DG15[7]

$ Publication(s) from which participant details have been taken

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 2016 [57]	Abbott ARCHITECT hs-cTnI	All	(<6 at 0 h AND 2h) AND Δ <2 at 0 to 2 h	NSTEMI	254	325	2	713	99 (97, 100)	69 (66, 72)
				<26.2 at 0 h AND 2 h		150	65	12	967	93 (87, 96)	94 (92, 95)
		Roche Elecsys hs-cTnT		(<14 at 0 h AND 2h) AND Δ <4 at 0 to 2 h		140	233	5	775	97 (92, 99)	77 (74, 79)
	Greenslade 2015 [71]	Abbott ARCHITECT hs-cTnI		<2 at 0 h		182	979	0	251	100 (98, 100)	20 (18, 23)
				<4 at 0 h		180	530	2	700	99 (96, 100)	57 (54, 60)
	Cullen 2014 [68]			<26.2 at 0 h		181	83	23	1284	89 (84, 93)	94 (93, 95)
				<26.2 at 0 h AND 2 h		195	103	9	1264	96 (92, 98)	92 (91, 94)
				<26.2 at 2 h			94		1273		93 (92, 94)
		Roche Elecsys hs-cTnT		<14 at 0 h		185	262	19	1105	91 (86, 94)	81 (79, 83)
				<14 at 2 h		191	258	13	1109	94 (89, 97)	81 (79, 83)
				<14 at 0 h AND 2 h		192	287	12	1080	94 (90, 97)	79 (77, 81)
	Eggers 2016 [69]	Abbott ARCHITECT hs-cTnI		<15.5 at 0 h AND 2 h		221	497	4	902	98 (96, 100)	64 (62, 67)
	Van der Linden 2018 [109]	Abbott ARCHITECT hs-cTnI AND		<4 at 0 h AND <9 at 0 h		403	1046	5	1083	99 (97, 100)	51 (49, 53)

Study	Publication	Assay	Participants	Threshold (ng/L)	Target condition	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
		Roche Elecsys hs-cTnT									
	Cullen 2013 [156]	Abbott ARCHITECT hs-cTnI		<26.2 at 0h AND 2h	MACE	227	96	20	1292	92 (88, 95)	93 (92, 94)
ADAPT/IMPACT	Nestelberger 2019 [171]	Beckman Coulter ACCESS hs-cTnI		(<4 at 0 h AND symptoms >3 hours) OR (<5 at 0 h AND Δ <5 at 0 to 2 h)	NSTEMI	86	197	2	995	98 (92, 100)	83 (81, 86)
APACE	Kaier 2017 [75]	Abbott ARCHITECT hs-cTnI		<2 at 0 h		224	881	0	199	100 (99, 100)	18 (16, 21)
		Roche Elecsys hs-cTnT		<5 at 0 h		218	763	1	326	100 (97, 100)	30 (27, 33)
	Boeddinghaus 2019 [60]	Beckman Coulter ACCESS hs-cTnI		ESC 0/1 hour pathway: (symptoms >3 hours AND <4 at 0 h) OR (<5 at 0 hand Δ <4 at 0 to 1 h)		95	176		408	99 (94, 100)	70 (66, 74)
	Boeddinghaus 2107 [58]	Abbott ARCHITECT hs-cTnI		<2 at 0 h		451	1924	0	453	100 (99, 100)	19 (17, 21)
				<5 at 0 h		438	874	13	1503	97 (95, 98)	63 (61, 65)
				<5 at 0 h AND Δ <2 at 0 to 1 h		444	925	7	1452	98 (97, 99)	61 (59, 63)

Study	Publication	Assay	Participants	Threshold (ng/L)	Target condition	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
				<2 at 0 h OR (<5 at 0 h AND Δ <2 at 0 to 1 h)			921		1456		61 (59, 63)
	Boeddinghaus 2018 [59]			ESC 0/1 hour pathway: (symtoms >3 hours AND <2 at 0 h) OR (<5 at 0 h AND Δ <2 at 0 to 1 h)		112	195	2	355	98 (94, 100)	65 (60, 69)
		Roche Elecsys hs-cTnT		ESC 0/1 hour pathway: (symptoms >3 hours AND <5 at 0 h) OR (<12 at 0 h AND Δ <3 at 0 to 1 h)		113	169	1	381	99 (95, 100)	69 (65, 73)
		Siemens ADVIA Centaur hs-cTnI		ESC 0/1 hour pathway: (symptoms >3 hous AND <3 at 0 h) OR (<6 at 0 h AND Δ <3 at 0 to 1 h)			243		307		56 (52, 60)
				<3 at 0 h OR (<8 at 0 h AND Δ <7 at 0 to 2 h)		61	100	0	200	100 (95, 100)	67 (61, 72)
	eddinghaus 2020 [173]	Quidel TriageTrue		ESC 0/1 hour pathway: (symptoms >3 hous AND <4 at 0 h) OR (<5 at 0 h AND Δ <3 at 0 to 1 h)		88	155	0	302	100 (97, 100)	66 (62, 70)
	Twerenbold 2019 [108]	Roche Elecsys hs-cTnT		ESC 0/1 hour pathway: (symptoms >3 hous AND <5 at	MACE	228	648	3	1417	99 (96, 100)	69 (67, 71)

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

Study	Publication	Assay	Participants	Threshold (ng/L)	Target condition	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
	[91]			h						100)	
	Rubini Gimenez 2015 [92]	Abbott ARCHITECT hs-cTnI		<5 at 0 h AND Δ <2 at 0 to 1 h		163	285	2	455	99 (96, 100)	61 (58, 65)
	Boeddinghaus 2019 [170]	Ortho VITROS hs-cTnI		ESC 0/1 hour pathway: (symptoms >3 hous AND <1 at 0 h) OR (<2 at 0 h AND Δ <1 at 0 to 1 h)		61	184	0	275	100 (95, 100)	60 (55, 64)
	Cullen 2013 [156]	Abbott ARCHITECT hs-cTnI		<26.2 at 0 h AND 2 h	MACE	129	62	27	691	83 (76, 88)	92 (90, 94)
	Lindahl 2017 [132]	bioMérieux VIDAS hs-cTnI		<2 at 0 h OR (<6 at 0 h AND 2 h)	NSTEMI	85	184	2	321	98 (92, 100)	64 (59, 68)
	Reichlin 2009 [167]	Abbott ARCHITECT hs-cTnI		≤10 at 0 h	AMI	116	77	7	518	94 (89, 98)	87 (84, 90)
		Roche Elecsys hs-cTnT		≤2 at 0 h		123	512	0	83	100 (98, 100)	14 (11, 17)
	Reiter 2011 [146]		>70 years	<14 at 0 h		96	157	2	151	98 (93, 100)	49 (43, 55)
				<5 at 0 h		98	305	0	3	100 (97, 100)	1 (0, 3)

Study	Publication	Assay	Participants	Threshold (ng/L)	Target condition	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
			≤70 years	<14 at 0 h		54	87	7	533	89 (78, 95)	86 (83, 89)
	Potocki 2012 [140]		with pre-existing CAD			73	142	5	213	94 (86, 98)	60 (55, 65)
			without pre-existing CAD			100	114	6	517	94 (88, 98)	82 (79, 85)
	Hochholzer 2011 [149]		All	<11 at 0 h		129	177	3	454	98 (94, 100)	72 (68, 75)
					NSTEMI	90				97 (91, 99)	72 (68, 75)
	Reichlin 2011 [145]			Δ30% at 0 to 2 h		43	84	24	439	64 (52, 76)	84 (81, 87)
APACE	Twerenbold 2018 [106]	Abbott ARCHITECT hs-cTnI	Normal renal function	ESC 0/1 hour pathway: ESC 0/1 hour pathway: (symptoms >3 hous AND <2 at 0 h) OR (<5 at 0 h AND Δ <2 at 0 to 1 h)		326	730	4	1444	99 (97, 100)	66 (64, 68)
			Renal dysfunction (eGFR <60 mL/min/1.73 m^2)			141	227	2	75	99 (95, 100)	25 (20, 30)
		Roche Elecsys hs-cTnT	Normal renal function	ESC 0/1 hour pathway: ESC 0/1 hour pathway: (symptoms >3 hous AND <5 at 0 h) OR (<12 at 0 h AND Δ <3 at 0 to 1 h)		360	528	4	1875	99 (97, 100)	78 (76, 80)
			Renal dysfunction (eGFR <60 mL/min/1.73 m^2)			150	249	0	88	100 (98, 100)	26 (22, 31)
	Jaeger 2016 [74]	Siemens Dimension	All	<5 at 0 h AND Δ <2 at 0 to 1 h		98	224		428	100 (97, 100)	66 (62, 69)

Study	Publication	Assay	Participants	Threshold (ng/L)	Target condition	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
		Vista hs-cTnI	Female			25	57		152	100 (89, 100)	73 (66, 79)
			Male			72	168	4	272	95 (87, 99)	62 (57, 66)
	Hoeller 2011 [168]	Abbott ARCHITECT hs-cTnI	All	<26.2 at 0 h	AMI	240	93	71	1163	77 (72, 82)	93 (91, 94)
		Roche Elecsys hs-cTnT		<14 at 0 h		398	363	46	1265	90 (86, 92)	78 (76, 80)
BACC	Neumann 2016 [84]	Abbott ARCHITECT hs-cTnI		≤27 at 0 h AND 3 h	NSTEMI	161	74	23	725	88 (82, 92)	91 (89, 93)
				≤6 at 0 h		170	312	14	487	92 (88, 96)	61 (57, 64)
				≤6 at 0 h AND 1 h		180	373	4	426	98 (95, 99)	53 (50, 57)
				≤6 at 0 h AND 3 h		182	402	2	397	99 (96, 100)	50 (46, 53)
				≤27 at 0 h AND 1 h		143	59	41	740	78 (71, 84)	93 (91, 94)
BEST	Body 2019 [115]	Roche Elecsys hs-cTnT		<5 at 0 h		76	313	1	275	99 (93, 100)	47 (43, 51)
	Body 2020[172]	Siemens ADVIA Centaur hs-cTnI		<3 at 0 h		131	580		287	99 (96, 100)	33 (30, 36)
Body 2015	Body 2015 [56]	Roche Elecsys hs-cTnT		<14 at 0 h	AMI	75	106	4	278	95 (88, 99)	72 (68, 77)
					MACE	88	92	10	272	90 (82, 95)	75 (70, 79)
				<3 at 0 h	AMI	79	360	0	24	100 (96,	6 (4, 9)

Study	Publication	Assay	Participants	Threshold (ng/L)	Target condition	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
										100)	
					MACE	99	352		13	100 (97, 100)	4 (2, 6)
				<5 at 0 h	AMI	78	289	1	95	99 (93, 100)	25 (21, 29)
					MACE	97	270			99 (94, 100)	26 (22, 31)
Cappellini 2019	Cappellini 2019 [62]			<14 at 0 h AND Δ ≤4 at 0 to 3 h	NSTEMI	473	3178	2	2758	100 (98, 100)	46 (45, 48)
			All	<14 at 0 h AND Δ ≤3 at 0 to 1 h		471	3284	4	2652	99 (98, 100)	45 (43, 46)
			Female			189	1560	0	1109	100 (98, 100)	42 (40, 43)
				<14 at 0 h AND Δ ≤4 at 0 to 3 h			1496		1173		44 (42, 46)
			Male	<14 at 0 h AND Δ ≤3 at 0 to 1 h		282	1702	4	1565	99 (96, 100)	48 (46, 50)
				<14 at 0 h AND Δ ≤4 at 0 to 3 h		285	1714	1	1553	100 (98, 100)	48 (46, 49)
CORE	Borna 2018 [116]		All	≤14 at 0 h AND 2h	MACE	78	152	12	509	87 (78, 93)	77 (74, 80)
	Mokhtari 2017 [120]			<5 at 0 h OR (<12 at 0 h AND Δ <3 at 0 to 1 h)		117	471	2	430	98 (94, 100)	48 (44, 51)
	Mokhtari 2016			<5 at 0 h		121	674	4	339	97 (92, 99)	33 (31, 36)

Study	Publication	Assay	Participants	Threshold (ng/L)	Target condition	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
	[121]			≤14 at 0 h		93	206	32	807	74 (66, 82)	80 (77, 82)
				<12 at 0 h AND Δ <3 at 0 to 1 h		117	163	2	146	98 (94, 100)	47 (42, 53)
High-STEACS	Bularga 2019 [61]	Abbott ARCHITECT hs-cTnI		<2 at 0 h		4289	27857	24	14931	99 (99, 100)	35 (34, 35)
				<5 at 0 h		4215	15386	98	27402	98 (97, 98)	64 (64, 64)
			Analysis population (excluding pts with cardiac troponin >99th centie at presentation, presenting ≤2 h from symptom onset, with STEMI, with missing presentation hs-cTnI)	<2 at 0 h		502	19619	15	12701	97 (95, 98)	39 (39, 40)
				<5 at 0 h		462	9115	55	23205	89 (86, 92)	72 (71, 72)
	Chapman 2020[174]	Roche Elecsys hs-cTnT	All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Study	Publication	Assay	Participants	Threshold (ng/L)	Target condition	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
				[redacted]							
	Chapman 2019 [67]	Siemens Atellica hs-cTnI		ESC 0/1 hour pathway: (symptoms ≥3 hours AND <3 at 0 h) OR (<6 at 0 h AND Δ <3 at 0 to 1 h)	NSTEMI	29	115	2	260	94 (79, 99)	69 (64, 74)
				ESC 0/3 hour pathway: (symptoms ≥6 hours AND ≤34 (F) ≤53 (M) at 0 h) OR (≤34 (F) ≤53 (M) at 3 h) OR Δ <50% of 99th centile at 0 to 3 h		252	420	25	1223	91 (87, 94)	74 (72, 77)
				High-STEACS pathway: (symptoms ≥2 h AND <5 at 0 h) OR (≤34 (F) ≤53 (M) at 3 h AND Δ <3 at 0 to 3 h)		272	430	6	1212	98 (95, 99)	74 (72, 76)
	Chapman 2018 [66]	Abbott ARCHITECT hs-cTnI		ESC 0/1 hour pathway: (symptoms ≥3 hours AND <3 at 0 h) OR (<6 at 0 h AND Δ <3 at 0 to 1 h)		33	83	0	290	100 (91, 100)	78 (73, 82)
				ESC 0/3 hour pathway: (symptoms ≥6 hours AND ≤16	MACE	327	231	49	1279	87 (83, 90)	85 (83, 86)

Study	Publication	Assay	Participants	Threshold (ng/L)	Target condition	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
				(F) ≤34 (M) at 0 h) OR (≤16 (F) ≤34 (M) at 3 h) OR Δ <50% of 99th centile at 0 to 3 h	NSTEMI	244	314	27	1301	90 (86, 93)	81 (79, 82)
				High-STEACS pathway: (symptoms ≥2 h AND <5 at 0 h) OR (≤16 (F) ≤34 (M) at 3 h AND Δ <3 at 0 to 3 h)	MACE	378	295	6	1238	98 (97, 99)	81 (79, 83)
					NSTEMI	273	400	2	1242	99 (97, 100)	76 (73, 78)
	Chapman 2017 [65]		Age <65 years	ESC 0/3 hour pathway: (symptoms ≥6 hours AND ≤16 (F) ≤34 (M) at 0 h) OR (≤16 (F) ≤34 (M) at 3 h) OR Δ <50% of 99th centile at 0 to 3 h		72	29	7	593	91 (83, 96)	95 (93, 97)
				High-STEACS pathway: (symptoms ≥2 h AND <5 at 0 h) OR (≤16 (F) ≤34 (M) at 3 h AND Δ <3 at 0 to 3 h)		78	39	1	583	99 (93, 100)	94 (92, 96)
			Age ≥65 years	ESC 0/3 hour pathway: (symptoms ≥6 hours AND ≤16 (F) ≤34 (M) at 0 h) OR (≤16 (F) ≤34 (M) at 3 h) OR Δ <50% of 99th centile at 0 to 3 h		99	57	13	348	88 (81, 94)	86 (82, 89)

Study	Publication	Assay	Participants	Threshold (ng/L)	Target condition	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
				High-STEACS pathway: (symptoms ≥2 h AND <5 at 0 h) OR (≤16 (F) ≤34 (M) at 3 h AND Δ <3 at 0 to 3 h)		109	88	3	317	97 (92, 99)	78 (74, 82)
			Female	ESC 0/3 hour pathway: (symptoms ≥6 hours AND ≤16 (F) ≤34 (M) at 0 h) OR (≤16 (F) ≤34 (M) at 3 h) OR Δ <50% of 99th centile at 0 to 3 h		61	48	5	362	92 (83, 97)	88 (85, 91)
				High-STEACS pathway: (symptoms ≥2 h AND <5 at 0 h) OR (≤16 (F) ≤34 (M) at 3 h AND Δ <3 at 0 to 3 h)		65	54	1	356	98 (92, 100)	87 (83, 90)
			Known ischaemic heart disease	ESC 0/3 hour pathway: (symptoms ≥6 hours AND ≤16 (F) ≤34 (M) at 0 h) OR (≤16 (F) ≤34 (M) at 3 h) OR Δ <50% of 99th centile at 0 to 3 h		73	52	16	377	82 (72, 89)	88 (84, 91)
				High-STEACS pathway: (symptoms ≥2 h AND <5 at 0 h) OR (≤16 (F) ≤34 (M) at 3 h AND Δ <3 at 0 to 3 h)		85	77	4	352	96 (89, 99)	82 (78, 86)

Study	Publication	Assay	Participants	Threshold (ng/L)	Target condition	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
			Male	ESC 0/3 hour pathway: (symptoms ≥6 hours AND ≤16 (F) ≤34 (M) at 0 h) OR (≤16 (F) ≤34 (M) at 3 h) OR Δ <50% of 99th centile at 0 to 3 h		110	38	15	579	88 (81, 93)	94 (92, 96)
				High-STEACS pathway: (symptoms ≥2 h AND <5 at 0 h) OR (≤16 (F) ≤34 (M) at 3 h AND Δ <3 at 0 to 3 h)		122	73	3	544	98 (93, 100)	88 (85, 91)
			No known ischaemic heart disease	ESC 0/3 hour pathway: (symptoms ≥6 hours AND ≤16 (F) ≤34 (M) at 0 h) OR (≤16 (F) ≤34 (M) at 3 h) OR Δ <50% of 99th centile at 0 to 3 h		95	33	4	548	96 (90, 99)	94 (92, 96)
				High-STEACS pathway: (symptoms ≥2 h AND <5 at 0 h) OR (≤16 (F) ≤34 (M) at 3 h AND Δ <3 at 0 to 3 h)		99	48	0	533	100 (97, 100)	92 (89, 94)
	Miller-Hodges 2018 [79]		Female patients with eGFR <60 mL/min/1.73 m^2	<16 at 0 h		105	121	1	243	99 (95, 100)	67 (62, 72)
			Female patients			160	156		1269	99 (97,	89 (87, 91)

Study	Publication	Assay	Participants	Threshold (ng/L)	Target condition	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
			with eGFR ≥60 mL/min/1.73 m^2							100)	
			Male patients with eGFR <60 mL/min/1.73 m^2	<34 at 0 h		98	82	2	252	98 (93, 100)	75 (70, 80)
			Male patients with eGFR ≥60 mL/min/1.73 m^2			280	109	4	1843	99 (96, 100)	94 (93, 95)
			Patients age <65 years with eGFR <60 mL/min/1.73 m^2	<16 (F) <34 (M) at 0 h		23	17	0	76	100 (88, 100)	82 (72, 89)
			Patients age <65 years with eGFR ≥60 mL/min/1.73 m^2			197	75	1	1926	99 (97, 100)	96 (95, 97)
			Patients age ≥65 years with eGFR <60 mL/min/1.73 m^2			180	186	3	419	98 (95, 100)	69 (65, 73)
			Patients age ≥65 years with eGFR			243	190	4	1186	98 (96, 100)	86 (84, 88)

Study	Publication	Assay	Participants	Threshold (ng/L)	Target condition	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
			≥60 mL/min/1.73 m^2								
			Patients with eGFR <60 mL/min/1.73 m^2	<1.2 at 0 h	MACE	224	661	0	19	100 (99, 100)	3 (2, 4)
				<16 (F) <34 (M) at 0 h	NSTEMI	203	203	3	495	99 (96, 100)	71 (67, 74)
				<5 at 0 h	MACE	222	525	2	155	99 (97, 100)	23 (20, 26)
			Patients with eGFR ≥60 mL/min/1.73 m^2	<1.2 at 0 h		455	2739	3	625	99 (98, 100)	19 (17, 20)
				<16 (F) <34 (M) at 0 h	NSTEMI	440	265	5	3112	99 (97, 100)	92 (91, 93)
				<5 at 0 h	MACE	451	1227	7	2137	98 (97, 99)	64 (62, 65)
high-US	Sandoval 2019 [176]	Siemens ADVIA Centaur hs-cTnI	All	<2 at 0 h		276	1481	1	454	100 (98, 100)	23 (22, 25)
					NSTEMI	259	1498	0	455	100 (99, 100)	23 (21, 25)
				<3 at 0 h	MACE	274	1248	3	687	99 (97, 100)	36 (33, 38)
					NSTEMI	257	1265	2	688		35 (33, 37)
				<5 at 0 h	MACE	273	924	4	1011	99 (96, 100)	52 (50, 54)
					NSTEMI	257	940	2	1013	99 (97,	52 (50, 54)

Study	Publication	Assay	Participants	Threshold (ng/L)	Target condition	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
		Siemens Atellica hs-cTnI		<2 at 0 h	MACE	275	1432		503	100)	26 (24, 28)
					NSTEMI	258	1449	1	504	100 (98, 100)	26 (24, 28)
				<3 at 0 h	MACE	273	1207	4	728	99 (96, 100)	38 (35, 40)
					NSTEMI	256	1224	3	729	99 (97, 100)	37 (35, 40)
				<5 at 0 h	MACE	274	899	4	1036	99 (96, 100)	54 (51, 56)
					NSTEMI	256	916	3	1037	99 (97, 100)	53 (51, 55)
Huang 2015	Huang 2015 [72]	Roche Elecsys hs-cTnT		≤14 at 0 h	AMI	1064	331	44	810	96 (95, 97)	71 (68, 74)
					NSTEMI	308		13		96 (93, 98)	71 (68, 74)
			Patients with eGFR ≥90 mL/min/1.73 m^2		AMI	363	70	19	367	95 (92, 97)	84 (80, 87)
					NSTEMI	59		5	370	92 (83, 97)	84 (80, 87)
			patients with eGFR 30 to 59 mL/min/1.73 m^2		AMI	197	87	2	75	99 (96, 100)	46 (38, 54)
					NSTEMI	78	86	0	77	100 (96, 100)	47 (39, 55)
			patients with eGFR 60 to 89		AMI	462	148	19	362	96 (94, 98)	71 (67, 75)
					NSTEMI	156	142	7	364	96 (91, 98)	72 (68, 76)

Study	Publication	Assay	Participants	Threshold (ng/L)	Target condition	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
			mL/min/1.73 m^2								
			patients with eGFR <30 mL/min/1.73 m^2		AMI	46	28	0	4	100 (94, 100)	13 (4, 29)
					NSTEMI	16				100 (83, 100)	13 (4, 29)
Lin 2019	Lin 2019 [117]		All	<10 at 0 h	MACE	165	328	108	1843	60 (54, 66)	85 (83, 86)
				<20 at 2 h		163	161	110	2010		93 (91, 94)
				<5 at 0 h AND 2h		185	367	88	1804	68 (62, 73)	83 (81, 85)
				Δ <10 at 0 to 2 h		115	63	158	2108	42 (36, 48)	97 (96, 98)
Peacock 2018	Chang 2018 [124]	Roche Elecsys hs-cTnT STAT		<19 at 0 h	AMI	125	164	8	1058	94 (88, 97)	87 (85, 88)
				Δ ≤10% at 0 to 3 h AND <19 at 3 h		129	549	4	673	97 (92, 99)	55 (52, 58)
				Δ ≤2 at 0 to 3 h AND <19 at 3 h		127	263	6	959	95 (90, 98)	78 (76, 81)
				Δ ≤50% at 0 to 3 h AND <19 at 3 h		125	187	8	1035	94 (88, 97)	85 (83, 87)
				Δ ≤8 at 0 to 3 h AND <19 at 3 h			169		1053		86 (84, 88)
	Peacock 2019 [89]			<19 at 0 h AND 3 h			178		1044		85 (83, 87)
					MACE	8	282	7	967	53 (27, 79)	77 (75, 80)
				<6 at 0 h AND 3 h	AMI	131	610	2	612	98 (95, 100)	50 (47, 53)

Study	Publication	Assay	Participants	Threshold (ng/L)	Target condition	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
					MACE	11	694	4	555	73 (45, 92)	44 (42, 47)
QUART	Parsonage 2014 [88]	Roche Elecsys hs-cTnT		≤14 at 0 h	AMI	52	113		595	93 (83, 98)	84 (81, 87)
				≤14 at 2 h		54	116	2	592	96 (88, 100)	84 (81, 86)
				≤14 at 0 h OR 2 h			123		585		83 (80, 85)
REACTION-US	Nowak 2018 [87]			<6 at 0 h		44	361	0	164	100 (93, 100)	31 (27, 35)
				<8 at 0 h AND Δ <3 at 0 to 0.5 h			274		221		45 (40, 49)
ROMI-3	Shortt 2017 [101]	Abbott ARCHITECT hs-cTnI		<1 at 0 h	NSTEMI	132	920	1	84	99 (96, 100)	8 (7, 10)
				<15 at 0 h		110	216	23	788	83 (75, 89)	78 (76, 81)
				<2 at 0 h		132	846	1	158	99 (96, 100)	16 (14, 18)
				<26 at 0 h		96	105	37	899	72 (64, 80)	90 (87, 91)
				<3 at 0 h		132	691	1	313	99 (96, 100)	31 (28, 34)
				<4 at 0 h		131	586	2	418	98 (95, 100)	42 (39, 45)
				<5 at 0 h		129	504	4	500	97 (92, 99)	50 (47, 53)
		Roche Elecsys hs-cTnT		<12 at 0 h		126	476	7	528	95 (89, 98)	53 (49, 56)
				<14 at 0 h		123	417	10	587	92 (87, 96)	58 (55, 62)
				<24 at 0 h		108	229	25	775	81 (74, 87)	77 (74, 80)
				<3 at 0 h		132	891	1	113	99 (96,	11 (9, 13)

Study	Publication	Assay	Participants	Threshold (ng/L)	Target condition	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
				<5 at 0 h			824		180	100)	18 (16, 20)
				<8 at 0 h		129	638	4	366	97 (92, 99)	36 (33, 40)
	Shortt 201 [101]	Abbott ARCHITECT hs-cTnI		<7 at 0 h		126	393	7	611	95 (89, 98)	61 (58, 64)
Shiozaki 2017	Shiozaki 2017 [100]	Roche Elecsys hs-cTnT		<13 at 0 h		57	246	0	110	100 (95, 100)	31 (26, 36)
				<13 at 0 h AND Δ <3 at 0 to 1 h			120		236		66 (61, 71)
Slagman 2017	Slagman 2017 [102]			<14 at 0 h		115	1086	9	2213	93 (87, 97)	67 (65, 69)
TRAPID-AMI	Body 2016 [114]				AMI	189	198	24	871	89 (84, 93)	81 (79, 84)
				<3 at 0 h		210	653	3	416	99 (96, 100)	39 (36, 42)
				<5 at 0 h		209	513	4	556	98 (95, 99)	52 (49, 55)
	Mueller 2016 [80]			<12 at 0 h AND Δ <3 at 0 to 1 h		206	263	7	806	97 (93, 99)	75 (73, 78)
					NSTEMI	185				96 (93, 99)	75 (73, 78)
	Mueller-Hennessen 2017 [230]			≤14 at 0 h AND Δ <9.2 at 0 to 1 h	AMI	98	9	115	1060	46 (39, 53)	99 (98, 100)
				≤14 at 0 h AND Δ <9.2 at 0 to 2 h		126	13	87	1056	59 (52, 66)	99 (98, 99)
				≤14 at 0 h AND Δ <20% at 0 to 1 h		83	28	130	1041	39 (32, 46)	97 (96, 98)

Study	Publication	Assay	Participants	Threshold (ng/L)	Target condition	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
				≤14 at 0 h AND Δ <20% at 0 to 2 h		119	46	94	1023	56 (49, 63)	96 (94, 97)
	Mueller-Hennessen 2017 [81]		<65 years	(≤14 at 0 h AND 1 h) AND Δ <20% at 0 to 1 h	MACE	76	23	79	547	49 (41, 57)	96 (94, 97)
			≥65 years			123	43	102	289	55 (48, 61)	87 (83, 90)
				(≤28 at 0 h AND 1 h) AND Δ <20% at 0 to 1 h		92	10	133	322	41 (34, 48)	97 (95, 99)
			Female	(≤14 at 0 h AND 1 h) AND Δ <20% at 0 to 1 h		62	17	37	361	63 (52, 72)	96 (93, 97)
				(≤9 at 0 h AND 1 h) AND Δ <20% at 0 to 1 h		71	37	28	341	72 (62, 80)	90 (87, 93)
			Male	(≤14 at 0 h AND 1 h) AND Δ <20%		137	49	144	475	49 (43, 55)	91 (88, 93)
				(≤15.5 at 0 h AND 1 h) AND Δ <20% at 0 to 1 h		129	41	152	483	46 (40, 52)	92 (90, 94)
TRUST	Carlton 2015 [64]	Abbott ARCHITECT hs-cTnI	All	≤26.2 at 0 h	NSTEMI	41	22	25	779	62 (49, 74)	97 (96, 98)
		Roche Elecsys hs-cTnT		≤14 at 0 h		66	127	13	753	84 (74, 91)	86 (83, 88)
	Carlton 2015 [63]			<3 at 0 h	MACE	94	755	1	72	99 (94, 100)	9 (7, 11)
					NSTEMI	78	771	0	73	100 (96,	9 (7, 11)

Study	Publication	Assay	Participants	Threshold (ng/L)	Target condition	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
										100)	
				<5 at 0 h	MACE	92	560	3	267	97 (91, 99)	32 (29, 36)
					NSTEMI	78	574	0	270	100 (96, 100)	32 (29, 35)
UTROPIA	Sandoval 2017 [96]	Abbott ARCHITECT hs-cTnI		<1.9 at 0 h		168	1018	2	443	99 (96, 100)	30 (28, 33)
				<5 at 0 h		161	657	9	804	95 (90, 98)	55 (52, 58)
	Sandoval 2017 [95]			Males <34 at 0 h Females <16 at 0 h		113	191	57	1270	66 (59, 74)	87 (85, 89)
				Males <34 Females <16 at 0 h AND 3h		104	137	5	822	95 (90, 98)	86 (83, 88)
Venge 2017	Venge 2017 [110]			<26.2 at 0 h	AMI	46	28	18	325	72 (59, 82)	92 (89, 95)
				<26.2 at 2 to 4 h		52	27	6	268	90 (79, 96)	91 (87, 94)
Aldous 2011	Aldous 2011 [147]	Roche Elecsys hs-cTnT		<13 at 0 h		92	38	18	184	84 (75, 90)	83 (77, 88)
				<14 at 0 h			36		186		84 (78, 88)
				<15 at 0 h		93	29	17	193	85 (76, 91)	87 (82, 91)
				<5 at 0 h		106	131	4	91	96 (91, 99)	41 (34, 48)
Aldous 2012	Aldous 2011 [143]			Peak <14 at 0 to 2 h	NSTEMI	189	149	11	590	95 (90, 97)	80 (77, 83)
				<14 at 0 to 2 h AND Δ <20% at 0 to 2 h		99	43	101	696	50 (42, 57)	94 (92, 96)
				<14 at 0 to 2 h OR Δ <20% at 0		195	260	5	479	98 (94, 99)	65 (61, 68)

Study	Publication	Assay	Participants	Threshold (ng/L)	Target condition	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
				to 2 h							
	Aldous 2012 [134]			<14 at 0 h	AMI	74	54	8	249	90 (82, 96)	82 (77, 86)
				<14 at 0 h AND 2 h		78	74	4	229	95 (88, 99)	76 (70, 80)
				<14 at 0 to 1 h		77	63	5	240	94 (86, 98)	79 (74, 84)
				<14 at 0 to 2 h		78	67	4	236	95 (88, 99)	78 (73, 82)
				<14 at 0 h AND Δ <20% at 0 to 2 h		49	81	33	222	60 (48, 70)	73 (68, 78)
				<14 at 0 h OR Δ <20% at 0 to 2 h		81	131	1	172	99 (93, 100)	57 (51, 62)
	Aldous 2012 [139]			<14 at 0 h	NSTEMI	181	134	24	600	88 (83, 92)	82 (79, 84)
				<3 at 0 h		196	383	9	351	96 (92, 98)	48 (44, 52)
				<5 at 0 h		192	305	13	429	94 (89, 97)	58 (55, 62)
				<14 at 2 h		189	149	16	585	92 (88, 95)	80 (77, 83)
				<5 at 2 h		196	340	9	394	96 (92, 98)	54 (50, 57)
				<3 at 2 h		201	424	4	310	98 (95, 99)	42 (39, 46)
Body 2011	Body 2011 [161]			<14 at 0 h	AMI	111	101	199	472	36 (30, 41)	82 (79, 85)
				<3 at 0 h		130	378	0	195	100 (98, 100)	34 (30, 38)
Christ 2010	Christ 2010 [150]			<14 at 0 h		19	45	1	72	95 (75, 100)	62 (52, 70)
				<3 at 0 h		20	92	0	25	100 (86, 100)	21 (14, 30)

Study	Publication	Assay	Participants	Threshold (ng/L)	Target condition	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
FASTER I and FAST II	Eggers 2012 [137]			<14 at 0 h	NSTEMI	101	59	27	173	79 (71, 86)	75 (68, 80)
				<45.7 at 0 h		65	11	63	221	51 (42, 60)	95 (92, 98)
Freund 2011	Freund 2011 [142]			<14 at 0 h		42	48	3	224	93 (82, 99)	82 (77, 87)
			Low/moderate pre-test probability			20	36	2	200	91 (71, 99)	85 (80, 89)
			High pre-test probability			22	12	1	24	96 (78, 100)	67 (49, 81)
Keller 2011	Keller 2011 [141]	Abbott ARCHITECT hs-cTnI	All	<3.4		282	633	0	345	100 (99, 100)	35 (32, 38)
							959		19		2 (1, 3)
				<3	AMI	232	77	50	901	82 (77, 87)	92 (90, 94)
				<30		277	94	5	884	98 (96, 99)	90 (88, 92)
				Δ <20% at 0 to 3 h		218	723	64	255	77 (72, 82)	26 (23, 29)
				<3.4 at 0 AND Δ <20% at 0 to 3 h		254	454	54	498	82 (78, 87)	52 (49, 56)
				<30 at 3 h AND Δ <20% at 0 to 3 h		187	34	110	929	63 (57, 68)	96 (95, 98)
				(<30 at 0 AND 3 h) AND Δ <20% at 0 to 3 h		52	26	4	869	93 (83, 98)	97 (96, 98)
Kurz 2011	Kurz 2011 [148]	Roche Elecsys hs-cTnT		<14 at 0 h	NSTEMI	16	7	10	24	62 (41, 80)	77 (59, 90)
				<9.5 at 0 h		38	11	8	37	83 (69, 92)	77 (63, 88)

Study	Publication	Assay	Participants	Threshold (ng/L)	Target condition	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
				<14 at 0h AND 3 h		26	7	0	23	100 (89, 100)	77 (58, 90)
				<14 at 0 h AND Δ <20% at 0 to 3 h		11	27	15	3	42 (23, 63)	10 (2, 27)
Melki 2011	Melki 2011 [144]			<14 at 0 h		112	21	2	98	98 (94, 100)	82 (74, 89)
				<14 at 2 h		114	25	0	94	100 (97, 100)	79 (71, 86)
PITAGORAS	Sanchis 2012 [135]			<3 at 0 h	MACE	53	207	9	177	85 (74, 93)	46 (41, 51)
RATPAC	Collinson 2013 [159]			<14 at 0 h	NSTEMI		33	14	733	79 (67, 88)	96 (94, 97)
				Peak <14 at 0 to 1.5 h		57	43	11	736	84 (73, 92)	94 (93, 96)
Saenger 2010	Saenger 2010 [165]			<14 at 0 h	AMI	92	38	6	152	94 (87, 98)	80 (74, 85)
				Δ <8 at 0 to 3 h		94	9	4	181	96 (90, 99)	95 (91, 98)
Sebbane 2013	Sebbane 2013 [157]			<14 at 0 h	NSTEMI	19	25	6	142	76 (55, 91)	85 (79, 90)
				<18 at 0 h			17		150		90 (84, 94)
TUSCA	Santaló 2013 [133]			<14 at 0 h		71	80	8	199	90 (81, 96)	71 (66, 77)

APPENDIX 3: STUDY QUALITY

a. QUADAS-2 Assessments

Study: ADAPT/IMPACT, Nestelberger 2019[171]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS

Adults presenting to the emergency department 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?	Tes
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

Bexkman 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 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

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 sane 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 2011*[147]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS

Consecutive adults presenting to the emergency department 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 hrs. Data reported for admission, for four thresholds No details of interpretation reported. One threshold was derived from ROC analysis; 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 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

Reference standard diagnosis of AMI based on joint European Cardiology Society an American College of Cardiology criteria and included serial conventional cTnI (10-12 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 2012*[139]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS

Patients presenting to the emergency department between 05:30 h and 20:00 h, and 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 pre-determined properties of the assay Frozen samples used, unclear whether 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 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

Reference standard final diagnosis of AMI, based on ACC criteria and including the results of serial conventional cTnI (10-12 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: BACC Neumann 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 TnI 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 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

2015 ESC guidelines and 3rd 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 TnI 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 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 point and limit of detection. Blinding not reported; objective test interpreted prior to reference standard 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 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

Thorgeson criteria; 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 included in 2x2 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 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 mixed AMI

Do the included patients match the question?	**Concerns: High**

DOMAIN 2: INDEX TEST(S)

A. RISK OF BIAS

Refernce 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 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

AMI diagnosis made based on cTnT (0 and 12 h) 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 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 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

2x2 Data were only available for the derivation cohort (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 pre-specified?	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 Myocardial Infarction. 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 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 99th centile cut point. Blinding not reported; retrospective analysis and so disease status may have been known when interpreting results. However, 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 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

Joint European Cardiology Society an American College of Cardiology criteria; time point not specified. Unclear whether clinicians were blinded to hs-cTn. A second consensus diagnosis incorporating 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: CORE[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 form those recruited

Do the included patients match the question?	**Concerns: HIGH**

DOMAIN 2: INDEX TEST(S)

A. RISK OF BIAS

MACE 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 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

The reference standard was adjudicated independently by multiple clinicians who were bline 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 uing 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: FASTER I and FAST II Eggers 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 coronoary 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. Threshold 99th centile cut point and 95% specificity value. Blinding not reported; objective test interpreted prior to reference standard 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 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

Joint European Cardiology Society an American College of Cardiology criteria; time point not specified. Unclear whether 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 2011*[142]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS

Consecutive adults presenting to the emergency department with chest pain (onset or peak within previous 6 hrs). 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 emergency department chest pain population, includes participants with a final diagnosis of STEMI; data also presented for subgroups with low-moderate and with 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 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

Reference standard final diagnosis, based on joint European Cardiology Society an American College of Cardiology criteria and included conventional cTnI on admission and at 3-9 hours if needed (10-12 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 2015[72]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS

A consecutive sample of patients with suspected AMI were enrolled. Patients reqiring 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 witjh 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 99th centile cut point. Blinding not reported; objective test interpreted prior to reference standard 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 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

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. 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 emergency physician and 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 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 hrs. Reference standard (final diagnosis) was adjudicated after hs-cTnI testing. Thresholds based on test properties, appeared to be pre-specified	
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

Reference standard diagnosis of AMI based on joint European Cardiology Society an American College of Cardiology criteria and included serial conventional cTnT (10-12 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 2011*[148]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS

Consecutive patients admitted to a chest pain unit. 206 Patients not included due to 'technical reasons' (not fully defined, e.g. venipuncture 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[231] is for a retrospectively selected subgroup of participants with a diagnosis of NSTEMI or unstable angina. 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 hr and 6 hr samples (6 hrs data not extracted) Reference standard troponin testing occurred after hs-cTnT. Threshold was pre-specified for data extracted from [231], but not from [148] (low risk of bias for[231] data)

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

Reference standard diagnosis of AMI based on joint European Cardiology Society and American College of Cardiology criteria and included serial conventional cTnT (10-12 hour time point not specified) Unclear whether 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 2019[117]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS

Convenience sample of patients presenting Monday to Friday, from 0800 to 2100 hours, with suspected ACS. Patients who did not have any data on cardiac troponin obtained as part of standard care as well as those lost to follow-up, and patients with STEMI were also 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

MACE was 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 pre-specified?	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 MACE

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 MACE 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 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 hrs. Reference standard (final diagnosis) determined after hs-cTnT testing. Threshold based on assay characteristics, appears pre-determined

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

Reference standard diagnosis of AMI based on joint European Cardiology Society an American College of Cardiology criteria and included serial conventional cTnT or cTnI (9-12 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 2018[89]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS

Patients with suspected ACS presenting to one 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 hospitalization within the last 3 months, recent cardioversion or defibrillation, acute noncardiac primary illness prior to enrollment (eg, 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 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. 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 2012*[135]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS

Patients excluded due to troponin elevation in any of 2 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 hrs (data reported for admission and peak values). Reference standard (30 day composite) occurred after testing. Thresholds were reported as pre-specified

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

Composite 30 day end point of AMI, death and revascularisation Not clear whether 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 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. Excluion 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 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. 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 Collinson 2013*[159]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS

Participants with chest pain and suspected AMI; Study uses subgroup of one arm of an RCT. Patients at high risk of NSTEMI 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 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 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

Reference standard diagnosis of AMI based on joint European Cardiology Society an American College of Cardiology criteria and included serial conventional cTnT or cTnI (10-12 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 enrolled, 25 no samples collected, 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: REACTION-US Nowak 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 were excluded, who did not meet the limited exclusion criteria.

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 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, 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 refernce standard. 30 (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 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, 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 hrs. Data reported for admission and Δ 0-3 hrs. No details of interpretation reported. Threshold for Δ value derived from ROC analysis; 99th centile 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 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

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 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 one month after acute episode. Optimal diagnostic thresholds were determined using within study ROC analyses; 99th centile 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 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

Diagnosis determined by two independent emergency department physicians, based on Joint European Cardiology Society an American College of Cardiology criteria. Reference standard included cTnI taken on admission, at 6 hrs and beyond, as needed (10-12 hr 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

54 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 2017[100]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS

Patients with chest pain suggestive of ACS. STEMI, trauma which could elevate troponins excluded. 30 patients >90 years and 16 with a poor prognosis were excluded (these reasons were not specified in the methods. An additional 21 patients were excluded for addition un-specified 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 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

Adjudicated by two cardiologists based on ESC/ACC guidelines, unclear whether this was done 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 2017[102]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS

All patients with routine POC-TnT 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 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 indx test.

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

Clinicians adjudicating the reference standard diagnosis had access to all clinical information including hs-cTnT results. Reference standard diagniosis was retrieved for ICD10 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 2016[80]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS

Adults presenting to the ED with symtoms 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), subgroup analysis excluding patients with STEMI (target condition NSTEMI) 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 refernce 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. Informantion 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: TUSCA Santalo 2013*[133]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS

Consecutive adult patients presenting to the emergency department	
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 emergency department 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 hs-cTnT 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 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

Final diagnosis adjudicated by committee, based on Roche cTnT at admission and 2, 4 and 6-8 hours or until discharge (10-12 hr time point not specified). NSTEMI defined as cTnT >10 ng/L and ΔcTnT >20%; also 99th centile. Unclear whether 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: UTROPIA, Sandoval 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?	
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

Final diagnosis adjudicated after the index test, pre-specified thresholds (IoD 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 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

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 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 mixed AMI

Do the included patients match the question?	**Concerns: High**

DOMAIN 2: INDEX TEST(S)

A. RISK OF BIAS

Reference standard TnT 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 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

Reference standard included TnT results at 2-4 nd 6-24 hours as well as clinical information and MI was adjudicated by a panel of cardiologists. Not clear whether cardiologists adjudicating final diagnosis had access to hs TnI 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 to 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**

b. QUADAS-2C Assessments

Study: ADAPT, Cullen 2014[68]

Domain: Patient selection			
Single test accuracy (QUADAS-2)		**Answers for Abbott ARCHITECT hs-cTnI**	**Answers for Roche Elecsys hs-cTnT**
Signaling 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 ARCHITECT hs-cTnI vs Roche Elecsys hs-cTnT**	
Signaling 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 randomized, was the allocation sequence random?	Not applicable	
	1.9 If patients were randomized, was the allocation sequence concealed until patients were enrolled and assigned to index tests?	Not applicable	
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 test ARCHITECT hs-cTnI**	**Answers Roche Elecsys hs-cTnT**
Signaling 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 ARCHITECT hs-cTnI vs Roche Elecsys hs-cTnT**	
Signaling 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	Unclear	

	test(s)?	
	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 ARCHITECT hs-cTnI**	**Answers for Roche Elecsys hs-cTnT**
Signaling 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 ARCHITECT hs-cTnI vs Roche Elecsys hs-cTnT**	
Signaling 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 ARCHITECT hs-cTnI**	**Answers for Roche Elecsys hs-cTnT**
Signaling 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 ARCHITECT hs-cTnI vs Roche Elecsys hs-cTnT**	
Signaling 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	Yes	

	the index tests?	
	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

Study: APACE, Boeddinghaus 2018,[59] Boeddinghaus 2019,[170] Boeddinghaus 2019,[178] (Comparison of assays using ESC 0/1 hour pathway or equivalent)

	Domain: Patient selection						
Single test accuracy (QUADAS-2)		**Answers for Abbott ARCHITECT hs-cTnI**	**Answers for Beckman Coulter ACCESS hs-cTnI**	**Answers for Ortho VITROS hs-cTnI**	**Answers for Quidel TriageTrue hs-cTnI**	**Answers for Roche Elecsys hs-cTnT**	**Answers for Siemens ADVIA Centaur hs-cTnI**
Signaling 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**				
Signaling 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 randomized, was the allocation sequence random?		Not applicable				
	1.9 If patients were randomized, was the allocation sequence		Not applicable				

	concealed until patients were enrolled and assigned to index tests?		
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 Abbott ARCHITECT hs-cTnI**	**Answers for Beckman Coulter ACCESS hs-cTnI**	**Answers for Ortho VITROS hs-cTnI**	**Answers for Quidel TriageTrue hs TnI**	**Answers for Roche Elecsys hs-cTnT**	**Answers for Siemens ADVIA Centaur hs-cTnI**
Signaling 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**				
Signaling 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 Abbott ARCHITECT hs-cTnI**	**Answers for Beckman Coulter ACCESS hs-cTnI**	**Answers for Ortho VITROS hs-cTnI**	**Answers for Quidel TriageTrue hs-cTnI**	**Answers for Roche Elecsys hs-cTnT**	**Answers for Siemens ADVIA Centaur hs-cTnI**
Signaling 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	Low	Low	Low	Low	Low	Low

	not match the review question?						
Comparative accuracy (QUADAS-2C)			**Answers for the comparison of all tests**				
Signaling 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 Abbott ARCHITECT hs-cTnI**	**Answers for Beckman Coulter ACCESS hs-cTnI**	**Answers for Ortho VITROS hs-cTnI**	**Answers for Quidel TriageTrue hs-cTnI**	**Answers for Roche Elecsys hs-cTnT**	**Answers for Siemens ADVIA Centaur hs-cTnI**
Signaling 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**				
Signaling 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)

Study: BEST, Body 2019,[115] Body 2020[172]

Domain: Patient selection			
Single test accuracy (QUADAS-2)		**Answers for Roche Elecsys hs-cTnT**	**Answers for Siemens ADVIA Centaur hs-cTnI**
Signaling 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 Roche Elecsys hs-cTnT vs Siemens ADVIA Centaur hs-cTnI**	
Signaling 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 randomized, was the allocation sequence random?	Not applicable	
	1.9 If patients were randomized, was the allocation sequence concealed until patients were enrolled and assigned to index tests?	Not applicable	
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 Roche Elecsys hs-cTnT**	**Answers for Siemens ADVIA Centaur hs-cTnI**
Signaling 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 Roche Elecsys hs-cTnT vs Siemens ADVIA Centaur hs-cTnI**	
Signaling 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 Roche Elecsys hs-cTnT**	**Answers for Siemens ADVIA Centaur hs-cTnI**
Signaling 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 Roche Elecsys hs-cTnT vs Siemens ADVIA Centaur hs-cTnI**	
Signaling 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 Roche Elecsys hs-cTnT**	**Answers for Siemens ADVIA Centaur hs-cTnI**
Signaling 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 Roche Elecsys hs-cTnT vs Siemens ADVIA Centaur hs-cTnI**	
Signaling 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

High-STEACS, Chapman 2018,[66] Chapman 2019[67]

Domain: Patient selection			
Single test accuracy (QUADAS-2)		**Answers for Abbott ARCHITECT hs-cTnI**	**Answers for Siemens Atellica hs-cTnI**
Signaling 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 ARCHITECT hs-cTnI vs Siemens Atellica hs-cTnI**	
Signaling 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 randomized, was the allocation sequence random?	Not applicable	
	1.9 If patients were randomized, was the allocation sequence concealed until patients were enrolled and assigned to index tests?	Not applicable	
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 ARCHITECT hs-cTnI**	**Answers for Siemens Atellica hs-cTnI**
Signaling 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 ARCHITECT hs-cTnI vs Siemens Atellica hs-cTnI**	
Signaling 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	Unclear	

	test(s)?	
	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 ARCHITECT hs-cTnI**	**Answers for Siemens Atellica hs-cTnI**
Signaling 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 ARCHITECT hs-cTnI vs Siemens Atellica hs-cTnI**	
Signaling 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 ARCHITECT hs-cTnI**	**Answers for Siemens Atellica hs-cTnI**
Signaling 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 ARCHITECT hs-cTnI vs Siemens Atellica hs-cTnI**	
Signaling 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	Yes	

	the index tests?	
	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

HIGH-US, Sandoval 2019[176]

Domain: Patient selection			
Single test accuracy (QUADAS-2)		**Answers for Siemens Atellica hs-cTnI**	**Answers for Siemens ADVIA Centaur hs-cTnI**
Signaling 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 Siemens Atellica hs-cTnI vs Siemens ADVIA Centaur hs-cTnI**	
Signaling 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 randomized, was the allocation sequence random?	Not applicable	
	1.9 If patients were randomized, was the allocation sequence concealed until patients were enrolled and assigned to index tests?	Not applicable	
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 Siemens Atellica hs-cTnI**	**Answers for Siemens ADVIA Centaur hs-cTnI**
Signaling 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 Siemens Atellica hs-cTnI vs Siemens ADVIA Centaur hs-cTnI**	
Signaling 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	Unclear	

	test(s)?	
	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 Siemens Atellica hs-cTnI**	**Answers for Siemens ADVIA Centaur hs-cTnI**
Signaling 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 Siemens Atellica hs-cTnI vs Siemens ADVIA Centaur hs-cTnI**	
Signaling 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 Siemens Atellica hs-cTnI**	**Answers for Siemens ADVIA Centaur hs-cTnI**
Signaling 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 Answers for the comparison of Siemens Atellica hs-cTnI vs Siemens ADVIA Centaur hs-cTnI**	
Signaling 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

ROMI-3, Shortt 2017[101]

Domain: Patient selection			
Single test accuracy (QUADAS-2)		**Answers for Abbott ARCHITECT hs-cTnI**	**Answers for Roche Elecsys hs-cTnT**
Signaling 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 Abbott ARCHITECT hs-cTnI vs Roche Elecsys hs-cTnT**	
Signaling 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 randomized, was the allocation sequence random?	Not applicable	
	1.9 If patients were randomized, was the allocation sequence concealed until patients were enrolled and assigned to index tests?	Not applicable	
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 Abbott ARCHITECT hs-cTnI**	**Answers for Roche Elecsys hs-cTnT**
Signaling 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 Abbott ARCHITECT hs-cTnI vs Roche Elecsys hs-cTnT**	
Signaling 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	Yes	

	the performance of the other index test(s)?	
	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 Abbott ARCHITECT hs-cTnI**	**Answers for Roche Elecsys hs-cTnT**
Signaling 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 Abbott ARCHITECT hs-cTnI vs Roche Elecsys hs-cTnT**	
Signaling 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 Abbott ARCHITECT hs-cTnI**	**Answers for Roche Elecsys hs-cTnT**
Signaling 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 Abbott ARCHITECT hs-cTnI vs Roche Elecsys hs-cTnT**	
Signaling 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

TRUST, Carlton 2015[64]

Domain: Patient selection			
Single test accuracy (QUADAS-2)		**Answers for Abbott ARCHITECT hs-cTnI**	**Answers for Roche Elecsys hs-cTnT**
Signaling 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 Abbott ARCHITECT hs-cTnI vs Roche Elecsys hs-cTnT**	
Signaling 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 randomized, was the allocation sequence random?	Not applicable	
	1.9 If patients were randomized, was the allocation sequence concealed until patients were enrolled and assigned to index tests?	Not applicable	
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 Abbott ARCHITECT hs-cTnI**	**Answers for Roche Elecsys hs-cTnT**
Signaling 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 Abbott ARCHITECT hs-cTnI vs Roche Elecsys hs-cTnT**	
Signaling 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	Yes	

	the performance of the other index test(s)?	
	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 Abbott ARCHITECT hs-cTnI**	**Answers for Roche Elecsys hs-cTnT**
Signaling 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 Abbott ARCHITECT hs-cTnI vs Roche Elecsys hs-cTnT**	
Signaling 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 Abbott ARCHITECT hs-cTnI**	**Answers for Roche Elecsys hs-cTnT**
Signaling 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 Abbott ARCHITECT hs-cTnI vs Roche Elecsys hs-cTnT**	
Signaling 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

APPENDIX 4: DETAILS OF EXCLUDED STUDIES WITH RATIONALE

To be included in the review studies had to fulfil the following criteria:

Population: Adults (≥18 yrs) 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: Abbott ARCHITECT hs-cTnI; Abbott Alinity hs-cTnI; Beckman Coulter Access hs-cTnI; Biomérieux VIDAS hs-cTnI; Ortho VITROS hs-cTnI; Quidel Triage True hs-cTnI Roche Elecsys (cTnT-hs or cTnT-hs STAT); Siemens Atellica hs-cTnI, Siemens Dimension EXL hs-cTnI; Siemens Dimension Vista hs-cTnI; Siemens ADVIA Centaur hs-cTnI; results available within 3 hours

Reference Standard: Third universal definition of AMI,[33] including measurement of troponin T or I (using any method) on presentation and 3-6 hours later **or** occurrence of MACE (any definition used in identified studies) during 30 day follow-up

Outcome: Sufficient data to construct 2x2 table of test performance

The table below summarises studies which 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. The table shows which of the criteria each study fulfilled ("Y") and on which item it failed ("N") or was unclear.

Study Details	Study Design	Setting	Population	Index Test	Reference Standard	Outcome
Aguirre, 2014[232]	Y	Y	Y	Y	Y	N
Ambavane, 2017[192]	Y	Y	Y	Y	Unclear	N
Badertscher, 2018[233]	Y	Y	Unclear	Unclear	Unclear	Y
Bandstein, 2014[234]	Y	Y	Y	Unclear	Y	N
Biener, 2013[235]	Y	Y	Y	N		
Borna, 2014[236]	Y	N				
Burgio, 2018[237]					N	
Burgio, 201[238]	Y	Y	Y	N		
Canadian Institutes of Health Research McMaster University, 2017[239]	N					
Chew, 2019[216]	Y	Y	Y	Y	Y	N

Study Details	Study Design	Setting	Population	Index Test	Reference Standard	Outcome
CortÉS, 2018[240]	Y	Y	Y	Y	Y	N
Costabel, 2014[241]	Y	Y	Y	Y	N	
Costabel, 2019[242]	Y	Y	Y	Unclear		
Croce, 2017[243]	Y	Y	N			
Cullen, 2013[244]	Y	Y	Y	N		
Cullen, 2013[245]	Y	Y	Y	Unclear	Unclear	N
Cullen, 2014[246]	Y	Y	Y	N		
Cullen, 2014[247]	Y	Y	Y	Y	Y	N
Dadkhah, 2017[248]	Y	Y	Y	N		
Druey, 2015[249]	Y	Y	Y	N		
Ferencik, 2017[250]	Y	Y	Y	Y	Unclear	Unclear
Gandolfo, 2017[251]	Y	Y	Y	Unclear	Y	
Gandolfo, 2017[252]	Unclear	Y	Unclear	Y	Unclear	N
Goorden, 2016[253]	Y	Y	Y	Y	Unclear	Y
Greenslade, 2017[254]	N					
Greenslade, 2018[255]	N					
Gunsolus, 2018[256]	Y	Y	Unclear	Unclear	Unclear	N
Hoeller, 2013[257]	Y[1]	Y	Y	Y	Y	Y
Ichise, 2017[258]	Y	Y	Y	Y	Unclear	N
Invernizzi, 2013[259]	Y	Y	Y	Unclear	N	
Isiksacan, 2017[260]	Y	Y	Y	Y	N	
Isiksacan, 2019[261]	Y	Y	Y	Y	N	
ISRCTN21109279, 2013[262]	Y[2]	Y	Y	Y	Y	Y
Kavsak, 2018[263]	N					
Kavsak, 2018[264]	Y	Unclear	Y	Y	Y	N
Kavsak, 2018[265]	Y	Y	Y	Y	Y	N
Kaysak, 2017[266]	Unclear	N				
Kellens, 2016[267]	Y	Y	Unclear	Y	Y	Unclear
Kitamura, 2013[77]	Y	Y	N			
Korley, 2014[268]	Y	Y	Y	Y	N	
Kovacs, 2015[269]	Y	Y	Y	Y	Y	N
Lin, 2018[270]	Y	Y	Y	Y	Y	N

Study Details	Study Design	Setting	Population	Index Test	Reference Standard	Outcome
Ljung, 2019[271]	N					
Mahler, 2017[78]	Y	Y	Y	Y	Y	N
McCord, 2017[272]	Y	Y	Y	Y	Y	N
McRae, 2017[273]	N					
McRae, 2017[274]	N					
McRae, 2019[275]	N					
Mohsen, 2016[276]	Y	Y	Y	N		
Mueller, 2018[277]	N					
Nacke, 2014[278]	Y	Y	Y	N		
Nasuruddin, 2017[279]	Y	Y	Y	Y	Unclear	N
Nejatian, 2017[280]	Y	Y	N	Unclear		
Nestelberger, 2016[281]	Y	Y	Y	Y	Y	N
Nestelberger, 2019[282]	Y	Y	Y	N		
Neumann, 2019[215]	N					
Neumann, 2019[283]	Y	Y	Y	N		
Nowak, 2017[284]	Y	Y	Y	Y	Y	N
Papendick, 2017[285]	Y	Y	Y	N		
Peitsmeyer, 2013[286]	Y	Y	Y	Y	N	
Peitsmeyer, 2013[287]	Y	Y	Y	N		
Pettersson, 2018[288]	Y	Y	Y	Y	N	
Pickering, 2015[289]	Y	Y	Y	Y	Y	N
Pickering, 2016[290]	N					
Pickering, 2016[291]	N					
Pickering, 2018[292]	Y	Y	Y	N		
Reddy, 2016[293]	Y	Y	Y	Y	N	
Reichlin, 2013[294]	Y	Y	Y	Y	N	
Renstroum, 2018[295]	Y	Y	Unclear	Unclear	Unclear	N
Riedlinger, 2018[296]	N					
Sandoval, 2017[297]	Y	Y	Y	Y	N	Unclear
Santi, 2017[298]	Y	Y	Y	Y	Y	N
Schoenenberger, 2016[299]	N					
Schofer, 2017[300]	Y	Y	Y	N		

Study Details	Study Design	Setting	Population	Index Test	Reference Standard	Outcome
Schonemann-Lund, 2015[301]	Y	N				
Shah, 2015[302]	Y	Y	Y	Y	N	
Shortt, 2015[303]	Y	Y	Y	N		
Stallone, 2016[304]	N					
Stoyanov, 2019[305]	N					
Su, 2015[306]	Y	Y	Y	Y	Unclear	N
Suh, 2018[307]	Y	N				
Teggert, 2015[308]	Y	Y	Y	N		
Than, 2014[309]	Y	Y	Y	N		
Than, 2016[310]	Y	Y	Y	N		
Thelin, 2013[311]	Y	Y	Y	Y	N	
Thet, 2019[312]	Y	Y	N			
Twerenbold, 2013[313]	Y	Y	Y	N		
Twerenbold, 2013[314]	Y	Y	Y	Y	Unclear	Y
Twerenbold, 2018[315]	N					
Vigen, 2018[316]	Y	Y	Y	Unclear	Y	Y
Wang, 2019[317]	N					
Wildi, 2018[318]	Y	Y	N			
Yip, 2014[319]	N					
Yokoyama, 2018[320]	Y	Y	Y	Y	N	
1 Duplicate; 2 Trial registry entry for TRUST, listed publications already included						

APPENDIX 5: 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 >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, EDACS) 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. 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 is suggested this is unlikely to be achieved in practice so a 1-2 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 choic . 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 life-time 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 timepoint 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.

Alternativey, 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 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 6: SCENARIO ANALYSES

Table 38: Scenario 1 conditional on base-case, MI treatment costs for FP

Strategy			Compared to Standard troponin			Full incremental ICER
	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts / ΔQALYs	ΔCosts / ΔQALYs
18 Beckman Coulter ACCESS hsTnI ((symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h))	£38,724	12.0763	-£152	-0.0011	£136,383	cheapest
5 Roche Elecsys hsTnT (<12 ng/L at 0 h AND Δ <3 ng/L at 0 to 1 h)	£38,764	12.0765	-£112	-0.0009	£118,636	ext dominated
17 Beckman Coulter ACCESS hsTnI (ESC pathway)	£38,781	12.0768	-£95	-0.0006	£170,370	ext dominated
9 Abbott ARCHITECT hsTnI (High-STEACS pathway)	£38,787	12.0768	-£89	-0.0006	£159,271	ext dominated
1 Roche Elecsys hsTnT (99th centile)	£38,788	12.0774	-£88	0.0000	£157,505,897	£57,659
3 Roche Elecsys hsTnT (ESC pathway)	£38,793	12.0768	-£83	-0.0006	£149,485	dominated
16 Siemens Atellica hsTnI (High-STEACS pathway)	£38,794	12.0763	-£82	-0.0011	£73,814	dominated
6 Siemens Dimension Vista hsTnI (<5 ng/L at 0 h AND Δ <2 ng/L at 0 to 1 h)	£38,809	12.0774	-£66	0.0000	£119,216,717	dominated
12 Siemens ADVIA Centaur hsTnI (<3 ng/L at 0 h OR (<8 ng/L at 0 h AND Δ <7 ng/L at 0 to 2 h))	£38,822	12.0774	-£54	0.0000	£96,913,928	dominated
20 bioMérieux VIDAS hsTnI (<2 ng/L at 0 h OR (<6 ng/l at 0 AND 2 h))	£38,828	12.0763	-£47	-0.0011	£42,608	dominated
21 Quidel TriageTrue hsTnI (ESC pathway)	£38,843	12.0774	-£33	0.0000	£58,544,594	dominated
19 Ortho VITROS hsTnI (ESC pathway)	£38,843	12.0774	-£32	0.0000	£58,315,678	dominated
8 Abbott ARCHITECT hsTnI (ESC pathway)	£38,855	12.0768	-£21	-0.0006	£36,935	dominated
13 Siemens ADVIA Centaur hsTnI (ESC pathway)	£38,862	12.0768	-£14	-0.0006	£24,942	dominated
14 Siemens ADVIA Centaur hsTnI (<5 ng/L at 0 h)	£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 hsTnI (<4 ng/L at 0 h)	£38,878	12.0767	£2	-0.0007	-£2,607	dominated
4 Roche Elecsys hsTnT (<8 ng/L at 0 h AND Δ <3 ng/L at 0 to 0.5 h)	£38,923	12.0774	£47	0.0000	-£84,642,503	dominated
2 Roche Elecsys hsTnT (LoD)	£38,969	12.0769	£93	-0.0005	-£185,857	dominated
15 Siemens Atellica hsTnI (<2 ng/L at 0 h)	£39,027	12.0774	£151	0.0000	-£271,257,977	dominated
11 Siemens ADVIA Centaur hsTnI (<2 ng/L at 0 h)	£39,047	12.0774	£171	0.0000	-£307,122,945	dominated

7 Abbott ARCHITECT hsTnI (LoD)	£39,055	12.0772	£179	-0.0002	-£1,073,915	dominated

Table 39: Scenario 1 conditional on secondary analysis, MI treatment costs for FP

Strategy			**Compared to Standard troponin**			**Full incremental ICER**
	Costs	**QALYs**	**ΔCosts**	**ΔQALYs**	**ΔCosts / ΔQALYs**	**ΔCosts / ΔQALYs**
Standard troponin (at presentation and after 10-12 hours)	£37,503	11.3230	£0	0.0000	NA	cheapest
18 Beckman Coulter ACCESS hsTnI ((symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h))	£38,151	11.4610	£648	0.1380	£4,698	£4,698
5 Roche Elecsys hsTnT (<12 ng/L at 0 h AND Δ <3 ng/L at 0 to 1 h)	£38,158	11.4510	£655	0.1280	£5,117	dominated
17 Beckman Coulter ACCESS hsTnI (ESC pathway)	£38,167	11.4488	£664	0.1259	£5,277	dominated
3 Roche Elecsys hsTnT (ESC pathway)	£38,172	11.4469	£670	0.1239	£5,403	dominated
6 Siemens Dimension Vista hsTnI (<5 ng/L at 0 h AND Δ <2 ng/L at 0 to 1 h)	£38,183	11.4455	£680	0.1225	£5,551	dominated
9 Abbott ARCHITECT hsTnI (High-STEACS pathway)	£38,192	11.4547	£689	0.1317	£5,233	dominated
16 Siemens Atellica hsTnI (High-STEACS pathway)	£38,192	11.4522	£690	0.1292	£5,336	dominated
20 bioMérieux VIDAS hsTnI (<2 ng/L at 0 h OR (<6 ng/l at 0 AND 2 h))	£38,196	11.4424	£693	0.1195	£5,799	dominated
1 Roche Elecsys hsTnT (99th centile)	£38,196	11.4562	£694	0.1333	£5,204	dominated
14 Siemens ADVIA Centaur hsTnI (<5 ng/L at 0 h)	£38,196	11.4313	£694	0.1083	£6,405	dominated
19 Ortho VITROS hsTnI (ESC pathway)	£38,198	11.4396	£695	0.1167	£5,958	dominated
12 Siemens ADVIA Centaur hsTnI (<3 ng/L at 0 h OR (<8 ng/L at 0 h AND Δ <7 ng/L at 0 to 2 h))	£38,198	11.4465	£696	0.1235	£5,633	dominated
8 Abbott ARCHITECT hsTnI (ESC pathway)	£38,200	11.4361	£698	0.1132	£6,162	dominated
10 Abbott ARCHITECT hsTnI (<4 ng/L at 0 h)	£38,201	11.4291	£698	0.1062	£6,572	dominated
13 Siemens ADVIA Centaur hsTnI (ESC pathway)	£38,204	11.4352	£701	0.1122	£6,247	dominated
21 Quidel TriageTrue hsTnI (ESC pathway)	£38,217	11.4455	£714	0.1225	£5,826	dominated
4 Roche Elecsys hsTnT (<8 ng/L at 0 h AND Δ <3 ng/L at 0 to 0.5 h)	£38,230	11.4250	£727	0.1020	£7,129	dominated
2 Roche Elecsys hsTnT (LoD)	£38,244	11.4147	£742	0.0918	£8,083	dominated
15 Siemens Atellica hsTnI (<2 ng/L at 0 h)	£38,274	11.4064	£771	0.0835	£9,239	dominated
11 Siemens ADVIA Centaur hsTnI (<2 ng/L at 0 h)	£38,284	11.4035	£782	0.0805	£9,705	dominated
7 Abbott ARCHITECT hsTnI (LoD)	£38,286	11.4014	£784	0.0784	£9,994	dominated

Table 40: Scenario 2 conditional on base-case, lifetime relative risk for mortality and reinfarction for FN:

Strategy			Compared to Standard troponin			Full incremental ICER
	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts / ΔQALYs	ΔCosts / ΔQALYs
18 Beckman Coulter ACCESS hsTnI ((symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h))	£38,654	12.0721	-£222	-0.0053	£42,267	cheapest
5 Roche Elecsys hsTnT (<12 ng/L at 0 h AND Δ <3 ng/L at 0 to 1 h)	£38,659	12.0729	-£216	-0.0045	£48,464	ext dominated
17 Beckman Coulter ACCESS hsTnI (ESC pathway)	£38,672	12.0748	-£204	-0.0026	£77,572	£6,962
3 Roche Elecsys hsTnT (ESC pathway)	£38,677	12.0748	-£199	-0.0026	£75,761	dominated
16 Siemens Atellica hsTnI (High-STEACS pathway)	£38,692	12.0721	-£183	-0.0053	£34,891	dominated
6 Siemens Dimension Vista hsTnI (<5 ng/L at 0 h AND Δ <2 ng/L at 0 to 1 h)	£38,693	12.0774	-£183	0.0000	£69,706,183	£7,874
20 bioMérieux VIDAS hsTnI (<2 ng/L at 0 h OR (<6 ng/l at 0 AND 2 h))	£38,693	12.0721	-£183	-0.0053	£34,815	dominated
14 Siemens ADVIA Centaur hsTnI (<5 ng/L at 0 h)	£38,696	12.0748	-£179	-0.0026	£68,270	dominated
10 Abbott ARCHITECT hsTnI (<4 ng/L at 0 h)	£38,698	12.0740	-£177	-0.0034	£51,980	dominated
9 Abbott ARCHITECT hsTnI (High-STEACS pathway)	£38,699	12.0748	-£177	-0.0026	£67,378	dominated
8 Abbott ARCHITECT hsTnI (ESC pathway)	£38,702	12.0748	-£174	-0.0026	£66,291	dominated
13 Siemens ADVIA Centaur hsTnI (ESC pathway)	£38,705	12.0748	-£171	-0.0026	£65,057	dominated
19 Ortho VITROS hsTnI (ESC pathway)	£38,706	12.0774	-£170	0.0000	£64,644,677	dominated
12 Siemens ADVIA Centaur hsTnI (<3 ng/L at 0 h OR (<8 ng/L at 0 h AND Δ <7 ng/L at 0 to 2 h))	£38,709	12.0774	-£167	0.0000	£63,673,276	dominated
1 Roche Elecsys hsTnT (99th centile)	£38,709	12.0774	-£167	0.0000	£63,440,707	dominated
21 Quidel TriageTrue hsTnI (ESC pathway)	£38,726	12.0774	-£149	0.0000	£56,850,305	dominated
4 Roche Elecsys hsTnT (<8 ng/L at 0 h AND Δ <3 ng/L at 0 to 0.5 h)	£38,734	12.0774	-£142	0.0000	£53,960,316	ext dominated
2 Roche Elecsys hsTnT (LoD)	£38,740	12.0750	-£135	-0.0024	£57,282	dominated
15 Siemens Atellica hsTnI (<2 ng/L at 0 h)	£38,773	12.0774	-£103	0.0000	£39,253,952	dominated
7 Abbott ARCHITECT hsTnI (LoD)	£38,782	12.0766	-£94	-0.0008	£118,920	dominated
11 Siemens ADVIA Centaur hsTnI (<2 ng/L at 0 h)	£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

Table 41: Scenario 2 conditional on secondary analysis, lifetime relative risk for mortality and reinfarction for FN:

Strategy			Compared to Standard troponin			Full incremental ICER
	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts / ΔQALYs	ΔCosts / ΔQALYs
Standard troponin (at presentation and after 10-12 hours)	£36,496	10.9853	£0	0.0000	NA	cheapest
7 Abbott ARCHITECT hsTnI (LoD)	£38,015	11.4007	£1,519	0.4155	£3,656	ext dominated
2 Roche Elecsys hsTnT (LoD)	£38,017	11.4128	£1,521	0.4276	£3,558	ext dominated
15 Siemens Atellica hsTnI (<2 ng/L at 0 h)	£38,022	11.4064	£1,525	0.4211	£3,622	dominated
11 Siemens ADVIA Centaur hsTnI (<2 ng/L at 0 h)	£38,022	11.4035	£1,526	0.4182	£3,648	dominated
10 Abbott ARCHITECT hsTnI (<4 ng/L at 0 h)	£38,022	11.4265	£1,526	0.4412	£3,460	ext dominated
14 Siemens ADVIA Centaur hsTnI (<5 ng/L at 0 h)	£38,027	11.4292	£1,531	0.4439	£3,448	ext dominated
4 Roche Elecsys hsTnT (<8 ng/L at 0 h AND Δ <3 ng/L at 0 to 0.5 h)	£38,042	11.4250	£1,546	0.4397	£3,517	dominated
8 Abbott ARCHITECT hsTnI (ESC pathway)	£38,048	11.4341	£1,552	0.4488	£3,457	ext dominated
13 Siemens ADVIA Centaur hsTnI (ESC pathway)	£38,048	11.4331	£1,552	0.4478	£3,465	dominated
5 Roche Elecsys hsTnT (<12 ng/L at 0 h AND Δ <3 ng/L at 0 to 1 h)	£38,054	11.4475	£1,558	0.4622	£3,371	ext dominated
3 Roche Elecsys hsTnT (ESC pathway)	£38,057	11.4448	£1,561	0.4595	£3,397	dominated
17 Beckman Coulter ACCESS hsTnI (ESC pathway)	£38,059	11.4468	£1,563	0.4615	£3,386	dominated
20 bioMérieux VIDAS hsTnI (<2 ng/L at 0 h OR (<6 ng/l at 0 AND 2 h))	£38,061	11.4383	£1,565	0.4530	£3,454	dominated
19 Ortho VITROS hsTnI (ESC pathway)	£38,061	11.4396	£1,565	0.4544	£3,445	dominated
6 Siemens Dimension Vista hsTnI (<5 ng/L at 0 h AND Δ <2 ng/L at 0 to 1 h)	£38,067	11.4455	£1,571	0.4602	£3,413	dominated
18 Beckman Coulter ACCESS hsTnI ((symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h))	£38,081	11.4568	£1,585	0.4716	£3,362	£3,362
12 Siemens ADVIA Centaur hsTnI (<3 ng/L at 0 h OR (<8 ng/L at 0 h AND Δ <7 ng/L at 0 to 2 h))	£38,086	11.4465	£1,590	0.4612	£3,447	dominated
16 Siemens Atellica hsTnI (High-STEACS pathway)	£38,092	11.4481	£1,596	0.4628	£3,448	dominated
21 Quidel TriageTrue hsTnI (ESC pathway)	£38,101	11.4455	£1,605	0.4602	£3,487	dominated
9 Abbott ARCHITECT hsTnI (High-STEACS pathway)	£38,104	11.4526	£1,608	0.4674	£3,441	dominated
1 Roche Elecsys hsTnT (99th centile)	£38,118	11.4562	£1,622	0.4710	£3,444	dominated

Table 42: Scenario 3 conditional on base-case, differential test costs:

Strategy			Compared to Standard troponin			Full incremental ICER
	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts / ΔQALYs	ΔCosts / ΔQALYs
18 Beckman Coulter ACCESS hsTnI ((symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h))	£38,666	12.0763	-£210	-0.0011	£188,442	cheapest
5 Roche Elecsys hsTnT (<12 ng/L at 0 h AND Δ <3 ng/L at 0 to 1 h)	£38,677	12.0765	-£199	-0.0009	£210,557	ext dominated
17 Beckman Coulter ACCESS hsTnI (ESC pathway)	£38,678	12.0768	-£197	-0.0006	£354,684	£22,200
3 Roche Elecsys hsTnT (ESC pathway)	£38,689	12.0768	-£187	-0.0006	£335,724	dominated
6 Siemens Dimension Vista hsTnI (<5 ng/L at 0 h AND Δ <2 ng/L at 0 to 1 h)	£38,692	12.0774	-£184	0.0000	£330,758,895	£23,949
14 Siemens ADVIA Centaur hsTnI (<5 ng/L at 0 h)	£38,702	12.0768	-£174	-0.0006	£312,438	dominated
16 Siemens Atellica hsTnI (High-STEACS pathway)	£38,704	12.0763	-£172	-0.0011	£154,774	dominated
19 Ortho VITROS hsTnI (ESC pathway)	£38,705	12.0774	-£171	0.0000	£307,200,566	dominated
9 Abbott ARCHITECT hsTnI (High-STEACS pathway)	£38,707	12.0768	-£169	-0.0006	£303,093	dominated
12 Siemens ADVIA Centaur hsTnI (<3 ng/L at 0 h OR (<8 ng/L at 0 h AND Δ <7 ng/L at 0 to 2 h))	£38,708	12.0774	-£168	0.0000	£302,143,335	dominated
10 Abbott ARCHITECT hsTnI (<4 ng/L at 0 h)	£38,708	12.0767	-£168	-0.0007	£232,351	dominated
13 Siemens ADVIA Centaur hsTnI (ESC pathway)	£38,710	12.0768	-£166	-0.0006	£298,174	dominated
8 Abbott ARCHITECT hsTnI (ESC pathway)	£38,710	12.0768	-£165	-0.0006	£297,336	dominated
20 bioMérieux VIDAS hsTnI (<2 ng/L at 0 h OR (<6 ng/l at 0 AND 2 h))	£38,711	12.0763	-£165	-0.0011	£148,321	dominated
1 Roche Elecsys hsTnT (99th centile)	£38,716	12.0774	-£159	0.0000	£286,628,255	dominated
21 Quidel TriageTrue hsTnI (ESC pathway)	£38,726	12.0774	-£149	0.0000	£268,289,079	dominated
4 Roche Elecsys hsTnT (<8 ng/L at 0 h AND Δ <3 ng/L at 0 to 0.5 h)	£38,741	12.0774	-£135	0.0000	£241,886,429	dominated
2 Roche Elecsys hsTnT (LoD)	£38,749	12.0769	-£126	-0.0005	£252,587	dominated
15 Siemens Atellica hsTnI (<2 ng/L at 0 h)	£38,772	12.0774	-£104	0.0000	£186,143,573	dominated
11 Siemens ADVIA Centaur hsTnI (<2 ng/L at 0 h)	£38,781	12.0774	-£94	0.0000	£169,540,501	dominated
7 Abbott ARCHITECT hsTnI (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

Table 43: Scenario 3 conditional on secondary analysis, differential test costs:

Strategy			Compared to Standard troponin			Full incremental ICER
	Costs	QALYs	ΔCosts	ΔQALYs	ΔCosts / ΔQALYs	ΔCosts / ΔQALYs
Standard troponin (at presentation and after 10-12 hours)	£37,503	11.3230	£0	0.0000	NA	Cheapest
7 Abbott ARCHITECT hsTnI (LoD)	£38,019	11.4014	£516	0.0784	£6,580	ext dominated
11 Siemens ADVIA Centaur hsTnI (<2 ng/L at 0 h)	£38,021	11.4035	£518	0.0805	£6,434	ext dominated
15 Siemens Atellica hsTnI (<2 ng/L at 0 h)	£38,021	11.4064	£518	0.0835	£6,210	ext dominated
2 Roche Elecsys hsTnT (LoD)	£38,026	11.4147	£524	0.0918	£5,706	ext dominated
10 Abbott ARCHITECT hsTnI (<4 ng/L at 0 h)	£38,032	11.4291	£529	0.1062	£4,982	ext dominated
14 Siemens ADVIA Centaur hsTnI (<5 ng/L at 0 h)	£38,032	11.4313	£530	0.1083	£4,889	ext dominated
4 Roche Elecsys hsTnT (<8 ng/L at 0 h AND Δ <3 ng/L at 0 to 0.5 h)	£38,050	11.4250	£547	0.1020	£5,360	Dominated
13 Siemens ADVIA Centaur hsTnI (ESC pathway)	£38,053	11.4352	£550	0.1122	£4,901	ext dominated
8 Abbott ARCHITECT hsTnI (ESC pathway)	£38,056	11.4361	£554	0.1132	£4,891	ext dominated
19 Ortho VITROS hsTnI (ESC pathway)	£38,060	11.4396	£558	0.1167	£4,778	ext dominated
17 Beckman Coulter ACCESS hsTnI (ESC pathway)	£38,065	11.4488	£562	0.1259	£4,468	ext dominated
6 Siemens Dimension Vista hsTnI (<5 ng/L at 0 h AND Δ <2 ng/L at 0 to 1 h)	£38,066	11.4455	£563	0.1225	£4,596	Dominated
3 Roche Elecsys hsTnT (ESC pathway)	£38,069	11.4469	£567	0.1239	£4,573	Dominated
5 Roche Elecsys hsTnT (<12 ng/L at 0 h AND Δ <3 ng/L at 0 to 1 h)	£38,072	11.4510	£569	0.1280	£4,442	ext dominated
20 bioMérieux VIDAS hsTnI (<2 ng/L at 0 h OR (<6 ng/l at 0 AND 2 h))	£38,079	11.4424	£576	0.1195	£4,821	dominated
12 Siemens ADVIA Centaur hsTnI (<3 ng/L at 0 h OR (<8 ng/L at 0 h AND Δ <7 ng/L at 0 to 2 h))	£38,085	11.4465	£582	0.1235	£4,714	dominated
18 Beckman Coulter ACCESS hsTnI ((symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h))	£38,094	11.4610	£591	0.1380	£4,281	£4,281
21 Quidel TriageTrue hsTnI (ESC pathway)	£38,101	11.4455	£598	0.1225	£4,880	dominated
16 Siemens Atellica hsTnI (High-STEACS pathway)	£38,103	11.4522	£600	0.1292	£4,643	dominated
9 Abbott ARCHITECT hsTnI (High-STEACS pathway)	£38,113	11.4547	£610	0.1317	£4,630	dominated
1 Roche Elecsys hsTnT (99th centile)	£38,125	11.4562	£622	0.1333	£4,669	dominated

Figure 17: Scenario 1 conditional on base-case cost effectiveness frontier

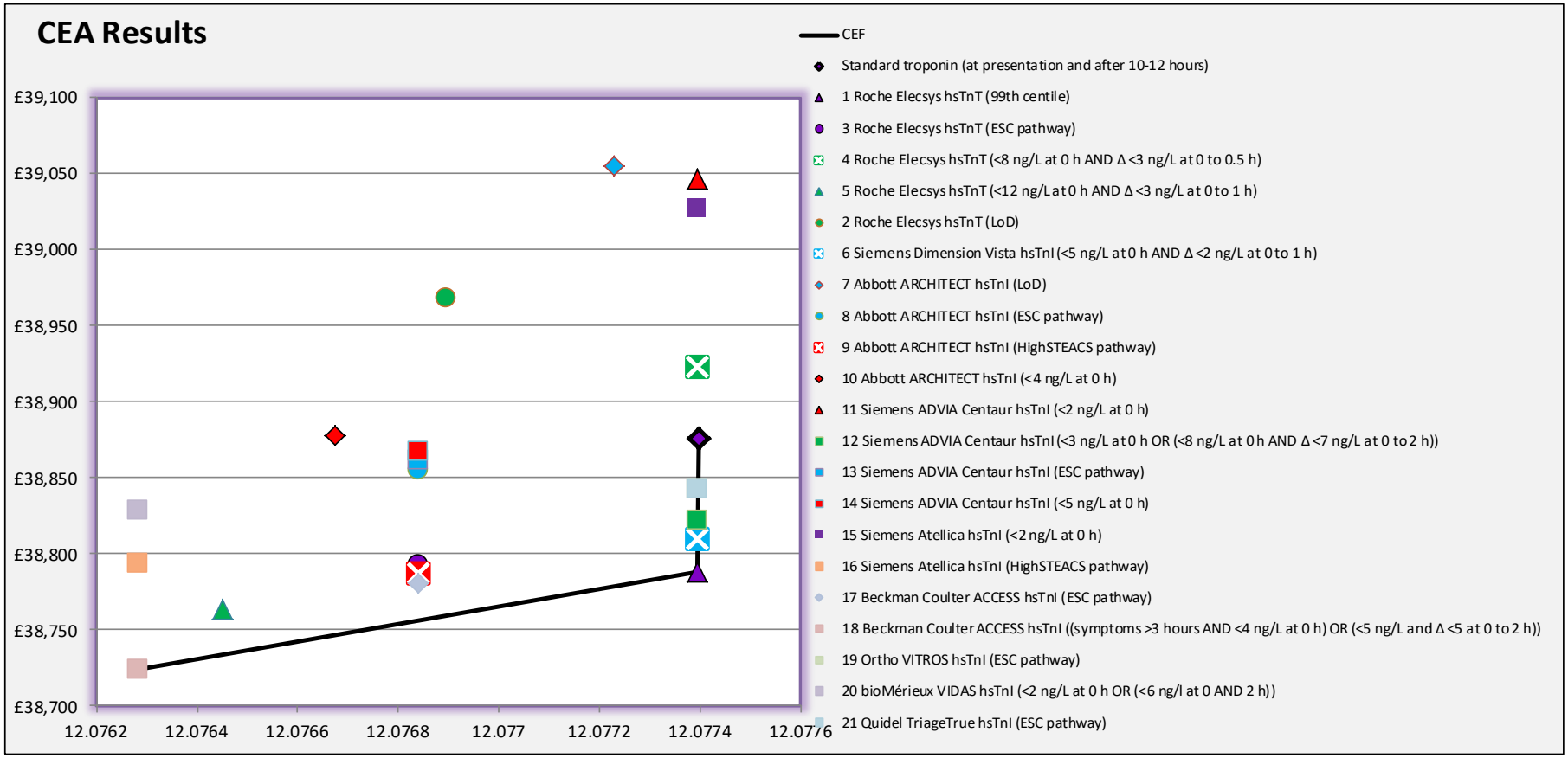


Figure 18: Scenario 1 conditional on secondary analysis cost effectiveness frontier

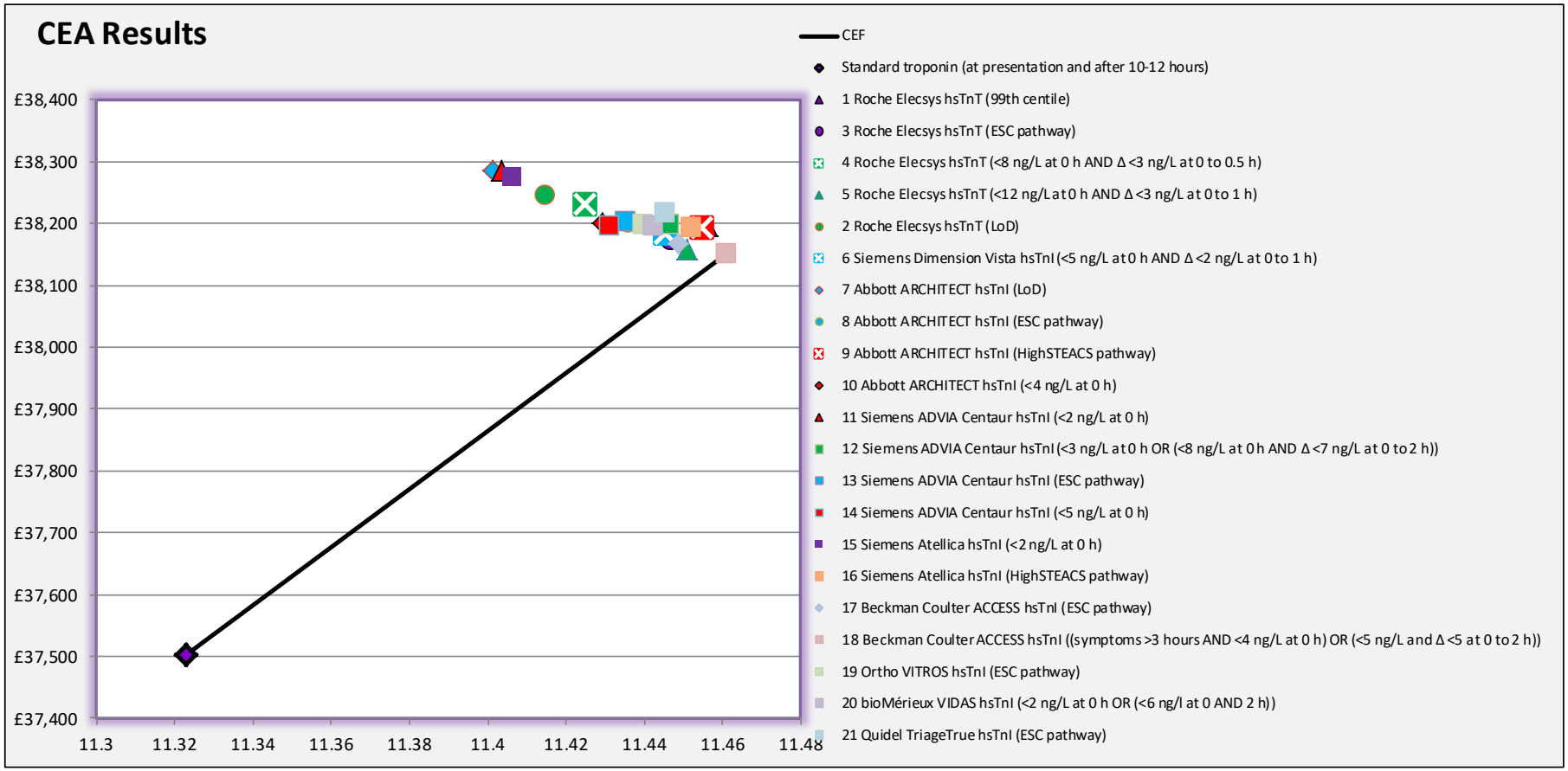


Figure 19: Scenario 2 conditional on base-case cost effectiveness frontier

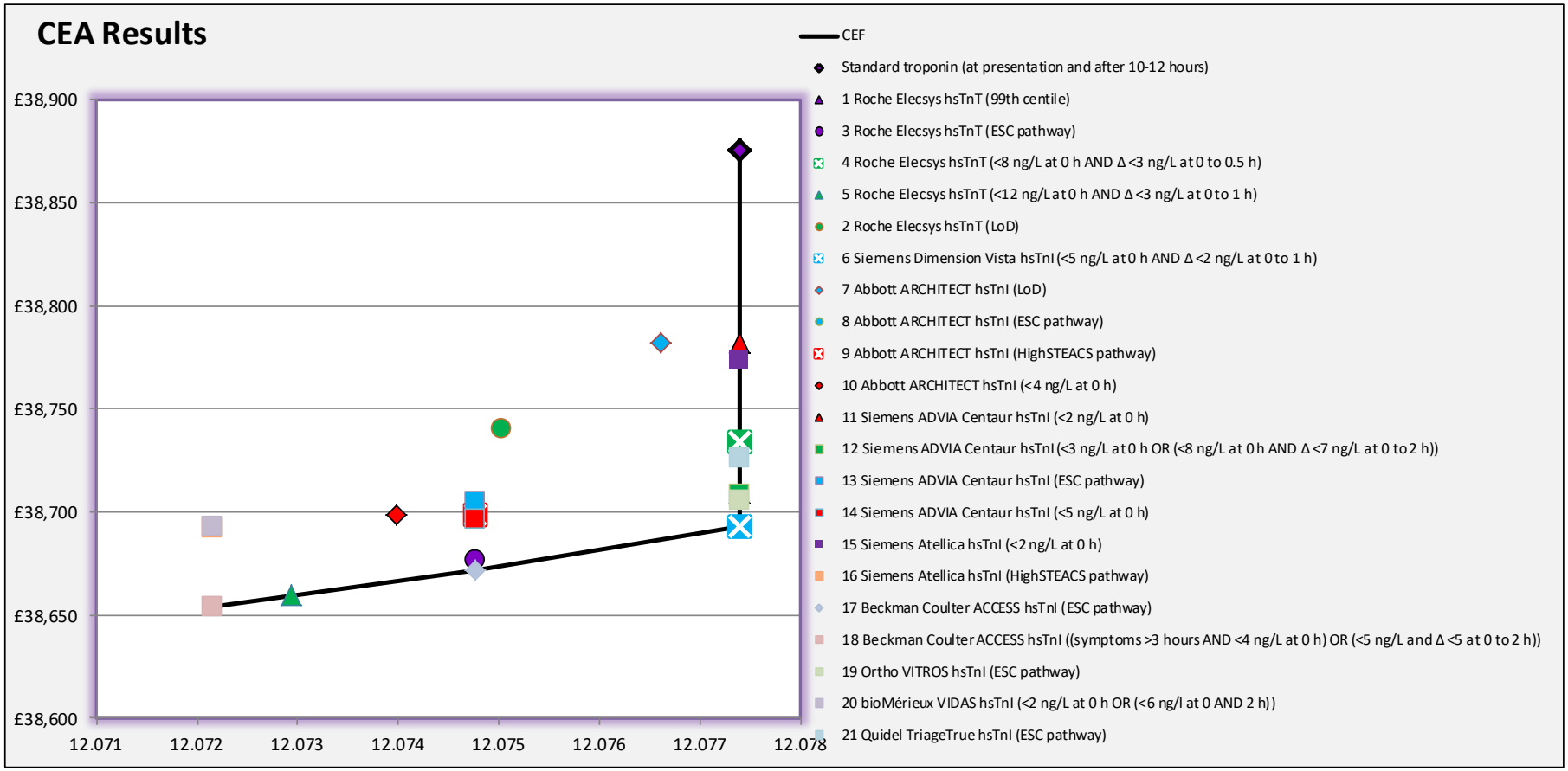


Figure 20: Scenario 2 conditional on secondary analysis cost effectiveness frontier

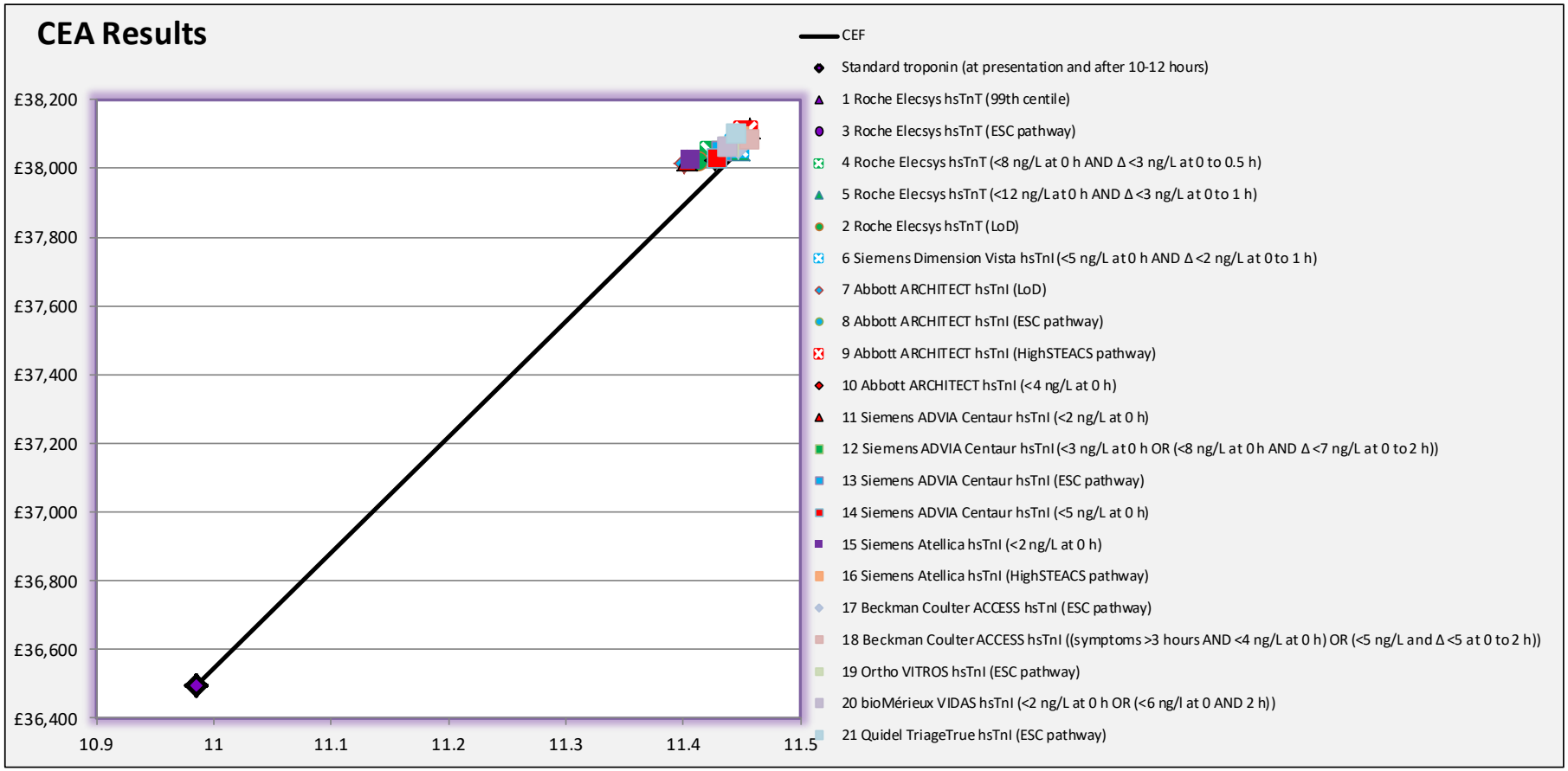


Figure 21: Scenario 3 conditional on base-case cost effectiveness frontier

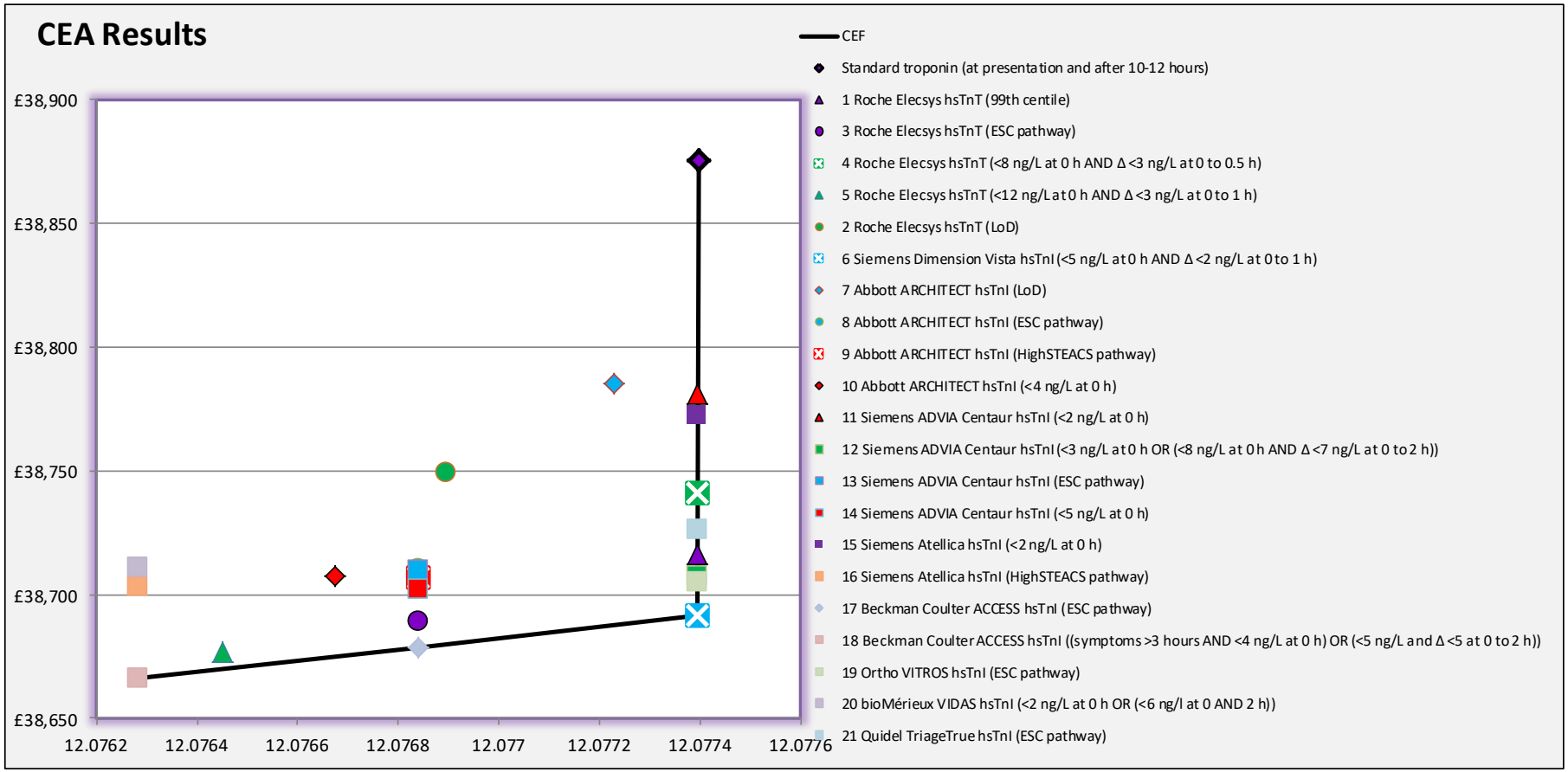
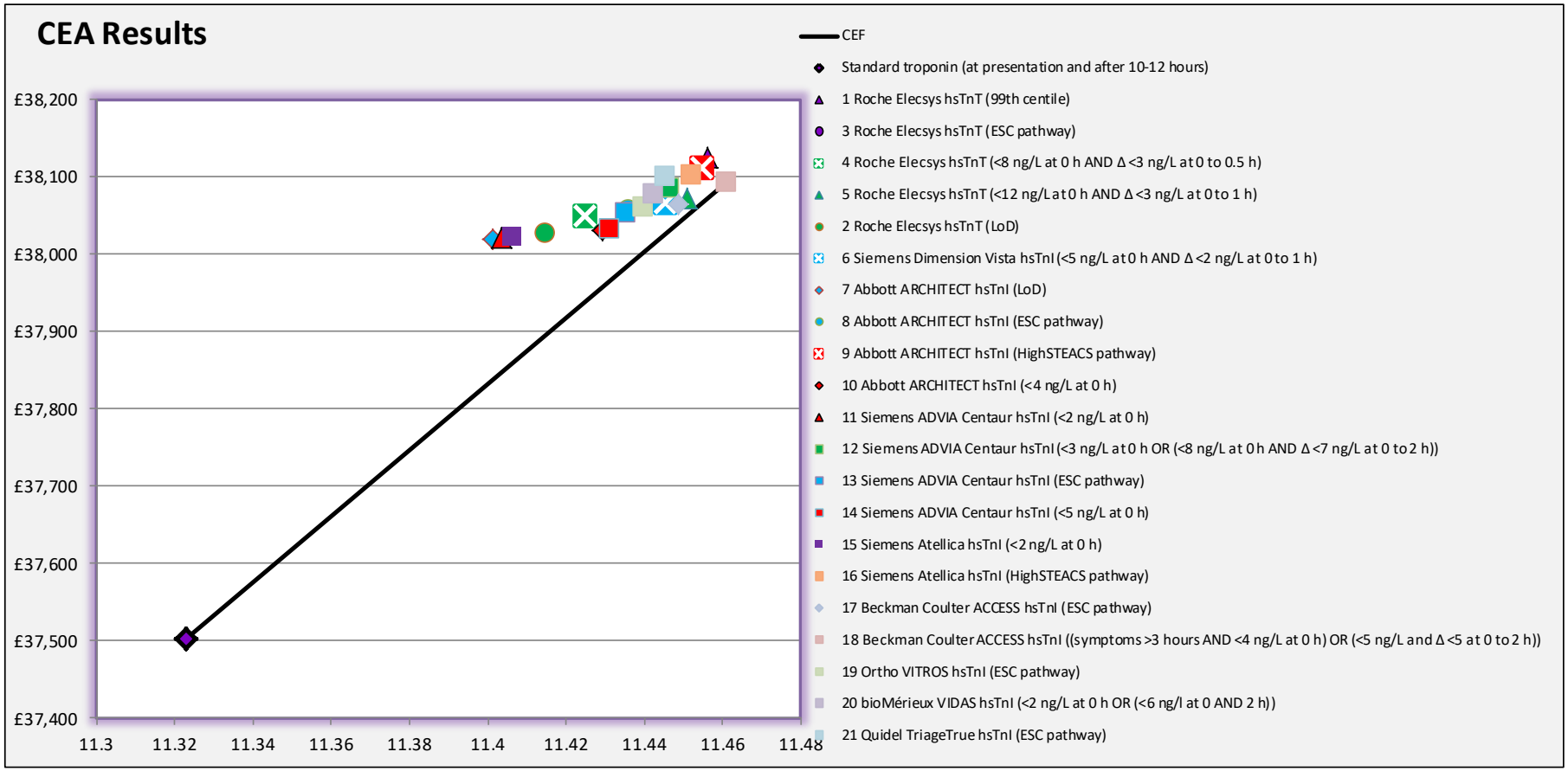


Figure 22: Scenario 3 conditional on secondary analysis cost effectiveness frontier



APPENDIX 7: DETERMINISTIC ONE-WAY SENSITIVITY ANALYSES

DOWSAs for base-case (based on incremental net benefit)

Figure 23: Tornado diagram for comparison between Roche Elecsys hsTnT (ESC 0/1 hour pathway: (symptoms >3 hours AND <5 ng/L at 0 h) OR (<12 ng/L at 0 h AND Δ <3 ng/L at 0 to 1 h)) and Beckman Coulter ACCESS hsTnI ((symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h))

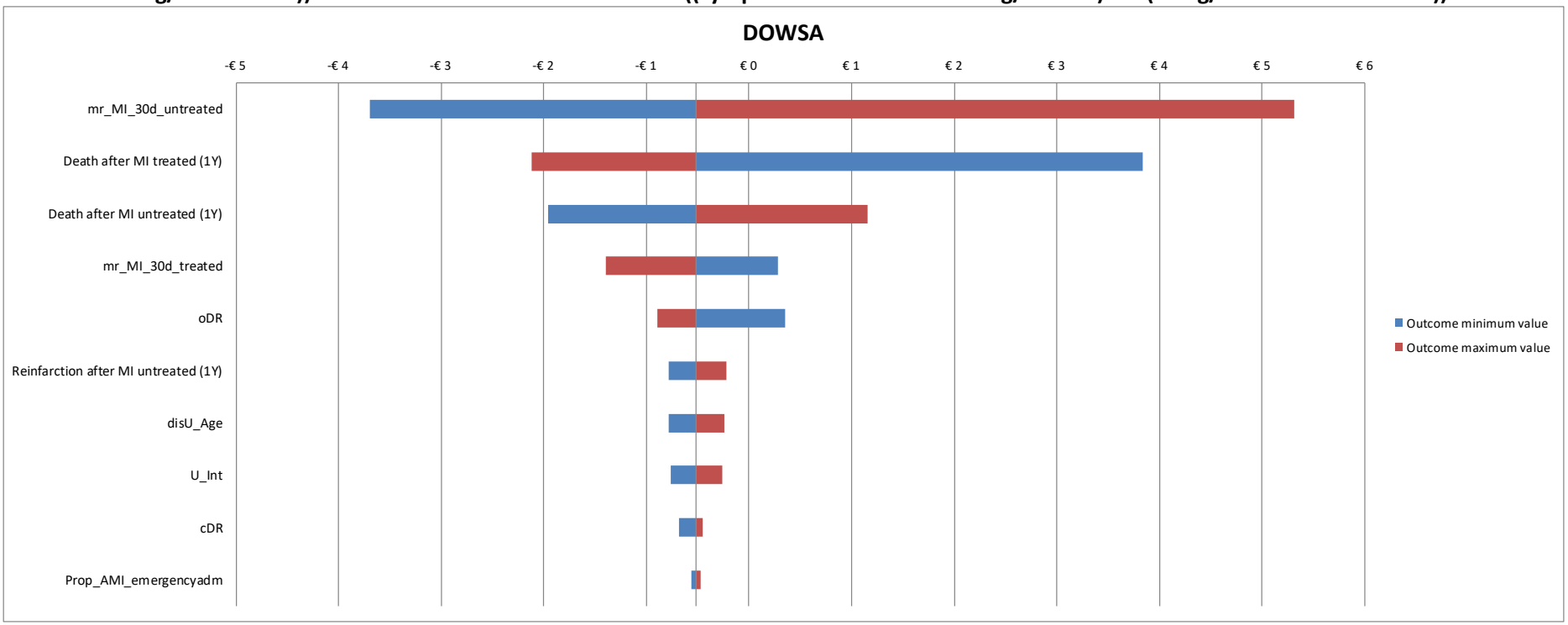


Figure 24: Tornado diagram for comparison between Siemens Dimension Vista hsTnI (<5 ng/L at 0 h AND Δ <2 ng/L at 0 to 1 h) and Roche Elecsys hsTnT (ESC 0/1 hour pathway: (symptoms >3 hours AND <5 ng/L at 0 h) OR (<12 ng/L at 0 h AND Δ <3 ng/L at 0 to 1 h))

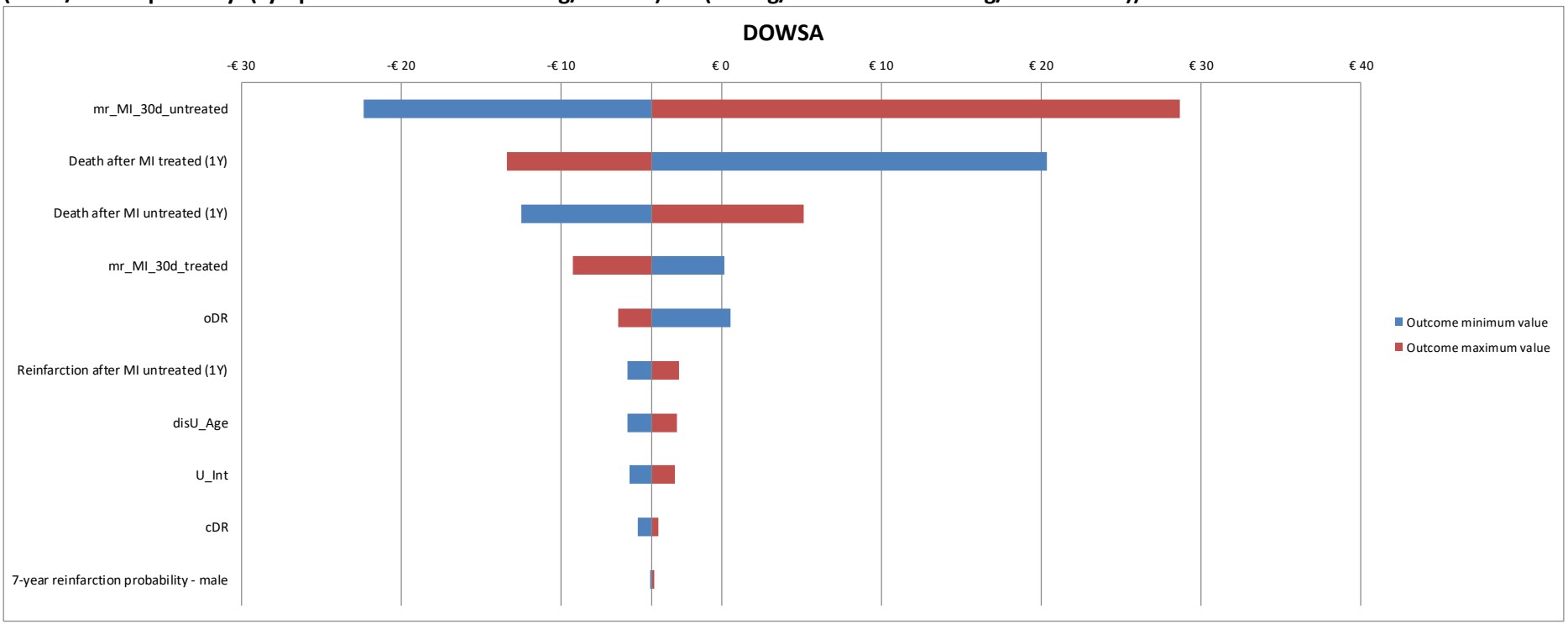
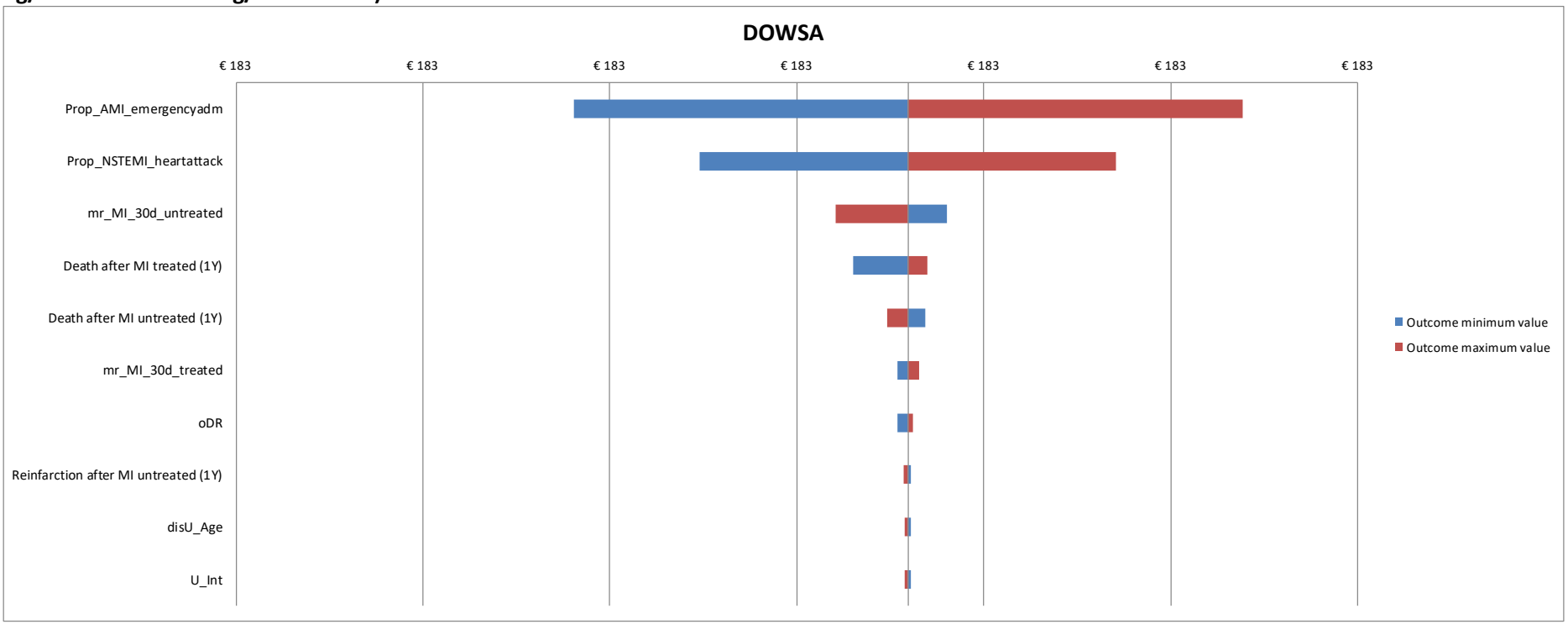
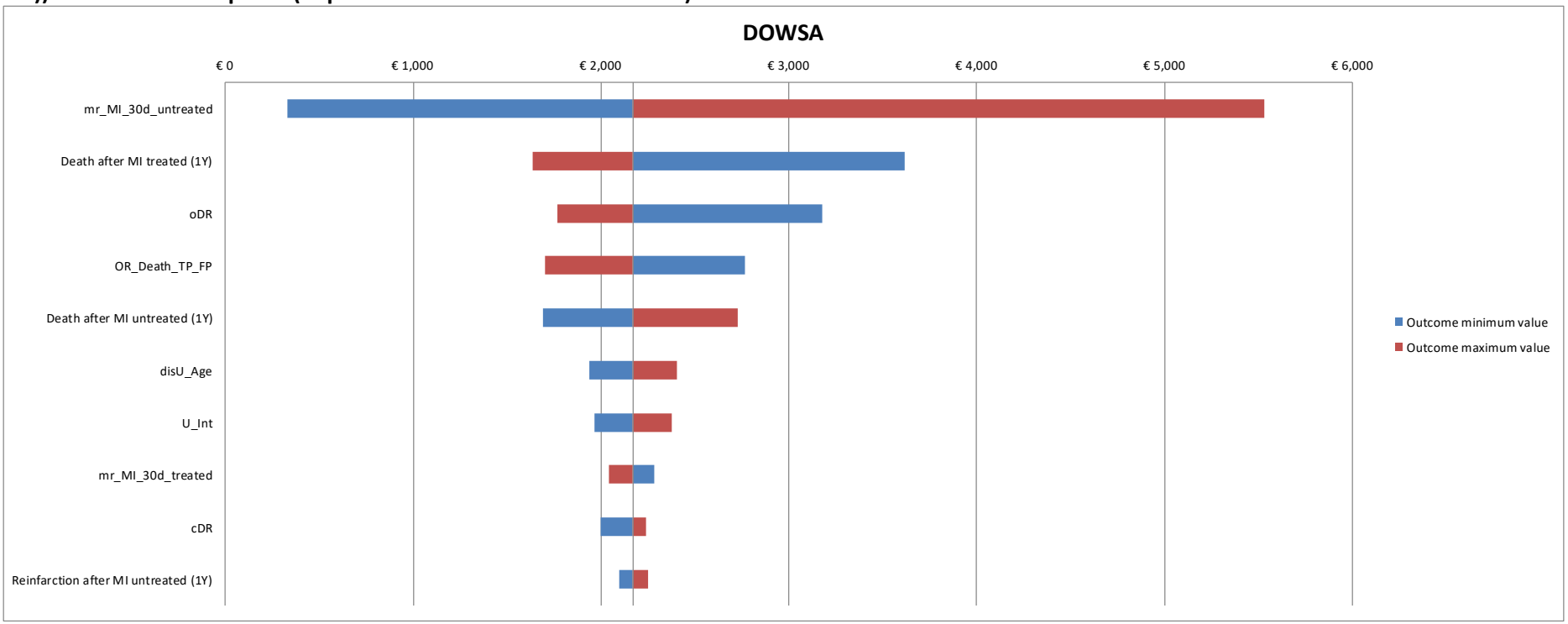


Figure 25: Tornado diagram for comparison between Standard troponin (at presentation and after 10-12 hours) and Siemens Dimension Vista hsTnI (<5 ng/L at 0 h AND Δ <2 ng/L at 0 to 1 h)



DOWSA for secondary analysis (based on incremental net benefit)

Figure 26: Tornado diagram for comparison between Beckman Coulter ACCESS hsTnI ((symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h)) and Standard troponin (at presentation and after 10-12 hours)



APPENDIX 8: NICE GUIDANCE RELEVANT TO THE MANAGEMENT OF SUPECTED ACS

Myocardial infarction: cardiac rehabilitation and prevention of further cardiovascular disease NICE clinical guideline CG172 (2013). Available from: http://guidance.nice.org.uk/CG172.

Recent-onset chest pain of suspected cardiac origin: assessment and diagnosis (2016). Available from: http://www.nice.org.uk/guidance/CG95.

Unstable angina and NSTEMI: early management. NICE clinical guideline CG94 (2013). Available from: https://www.nice.org.uk/guidance/CG94.

Myocardial infarction with ST-segment elevation: acute management. NICE clinical guideline CG167 (2013). Available from: http://guidance.nice.org.uk/CG167.

Myocardial infarction (acute): Early rule out using high-sensitivity troponin tests (Elecsys Troponin T high-sensitive, ARCHITECT STAT High Sensitive Troponin-I and AccuTnI+3 assays) (2014). NICE diagnostic guidance (DG15) Available from: https://www.nice.org.uk/guidance/dg15.

CG94/CG172/CG167 are currently under revision to become a single guideline; expected publication date, July 2020 (GID-NG10085).

APPENDIX 9: PRISMA CHECK LIST

Section/topic	#	Checklist item	Reported on page #
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; systematic review registration number.	Pages 14 to 16
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Section 1
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Sections 1 and 2
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.	Section 3.1.2 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.	Section 3.1.1
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).	Section 3.1.3
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.	Section 3.1.3

Section/topic	#	Checklist item	Reported on page #
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Section 3.1.3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Section 3.1.4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Section 3.1.5
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.	Section3.1.5
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 pre-specified.	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.	Section 3.2.1 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.	Sections 3.2.3 to 3.2.13, 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).	Section 3.2.2 and appendix 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Sections 3.2.3 to 3.2.13 and appendix 2c
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Sections 3.2.4 and 3.2.5
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			

Section/topic	#	Checklist item	Reported on page #
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Section 5.1.1
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).	Sections 5.2.1 and 5.3.1
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Section 6
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 2