National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

Evidence overview

High-sensitivity troponin tests for the early rule out of acute myocardial infarction

This overview summarises the key issues for the diagnostics advisory committee's consideration. It is intended to be used with NICE's final scope for the assessment and the diagnostics assessment report. A glossary of terms can be found in appendix B.

1 Background

1.1 Introduction

The purpose of this assessment is to evaluate the clinical and cost effectiveness of high-sensitivity troponin tests, used as single tests or repeated over a short time (within 4 hours), for the early rule-out of myocardial infarction in people who present to hospital with chest pain.

Chest pain and suspected myocardial infarction were the cause of about 5% of all emergency hospital admissions in 2017 to 2018. However, myocardial infarction will have occurred in only about 20% of those admissions. Tests that can quickly tell whether a person is having a myocardial infarction or not could mean that unnecessary hospital admissions are avoided, so reducing waiting time and anxiety for many people.

Cardiac troponins I and T are biological markers of cardiac muscle death (cardiomyocyte necrosis). They are released into the circulation, so rise, when cardiac muscle is damaged. They are used as markers of acute myocardial infarction along with clinical history taking and electrocardiography (ECG)

monitoring. ST-segment elevation myocardial infarction (STEMI) can usually be diagnosed by ECG alone. So, the main diagnostic challenge is detecting or ruling out non-ST segment elevation myocardial infarction (NSTEMI).

The optimum sensitivity of older (non-high-sensitivity) troponin assays (referred to here as standard troponin assays) for acute myocardial infarction is 10 to 12 hours after the onset of symptoms. For many people, this means hospital admission and observation while serial troponin testing is done. To overcome this, high-sensitivity troponin assays have been developed. These can detect lower levels of troponin in the blood earlier than standard troponin assays, so enable early rule out of NSTEMI after the onset of acute chest pain. This could lead to earlier discharge for people with normal troponin levels and earlier intervention for those with a confirmed NSTEMI.

NICE diagnostics guidance on myocardial infarction (acute): early rule out using high-sensitivity troponin tests recommends using the Elecsys Troponin T high-sensitive assay and ARCHITECT STAT High Sensitivity Troponin-I assay as options for the early rule out of NSTEMI in people presenting to an emergency department with chest pain and suspected acute coronary syndrome. Since this guidance was published, NICE's guideline on recent-onset chest pain of suspected cardiac origin has been updated to include high-sensitivity troponin tests. But stakeholder feedback suggests that high-sensitivity troponin testing used with early rule-out protocols has not been routinely adopted in the NHS and, if it has, there is wide variation in how it is being done. This update assessment is being done to:

- ensure that guidance is based on evidence including new high-sensitivity assays developed and marketed since publication of the NICE guidance to provide more detailed recommendations on how to use high-sensitivity assays (for example, timing of testing and using sequential testing strategies) when possible.

Like the previous evaluation, the comparator for this assessment is standard troponin testing over 10 to 12 hours from symptom onset. The aim is to

capture the benefit of high-sensitivity troponin assays used with early rule-out protocols.

Provisional recommendations on the use of these technologies will be made by the diagnostics advisory committee at the committee meeting on 2 April 2020.

1.2 Scope of the assessment

Table 1 Scope of the assessment

Decision question	Does early rule out of acute myocardial infarction using high-sensitivity troponin testing within 4 hours of presentation (including 1 hour and 3 hour rule out) represent a more cost-effective use of NHS resources compared to serial troponin measurement over 10 to 12 hours?
Populations	People with chest pain and suspected non-ST segment elevation acute coronary syndrome. Subgroups for consideration include groups where different cut-off levels for determining a positive troponin test may be required. Subgroups may include: • sex • people who may have chronically elevated troponin levels, for example, older people and people with renal disease The analysis should also consider subgroups with low and high pre-test probabilities for non-ST segment elevation myocardial infarction, for example, people with a history of previous acute myocardial infarction, and time since symptom onset.
Interventions	High-sensitivity troponin tests, used either as a single test or series of tests, within 4 hours of presentation (including 1 hour and 3 hour rule out). High-sensitivity troponin assays identified as of interest to the NHS are: • Access hsTnI (Beckman Coulter) • ADVIA Centaur high-sensitivity troponin I (Siemens Healthineers) • Alinity i STAT High Sensitive Troponin-I assay (Abbott Diagnostics) • ARCHITECT STAT High Sensitivity Troponin-I (Abbott Diagnostics) • Atellica IM high-sensitivity troponin I (Siemens

	Healthineers) • Dimension EXL high-sensitivity troponin I (Siemens Healthineers) • Dimension Vista high-sensitivity troponin I (Siemens Healthineers) • Elecsys cTnT-hs (Roche Diagnostics) • Elecsys cTnT-hs STAT (Roche Diagnostics) • TriageTrue High Sensitivity Troponin I Test (Quidel Cardiovascular) • VIDAS High sensitive Troponin I assay (bioMérieux) • VITROS High Sensitivity Troponin I Assay (Ortho Clinical Diagnostics).
Comparator	Serial cardiac troponin testing with a 10 to 12 hour peak measurement test strategy. Comparator technologies may include any troponin assay not previously defined as an intervention.
Healthcare setting	Emergency department
Outcomes	Intermediate measures for consideration may include: • diagnostic accuracy including at 99th percentile cut-off levels, limit of detection and limit of quantitation, and considering delta change • turnaround time • time to discharge • proportion of people admitted and discharged • proportion of people diagnosed with non-ST segment elevation myocardial infarction.
Clinical outcomes	Clinical outcomes for consideration may include: • subsequent emergency department attendance or hospital admission for chest pain • patient anxiety associated with waiting for a clinical decision and the initiation of further treatment • morbidity and mortality, including fatal and non-fatal acute myocardial infarction after discharge from the emergency department • frequency of coronary revascularisation • prognostic accuracy for major adverse cardiac events, that is death, non-fatal myocardial infarction, revascularisation, or hospitalisation for myocardial ischaemia.

	• health related quality of life
Costs	Costs will be considered from an NHS and personal social services perspective. Costs for consideration may include: • costs for high-sensitivity troponin testing including early rule-out test strategies at various time points within 4 hours of presentation • costs associated with a diagnosis of non-ST segment elevation myocardial infarction including additional tests such as electrocardiography, hospital admission, treatment and follow up • cost of adverse events arising as a result of testing including subsequent emergency department attendances or re-admissions. The cost effectiveness of interventions should be expressed in terms of incremental cost per quality-adjusted life year.
Time horizon	The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.

Further details including descriptions of the interventions, comparator, care pathway and outcomes can be found in the final scope.

2 The evidence

This section summarises data from the diagnostics assessment report compiled by the external assessment group (EAG).

2.1 Clinical effectiveness

The EAG did a systematic review to identify evidence on the clinical effectiveness of high-sensitivity troponin tests to for the early rule out of acute myocardial infarction in people who present to hospital with chest pain. Studies that were included in the previous diagnostic assessment report, done to support the development of NICE diagnostics guidance on myocardial infarction (acute): early rule out using high-sensitivity troponin tests (DG15), were also included in this review.

The EAG identified 37 studies that met the inclusion criteria (see table 2 on page 42 of the diagnostics assessment report).

Test accuracy data was reported for the following high-sensitivity troponin assays:

- Roche Elecsys (30 studies)
- Abbott ARCHITECT (9 studies)
- Siemens Healthineers Atellica (2 studies)
- Siemens Healthineers ADVIA Centaur (3 studies)
- Beckman Coulter Access (2 studies) and
- 1 study each reported accuracy data for Siemens Healthineers Dimension Vista, Ortho VITROS, bioMérieux VIDAS and Quidel Cardiovascular TriageTrue.

Seven studies reported diagnostic accuracy data for more than 1 test. No studies were identified that matched the inclusion criteria for the review for Abbott Alinity or Siemens Healthineers Dimension EXL high sensitivity Troponin I assays. Two randomised controlled trials were included in the review: High-STEACS and HiSTORIC trials (an unpublished report provided as academic in confidence).

Of the 37 included studies, 22 were done in Europe (7 in the UK), 5 in Australia and New Zealand, 6 in the US, 3 in East Asia and 1 was a worldwide study.

Study quality

The EAG did a quality assessment of the 2 randomised controlled trials using the revised Cochrane risk of bias tool for cluster randomised trials. Overall, the trials were done well, with procedures to ensure randomisation and blinding. The full results of this assessment can be found in table 4 (on page 54 of the diagnostics assessment report).

The methodological quality assessment of the diagnostic test accuracy studies is described in the diagnostics assessment report (see page 54). Studies that evaluated a single high-sensitivity test were assessed using the QUADAS-2 tool. Studies that provided data for 2 or more high-sensitivity tests were assessed using the QUADAS-2C tool. The main potential sources of bias related to patient spectrum (for example, not enrolling consecutive patients or excluding patients for reasons not specified in the protocol) and patient flow (for example, withdrawals from the study). There were also concerns about the applicability of the patient population and the reference standard for some studies. The results of the QUADAS-2 and QUADAS-2C assessments are summarised in tables 5 and 6 of the diagnostics assessment report (on pages 56 to 59).

Randomised controlled trials

High-STEACS evaluated the implementation of an early rule-out pathway in 10 secondary and tertiary care hospitals in Scotland. It assessed rates at which conditions were reclassified after high-sensitivity troponin tests compared with standard troponin testing, and the subsequent incidence of myocardial infarction and cardiovascular death. HiSTORIC (an unpublished report provided as academic in confidence) also evaluated the implementation of an early rule-out pathway in 7 acute hospitals in Scotland. The primary outcomes were length of stay and myocardial infarction or cardiac death after discharge (at 30 days).

Both trials used the Abbott ARCHITECT high-sensitivity assay. During the validation phase of High-STEACS (6 to 12 months), results of the high-sensitivity troponin I assay were concealed from the attending clinician and a standard cardiac troponin assay was used to guide care. A high-sensitivity test was introduced after 6 months (early implementation) or 12 months (late implementation). In the validation phase of HiSTORIC, standard troponin testing was done at presentation and repeated 6 to 12 hours after symptom onset if indicated. The validation phase in HiSTORIC also used the High-STEACS early rule-out pathway:

- symptoms for 2 hours or more and less than 5 ng/litre of troponin at 0 hours, or
- in women, 16 ng/litre troponin or lower at 3 hours and a delta change of less than 3 ng/litre troponin at 0 to 3 hours or
- in men, 34 ng/litre troponin or lower at 3 hours and delta change of less than 3 ng/litre troponin at 0 to 3 hours.

In patients whose condition was reclassified in the High-STEACS trial, there were no differences in any of the secondary efficacy and safety outcome measures (myocardial infarction, unplanned coronary revascularisation, all-cause death, death from cardiovascular causes, hospital admission for heart failure and ischaemic stroke). The median length of stay was 7 hours (interquartile range 3 to 24) in the implementation phase compared with 4 hours (interquartile range 3 to 20) in the validation phase. The authors of High-STEACS concluded that implementing an early rule-out pathway was not associated with any increase in myocardial infarction or cardiac death after discharge, at 30 days or 1 year.

In HiSTORIC, at 1 year, [redacted]. Further details on the results from High-STEACS and HiSTORIC are provided from page 61 of the diagnostics assessment report.

Diagnostic test accuracy

Roche Elecsys hs-cTnT assay

Summary estimates of sensitivity and specificity from testing a single sample and a 99th percentile diagnostic threshold for the general population were 90% (95% CI 85% to 94%) and 78% (95% CI 72% to 83%), based on data from 22 studies. The summary estimates of sensitivity and specificity, using a single sample and a limit of detection threshold, were 99% (95% CI 97% to 99%) and 36% (95% CI 28% to 45%) based on data from 9 studies. The 8 studies that assessed the diagnostic performance of a limit of blank threshold in a single sample gave a similarly high summary estimate of sensitivity of 100% (95% CI 98% to 100%), but a reduced specificity of 19% (95% CI 11% to 31%). All estimates were similar when the analyses were restricted to studies that excluded people with STEMI.

The use of multiple sample strategies in general appears to offer increased specificity without substantial loss of sensitivity compared with a single sample on presentation and a very low limit of detection or limit of blank threshold. The European Society of Cardiology's (ESC) 0/1-hour rule-out pathway combines an initial sample and a very low limit of detection ng/litre threshold (5 ng/litre troponin) in patients reporting a minimum symptom duration of 3 hours. The pathway uses repeat testing at 1 hour for patients who have an initial result of less than 12 ng/litre troponin and who have symptoms lasting less than 3 hours, that is, it uses an 'OR' combination. For the target condition NSTEMI (taken from the APACE study), the sensitivity and specificity estimates for this strategy were 99% (95% CI 98 to 100%) and 68% (95% CI 67 to 70%) respectively. Similar estimates of diagnostic performance were obtained for strategies involving an 'AND' combination of initial high-sensitivity troponin level and absolute change.

The summary estimates for the various test strategies using the Roche Elecsys hs-cTnT assay are shown in table 2. Further details can be found starting on page 62 of the diagnostics assessment report.

Table 2 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 percentile threshold (14 ng/litre) 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)
LoD (<5ng/litre) at 0 h	All	Any AMI	9	99 (97, 99)	36 (28, 45)
	All	NSTEMI	6[1]	99 (97, 100)	35 (25, 46)
	All	MACE	3	98 (95, 99)	32 (30, 34)
LoB (<3ng/litre) 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 percentile threshold (14 ng/litre) at 2 h	All	NSTEMI	2	95 (92, 96)	81 (79, 82)
Multiple sample strategies					
ESC 0/1-hour pathway: (symptoms >3 hours AND <5 ng/litre at 0 h) OR (<12 ng/litre at 0 h AND Δ <3 ng/litre at 0 to 1 h)	All	NSTEMI	1[1]	99 (98, 100)	68 (67, 70)
	All	MACE	2	99 (97, 100)	62 (61, 64)
(<14 ng/litre at 0 h AND 2h) AND Δ <4 ng/litre	All	NSTEMI	2	98 (96, 99)	74 (72, 76)
<12 ng/litre at 0 h AND Δ <3 ng/litre at 0 to 1 h	All	NSTEMI	3[1]	98 (97, 99)	73 (71, 74)
<8 ng/litre at 0 h AND Δ <3 ng/litre at 0 to 0.5 h	All	NSTEMI	1[1]	100 (93, 100)	45 (40, 49)
99th percentile threshold (<14 ng/litre at 0 h AND 3 h)	All	NSTEMI	1[1]	100 (89, 100)	77 (58, 90)

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

[1] Key results used in cost-effectiveness modelling

Abbott ARCHITECT hs-cTnI assay

Summary estimates of sensitivity and specificity for a single sample and a diagnostic threshold of the 99th percentile for the general population were 75% (95% CI 65% to 82%) and 94% (95% CI 94% to 96%), based on data from 5 studies. These estimates were similar if the analysis was restricted to studies that excluded people with STEMI. The summary estimates of sensitivity and specificity, using a limit of detection threshold (2 ng/litre troponin) in a single sample taken on presentation, were 100% (95% CI 99% to 100%) and 21% (95% CI 16% to 26%),respectively, based on data from 4 studies in NSTEMI.

For multiple sample strategies, the High-STEACS pathway was used as follows:

- symptoms for 2 hours or more and less than 5 ng/litre of troponin at 0 hours, or
- in women, 16 ng/litre troponin or lower at 3 hours and a delta change of less than 3 ng/litre troponin at 0 to 3 hours or
- in men, 34 ng/litre troponin or lower at 3 hours and delta change of less than 3 ng/litre troponin at 0 to 3 hours.

This strategy appears to offer increased specificity without substantial loss of sensitivity compared with a single sample on presentation and a very low limit of detection threshold. 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. The ESC 0/1-hour rule-out pathway reported a lower specificity than the High-STEACS pathway, with summary sensitivity and specificity estimates of 99% (95% CI 98% to 100%) and 57% (95% CI 56% to 59%) respectively, for the target condition NSTEMI.

The summary estimates for the various test strategies using the Abbott ARCHITECT high sensitivity troponin I assay are shown in table 3 and in full starting on page 71 of the diagnostics assessment report.

Table 3 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 percentile threshold (26.2 ng/litre) at 0 h	All	Any AMI	5	75 (65, 82)	94 (91, 96)
		NSTEMI	4	75 (64, 84)	94 (90, 96)
LoD (<2ng/litre) at 0 h	All	NSTEMI	4	100 (99, 100)	21 (16, 26)
	All	MACE	1	97 (95, 98)	39 (39, 40)
<4 ng/litre at 0 h	All	NSTEMI	2	99 (97, 100)	50 (48, 52)
<5 ng/litre 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/litre at 0 h) OR (<5 ng/litre at 0 h AND Δ <2 ng/litre at 0 to 1 h)	All	NSTEMI	2	99 (98, 100)	57 (56, 59)
High-STEACS pathway: (symptoms ≥2 h AND <5 ng/litre at 0 h) OR (≤16 ng/litre (F) ≤34 ng/litre (M) at 3 h AND Δ <3 ng/litre at 0 to 3 hours)	All	NSTEMI	1	99 (97, 100)	76 (73, 78)
	All	MACE	1	98 (97, 99)	81 (79, 83)
AMI: acute myocardial infarction; ESC: European Society of Cardiology; h, hours; MACE: major adverse cardiac event; NSTEMI: non-ST segment elevation myocardial infarction					

Beckman Coulter Access high-sensitivity Troponin I assay

The 2 studies evaluating the Beckman Coulter Access assay each assessed a different multiple sample strategy. One followed the ESC 0/1-hour rule-out pathway, giving sensitivity and specificity estimates of 99% (95% CI 94% to 100%) and 70% (95% CI 66% to 74%) respectively, for the target condition NSTEMI. The second study assessed a similar strategy, but with repeat testing at 2 hours. The sensitivity estimates were similar for the 2 strategies, but the specificity of the 2-hour repeat testing strategy was higher than that of the 1-hour strategy (see table 4).

bioMérieux VIDAS high-sensitivity Troponin I assay

The study evaluating the bioMérieux VIDAS assay assessed the performance of a multiple sample strategy, with samples taken on presentation and at 2 hours. The reported sensitivity and specificity estimates were 98% (95% CI 92% to 100%) and 64% (95% CI 5%9 to 68%) respectively, for the target condition NSTEMI (see table 5).

Ortho VITROS high-sensitivity Troponin I assay

The study evaluating the Ortho VITROS assay assessed the performance of a strategy following the ESC 0/1-hour rule-out pathway. The reported sensitivity and specificity estimates were 100% (95% CI 95% to 100%) and 60% (95% CI 55% to 64%) respectively, for the target condition NSTEMI (see table 6).

Quidel TriageTrue high-sensitivity Troponin I assay

The study evaluating the Quidel TriageTrue assay assessed the performance of a strategy following the ESC 0/1-hour rule-out pathway. The reported sensitivity of this strategy was 100% (95% CI 97% to 100%) and the specificity was 66% (95% CI 62% to 70%) for the target condition NSTEMI (see table 7).

Siemens ADVIA Centaur high-sensitivity Troponin I assay

There were 2 studies that evaluated the use of the Siemens ADVIA Centaur assay. Using a rule-out threshold of 2 ng/litre troponin, the sensitivity and

specificity estimates on a single sample were 100% (95% CI 99% to 100%) and 23% (95% CI 21% to 25%) for the target condition NSTEMI. Two different multiple sample strategies were evaluate. One followed the structure of the ESC 0/1-hour rule-out pathway. The sensitivity and specificity estimates for this strategy were 99% (95% CI 95% to 100%) and 56% (95% CI 52% to 60%) respectively, for the target condition NSTEMI. The second study assessed a similar strategy, but with higher thresholds and repeat testing at 2 hours. The sensitivity and specificity estimates for this strategy were 100% (95% CI 95% to 100%) and 67% (95% CI 61 to 72%) respectively, for the target condition NSTEMI (see table 8).

Siemens Atellica high-sensitivity Troponin I assay

Using a rule-out threshold of 2 ng/litre troponin, the sensitivity and specificity estimates on a single sample were 100% (95% CI 98% to 100%) and 26% (95% CI 24% to 28%) respectively, for the target condition NSTEMI. Sensitivity and specificity estimates for the High-STEACS pathway were 98% (95% CI 95 to 100% and 74% (95% CI 72% to 76%) for the target condition NSTEMI (see table 9).

Siemens Dimension Vista high-sensitivity Troponin I assay

The study of the Siemens Dimension Vista assay assessed the performance of a strategy using measurements done at baseline and the absolute change within 1 hour. The sensitivity of the strategy was 100% (95% CI 97% to 100%) and specificity was 66% (95% CI 62% to 69%) for the target condition NSTEMI (see table 10).

Table 4 Accuracy of the Beckman Coulter hs-cTnI assay: summary estimates (95% CI)

Test strategy	Population	Target condition	Number of studies	Sensitivity (%)	Specificity (%)
ESC 0/1-hour pathway: (symptoms >3 hours AND <4 ng/litre at 0 hours) OR (<5 ng/litre and Δ <4 ng/litre at 0 to 1 hours)	All	NSTEMI	1	99 (94, 100)	70 (66, 74)
(symptoms >3 hours AND <4 ng/litre at 0 hours) OR (<5 ng/litre and Δ <5 ng/litre at 0 to 2 hours)			1	98 (92, 100)	83 (81, 86)

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

Table 5 Accuracy of the bioMérieux VIDAS hs-cTnI assay: summary estimates (95% confidence intervals)

Test strategy	Population	Target condition	Number of studies	Sensitivity (%)	Specificity (%)
<2 ng/litre at 0 hours OR (<6 ng/litre at 0 AND 2 hours)	All	NSTEMI	1	98 (92, 100)	64 (59, 68)

NSTEMI: non-ST segment elevation myocardial infarction

Table 6 Accuracy of the Ortho VITROS hs-cTnI assay: summary estimates (95% confidence intervals)

Test strategy	Population	Target condition	Number of studies	Sensitivity (%)	Specificity (%)
ESC 0/1-hour pathway: (symptoms >3 hours AND <1 ng/litre at 0 hours) OR (<2 ng/litre at 0 hours AND Δ <1 ng/litre at 0 to 1 hours)	All	NSTEMI	1	100 (95, 100)	60 (55, 64)

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

Table 7 Accuracy of the Quidel TriageTrue hs-cTnI assay: summary estimates (95% confidence intervals)

Test strategy	Population	Target condition	Number of studies	Sensitivity (%)	Specificity (%)
ESC 0/1-hour pathway: (symptoms >3 hours AND <4 ng/litre at 0 hours) OR (<5 ng/litre at 0 hours AND Δ <3 ng/litre at 0 to 1 hours)	All	NSTEMI	1	100 (97, 100)	66 (62, 70)

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

Table 8 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/litre at 0 h	All	NSTEMI	1	100 (99, 100)	23 (21, 25)
<2 ng/litre at 0 h	All	MACE	1	100 (98, 100)	23 (22, 25)
<3 ng/litre at 0 h	All	NSTEMI	2	99 (98, 100)	35 (33, 36)
<3 ng/litre at 0 h	All	MACE	1	99 (97, 100)	36 (33, 38)
<5 ng/litre at 0 h	All	NSTEMI	1	99 (97, 100)	52 (50, 54)
<5 ng/litre at 0 h	All	MACE	1	99 (96, 100)	52 (50, 54)
Multiple sample strategies					
ESC 0/1-hour pathway: (symptoms >3 h AND <3 ng/litre at 0 h) OR (<6 ng/litre at 0 h AND Δ <3 ng/litre at 0 to 1 h)	All	NSTEMI	1	99 (95, 100)	56 (52, 60)
<3 ng/litre at 0 h OR (<8 ng/litre at 0 h AND Δ <7 ng/litre at 0 to 2 h)	All	NSTEMI	1	100 (95, 100)	67 (61, 72)

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

Table 9 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/litre at 0 hours	All	NSTEMI	1	100 (98, 100)	26 (24, 28)
<2 ng/litre at 0 hours	All	MACE	1	99 (97, 100)	26 (24, 28)
Multiple sample strategies					
ESC 0/1-hour pathway: (symptoms ≥3 h AND <3 ng/litre at 0 hours) OR (<6 ng/litre at 0 hour AND Δ <3 ng/litre at 0 to 1 hours)	All	NSTEMI	1	94 (79, 99)	69 (64, 74)
ESC 0/3 hour pathway: (symptoms ≥6 hours AND ≤34 ng/litre (F) ≤53 ng/litre (M) at 0 hours) OR (≤34 ng/litre (F) ≤53 ng/litre (M) at 3 hours) OR Δ <50% of 99th percentile at 0 to 3 hours	All	NSTEMI	1	91 (87, 94)	74 (72, 77)
High-STEACS pathway: (symptoms ≥2 h AND <5 ng/litre at 0 hours) OR (≤34 ng/litre (F) ≤53 ng/litre (M) at 3 h AND Δ <3 ng/litre at 0 to 3 hours)	All	NSTEMI	1	98 (95, 99)	74 (72, 76)

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

Table 10 Accuracy of the Siemens Dimension Vista hs-cTnI assay: summary estimates (95% CI)

Test strategy	Population	Target condition	Number of studies	Sensitivity (%)	Specificity (%)
<5 ng/litre at 0 hours AND Δ <2 ng/litre at 0 to 1 hours	All	NSTEMI	1	100 (97, 100)	66 (62, 69)

NSTEMI: non-ST segment elevation myocardial infarction

Diagnostic accuracy in relevant subgroups

The EAG identified some data on the subgroups from the scope. In a study using the Roche Elecsys assay and a 99th percentile threshold on a single sample at presentation, a higher estimate of sensitivity for any acute myocardial infarction was estimated in people older than 70 than for people aged 70 or younger (97%, 95% CI 92% to 99%; and 88%, 95% CI 78% to 94% respectively). The estimate of sensitivity for people aged over 70 was also higher than the corresponding summary estimates from all 22 studies that used the 99th percentile diagnostic threshold. A similar pattern was apparent for people with a high pre-test probability (determined by clinical judgement based on cardiovascular risk factors, type of chest pain, physical findings, and ECG abnormalities) compared with those with a low to moderate pre-test probability. The same was found for people without pre-existing cardiovascular disease compared with those with pre-existing cardiovascular disease (table 11).

Considering the test strategies included in the assessment and the cost-effectiveness modelling, only the High-STEACS study reported using sex-specific thresholds. Data from this study appeared to show that the sensitivity of testing a single sample taken on presentation can be markedly increased by using sex-specific 99th percentile cut-offs (table 12). This study also used sex-specific thresholds as part of a multiple test strategy: the High-STEACS pathway. It is unclear whether the use of sex-specific thresholds in this pathway offers any advantage over using a single general population threshold. This is because no equivalent pathway was evaluated. Other studies reported data on male and female subgroups using a single general population threshold in each group. Results from a study on the Roche Elecsys assay showed very similar accuracy estimates for the subgroups (table 11), although a study on the Siemens Dimension Vista reported a lower sensitivity and specificity in the subgroup of men than in the subgroup of women (table 13).

Two studies on the Roche Elecsys high sensitivity troponin assay and 2 on the Abbott ARCHITECT high-sensitivity troponin assay reported data on how diagnostic performance varies with renal function. All studies show a decrease in specificity as renal function decreases (tables 11 and 12).

Table 11 Accuracy of the Roche hs-cTnT assay in subgroup populations: summary estimates (95% CI)

Test strategy	Population	Target condition	Number of studies	Sensitivity (%)	Specificity (%)
99th percentile threshold (14 ng/litre) at 0 hours	All	Any AMI	22	90 (85,94)	78 (72, 83)
	age ≤70 years	Any AMI	1	88 (78, 94)	86 (83, 89)
	age >70 years	Any AMI	1	97 (92, 99)	49 (44, 55)
	patients with pre-existing coronary artery disease (CAD)	Any AMI	1	93 (85, 97)	60 (55, 65)
	patients without pre-existing CAD	Any AMI	1	94 (88, 97)	82 (79, 85)
	Mixed; Low to moderate pre-test probability	Any AMI	1	89 (70, 97)	85 (79, 89)
	Mixed; High pre-test probability	Any AMI	1	94 (77, 99)	66 (50, 79)
	All	NSTEMI	14	90 (85, 94)	77 (68, 84)
	Female	NSTEMI	1	91 (85, 96)	79 (76, 82)
	Male	NSTEMI	1	91 (87, 94)	79 (76, 81)
	patients with eGFR <30 mL/min/1.73 m^2	NSTEMI	1	100 (83, 100)	13 (4, 29)
	patients with eGFR 30 to 59 mL/min/1.73 m^2	NSTEMI	1	100 (96, 100)	47 (39, 55)
	patients with eGFR 60 to 89 mL/min/1.73 m^2	NSTEMI	1	96 (91, 98)	72 (68, 76)
	patients with eGFR >90 mL/min/1.73 m^2	NSTEMI	1	92 (83, 97)	84 (80, 87)
ESC 0/1-hour pathway: (symptoms >3 hours AND <5 ng/litre at 0 hours) OR (<12 ng/litre at 0 hours AND Δ <3 ng/litre at 0 to 1 hours)	All	NSTEMI	1	99 (98, 100)	68 (67, 70)
	patients with normal renal function	NSTEMI	1	99 (97, 100)	78 (76, 80)
	patients with impaired renal function (eGFR <60 mL/min/1.73 m^2)	NSTEMI	1	100 (98, 100)	26 (22, 31)

AMI: acute myocardial infarction; CAD: coronary artery disease; eGFR: estimated glomerular filtration rate; ESC: European Society of Cardiology; NSTEMI: non-ST segment elevation myocardial infarction

Table 12 Accuracy of the Abbott ARCHITECT hs-cTnI assay in subgroup populations: summary estimates (95% CI)

Test strategy	Population	Target condition	Number of studies	Sensitivity (%)	Specificity (%)
Sex-specific 99th percentile threshold (female 16 ng/litre, male 34 ng/litre at 0 h)	patients with eGFR <60 mL/min/1.73 m^2)	NSTEMI	1	99 (96, 100)	71 (67, 74)
	patients with eGFR ≥60 mL/min/1.73 m^2)		1	99 (97, 100)	92 (91, 93)
	patients age ≥65 years with eGFR ≥60 mL/min/1.73 m^2		1	98 (96, 100)	86 (84, 88)
	patients age ≥65 years with eGFR <60 mL/min/1.73 m^2		1	98 (95, 100)	69 (65, 73)
	patients age <65 years with eGFR ≥60 mL/min/1.73 m^2		1	99 (97, 100)	96 (95, 97)
	patients age <65 years with eGFR <60 mL/min/1.73 m^2		1	100 (88, 100)	82 (72,89)
ESC 0/1-hour pathway: (symptoms >3 hours AND <2 ng/litre at 0 h) OR (<5 ng/litre at 0 h AND Δ <2 ng/litre at 0 to 1 h)	All	NSTEMI	2	99 (98, 100)	57 (56, 59)
	Normal renal function	NSTEMI	1	99 (97, 100)	66 (64, 68)
	Impaired renal function (eGFR <60 mL/min/1.73 m^2)	NSTEMI	1	99 (95, 100)	25 (20, 30)
High-STEACS pathway: (symptoms ≥2 h AND <5 ng/litre at 0 h) OR (≤16 ng/litre (F) ≤34 ng/litre (M) at 3 h AND Δ <3 ng/litre at 0 to 3 h)	All	NSTEMI	1	99 (97, 100)	76 (73, 78)
	Male	NSTEMI	1	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)

eGFR: estimated glomerular filtration rate; ESC: h, hours; European Society of Cardiology; NSTEMI: non-ST segment elevation myocardial infarction

Table 13 Accuracy of the Siemens Dimension Vista hs-cTnI assay in subgroup populations: summary estimates (95% CI)

Test strategy	Population	Target condition	Number of studies	Sensitivity (%)	Specificity (%)
<5 ng/litre at 0 hours AND Δ <2 ng/litre at 0 to 1 hours	All	NSTEMI	1	100 (97, 100)	66 (62, 69)
	Male	NSTEMI	1	95 (87, 99)	62 (57, 66)
	Female			100 (89, 100)	73 (66, 79)

NSTEMI: non-ST segment elevation myocardial infarction

Comparative diagnostic accuracy for more than one assay

Seven studies reported accuracy data for more than 1 assay. Further details can be found starting on page 88 of the diagnostics assessment report.

The APACE study provided data on the performance of the ESC 0/1-hour pathway using Roche Elecsys hs-cTnT, Abbott ARCHITECT hs-cTnI and Siemens ADVIA Centaur hs-cTnI assays. It also provided data on the performance of the ESC 0/1-hour pathway using the Beckman Coulter Access hs-cTnI, Ortho VITROS hs-cTnI and Quidel TriageTrue hs-cTnI assays, but these results came from different patient subgroups and were reported in different publications. Data showed that the ESC 0/1-hour rule-out pathway performed consistently across all 6 high-sensitivity troponin assays evaluated (sensitivity estimates were always 98% or higher).

3 other studies, ADAPT, ROMI-3, and TRUST, compared the Roche Elecsys hs-cTnT assay and the Abbott ARCHITECT hs-cTnI assay. Although the sensitivity estimates for the Roche Elecsys hs-cTnT assay, using the 99th percentile and a single sample at presentation, were higher than those for the Abbott ARCHITECT hs-cTnI assay, both had sensitivity estimates of less than 97%. When the limit of detection 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, and were always 99% or higher.

The High-STEACS study provided data on the rule-out performance of the 3 strategies using the Abbott ARCHITECT hs-cTnI assay and the Siemens Atellica hs-cTnI assay. It is unclear whether both tests were evaluated in the same subgroup of people in the study. Data showed that the sensitivity of the ESC 0/1-hour pathway was lower using the Siemens Atellica hs-cTnI assay (94% [95% CI 79% to 99%]) than using the Abbott ARCHITECT hs-cTnI assay (100% [95% CI 91% to 100%]). The sensitivity and specificity estimates for the ESC 0/3-hour rule-out pathway were similar using either assay (both

had sensitivity estimates of less than 97%). The sensitivity and specificity estimates for the High-STEACS 0/3-hour rule-out pathway were also similar using either assay (both had sensitivity estimates of 98% or more).

The HIGH-US study compared the performance of 2 Siemens hs-cTnI assays (Atellica and ADVIA Centaur), using 3 low thresholds and a single sample at presentation. The results showed consistent performance between the 2 assays for all thresholds (sensitivity estimates were 99% or more).

The BEST study compared the performance of 2 single sample at presentation strategies based on the Siemens ADVIA Centaur assay (threshold of 3 ng/litre troponin) and the Roche Elecsys hs-cTnT assay (limit of detection [5 ng/litre troponin] threshold). Data were reported in separate publications with different numbers of people. The sensitivity estimates were similar for the Roche Elecsys hs-cTnT assay and the Siemens ADVIA hs-cTnI assay (both 99%), but the Roche Elecsys hs-cTnT assay had a higher specificity of 47% (95% CI 43% to 51%), than the Siemens ADVIA Centaur hs-cTnI assay, which was 33% (95% CI 30% to 36%).

Test strategies included in the cost-effectiveness modelling

Because the final dataset consisted of over 60 test strategies (combination of different assays, timing and thresholds), it was necessary for the EAG to reduce the number of strategies to include in the economic model. Strategies were excluded if it was obvious that they would be more expensive and less effective than other test strategies based on sensitivity, specificity, test costs, the number of tests and the timing of testing. Secondly, strategies that had a sensitivity less than 97% were excluded. This was based on expert opinion about the minimum sensitivity that would be acceptable in clinical practice. The number of strategies was reduced to 21, and these are listed in table 14 below and on page 96 of the diagnostics assessment report.

When considering single test strategies, only those using a threshold at or near to the limit of detection for the assay, in a sample taken at presentation, met the minimum clinically acceptable sensitivity criterion.

Most of the multiple test strategies meeting the minimum clinically acceptable sensitivity comprised an initial rule-out step, based on high-sensitivity troponin levels in a sample taken on presentation and a minimum symptom duration, and a second stage (for people not meeting the initial rule-out criteria) based on presentation levels of high-sensitivity troponin and absolute change in high-sensitivity troponin between presentation and a second sample taken after 1, 2 or 3 hours.

Table 14 Test strategies selected for cost-effectiveness modelling

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

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

CI, confidence intervals, ESC, European Society of cardiology; h, hour; hs-cTn, high-sensitivity troponin; LoD, limit of detection; ng, nanograms.

2.2 Costs and cost effectiveness

The EAG did a search to identify evidence on the cost effectiveness of high-sensitivity troponin assays for the early rule out of acute myocardial infarction. The EAG also developed a de novo economic model to assess the cost effectiveness of the different testing strategies.

Systematic review of the cost-effectiveness evidence

Studies reporting a full economic analysis of the cost effectiveness of either high-sensitivity troponin testing or standard troponin testing that included survival or quality-adjusted life years (QALYs) as an outcome measure, were eligible for inclusion. Full details of the systematic review can be found from page 98 of the diagnostics assessment report.

Five studies identified in the original assessment report and 1 new study were included in the systematic review. Results varied in the 5 studies from the original report, and the EAG concluded that there was uncertainty about the cost effectiveness of diagnostic strategies using high-sensitivity troponin testing. One of the included studies, done in Europe and reported as a conference abstract only, concluded that high-sensitivity troponin testing is a cost-effective option compared with standard troponin testing. The study reported an incremental cost-effectiveness ratio (ICER) of 3,748 euros per QALY gained (Vaidya et al. 2012). Another study investigated a number of diagnostic strategies for acute myocardial infarction and adopted the perspective of the NHS. The authors concluded that the optimal diagnostic strategy in all but 1 of the scenarios modelled was a single high-sensitivity troponin test at presentation, with people having a negative result being discharged and those having a positive result being admitted for a second troponin test at 10 hours (Goodacre et al. 2013). The remaining 3 studies, including 2 taking the perspective of the NHS, reported substantially higher ICERs and greater uncertainty. The EAG noted that the key drivers of cost effectiveness in the included studies were the accuracy of high-sensitivity

troponin assays, and the efficiency of decision making once test results were available.

The more recent study (Ambavane et al. 2017) reported that a 1-hour algorithm using high-sensitivity troponin testing had higher sensitivity (87% compared with 69%) but lower specificity (96% compared with 97%) than standard care. Total costs were reduced for the 1-hour algorithm compared with standard care (£2,480 compared with £4,561). This was mainly because of a shorter length of stay in the emergency department.

Economic analysis

The EAG developed a de novo economic model to explore the cost effectiveness of high-sensitivity troponin assays for the early rule out of acute myocardial infarction in people with acute chest pain (used up to 4 hours from the onset of chest pain or at presentation). The model compared high-sensitivity assays with standard troponin T or I testing, or both, on admission and at 10 to 12 hours after the onset of symptoms. The population in the model was people presenting to the emergency department with suspected non-ST segment elevation acute coronary syndrome, who have no major comorbidities needing hospitalisation (for example, heart failure or arrhythmia) and in whom STEMI has been ruled out.

For the economic model, only high-sensitivity troponin tests that had a sensitivity of 97% or above were selected (based on expert opinion about the minimum sensitivity that would be acceptable in clinical practice). This resulted in the following strategies being evaluated in the economic model:

1. Roche Elecsys hs-cTnT (99th percentile threshold [under 14 ng/litre troponin at 0 hours AND 3 hours])
2. Roche Elecsys hs-cTnT (limit of detection under 5ng/litre troponin at 0 hours)
3. Roche Elecsys hs-cTnT (ESC 0/1-hour pathway [symptoms over 3 hours AND under 5 ng/litre troponin at 0 hours] OR [under 12 ng/litre

troponin at 0 hours AND a delta change of less than 3 ng/litre at 0 to 1 hour])

4. Roche Elecsys hs-cTnT (under 8 ng/litre troponin at 0 hours AND a delta change of less than 3 ng/litre at 0 to 0.5 hours)
5. Roche Elecsys hs-cTnT (under 12 ng/litre troponin at 0 hours AND a delta change of less than 3 ng/litre at 0 to 1 hour)
6. Siemens Dimension Vista hs-cTnI (under 5 ng/litre troponin at 0 hours AND a delta change of less than 2 ng/litre at 0 to 1 hours)
7. Abbott ARCHITECT hs-cTnI (limit of detection under 2ng/litre troponin at 0 hours)
8. Abbott ARCHITECT hs-cTnI (ESC 0/1-hour pathway [symptoms over 3 hours AND under 2 ng/litre troponin at 0 hours] OR [under 5 ng/litre troponin at 0 hours AND a delta change of less than 2 ng/litre at 0 to 1 hours])
9. Abbott ARCHITECT hs-cTnI (High-STEACS pathway [symptoms 2 hours or more AND under 5 ng/litre troponin at 0 hours OR 16 ng/litre or more (women) and 34 ng/litre or more (men) at 3 hours AND a delta change of less than 3 ng/litre])
10. Abbott ARCHITECT hs-cTnI (under 4 ng/litre troponin at 0 hours)
11. Siemens ADVIA Centaur hs-cTnI (under 2 ng/litre troponin at 0 hours)
12. Siemens ADVIA Centaur hs-cTnI (under 3 ng/litre troponin at 0 hours OR under 8 ng/litre troponin at 0 hours AND a delta change of less than 7 ng/litre at 0 to 2 hours)
13. Siemens ADVIA Centaur hs-cTnI (ESC 0/1-hour pathway [symptoms over 3 hours AND under 3 ng/litre troponin at 0 hours OR under 6 ng/litre troponin at 0 hours AND a delta change of less than 3 ng/litre at 0 to 1 hour])
14. Siemens ADVIA Centaur hs-cTnI (under 5 ng/litre troponin at 0 hours)
15. Siemens Atellica hs-cTnI (under 2 ng/litre troponin at 0 hours)
16. Siemens Atellica hs-cTnI (High-STEACS pathway [symptoms 2 hours or more AND under 5 ng/litre troponin at 0 hours OR 34 ng/litre or less

(women) and 53 ng/litre or less (men) at 3 hours AND a delta change of less than 3 ng/litre])

17. Beckman Coulter Access hs-cTnI (ESC 0/1-hour pathway [symptoms over 3 hours AND under 4 ng/litre troponin at 0 hours OR under 5 ng/litre and a delta change of less than 4 ng/litre at 0 to 1 hour])
18. Beckman Coulter Access hs-cTnI (symptoms over 3 hours AND under 4 ng/litre troponin at 0 hours OR under 5 ng/litre troponin and a delta change of less than 5 ng/litre at 0 to 2 hours)
19. Ortho VITROS hs-cTnI (ESC 0/1-hour pathway [symptoms over 3 hours AND under 1 ng/litre troponin at 0 hours OR under 2 ng/litre troponin at 0 hours AND delta change under 1 ng/litre at 0 to 1 hour])
20. bioMérieux VIDAS hs-cTnI (under 2 ng/litre troponin at 0 hours OR under 6 ng/litre troponin at 0 AND 2 hours)
21. Quidel TriageTrue hs-cTnI (ESC 0/1-hour pathway [symptoms over 3 hours AND under 4 ng/litre troponin at 0 hours OR under 5 ng/litre troponin at 0 hours AND a delta change of less than 3 ng/litre at 0 to 1 hour])

Model structure

An identical model structure as reported in the original diagnostic assessment report was used. This model structure was developed by adapting the health technology assessment report from Goodacre et al. (2013) to the scope of the assessment. The model consists of a decision tree and a state-transition model. The decision tree was used to model the 30-day outcomes after presentation, based on test results and the accompanying treatment decision. The decision tree is shown in figure 1. The following health states were included:

- no acute coronary syndrome and no unstable angina (no ACS, no UA)
- unstable angina (UA)
- post-acute myocardial infarction, treated and untreated (post-AMI)
- post-acute myocardial infarction with reinfarction (post-AMI with reinfarction)

- death.

People presenting at the emergency department with suspected non-ST elevation acute coronary syndrome were tested and results were classified as either true positive, false positive, false negative or true negative. These people entered health states as listed above. People could also die after treatment or be discharged.

- People with true-positive test results were correctly treated for acute myocardial infarction and were allocated to ‘non-fatal AMI (treated)’.
- People with false-positive test results were considered to have no acute myocardial infarction, but did not meet early rule-out criteria. They were subdivided between ‘no ACS, no UA’ and ‘UA’. It was assumed that people with false positive test results would remain in the hospital longer but would not be treated for acute myocardial infarction.
- People with true negative test results were considered not to be treated for acute myocardial infarction and were subdivided between ‘no ACS, no UA’ and ‘UA’.
- People with false negative test results were assumed to have untreated acute myocardial infarction resulting in increased reinfarction and mortality probabilities for 1 year and were allocated to ‘non-fatal AMI (untreated)’.

The long-term consequences in terms of costs and QALYs were estimated using a state-transition cohort model (figure 2) with a lifetime time horizon (60 years) and a cycle time of 1 year (except for the first cycle which was adjusted to 335.25 days to ensure that the decision tree period and the first cycle summed to 1 year). Discount rates of 3.5% and a half-cycle correction were applied for both costs and effects.

Figure 1: Decision tree model structure

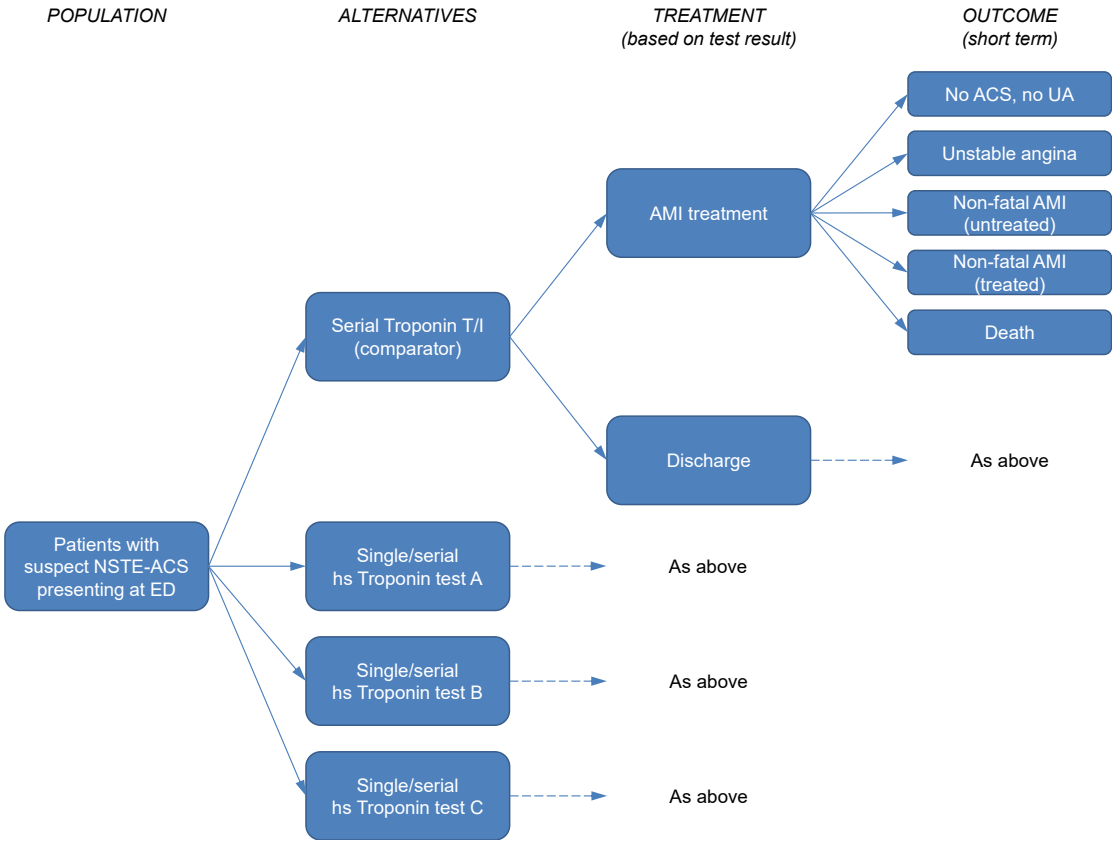
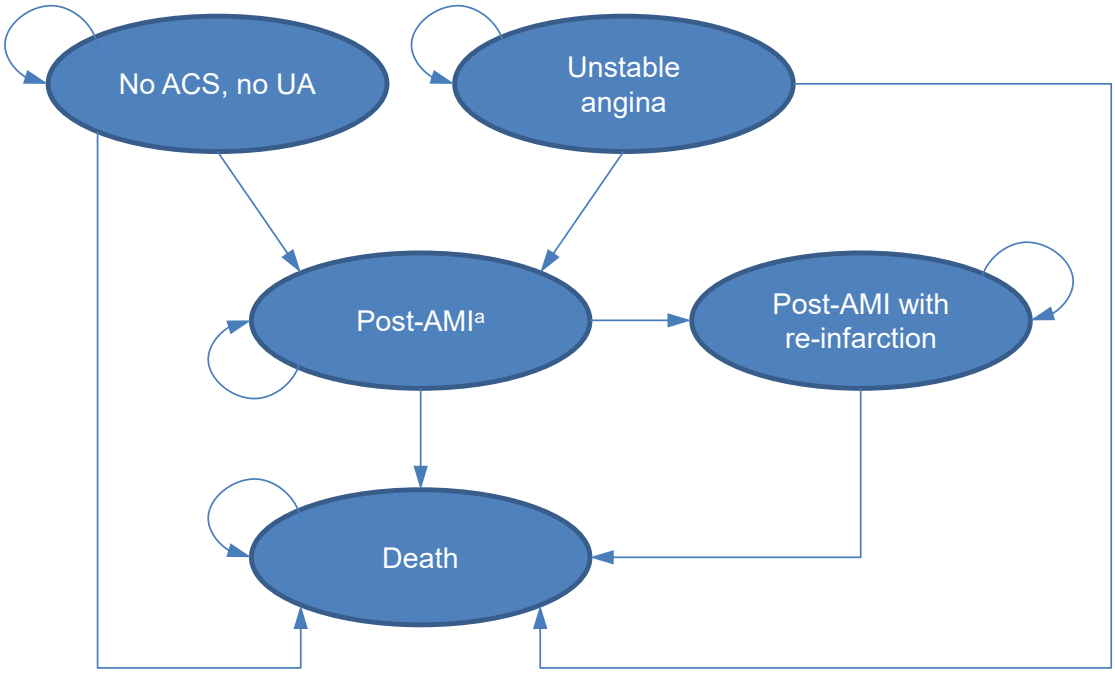


Figure 2: State-transition model structure



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

Model inputs

Estimates for the model input parameters were retrieved from the literature and from consulting experts. Accuracy estimates were derived from the systematic review component of the assessment.

The proportion of people testing positive or negative were based on the estimated accuracy of the testing strategies considered (table 16) and the estimated prevalence of NSTEMI in the UK (12.2%). All other clinical input parameters for the decision tree and state-transition model are reported in table 17 and further details on how inputs were used are provided in the diagnostics assessment report starting on page 119.

Table 15 Test accuracy and outcomes

Test strategy	Sens (Se)	Spec (Se)	FP	TN	PPV
Standard troponin (at presentation and after 10-12 h)	1.00 (-)	1.00 (-)	0.00	0.88	1.00
1 Roche Elecsys hs-cTnT (99th percentile)	1.00 (0.03)	0.77 (0.08)	0.20	0.68	0.38
2 Roche Elecsys hs-cTnT (LoD)	0.99 (0.01)	0.35 (0.05)	0.57	0.31	0.18
3 Roche Elecsys hs-cTnT (ESC pathway)	0.99 (0.01)	0.68 (0.01)	0.28	0.60	0.30
4 Roche Elecsys hs-cTnT (<8 ng/litre at 0 h AND Δ <3 ng/litre at 0 to 0.5 h)	1.00 (0.02)	0.45 (0.02)	0.48	0.40	0.20
5 Roche Elecsys hs-cTnT (<12 ng/litre at 0 h AND Δ <3 ng/litre at 0 to 1 h)	0.98 (0.01)	0.73 (0.01)	0.24	0.64	0.33
6 Siemens Dimension Vista hs-cTnI (<5 ng/litre at 0 h AND Δ <2 ng/litre at 0 to 1 h)	1.00 (0.02)	0.66 (0.02)	0.30	0.58	0.29
7 Abbott ARCHITECT hs-cTnI (LoD)	1.00 (0.00)	0.21 (0.03)	0.69	0.18	0.15
8 Abbott ARCHITECT hs-cTnI (ESC pathway)	0.99 (0.00)	0.57 (0.01)	0.38	0.50	0.24
9 Abbott ARCHITECT hs-cTnI (High-STEACS pathway)	0.99 (0.01)	0.76 (0.01)	0.21	0.67	0.36
10 Abbott ARCHITECT hs-cTnI (<4 ng/litre at 0 h)	0.99 (0.01)	0.50 (0.01)	0.44	0.44	0.22
11 Siemens ADVIA Centaur hs-cTnI (<2 ng/litre at 0 h)	1.00 (0.00)	0.23 (0.01)	0.68	0.20	0.15
12 Siemens ADVIA Centaur hs-cTnI (<3 ng/litre at 0 h OR (<8 ng/litre at 0 h AND Δ <7 ng/litre at 0 to 2 h))	1.00 (0.01)	0.67 (0.03)	0.29	0.59	0.30
13 Siemens ADVIA Centaur hs-cTnI (ESC pathway)	0.99 (0.01)	0.56 (0.02)	0.39	0.49	0.24
14 Siemens ADVIA Centaur hs-cTnI (<5 ng/litre at 0 h)	0.99 (0.01)	0.52 (0.01)	0.42	0.46	0.22
15 Siemens Atellica hs-cTnI (<2 ng/litre at 0 h)	1.00 (0.01)	0.26 (0.01)	0.65	0.23	0.16
16 Siemens Atellica hs-cTnI (High-STEACS pathway)	0.98 (0.01)	0.74 (0.01)	0.23	0.65	0.34
17 Beckman Coulter Access hs-cTnI (ESC pathway)	0.99 (0.02)	0.70 (0.02)	0.26	0.61	0.00
18 Beckman Coulter Access hs-cTnI ((symptoms >3 h AND <4 ng/litre at 0 h) OR (<5 ng/litre and Δ <5 at 0 to 2 h))	0.98 (0.02)	0.83 (0.01)	0.15	0.73	0.45
19 Ortho VITROS hs-cTnI (ESC pathway)	1.00 (0.01)	0.60 (0.02)	0.35	0.53	0.26
20 bioMérieux VIDAS hs-cTnI (<2 ng/litre at 0 h OR (<6 ng/litre at 0 AND 2 h))	0.98 (0.02)	0.64 (0.02)	0.32	0.56	0.27
21 Quidel TriageTrue hs-cTnI (ESC pathway)	1.00 (0.01)	0.66 (0.02)	0.30	0.58	0.29
Abbreviations: h, hours; Sens, sensitivity; spec, specificity, SE, standard error; FP, false positive; TN, true negative; PPV, positive predictive value					

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. This correlation was assumed to be equal for other tests. The proportion of true positives was 0.12 for all tests. The proportion of false negatives was 0.00 for all tests. Negative predictive value was 1.00 for all tests.

Table 16 Model inputs

	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
Proportion of NSTEMIs of all confirmed cases of heart attack	0.613	0.002	Beta	Healthcare Quality Improvement Programme
NSTEMI prevalence [a]	0.122	-	-	Calculated
Proportion of UA (of all non-NSTEMI patients)	0.160	0.038	Beta	CADTH (2013)
Decision tree (30-day) probabilities				
Mortality (30-day) treated AMI	0.097	0.012	Beta	Pope (2000)
Mortality (30-day) untreated AMI	0.105	0.069	Beta	Pope (2000)
Mortality (30-day) treated UA	0.021	0.005	Beta	Pope (2000)
Mortality (30-day) no ACS	Age dependent [b]	-	Fixed	ONS
State-transition model (long term)				
AMI incidence	Age dependent [c]	-	Fixed	British Heart Foundation
Annual reinfarction (treated) [d]	0.023	0.001	Beta	Smolina (2012)
Relative risk for reinfarction (untreated versus treated) [e]	2.568	1.366 - 5.604	LogNormal	Mills (2011)
Annual mortality no ACS	Age dependent [b]	-	Fixed	ONS
Annual mortality post-MI [d]	0.066	0.000	Beta	Smolina (2012)
Annual mortality post reinfarction [d]	0.142	0.002	Beta	Smolina (2012)
Hazard ratio for mortality (UA versus NSTEMI)	0.781	0.581 - 1.053	LogNormal	Allen (2006)
Relative risk for mortality (untreated versus treated) [d]	1.877	0.951 - 4.239	LogNormal	Mills (2011)
Secondary analysis (adjusted relative risk for patients tested false positive)				
Odds ratio for AMI [f]	1.210	0.830 – 1.760	LogNormal	Liplinski (2015)
Odds ratio for death [f]	1.600	1.140 – 2.240	LogNormal	Liplinski (2015)
Proportion of AMI [g]	0.109	0.011	Beta	Liplinski (2015)
Proportion of death [g]	0.110	0.011	Beta	Liplinski (2015)
Relative risk for AMI [f, h]	0.842	-	Calculated	Liplinski (2015)
Relative risk for death [f, h]	0.652	-	Calculated	Liplinski (2015)
Abbreviations: ACS, acute coronary syndrome; AMI, acute myocardial infarction; NSTEMI, non-ST segment elevation myocardial infarction; ONS, Office for National Statistics; UA, unstable angina				

[a] Prevalence was used to calculate proportions of true/false positives/negatives with 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 sex (58.1% males).
[e] Increased reinfarction and mortality risk for untreated (versus treated) was assumed for the 1st year after presentation, after which no increased risk was assumed (relative risk = 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] Odds ratios were converted to relative risks using the method described by Zhang and Yu.

Costs

Test-specific resource use consisted of the number of tests done and the duration of hospital stay (hours) before discharge or acute myocardial infarction treatment. For test strategies that involved a subsequent test conditional on the outcome of the first test, the rule-out rate for the presentation sample was used to calculate the number of subsequent tests.

Table 17 Test-specific resource use

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

[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)
AMI, acute myocardial infarction; ESC, European Society of cardiology; h, hour; hs-cTn, high-sensitivity troponin; LoD, limit of detection; ng, nanograms.

Health state costs were taken from a retrospective cohort study done in the UK (Danese et al. 2016). Acute myocardial infarction treatment costs were based on NHS reference costs and hospital stay costs were based on data from the Personal Social Services Research Unit. Further details can be found in the diagnostics assessment report starting on page 123.

In the base case, test costs were assumed to be identical for all tests (£2.50) except for the point-of-care test (£25.00, based on information provided by Quidel). A scenario analysis was done using test-specific costs and assuming that costs relating to the analyser and staff time were identical for all strategies. Assay-specific costs are shown in table 18.

Table 18 Test costs

Test	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 hsTn	£1.85
bioMérieux VIDAS hsTnI [a]	£6.05
Quidel TriageTrue hsTnI (point-of-care)	£25.00

[a] No information provided by company, so cost assumed to be identical to the highest laboratory-based test cost.

Health-related quality of life and QALY decrements

Age-dependent utility scores from the UK general population were calculated for people in the ‘no ACS, no UA’ health state. These age-dependent utility scores were combined with age-dependent disutility values for acute myocardial infarction, to calculate utility values for the ‘post-AMI’ health states (with or without reinfarction). Utility values for the ‘UA’ health state were calculated based on the ‘post-MI’ utility values and a utility increment of 0.010.

Further details on utility values can be found on page 120 of the diagnostics assessment report.

Key assumptions

The following assumptions were applied in the base-case analysis:

- Standard troponin testing (at presentation and after 10 to 12 hours) has perfect accuracy.
- The life expectancy and quality of life for people with false-positive test results is equal to the life expectancy, quality of life and costs of people with true-negative results.
- Compared with acute myocardial infarctions occurring during the decision tree period, all acute myocardial infarctions (either first or reinfarction) occurring in the state-transition model are diagnosed correctly, so are treated.
- Unstable angina is always correctly diagnosed, so is treated.
- The reinfarction probability for the 'post-AMI with reinfarction' health state is equal to the reinfarction probability for the 'post-AMI' health state.
- The increased post-acute myocardial infarction reinfarction and mortality probabilities for untreated acute myocardial infarction were assumed to last 1 year. After this a relative risk of 1.0 was applied (for untreated versus treated acute myocardial infarction).
- There is no additional benefit of starting treatment early, so treatment effect for high-sensitivity strategies is equal to treatment effect for standard troponin strategies.
- All 30-day deaths (after presentation at the emergency department) are due to fatal acute myocardial infarction events and will receive the associated costs.

Base-case results

For the purposes of decision making, the costs per QALY gained or lost will be considered. Standard troponin testing was the most effective and the most expensive strategy with an ICER of £38,871 per QALY gained (probabilistic

analysis). But, other testing strategies with a sensitivity of 100% (subject to uncertainty) were almost equally as effective, resulting in the same QALY gain. Compared with standard troponin testing, high-sensitivity troponin testing resulted in probabilistic ICERs ranging between £34,307 and £36,842,603 savings per QALY lost (table 18). Full results of the base-case analysis can be found in the diagnostics assessment report starting on page 127.

Table 19 Probabilistic results for base-case analysis: hs-troponin testing compared with standard troponin testing

	Strategy	Costs	QALYs	Incremental Costs	Incremental QALYs	ICER[1]
18	Beckman Coulter Access hs-cTnI ((symptoms >3 h AND <4 ng/litre at 0 h) OR (<5 ng/litre and Δ <5 at 0 to 2 h))	£38,625	12.0768	-£246	-0.0058	£42,753
17	Beckman Coulter Access hs-cTnI (ESC pathway)	£38,650	12.0790	-£221	-0.0036	£62,121
3	Roche Elecsys hs-cTnT (ESC pathway)	£38,662	12.0798	-£209	-0.0027	£77,589
20	bioMérieux VIDAS hs-cTnI (<2 ng/litre at 0 h OR (<6 ng/litre at 0 AND 2 h))	£38,662	12.0764	-£209	-0.0061	£34,307
5	Roche Elecsys hs-cTnT (<12 ng/litre at 0 h AND Δ <3 ng/litre at 0 to 1 h)	£38,663	12.0813	-£208	-0.0012	£169,682
14	Siemens ADVIA Centaur hs-cTnI (<5 ng/litre at 0 h)	£38,678	12.0794	-£193	-0.0032	£60,899
9	Abbott ARCHITECT hs-cTnI (High-STEACS pathway)	£38,681	12.0795	-£190	-0.0030	£63,659
13	Siemens ADVIA Centaur hs-cTnI (ESC pathway)	£38,684	12.0791	-£187	-0.0034	£54,645
6	Siemens Dimension Vista hs-cTnI (<5 ng/litre at 0 h AND Δ <2 ng/litre at 0 to 1 h)	£38,688	12.0825	-£183	0.0000	£36,842,603
16	Siemens Atellica hs-cTnI (High-STEACS pathway)	£38,698	12.0811	-£173	-0.0014	£119,994
10	Abbott ARCHITECT hs-cTnI (<4 ng/litre at 0 h)	£38,699	12.0815	-£171	-0.0010	£169,198
19	Ortho VITROS hs-cTnI (ESC pathway)	£38,701	12.0825	-£170	0.0000	£28,179,082
8	Abbott ARCHITECT hs-cTnI (ESC pathway)	£38,702	12.0818	-£169	-0.0007	£233,736
12	Siemens ADVIA Centaur hs-cTnI (<3 ng/litre at 0 h OR (<8 ng/litre at 0 h AND Δ <7 ng/litre at 0 to 2 h))	£38,704	12.0825	-£167	0.0000	£25,072,373
1	Roche Elecsys hs-cTnT (99th percentile)	£38,706	12.0825	-£165	0.0000	£15,661,356
21	Quidel TriageTrue hs-cTnI (ESC pathway)	£38,721	12.0825	-£149	0.0000	£28,167,521
4	Roche Elecsys hs-cTnT (<8 ng/litre at 0 h AND Δ <3 ng/litre at 0 to 0.5 h)	£38,729	12.0825	-£142	0.0000	£17,442,604
2	Roche Elecsys hs-cTnT (LoD)	£38,738	12.0817	-£132	-0.0008	£169,952
15	Siemens Atellica hs-cTnI (<2 ng/litre at 0 h)	£38,768	12.0825	-£103	0.0000	£21,210,686

11	Siemens ADVIA Centaur hs-cTnI (<2 ng/litre at 0 h)	£38,777	12.0825	-£94	0.0000	£31,584,800
7	Abbott ARCHITECT hs-cTnI (LoD)	£38,778	12.0823	-£93	-0.0002	£381,602
	Standard troponin (at presentation and after 10-12 h)	£38,871	12.0825	£0	0.0000	NA

[1] ICERs are costs saved per QALY lost

ESC, European Society of cardiology; h, hour; hs-cTn, high-sensitivity troponin; ICER, incremental cost effectiveness ratio; LoD, limit of detection; QALY, quality adjusted life year; ng, nanograms.

Secondary analysis

For the base case, it was assumed that people who tested negative on standard troponin tests and positive on high-sensitivity troponin tests would have a life expectancy and quality of life equal to people with true-negative test results, but this assumption is debatable. A meta-analysis by Liplinski et al. (2015) showed that people with a negative standard troponin test and positive high-sensitivity troponin test have an increased risk of reinfarction and mortality compared with those who test negative on both standard troponin and high-sensitivity troponin tests. Although this risk was not as high as in people with both positive standard troponin and positive high-sensitivity troponin tests, it could still be considered prognostically important. So, a secondary analysis was done in which the risk of acute myocardial infarction and mortality was adjusted for people with false positive results.

In this analysis, standard troponin was the cheapest and the least effective testing strategy with an ICER of £37,517 per QALY gained (probabilistic analysis). Compared with standard troponin testing, high-sensitivity troponin testing resulted in probabilistic ICERs ranging between £4,043 and £6,148 per QALY gained (table 20). Full deterministic and probabilistic results for the secondary analysis can be found in the diagnostics assessment report starting on page 133.

Table 20 Probabilistic results for secondary analysis: hs-troponin test strategies compared with standard troponin

Strategy	Costs	QALYs	ΔCosts	ΔQALYs	ICER
Standard troponin (at presentation and after 10-12 h)	£37,517	11.3340	£0	0.0000	NA
14 Siemens ADVIA Centaur hs-cTnI (<5 ng/litre at 0 h)	£38,039	11.4463	£522	0.1123	£4,648
7 Abbott ARCHITECT hs-cTnI (LoD)	£38,046	11.4201	£529	0.0861	£6,148
2 Roche Elecsys hs-cTnT (LoD)	£38,050	11.4328	£532	0.0988	£5,389
15 Siemens Atellica hs-cTnI (<2 ng/litre at 0 h)	£38,051	11.4249	£534	0.0909	£5,868
11 Siemens ADVIA Centaur hs-cTnI (<2 ng/litre at 0 h)	£38,051	11.4221	£534	0.0881	£6,064
10 Abbott ARCHITECT hs-cTnI (<4 ng/litre at 0 h)	£38,055	11.4466	£538	0.1126	£4,778
13 Siemens ADVIA Centaur hs-cTnI (ESC pathway)	£38,057	11.4497	£540	0.1157	£4,662
20 bioMérieux VIDAS hs-cTnI (<2 ng/litre at 0 h OR (<6 ng/litre at 0 AND 2 h))	£38,060	11.4547	£543	0.1207	£4,500
17 Beckman Coulter Access hs-cTnI (ESC pathway)	£38,066	11.4628	£548	0.1288	£4,258
4 Roche Elecsys hs-cTnT (<8 ng/litre at 0 h AND Δ <3 ng/litre at 0 to 0.5 h)	£38,070	11.4430	£553	0.1089	£5,072
3 Roche Elecsys hs-cTnT (ESC pathway)	£38,072	11.4619	£555	0.1279	£4,337
18 Beckman Coulter Access hs-cTnI ((symptoms >3 hours AND <4 ng/litre at 0 h) OR (<5 ng/litre and Δ <5 at 0 to 2 h))	£38,077	11.4725	£560	0.1385	£4,043
8 Abbott ARCHITECT hs-cTnI (ESC pathway)	£38,079	11.4535	£562	0.1195	£4,699
19 Ortho VITROS hs-cTnI (ESC pathway)	£38,087	11.4571	£570	0.1231	£4,630
5 Roche Elecsys hs-cTnT (<12 ng/litre at 0 h AND Δ <3 ng/litre at 0 to 1 h)	£38,088	11.4678	£570	0.1338	£4,263
6 Siemens Dimension Vista hs-cTnI (<5 ng/litre at 0 h AND Δ <2 ng/litre at 0 to 1 h)	£38,092	11.4627	£575	0.1287	£4,467
12 Siemens ADVIA Centaur hs-cTnI (<3 ng/litre at 0 h OR (<8 ng/litre at 0 h AND Δ <7 ng/litre at 0 to 2 h))	£38,111	11.4636	£594	0.1296	£4,580
9 Abbott ARCHITECT hs-cTnI (High-STEACS pathway)	£38,115	11.4691	£598	0.1351	£4,425
21 Quidel TriageTrue hs-cTnI (ESC pathway)	£38,126	11.4627	£609	0.1287	£4,729
16 Siemens Atellica hs-cTnI (High-STEACS pathway)	£38,126	11.4689	£609	0.1349	£4,517
1 Roche Elecsys hs-cTnT (99th percentile)	£38,139	11.4718	£622	0.1378	£4,514

ESC, European Society of cardiology; h, hour; hs-cTn, high-sensitivity troponin; ICER, incremental cost effectiveness ratio; LoD, limit of detection; QALY, quality adjusted life year; ng, nanograms.

Analysis of alternative scenarios

During the original evaluation of high-sensitivity troponin testing, the committee concluded that the secondary analysis was the most robust analysis because it is likely that high-sensitivity troponin testing will detect additional people who would benefit from treatment in practice. So, results presented in this overview focus on scenario and sensitivity analyses done on secondary analysis. The following scenario analyses were done deterministically on both the base-case and the secondary analysis:

1. Acute myocardial infarction treatment costs (£2,496 based on NHS reference costs) were applied for people who tested false positive rather than using no treatment costs, as assumed in the base-case analysis.

2. The assumption that the increased post-acute myocardial infarction reinfarction and mortality probabilities for untreated acute myocardial infarction AMI only lasts for 1 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, see table 18).

For all scenario analyses of the secondary analysis, results were similar to those from the secondary analysis base case. Standard troponin remained the cheapest and the least effective testing strategy (deterministic analysis). In all scenario analyses of the secondary analysis, high-sensitivity troponin testing compared with standard troponin testing resulted in ICERs less than £10,000 per QALY gained. Full results for scenario analyses can be found in the diagnostics assessment report starting on page 139 and in appendix 6.

Sensitivity analyses

For both the base-case and the secondary analysis, one-way sensitivity analyses were done including all probabilistic parameters (NHS reference

costs were included plus or minus 20%), creating tornado diagrams for the relevant comparisons.

In the secondary analysis, the parameters that had a notable effect on the estimated cost-effectiveness estimates were:

- 30-day mortality for untreated acute myocardial infarction
- mortality 1 year after treated and untreated acute myocardial infarction
- discount rate used for outcomes, and
- relative mortality for people who had a true positive result compared with those that had a false positive result.

At extreme values (based on 95% confidence intervals) of these inputs, standard troponin testing remains cheaper and less effective than the high-sensitivity troponins assays. Further details can be found in the diagnostics assessment report, starting on page 140 and in appendix 7.

Incremental analyses per assay

Per-assay analyses based on the secondary analysis show which test strategies would be the most cost-effective for each individual assay (table 21). More details can be found starting on page 141 of the diagnostics assessment report.

Table 21 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/litre at 0 h AND Δ <3 ng/litre at 0 to 0.5 h)	£38,070	11.4430	Extendedly dominated
3 Roche Elecsys hs-cTnT (ESC pathway)	£38,072	11.4619	£769
5 Roche Elecsys hs-cTnT (<12 ng/litre at 0 h AND Δ <3 ng/litre at 0 to 1 h)	£38,088	11.4678	£2,658
1 Roche Elecsys hs-cTnT (99th percentile)	£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/litre at 0 h)	£38,055	11.4466	£326
8 Abbott ARCHITECT hs-cTnI (ESC pathway)	£38,079	11.4535	Extendedly dominated
9 Abbott ARCHITECT hs-cTnI (High-STEACS pathway)	£38,115	11.4691	£2,666

Siemens ADVIA Centaur hs-cTnI assay			
14 Siemens ADVIA Centaur hs-cTnI (<5 ng/litre at 0 h)	£38,039	11.4463	cheapest
11 Siemens ADVIA Centaur hs-cTnI (<2 ng/litre at 0 h)	£38,051	11.4221	dominated
13 Siemens ADVIA Centaur hs-cTnI (ESC pathway)	£38,057	11.4497	Extendedly dominated
12 Siemens ADVIA Centaur hs-cTnI (<3 ng/litre at 0 h OR (<8 ng/litre at 0 h AND Δ <7 ng/litre at 0 to 2 h))	£38,111	11.4636	£4,140
Siemens Atellica hs-cTnI assay			
15 Siemens Atellica hs-cTnI (<2 ng/litre 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 h AND <4 ng/litre at 0 h) OR (<5 ng/litre and Δ <5 at 0 to 2 h))	£38,077	11.4725	£1,197
ESC, European Society of cardiology; h, hour; hs-cTn, high-sensitivity troponin; ICER, incremental cost effectiveness ratio; LoD, limit of detection; QALY, quality adjusted life year; ng, nanograms.			

3 Summary

Clinical effectiveness

The EAG identified 37 studies that met the inclusion criteria for the review. These included 2 randomised controlled trials, High-STEACS and HiSTORIC. Test accuracy data was reported for the following high-sensitivity troponin assays:

- Roche Elecsys (30 studies)
- Abbott ARCHITECT (9 studies)
- Siemens Healthineers Atellica (2 studies)
- Siemens Healthineers ADVIA Centaur (3 studies)
- Beckman Coulter Access (2 studies) and
- 1 study each reported accuracy data for Siemens Healthineers Dimension Vista, Ortho VITROS, bioMérieux VIDAS and Quidel Cardiovascular TriageTrue.

There were 7 studies that reported diagnostic accuracy data for more than 1 test. No studies matching the inclusion criteria for the review were identified for the Abbott Alinity or Siemens Healthineers Dimension EXL high sensitivity Troponin I assays.

When considering single test strategies, only those using a threshold at or near to the limit of detection for the assay, in a sample taken at presentation, met the minimum clinically acceptable sensitivity criterion of 97%. Most of the multiple test strategies meeting the minimum clinically acceptable sensitivity comprised an initial rule-out step, based on high-sensitivity troponin levels in a sample taken on presentation and a minimum symptom duration. These strategies also had a second stage (for people not meeting the initial rule-out criteria) based on presentation levels of high-sensitivity troponin, and absolute change in levels between presentation and a second sample taken after 1, 2 or 3 hours.

There is evidence that high-sensitivity troponin assays can be used to rule out NSTEMI in adults presenting with acute chest pain, within the 4-hour NHS emergency department target. Test strategies that included a second rule-out step appeared to offer consistently higher specificity compared with rule-out strategies based on very low high-sensitivity troponin levels in a single sample taken on presentation alone. Sensitivity estimates also remained high for these multiple sample strategies. So, a multiple test strategy is likely to produce the highest rule-out rates while maintaining clinically acceptable sensitivity (very low rates of missed NSTEMI).

Cost effectiveness

The EAG considered the long-term costs and QALYs associated with different troponin testing methods for people presenting at the emergency department with suspected non-ST segment elevation acute coronary syndrome. The de novo model consisted of a decision tree and a state-transition cohort model. The decision tree was used to model the 30-day outcomes after presentation, based on test results and the accompanying treatment decision. The long-term consequences in terms of costs and QALYs were estimated using a state-transition cohort model with a lifetime time horizon (60 years). For the economic analyses only high-sensitivity troponin tests that had a sensitivity of 97% or above were selected, so 21 test strategies and standard troponin testing were included in the model.

In the base case, it was assumed that standard troponin testing had perfect sensitivity and specificity for diagnosing acute myocardial infarction. Also, it was assumed that only people testing positive with standard troponin testing were at increased risk for adverse events (acute myocardial infarction and mortality) so would benefit from immediate treatment. In a secondary analysis, a proportion of people testing positive only with a high-sensitivity troponin test and not with standard troponin testing, that is, false positives, were assumed to be at increased risk of acute myocardial infarction and mortality.

In the base case, standard troponin testing was the most effective and the most expensive strategy. However, other testing strategies with a sensitivity of 100% (subject to uncertainty) were almost equally as effective, resulting in the same QALY gain. Compared with standard troponin testing, high-sensitivity troponin testing resulted in probabilistic ICERs ranging between £34,307 and £36,842,603 savings per QALY lost.

In the secondary analysis, standard troponin was the cheapest and the least effective testing strategy. Compared with standard troponin testing, high-sensitivity troponin testing resulted in probabilistic ICERs ranging between £4,043 and £6,148 per QALY gained.

4 Issues for consideration

Clinical effectiveness

There was a lot of evidence about high-sensitivity troponin assays. This assessment used 37 studies from 123 publications, while the previous guidance used 18 studies from 37 publications. The main areas of change were an expansion of the number of assays available for use in the NHS, and an increase in the number of studies about how to use high-sensitivity troponin assays in clinical practice, that is, exploring different testing strategies. The large number of alternative test strategies (combining different assays, different timing and different thresholds) made interpreting the results complex.

Most results related to 2 assays, the Roche Elecsys hs-cTnT assay and the Abbott ARCHITECT hs-cTnI assay. There was some data (1 to 3 studies) on the following assays: Siemens Healthineers Atellica hs-cTnI, Siemens Healthineers ADVIA Centaur hs-cTnI, Beckman Coulter Access hs-cTnI, Siemens Healthineers Dimension Vista hs-cTnI, Ortho VITROS hs-cTnI, bioMérieux VIDAS hs-cTnI and Quidel Cardiovascular TriageTrue hs-cTnI. No studies were identified for the Abbott Alinity hs-cTnI, or Siemens Healthineers Dimension EXL hs-cTnI.

Many studies reported data for the performance of a single presentation sample rule-out strategy, using a threshold at or near to the limit of detection for the assay. These strategies often had high sensitivities but low specificities for the rule out of NSTEMI. During the original evaluation of high-sensitivity troponins, the committee concluded that although the limit of blank and limit of detection showed promise as cut-off thresholds in early rule-out test strategies, the clinical and practical implications of introducing limit of blank and limit of detection cut-off thresholds into practice were uncertain. Doing a second test 1 to 3 hours after the first appears to offer consistently higher specificity than strategies using a single sample on presentation, with sensitivity estimates remaining high.

The product information leaflets for all the high-sensitivity troponin assays included in this assessment reported separate thresholds for women and men, as well as overall 99th percentile for the general population. While there are some subgroup data comparing the performance of a common threshold in males and females, few studies have evaluated the diagnostic performance of sex-specific thresholds. The High-STEACS pathway utilises sex-specific thresholds, but it remains unclear if the use of sex-specific thresholds in the High-STEACS pathway offers any advantage over the use of a single general population threshold.

Some data were identified about the performance of high-sensitivity troponin test strategies in people with normal renal function and those with impaired

renal function, people with known ischaemic heart disease and those with no known ischaemic heart disease, and people 65 years old and over compared with those under 65 years old. The renal function subgroup data for the ESC 0/1-hour pathway, using the Abbott ARCHITECT hs-cTnI assay, show that the sensitivity of the rule-out pathway is high for both people with normal renal function and those with impaired renal function. However, the specificity of this test strategy was markedly lower in people with impaired renal function than in those with normal renal function and would reduce the number of people discharged within 4 hours. Subgroup data for the High-STEACS pathway, also using the Abbott ARCHITECT hs-cTnI assay, show that this test strategy may fall below the clinically acceptable threshold for sensitivity (97%) defined from this assessment, when used in people with known ischaemic heart disease compared with those with no known ischaemic heart disease. Overall, 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.

Cost effectiveness

In the base-case, standard troponin testing at 10 to 12 hours was considered the reference standard, assuming perfect sensitivity and specificity. But there is evidence that the prognostic performance of standard troponin testing may be imperfect. For example, a negative standard troponin test might assess correctly that a person is not experiencing a NSTEMI, but some people with a negative standard test result and a positive high-sensitivity troponin test result may still benefit from treatment because of the prognostic significance of the high-sensitivity test result. To take this possibility into account, a secondary analysis was done that assumed an increased risk of adverse events (acute myocardial infarction and mortality) for people with a false positive high-sensitivity test result (negative standard troponin result, positive high-sensitivity troponin result). This resulted in the standard troponin strategy being less effective than the high-sensitivity troponin testing strategies. During the original evaluation of high-sensitivity troponins, the committee concluded

that the secondary analysis was the most robust analysis, because it is likely that high-sensitivity troponin testing will detect more people who would benefit from treatment in practice.

The differences between the strategies in both costs and QALYs gained were very small. Given these minimal differences in cost effectiveness, it is worth noting that the high-sensitivity test strategies with the highest proportion of true negatives (that is, where 65% or more people can be safely discharged from hospital) involve high-sensitivity test strategies with a second test 2 to 3 hours after the first test (Siemens Atellica hs-cTnI [High-STEACS pathway], Abbott ARCHITECT hs-cTnI [High-STEACS pathway], Roche Elecsys hs-cTnT [99th percentile] and Beckman Coulter Access hs-cTnI [symptoms over 3 hours AND under 4 ng/litre troponin at 0 hours OR under 5 ng/litre troponin and a delta change of less than 5 at 0 to 2 hours]).

A major assumption that was maintained throughout all analyses was the conservative assumption of no health benefit of early treatment in the high-sensitivity troponin strategies as compared to 'late' treatment in the standard troponin strategy. Although many experts think that there must be a benefit, at least to some extent, of treating people early, there is no evidence yet to support or quantify a timing effect.

5 Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

Troponin levels may differ in men and women. They may also be chronically elevated in some groups; this includes people who are older and people with comorbidities such as chronic kidney disease. Sex and people who may have chronically elevated troponin levels were included as population subgroups in the scope. Evidence was identified for these subgroups and is discussed on

page 18 of this overview and in the diagnostics assessment report starting on page 155.

6 Implementation

The NICE adoption team identified potential barriers to the implementation of high-sensitivity troponin testing:

- Agreement between emergency department, cardiology, clinical biochemistry and acute medicine about the most appropriate early rule-out protocol.
- Inappropriate testing reducing clinical confidence in the test.
- Allocation of resources: anticipated savings will be seen in emergency department, cardiology and acute medicine through quicker discharge; costs are likely to be incurred by the laboratory (assay, consumables and staff costs).

Any laboratories using high-sensitivity assays should be able to show compliance with an accredited external quality assurance scheme. Internal quality assurance and calibration of all tests should also be conducted in accordance with the manufacturer's instructions for use.

7 Authors

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Appendix A: Sources of evidence considered in the preparation of the overview

A. The diagnostics assessment report for this assessment was prepared by Kleijnen Systematic Reviews Ltd in collaboration with Maastricht University:

Westwood ME, Ramaekers BLT, Grimm S, Worthy G, Fayter D, Armstrong N, Buksnys T, Ross J, Joore MA, Kleijnen J. High sensitivity troponin assays for the early rule-out or diagnosis of acute myocardial infarction in people with acute chest pain: a systematic review and cost-effectiveness analysis. A Diagnostic Assessment Report. Kleijnen Systematic Reviews Ltd, 2020.

B. The following organisations accepted the invitation to participate in this assessment as stakeholders. They were invited to comment on the draft scope and the diagnostics assessment report.

Manufacturer(s) of technologies included in the final scope:

- Abbott Laboratories
- Beckman Coulter
- bioMérieux
- Ortho Clinical Diagnostics
- Quidel Ireland
- Roche Diagnostics
- Siemens Healthineers

Other commercial organisations:

- Radiometer Ltd
- Randox Laboratories
- Thermo Fisher Scientific

Professional groups and patient/carer groups:

- Association of Clinical Biochemistry
- British Cardiovascular Society
- Royal College of Physicians
- Society for Acute Medicine

Research groups:

- King's College London School of Cardiovascular Medicine and Sciences

Associated guideline groups:

- None

Others:

- NHS England
- Department of Health
- Healthcare Improvement Scotland
- Medicines and Healthcare products Regulatory Agency
- Welsh Government

Appendix B: Glossary of terms

Acute coronary syndrome (ACS)

An umbrella term for a range of conditions where myocardial ischaemia may be present. ACS includes STEMI, NSTEMI and unstable angina. Suspected ACS is a challenge for clinicians who must use a range of diagnostic tests to determine the underlying condition and instigate the correct management.

Coefficient of variation (CV)

Intra-assay coefficient of variation is used to describe the precision, or repeatability, of immunoassays. In order to be classified as high-sensitivity, troponin assays need to show a CV of less than 10%.

Delta change

A measure of the magnitude of change between baseline and serial test values.

Limit of detection

The lowest level of an analyte that can be reliably detected or distinguished from the absence of the analyte.

Limit of quantitation

The lowest level of an analyte that can be reliably detected and for which predefined targets for bias and imprecision can be met.

Non-ST segment elevation acute coronary syndrome

A working diagnosis given to patients who present with a suspected acute coronary syndrome, without persistent ST-elevation changes on a 12-lead ECG.

Non-ST segment elevation myocardial infarction (NSTEMI)

A less severe myocardial infarction which occurs when the coronary artery is partially blocked, meaning that less damage to the myocardium occurs than would be observed with a STEMI. NSTEMI does not produce ST elevation on ECG and the use of cardiac biomarkers is needed to distinguish a NSTEMI

from unstable angina. NSTEMI is distinguished from unstable angina based on raised cardiac biomarkers, usually troponin.

Short turnaround time (STAT) test

Tests that must be processed quickly to help with managing an emergency. Tests marked as STAT are treated as the highest priority for processing and reporting by a laboratory.

ST-segment elevation myocardial infarction (STEMI)

A more severe myocardial infarction which is diagnosed by observing a characteristic elevation of the ST segment on an ECG. An elevation of the ST segment shows that there has been a relatively large amount of damage to the myocardium, usually because the coronary artery is blocked.