NICE National Institute for Health and Care Excellence

NICE guidance

High-sensitivity troponin tests for the early rule out of NSTEMI

HealthTech guidance
Published: 26 August 2020

www.nice.org.uk/guidance/htg552

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Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

This guidance replaces DG15 and DG40.

1 Recommendations

1.1 The following high-sensitivity troponin tests are recommended as options for the early rule out of non-ST-segment elevation myocardial infarction (NSTEMI) in people presenting to an emergency department with chest pain and suspected acute coronary syndrome:

- Access High-Sensitivity Troponin I Assay
- ADVIA Centaur High-Sensitivity Cardiac Troponin-I Assay
- Alinity High Sensitive Troponin-I assay
- ARCHITECT STAT High Sensitive Troponin-I assay
- Atellica IM High-Sensitivity Cardiac Troponin I Assay
- Dimension Vista High-Sensitivity Cardiac Troponin I Assay
- Dimension EXL High-Sensitivity Cardiac Troponin I Assay
- Elecsys Troponin T-high sensitive assay
- Elecsys Troponin T-high sensitive STAT assay
- VIDAS High sensitive Troponin I assay
- VITROS High Sensitivity Troponin I Assay.

1.2 The tests are recommended for use with different early rule-out test strategies alongside clinical judgement, including:

- A single sample on presentation using a threshold at or near the limit of detection, which will vary depending on the assay being used. If this sample is positive it should not be used to rule in NSTEMI.
- Multiple sample strategies, which typically include a sample at initial

assessment followed by a second sample taken at 30 minutes to 3 hours (if clinically appropriate) and use of 99th percentile thresholds or thresholds at or near the limit of detection of the assay.

Healthcare professionals should consider the likely time since the onset of symptoms when interpreting test results.

1.3 When NSTEMI is not ruled out using early rule-out test strategies, use NICE's guideline on recent-onset chest pain of suspected cardiac origin to help diagnose myocardial infarction, and consider using sex-specific thresholds at the 99th percentile (see section 4.7 and section 5.2).

More research is needed

1.4 Further research is recommended on the diagnostic performance of the TriageTrue High Sensitivity Troponin I test when using samples at point of care (see section 5.1).

Why the committee made these recommendations

When someone comes to a hospital emergency department with chest pain, tests are needed to work out if they're having a myocardial infarction (heart attack), and if so, what type it is and what treatment they need. Standard troponin tests take 10 to 12 hours, so people need to be admitted to hospital while they wait for the results.

High-sensitivity troponin tests can help to quickly rule out a type of heart attack called an NSTEMI. Doing these tests can mean people with normal troponin levels do not need to be admitted to hospital, and those with a confirmed NSTEMI can get earlier treatment.

Evidence shows that, of the high-sensitivity troponin tests, 9 are similarly effective in terms of diagnostic performance. Of these, 8 are also similarly cost effective compared with standard troponin tests in different early rule-out test strategies and so are recommended for use in the NHS.

There is only 1 diagnostic accuracy study for Elecsys STAT, and no diagnostic accuracy

evidence for Alinity and Dimension EXL. But they use the same methods, principles and reagents as alternative versions of the tests that do have diagnostic accuracy evidence and were included in the economic model. The main difference is that they are run on different analysers. They are therefore also recommended.

Although the TriageTrue test has the potential to be cost effective, its diagnostic accuracy when used on whole blood is uncertain.

2 The diagnostic tests

Clinical need and practice

2.1 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, reducing waiting time and anxiety for many people.

2.2 Cardiac troponins I and T are biological markers of cardiac muscle death (cardiomyocyte necrosis). They are released into the circulation, so rise when the 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).

2.3 The optimum sensitivity of older (non-high-sensitivity) troponin tests (referred to here as standard troponin tests) 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 tests have been developed. These can detect lower levels of troponin in the blood earlier than standard troponin tests, so enable early rule out of NSTEMI after the onset of acute chest pain. This could lead to fewer people being admitted to hospital, earlier discharge for people with normal troponin levels and earlier intervention for those with a confirmed NSTEMI.

2.4 NICE's 2014 guidance on high-sensitivity troponin tests recommended the Elecsys troponin T-high sensitive test and ARCHITECT STAT High Sensitive Troponin-I test 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 that 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 strategies has not been routinely adopted in the NHS and, if it has, there is wide variation in how it is being done. This updated assessment is being done to ensure that guidance is based on evidence including new high-sensitivity tests developed and marketed since publication of the NICE guidance. It is also to provide more detailed recommendations on how to use high-sensitivity tests (for example, timing of testing and using sequential testing strategies) when possible.

The interventions

2.5 All tests included in the assessment are CE marked and available to the NHS.

Access High-Sensitivity Troponin I Assay (Beckman Coulter)

2.6 The Access test is designed to be used in a laboratory with the Beckman Coulter Access 2 and DxI/DxC analysers. The company says that the test's performance is the same regardless of analyser. It is a paramagnetic particle chemiluminescent immunoassay for in-vitro quantitative determination of troponin I in serum and plasma samples. Results are available in 17 minutes. Recommended 99th percentile cut-offs are:

- 17.5 ng/litre for the whole population
- 11.6 ng/litre for women
- 19.8 ng/litre for men.

Each 99th percentile has a coefficient of variation (CV) of less than 10%. The test can detect troponin I in more than 97% of the reference population.

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

2.7 The ARCHITECT test is designed to be used in a laboratory with the Abbott ARCHITECT i2000SR and i1000SR analysers. The test is a chemiluminescent microparticle immunoassay for in-vitro quantitative determination of troponin I in serum and plasma samples. Results are available in 18 minutes. The ARCHITECT test can detect troponin I in 96% of the reference population. Recommended 99th percentile cut-offs are:

- 26.2 ng/litre for the whole population with a CV of 4%
- 15.6 ng/litre for women (CV 5.3%)
- 34.2 ng/litre for men (CV 3.5%).

Alinity High Sensitive Troponin-I assay (Abbott Diagnostics)

2.8 The Alinity test is designed to be used in a laboratory with the Alinity i analyser. It is a chemiluminescent microparticle immunoassay for the quantitative determination of troponin I in plasma and serum samples. Results are available in 18 minutes. Recommended 99th percentile cut-offs are:

- 26.2 ng/litre for the whole population with a CV of 4.6%
- 15.6 ng/litre for women (CV 5.0%)
- 34.2 ng/litre for men (CV 4.5%).

ADVIA Centaur High-Sensitivity Cardiac Troponin I Assay (Siemens Healthineers)

2.9 The ADVIA Centaur test is designed to be used in a laboratory with the Siemens ADVIA Centaur XP and ADVIA Centaur XPT analysers. It is a magnetic latex particle chemiluminescent immunoassay for the in-vitro quantitative determination of troponin I in serum and plasma samples. Test results are available in 18 minutes. Recommended 99th percentile cut-offs are:

- 47.34 ng/litre in lithium heparin and 46.47 ng/litre in serum for the whole population
- 36.99 ng/litre in lithium heparin and 39.59 ng/litre in serum for women
- 57.27 ng/litre in lithium heparin and 58.05 ng/litre in serum for men.

  Each 99th percentile has a CV of less than 10%. The test can detect troponin I in more than 50% of the reference population.

Atellica IM High-Sensitivity Cardiac Troponin I Assay (Siemens Healthineers)

2.10 The Atellica test is designed to be used in a laboratory with the Siemens Atellica IM analyser. It is a magnetic latex particle chemiluminescent immunoassay for the in-vitro quantitative determination of troponin I in serum and plasma samples. Test results are available in 10 minutes. Recommended 99th percentile cut-offs are:

- 45.2 ng/litre in lithium heparin and 45.43 ng/litre in serum for the whole population
- 34.11 ng/litre in lithium heparin and 38.64 ng/litre in serum for women
- 53.48 ng/litre in lithium heparin and 53.53 ng/litre in serum for men.

  Each 99th percentile has a CV of less than 10%. The test can detect troponin I in more than 50% of the reference population.

Dimension EXL High-Sensitivity Cardiac Troponin I Assay (Siemens Healthineers)

2.11 The Dimension EXL test is designed to be used in a laboratory with the Siemens Dimension EXL analyser. It is a magnetic latex particle chemiluminescent immunoassay for the in-vitro quantitative determination of troponin I in serum and plasma samples. Test results are available in 18 minutes. Recommended 99th

percentile cut-offs are:

- 60.4 ng/litre in lithium heparin and 58.2 ng/litre in serum for the whole population
- 51.4 ng/litre in lithium heparin and 47.8 ng/litre in serum for women
- 76.2 ng/litre in lithium heparin and 71.8 ng/litre in serum for men.

  Each 99th percentile has a CV of less than 10%. The test can detect troponin I in more than 50% of the reference population.

Dimension Vista High-Sensitivity Cardiac Troponin I Assay (Siemens Healthineers)

2.12 The Dimension Vista test is designed to be used in a laboratory with the Siemens Dimension Vista analysers. 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 10 minutes. Recommended 99th percentile cut-offs are:

- 58.9 ng/litre in lithium heparin and 57.9 ng/litre in serum for the whole population
- 53.77 ng/litre in lithium heparin and 51.1 ng/litre in serum for women
- 78.5 ng/litre in lithium heparin and 74.9 ng/litre in serum for men.

  Each 99th percentile has a CV of less than 10%. The test can detect troponin I in more than 50% of the reference population.

Elecsys troponin T-high sensitive assay (Roche)

2.13 The Elecsys and Elecsys STAT tests are designed to be used in a laboratory on the Roche cobas e411, e601, and e602 analysers. The company says that performance is the same when used on these analysers. The test can also be run on the cobas e801 analyser, which is designed for very high throughput as both a

standard and STAT test. The Elecsys test is a sandwich electrochemiluminescence immunoassay for in-vitro quantitative determination of troponin T in serum and plasma samples. Results are available in 18 minutes with the standard test and in 9 minutes with the STAT test. Both tests can detect troponin T in 57% of the reference population. Recommended 99th percentile cut-offs are:

- 14.0 ng/litre for the whole population with a CV of less than 10%
- 9.0 ng/litre for women
- 16.8 ng/litre for men.

TriageTrue High Sensitivity Troponin I Test (Quidel Cardiovascular)

2.14 The TriageTrue test can be used at point of care or in a laboratory with the Triage MeterPro analyser. It is a fluorescence immunoassay for the in-vitro quantitative determination of troponin I in EDTA anticoagulated whole blood and plasma samples. Test results are available in less than 20 minutes. Recommended 99th percentile cut-offs are:

- 20.5 ng/litre for the whole population with a CV of less than 10%
- 14.4 ng/litre for women
- 25.7 ng/litre for men.

The test can detect troponin I in more than 50% of the reference population.

VITROS High Sensitivity Troponin I Assay (Ortho Clinical Diagnostics)

2.15 The VITROS test is designed to be used in a laboratory on the following analysers: VITROS ECi/ECiQ/3600 Immunodiagnostic Systems and the VITROS 5600/XT 7600 Integrated System. It is an immunometric immunoassay for the in-vitro quantitative determination of troponin I in serum and plasma samples. Test

results are available in 15 minutes. Recommended 99th percentile cut-offs are:

- 11 ng/litre in lithium heparin and serum for the whole population
- 9 ng/litre in lithium heparin and serum for women
- 13 ng/litre in lithium heparin and 12 ng/litre in serum for men.

The test can detect troponin I in more than 50% of the reference population.

VIDAS High sensitive Troponin I assay (bioMérieux)

2.16 The VIDAS test is designed to be used in a laboratory on the following analysers: VIDAS, MINI VIDAS and VIDAS 3. It is for the in-vitro quantitative determination of troponin I in serum and plasma (lithium heparin) samples. Test results are available in 20 minutes. Recommended 99th percentile cut-offs are:

- 19 ng/litre for the whole population
- 11 ng/litre for women
- 25 ng/litre for men.

The comparator

2.17 The comparator was standard troponin testing over 10 to 12 hours from symptom onset used with early rule-out strategies.

3 Evidence

The diagnostics advisory committee considered evidence on high-sensitivity troponin tests for the early rule out of non-ST-segment elevation myocardial infarction (NSTEMI) from several sources. Full details of all the evidence are in the committee papers.

Clinical effectiveness

3.1 The external assessment group (EAG) did a systematic review to identify evidence on the clinical effectiveness of high-sensitivity troponin tests for the early rule out of acute myocardial infarction, including NSTEMI, in people who come to hospital with chest pain. It also considered studies used to develop the original diagnostics guidance on early rule out of myocardial infarction using high-sensitivity troponin tests.

3.2 The EAG identified 37 studies that met the inclusion criteria. Test accuracy data were reported for the following high-sensitivity troponin tests: Elecsys (30 studies), ARCHITECT (9 studies), Atellica (2 studies), ADVIA Centaur (3 studies), Access (2 studies). One study each reported accuracy data for Dimension Vista, VITROS, VIDAS and TriageTrue.

3.3 Seven studies reported diagnostic accuracy data for more than 1 test. No studies were identified that matched the inclusion criteria for the review for Alinity or Dimension EXL tests. Two randomised controlled trials were included in the review: High-STEACS and HiSTORIC.

3.4 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.

3.5 The randomised controlled trials were quality assessed using the revised Cochrane risk of bias tool for cluster randomised trials. 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.

Randomised controlled trials

3.6 Both trials used the ARCHITECT test.

3.7 The High-STEACS trial evaluated the implementation of an early rule-out strategy in 10 secondary and tertiary care hospitals in Scotland. It compared the rates at which conditions were reclassified after high-sensitivity troponin tests with the rates of reclassification after standard troponin testing. It also compared the subsequent incidence of myocardial infarction and cardiovascular death.

3.8 The HiSTORIC trial also evaluated the implementation of an early rule-out strategy in 7 acute hospitals in Scotland. The primary outcomes were length of stay and myocardial infarction or cardiac death after discharge at 30 days. The results are academic in confidence.

3.9 During the validation phase of High-STEACS (6 to 12 months), results of the high-sensitivity troponin I test were concealed from the attending clinician, and a standard cardiac troponin test was used to guide care. A high-sensitivity test was introduced after 6 months (early implementation) or 12 months (late implementation).

3.10 In patients whose condition was reclassified in the High-STEACS trial, there were no differences between high-sensitivity and standard troponin tests in the primary or 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 for patients without myocardial injury was 7 hours (interquartile range 3 to 24) in the validation phase and 4 hours (interquartile range 3 to 20) in the implementation phase. The authors of High-STEACS concluded that implementing an early rule-out strategy was not associated with any increase in myocardial infarction or cardiovascular death within 1 year of initial presentation.

Diagnostic test accuracy

Elecsys troponin T-high sensitive assay

3.11 Summary estimates of sensitivity and specificity from testing a single sample, using a 99th percentile diagnostic threshold for the general population, were 90% (95% confidence interval [CI] 85 to 94) and 78% (95% CI 72 to 83) respectively, 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) respectively, 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 ST-segment elevation myocardial infarction (STEMI).

3.12 Using multiple sample strategies appears to offer better specificity without substantial loss of sensitivity than using 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 threshold (5 ng/litre) in patients reporting a minimum symptom duration of 3 hours. The strategy tests at presentation and 1 hour later for patients whose acute myocardial infarction is not ruled out by the initial test, that is, it uses an 'OR' combination. The threshold for repeat testing is an initial troponin concentration of less than 12 ng/litre with an absolute change in troponin concentration, from 0 to 1 hour, of less than 3 ng/litre. For NSTEMI, the sensitivity and specificity estimates for this strategy were 99% (95% CI 98 to 100) and 68% (95% CI 67 to 70), respectively. Estimates of diagnostic performance were similar for strategies using an 'AND' combination of initial high-sensitivity troponin level and absolute change in troponin level.

ARCHITECT STAT High Sensitive Troponin-I assay

3.13 Summary estimates of sensitivity and specificity for a single sample using 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) respectively, 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) 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.

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

- in the whole population, symptoms for 2 hours or more and a troponin concentration of less than 5 ng/litre at 0 hours, or
- in women, 16 ng/litre or lower when measured 3 hours from presentation and an absolute change of less than 3 ng/litre at 0 to 3 hours, or
- in men, 34 ng/litre or lower when measured 3 hours from presentation and an absolute change of less than 3 ng/litre at 0 to 3 hours.

3.15 Using the High-STEACS pathway in this way appeared to offer increased specificity without substantial loss of sensitivity compared with a single sample on presentation and a risk stratification threshold of less than 5 ng/litre. The sensitivity and specificity estimates for this strategy were 99% (95% CI 97 to 100) and 76% (95% CI 73 to 78) respectively, for NSTEMI. The ESC 0/1-hour rule-out pathway reported a lower specificity than the High-STEACS pathway. It used an initial sample and a limit of detection threshold of less than 2 ng/litre, or repeat testing combining an initial troponin concentration of less than 5 ng/litre and an absolute change in troponin concentration, from 0 to 1 hour, of less than 2 ng/litre. Summary sensitivity and specificity estimates were 99% (95% CI 98 to 100) and 57% (95% CI 56 to 59) respectively for NSTEMI.

Access High-Sensitivity Troponin I Assay

3.16 The 2 studies evaluating the Access test each assessed a different multiple sample strategy. One followed the ESC 0/1-hour rule-out pathway (initial sample and a limit of detection threshold of less than 4 ng/litre, or repeat testing combining an initial concentration of less than 5 ng/litre and an absolute change in troponin concentration, from 0 to 1 hour, of less than 4 ng/litre), giving sensitivity and specificity estimates of 99% (95% CI 94 to 100) and 70% (95% CI

66 to 74) respectively for 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.

VIDAS High sensitive Troponin I assay

3.17 The study evaluating the VIDAS test assessed a multiple sample strategy, with samples taken on presentation and at 2 hours using a threshold of less than 2 ng/litre at presentation, or less than 6 ng/litre at presentation and at 2 hours. The reported sensitivity and specificity estimates were 98% (95% CI 92 to 100) and 64% (95% CI 59 to 68) respectively for NSTEMI.

VITROS High Sensitivity Troponin I Assay

3.18 The study evaluating the VITROS test assessed the ESC 0/1-hour rule-out pathway. This combined an initial sample and a limit of detection threshold of less than 1 ng/litre, or repeat testing combining an initial troponin concentration of less than 2 ng/litre and an absolute change in troponin concentration, from 0 to 1 hour, of less than 1 ng/litre. The reported sensitivity and specificity estimates were 100% (95% CI 95 to 100) and 60% (95% CI 55 to 64) respectively for NSTEMI.

TriageTrue High-Sensitivity Troponin I Test

3.19 The study evaluating the TriageTrue test assessed the ESC 0/1-hour rule-out pathway. This combined an initial sample and a limit of detection threshold of less than 4 ng/litre, or repeat testing combining an initial troponin concentration of less than 5 ng/litre and an absolute change in troponin concentration, from 0 to 1 hour, of less than 3 ng/litre. The reported sensitivity of this strategy was 100% (95% CI 97 to 100) and the specificity was 66% (95% CI 62 to 70) for NSTEMI.

ADVIA Centaur high-sensitivity Troponin I assay

3.20 Three studies evaluated the ADVIA Centaur test. Using a rule-out threshold of 2 ng/litre in a single sample taken on presentation, the sensitivity and specificity estimates were 100% (95% CI 99 to 100) and 23% (95% CI 21 to 25) respectively for NSTEMI. Two multiple sample strategies were evaluated. One followed the ESC 0/1-hour rule-out pathway. This combined an initial sample and a limit of detection threshold of less than 3 ng/litre, or repeat testing combining an initial concentration of less than 6 ng/litre and an absolute change in troponin concentration, from 0 to 1 hour, of less than 3 ng/litre. The sensitivity and specificity estimates for this strategy were 99% (95% CI 95 to 100) and 56% (95% CI 52 to 60) respectively for 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 NSTEMI.

Atellica High-Sensitivity Troponin I Assay

3.21 Using a rule-out threshold of 2 ng/litre, in a single sample taken on presentation, the sensitivity and specificity estimates for the Atellica test were 100% (95% CI 98 to 100) and 26% (95% CI 24 to 28) respectively for NSTEMI. Sensitivity and specificity estimates for the High-STEACS pathway (symptoms for at least 2 hours and an initial troponin concentration of less than 5 ng/litre, or a troponin concentration of 34 ng/litre or less in women, or 53 ng/litre or less in men at 3 hours and an absolute change in concentration from 0 to 3 hours, of less than 3 ng/litre) were 98% (95% CI 95 to 100) and 74% (95% CI 72 to 76) respectively for NSTEMI.

Dimension Vista High-Sensitivity Cardiac Troponin I Assay

3.22 The study of the Dimension Vista test assessed a strategy using measurements done at baseline using a troponin concentration threshold of less than 5 ng/litre and an absolute change of less than 2 ng/litre 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 NSTEMI.

Diagnostic accuracy in relevant subgroups

3.23 The EAG identified some data on the subgroups described in the scope for this guidance. In a study using the Elecsys test and a 99th percentile threshold on a single sample at presentation, a higher sensitivity for any acute myocardial infarction was estimated in people over 70 than for people aged 70 or under (97% [95% CI 92 to 99] and 88% [95% CI 78 to 94] respectively). The estimate of sensitivity for people over 70 was also higher than the corresponding summary estimates from all 22 studies that used the 99th percentile diagnostic threshold. There was a similar pattern for people with a high pre-test probability (determined by clinical judgement of cardiovascular risk factors, type of chest pain, physical findings and electrocardiography [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.

3.24 Only the High-STEACS trial reported using sex-specific thresholds. Data from this study appeared to show that testing using a single sample taken on presentation is markedly more sensitive if sex-specific 99th percentile cut-offs are used, compared with a standard troponin test with a uniform threshold. This is particularly true in women, for whom the 99th percentile is lower. This study also used sex-specific thresholds as part of a multiple test strategy: the High-STEACS pathway. It is unclear whether using sex-specific thresholds in this strategy offers any advantage over using a single general population threshold. This is because no equivalent strategy, using a single universal threshold, was evaluated. Other studies reported data on men and women using a single general population threshold in each group. Results from a study on the Elecsys test showed very similar accuracy estimates for the subgroups, although a study on the Dimension Vista reported a lower sensitivity and specificity in men than in women.

3.25 Two studies on the Elecsys test and 2 on the ARCHITECT test reported data on how diagnostic performance varies with renal function. All studies show a decrease in specificity as renal function decreases.

Comparative diagnostic accuracy for more than 1 test

3.26 Seven studies reported accuracy data for more than 1 test.

3.27 The APACE study provided data on the ESC 0/1-hour pathway using the Elecsys, ARCHITECT and ADVIA Centaur tests. It also provided data on the ESC 0/1-hour pathway using the Access, VITROS and TriageTrue tests, but these results came from different patient subgroups and were reported in different publications. Data showed that the ESC 0/1-hour pathway performed consistently across all 6 high-sensitivity troponin tests evaluated with sensitivity estimates of 98% or higher.

3.28 Three other studies, ADAPT, ROMI-3, and TRUST, compared the Elecsys and ARCHITECT tests. Although the sensitivity estimates for the Elecsys test, using the 99th percentile and a single sample at presentation, were higher than those for the ARCHITECT test, 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 Elecsys test and the ARCHITECT test, and were always 99% or higher.

3.29 The High-STEACS trial provided data on the rule-out performance of 3 strategies (ESC 0/1-hour, ESC 0/3-hour and High-STEACS 0/3-hour) using the ARCHITECT and Atellica tests. 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 Atellica test (94% [95% CI 79 to 99]) than using the ARCHITECT test (100% [95% CI 91 to 100]). The sensitivity and specificity estimates for the High-STEACS 0/3-hour rule-out pathway were similar using either test (both had sensitivity estimates of 98% or more). The ESC 0/3-hour rule-out pathway in this study consisted of:

- symptoms for 6 hours or more and a troponin concentration of 16 ng/litre or less in women or 34 ng/litre or less in men at 0 hours, or
- a troponin concentration of 16 ng/litre or less in women or 34 ng/litre or less in men at 3 hours, or
- an absolute change of less than 50% of the 99th percentile at 0 to 3 hours.

The sensitivity and specificity estimates for the ESC 0/3-hour rule-out

pathway were both less than 97% using either test.

3.30 The HIGH-US study compared 2 Siemens tests (Atellica and ADVIA Centaur), using 3 low thresholds and a single sample at presentation. The results showed sensitivity estimates were 99% or more for both tests for all thresholds.

3.31 The BEST study compared 2 single sample at presentation strategies using the ADVIA Centaur test (threshold of 3 ng/litre) and Elecsys test (limit of detection [5 ng/litre] threshold). Data were reported in separate publications with different numbers of people. The sensitivity estimates were 99% for both tests, but the Elecsys test had a higher specificity (47% [95% CI 43 to 51]) than the ADVIA Centaur test (33% [95% CI 30 to 36]).

Cost effectiveness

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

Review of economic evidence

3.33 Studies were eligible if they reported a full economic analysis of the cost effectiveness of either high-sensitivity troponin testing or standard troponin testing. They also had to include survival or quality-adjusted life years (QALYs) as an outcome measure.

3.34 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. The EAG noted that the key drivers of cost effectiveness in the included studies were the accuracy of high-sensitivity troponin tests, and the efficiency of decision making once test results were available.

3.35 The most recent study (Ambavane et al. 2017) reported that a 1-hour strategy using high-sensitivity troponin testing had higher sensitivity (87% compared with 69%) but lower specificity (96% compared with 97%) than standard care. The reference standard used to calculate diagnostic accuracy was determination of final diagnosis based on a comprehensive review of medical records. Total costs were less for the 1-hour strategy 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

3.36 The EAG developed a de novo economic model to explore the cost effectiveness of high-sensitivity troponin tests for the early rule out of acute myocardial infarction, including NSTEMI, 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 tests 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.

3.37 Only high-sensitivity troponin tests with a sensitivity of 97% or above were used in the economic model, based on expert opinion of the minimum sensitivity acceptable in clinical practice. The strategies evaluated are described in table 1.

Table 1 Test strategies evaluated in the economic model

Strategy number	Test	Strategy
1	Elecsys	99th percentile threshold (under 14 ng/litre at 0 hours AND 3 hours)
2	Elecsys	Limit of detection under 5 ng/litre at 0 hours
3	Elecsys	ESC 0/1-hour pathway: symptoms over 3 hours AND under 5 ng/litre at 0 hours OR under 12 ng/litre at 0 hours AND an absolute change of less than 3 ng/litre at 0 to 1 hour

Strategy number	Test	Strategy
4	Elecsys	Under 8 ng/litre at 0 hours AND an absolute change of less than 3 ng/litre at 0 to 0.5 hours
5	Elecsys	Under 12 ng/litre at 0 hours AND an absolute change of less than 3 ng/litre at 0 to 1 hour
6	Dimension Vista	Under 5 ng/litre at 0 hours AND an absolute change of less than 2 ng/litre at 0 to 1 hours
7	ARCHITECT	Under 12 ng/litre at 0 hours AND an absolute change of less than 3 ng/litre at 0 to 1 hour
8	ARCHITECT	ESC 0/1-hour pathway: symptoms over 3 hours AND under 2 ng/litre at 0 hours OR under 5 ng/litre at 0 hours AND an absolute change of less than 2 ng/litre at 0 to 1 hours
9	ARCHITECT	High-STEACS pathway: symptoms for 2 hours or more AND under 5 ng/litre at 0 hours OR 16 ng/litre or more (women) and 34 ng/litre or more (men) at 3 hours AND an absolute change of less than 3 ng/litre
10	ARCHITECT	Under 4 ng/litre at 0 hours
11	ADVIA Centaur	Under 2 ng/litre at 0 hours
12	ADVIA Centaur	Under 3 ng/litre at 0 hours OR under 8 ng/litre at 0 hours AND an absolute change of less than 7 ng/litre at 0 to 2 hours
13	ADVIA Centaur	ESC 0/1-hour pathway: symptoms over 3 hours AND under 3 ng/litre at 0 hours OR under 6 ng/litre at 0 hours AND an absolute change of less than 3 ng/litre at 0 to 1 hour
14	ADVIA Centaur	Under 5 ng/litre at 0 hours
15	Atellica	Under 2 ng/litre at 0 hours

Strategy number	Test	Strategy
16	Atellica	High-STEACS pathway: symptoms for 2 hours or more AND under 5 ng/litre at 0 hours OR 34 ng/litre or less (women) and 53 ng/litre or less (men) at 3 hours AND an absolute change of less than 3 ng/litre
17	Access	ESC 0/1-hour pathway: symptoms over 3 hours AND under 4 ng/litre at 0 hours OR under 5 ng/litre and an absolute change of less than 4 ng/litre at 0 to 1 hour
18	Access	Symptoms over 3 hours AND under 4 ng/litre at 0 hours OR under 5 ng/litre and an absolute change of less than 5 ng/litre at 0 to 2 hours
19	VITROS	ESC 0/1-hour pathway: symptoms over 3 hours AND under 1 ng/litre at 0 hours OR under 2 ng/litre at 0 hours AND an absolute change of under 1 ng/litre at 0 to 1 hour
20	VIDAS	Under 2 ng/litre at 0 hours OR under 6 ng/litre at 0 AND 2 hours
21	TriageTrue	ESC 0/1-hour pathway: symptoms over 3 hours AND under 4 ng/litre at 0 hours OR under 5 ng/litre at 0 hours AND an absolute change of less than 3 ng/litre at 0 to 1 hour

Model structure

3.38 The model structure from the original diagnostics assessment report was used. This model structure was adapted from the health technology assessment report from Goodacre et al. (2013). It 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 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.

3.39 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 (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)'.

3.40 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) 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.

Model inputs

3.41 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 was based on the estimated accuracy of the testing strategies considered (table 2) and the estimated prevalence of NSTEMI in the UK (12.2%).

Table 2 Test accuracy inputs

Number	Test	Strategy	Sensitivity (SE)	Specificity (SE)
0	Standard troponin	At presentation and after 10 to 12 hours	1.00 (-)	1.00 (-)
1	Elecsys	99th percentile at 0 hours AND 3 hours	1.00 (0.03)	0.77 (0.08)
2	Elecsys	Limit of detection at 0 hours	0.99 (0.01)	0.35 (0.05)
3	Elecsys	ESC 0/1-hour pathway	0.99 (0.01)	0.68 (0.01)
4	Elecsys	Less than 8 ng/litre at 0 hours AND change of less than 3 ng/litre at 0 to 0.5 hours	1.00 (0.02)	0.45 (0.02)
5	Elecsys	Less than 12 ng/litre at 0 hours AND change of less than 3 ng/litre at 0 to 1 hour	0.98 (0.01)	0.73 (0.01)
6	Dimension Vista	Less than 5 ng/litre at 0 hours AND change less than 2 ng/litre at 0 to 1 hour	1.00 (0.02)	0.66 (0.02)
7	ARCHITECT	Limit of detection at 0 hours	1.00 (0.00)	0.21 (0.03)
8	ARCHITECT	ESC 0/1-hour pathway	0.99 (0.00)	0.57 (0.01)
9	ARCHITECT	High-STEACS pathway	0.99 (0.01)	0.76 (0.01)
10	ARCHITECT	Less than 4 ng/litre at 0 hours	0.99 (0.01)	0.50 (0.01)

Number	Test	Strategy	Sensitivity (SE)	Specificity (SE)
11	ADVIA Centaur	Less than 2 ng/litre at 0 hours	1.00 (0.00)	0.23 (0.01)
12	ADVIA Centaur	Less than 3 ng/litre at 0 hours OR less than 8 ng/litre at 0 hours AND change of less than 7 ng/litre at 0 to 2 hours	1.00 (0.01)	0.67 (0.03)
13	ADVIA Centaur	ESC 0/1-hour pathway	0.99 (0.01)	0.56 (0.02)
14	ADVIA Centaur	Less than 5 ng/litre at 0 hours	0.99 (0.01)	0.52 (0.01)
15	Atellica	Less than 2 ng/litre at 0 hours	1.00 (0.01)	0.26 (0.01)
16	Atellica	High-STEACS pathway	0.98 (0.01)	0.74 (0.01)
17	Access	ESC 0/1-hour pathway	0.99 (0.02)	0.70 (0.02)
18	Access	Symptoms at more than 3 hours AND less than 4 ng/litre at 0 hour OR less than 5 ng/litre and change of less than 5 ng/litre at 0 to 2 hours	0.98 (0.02)	0.83 (0.01)
19	VITROS	ESC 0/1-hour pathway	1.00 (0.01)	0.60 (0.02)
20	VIDAS	Less than 2 ng/litre at 0 hour OR less than 6 ng/litre at 0 AND 2 hours	0.98 (0.02)	0.64 (0.02)
21	TriageTrue	ESC 0/1-hour pathway	1.00 (0.01)	0.66 (0.02)

ESC, European Society of Cardiology; SE, standard error; ng/litre is nanograms troponin per litre of blood.

3.42 Test-specific resource use consisted of the number of tests done and the duration of hospital stay in 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. The resource use included a delay from the time at which sampling could be done to the time at which results became available (2 hours) and delay between arrival at hospital and troponin assessment starting (1 hour).

3.43 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.

3.44 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.

3.45 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 assuming a utility increment of 0.010.

Assumptions

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

- Standard troponin testing (at presentation and after 10 to 12 hours) has perfect accuracy.
- 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 compared with 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.

3.47 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. A secondary analysis was done in which the risk of acute myocardial infarction and mortality was adjusted for people with false positive results.

Results

3.48 In the base case, standard troponin testing was the most effective and the most expensive strategy. But other testing strategies with a sensitivity of 100% (subject to uncertainty) were almost equally as effective, resulting in the same QALY gain up to 4 decimal places. Compared with standard troponin testing, high-sensitivity troponin testing resulted in probabilistic incremental cost-effectiveness ratios (ICERs) ranging between £34,307 and £36,842,603 savings per QALY lost.

3.49 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.

3.50 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.

3.51 One-way sensitivity analyses were done including all parameters that were changed in the probabilistic sensitivity analysis. 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
- relative mortality for people who had a true positive result compared with those who 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 troponin tests.

4 Committee discussion

Quick, accurate tests may reduce anxiety for patients and carers

4.1 The committee heard from a patient expert who highlighted the stresses and fears that patients and their families experience when attending the emergency department with chest pain. Reducing waiting times is important for patients. Technologies that reduce the time taken from sample to clinical decision, while providing good diagnostic accuracy, may help reduce patient anxiety. Patients may be reassured that they are having the most appropriate treatment with tests that provide an accurate result.

Flexibility on tests and strategies helps hospitals

4.2 NICE has previously recommended high-sensitivity troponin for early rule out of acute myocardial infarction, so most emergency departments are already set up for high-sensitivity troponin testing. Many have implemented early rule-out strategies as routine practice. The committee considered that there were practical issues around early rule-out strategies that incorporate serial testing but that these could be resolved in practice. It also considered that, if more tests and different testing strategies were found to be cost effective and were recommended, this would help with procurement and give hospitals more flexibility to implement a strategy that works for them.

Clinical effectiveness

The comparative accuracy of the different tests is uncertain

4.3 There were concerns about the level of clinical evidence available for some of the tests. Most diagnostic accuracy results related to the Elecsys (30 studies) and

ARCHITECT (9 studies) tests. Other tests had less evidence available but were mostly still acceptable. The committee noted that there was also limited evidence comparing the diagnostic performance of 1 test with another. This meant that although there may be differences in performance between the tests, it is difficult to estimate these differences with any certainty.

The sensitivity of single-sample early rule-out strategies varies depending on which threshold is used

4.4 Results from the diagnostic accuracy studies showed that strategies that test a single sample on presentation using a threshold at or close to the limit of detection gave high sensitivity but low specificity. However, the committee commented that single sample strategies can be useful to rule out non-ST-segment elevation myocardial infarction (NSTEMI) early in emergency departments and, for this purpose, specificity is not a priority. There were concerns about the consistency of different analysers to provide accurate results at these low thresholds. However, clinical experts commented that samples with results close to these low thresholds would be from people considered very low risk and would have a good prognosis regardless of treatment. In contrast, results from diagnostic accuracy studies showed that a single test strategy using the 99th percentile threshold had sensitivity estimates too low to be safely used in clinical practice.

Multiple sample early rule-out strategies have better specificity than single-sample strategies

4.5 Results from the diagnostic accuracy studies showed that multiple sample early rule-out strategies, that is, those that included a second rule-out step, had better specificity than single-sample strategies using a very low threshold. Multiple sample strategies also maintained high levels of sensitivity. However, clinical experts commented that it was difficult to make direct comparisons of the different test strategies based on specificity because the number of true negatives would be affected by the prevalence of NSTEMI in each of the different study populations.

High-sensitivity troponin tests should be used alongside clinical judgement

4.6 Clinical experts noted that the clinical context in which decisions on discharging or admitting someone to hospital is important, and that decisions should never be based solely on the results of a high-sensitivity troponin test. For example, a person with a negative high-sensitivity troponin test result should not be discharged without further investigations if they look visibly unwell or if the sample was collected too soon after the suspected cardiac event, a practice that could result in a false negative result.

Using sex-specific 99th percentile thresholds could reduce inequality in women's treatment

4.7 Clinical experts explained that there was consistent evidence from reference range studies that the 99th percentile threshold differs between men and women. For the Elecsys and ARCHITECT tests, the 99th percentile upper reference limit for women is much lower than the general (mixed) population 99th percentile. The High-STEACS trial was the only strategy included in the cost-effectiveness modelling to use sex-specific 99th percentile thresholds in an early rule-out strategy. But it did not provide a direct comparison with a general population 99th percentile threshold. The committee therefore considered that the evidence on using sex-specific 99th percentile thresholds in early rule-out strategies was unclear. Clinical experts noted that sex-specific 99th percentile thresholds were sometimes used in clinical practice to help diagnose NSTEMI, but that there was no evidence that using them affected clinical outcomes. They noted that the ongoing CODE-MI study aims to evaluate the effect of using the sex-specific 99th percentile threshold for women for high-sensitivity cardiac troponin. This will be compared with the general (mixed) population 99th percentile threshold, for the diagnosis, treatment and outcomes of women presenting to the emergency department with cardiac chest pain. The committee noted that there was a wider equality issue because women with acute myocardial infarction are generally under-diagnosed and under-treated compared with men. The committee considered that using sex-specific 99th percentile thresholds to help diagnose NSTEMI could be a step towards reducing this health inequality. It concluded that, when NSTEMI is not ruled out using early rule-out

test strategies, NICE's guideline on recent-onset chest pain of suspected cardiac origin may be used to help diagnose myocardial infarction, and the use of sex-specific thresholds at the 99th percentile should be considered (see section 5.2).

Randomised controlled trial evidence shows early rule-out strategies do not negatively affect health

4.8 The committee considered evidence from 2 randomised controlled trials, High-STEACS and HiSTORIC. It noted that the authors of High-STEACS concluded that the implementation of an early rule-out strategy was not associated with any increase in myocardial infarction or cardiovascular death within 1 year of initial presentation. The HiSTORIC trial was submitted to NICE as academic-in-confidence evidence. The committee concluded that evidence from the randomised controlled trials, which reported end clinical outcomes, strongly supported using high-sensitivity troponin tests with early rule-out strategies in clinical practice.

The TriageTrue point-of-care test is innovative but its diagnostic accuracy is uncertain

4.9 The committee noted that the TriageTrue point-of-care test had a turnaround time of around 20 minutes and had the potential to be an important development in the field. The rapid time to test results could have benefits because of a reduced length of time spent waiting for a result in the emergency department (see section 4.1). Only 1 study was available on the TriageTrue test. In this study troponin levels were tested in stored plasma samples rather than the whole blood samples used in clinical practice. The committee noted that the evidence did not reflect how the test would be used in clinical practice at the point of care. It concluded that further evidence on TriageTrue's diagnostic performance when used on whole blood at the point of care is needed before the test can be recommended for use in clinical practice.

The Alinity, Dimension EXL and Elecsys STAT tests are likely to have the same performance as alternative versions of tests

4.10 The Alinity and Dimension EXL tests were not included in the economic model because there were no direct diagnostic accuracy data for them in the systematic review. However, the committee noted that these tests were based on the same methods and principles, and used the same reagents as other tests that were included in the modelling. The committee heard that the Alinity test was a newer version of the ARCHITECT test and that the Dimension EXL test was a different version of the Vista test, but the tests were all run on different analysers. It noted further that the Elecsys STAT test was the same in terms of technical specification and performance as the Elecsys troponin T-high sensitive test, and is run on the same analysers. The committee concluded that the diagnostic accuracy of these different versions of the tests should be comparable. It also concluded that it was the responsibility of individual laboratories to assess the equivalency of these tests in practice, and to validate their diagnostic performance against their current system. This would be achieved in part by participating in external quality assessment schemes.

Cost effectiveness

Only including early rule-out strategies with a minimum sensitivity of 97% in the economic analysis is acceptable

4.11 Only early rule-out strategies with a sensitivity of 97% or more were used in the cost-effectiveness modelling, based on expert opinion about the minimum sensitivity acceptable in clinical practice. The committee noted that this approach could mean that some potentially cost-effective strategies were excluded from the economic modelling. But overall it agreed that it was an acceptable approach that was necessary to keep the number of test strategies in the economic model manageable and ensure that those considered were likely to be safe in practice.

The prognostic benefits associated with a false positive high-sensitivity troponin test should be incorporated into decision

making

4.12 The secondary analysis incorporated prognostic benefits associated with false positive high-sensitivity troponin test results. Clinical experts noted that it is now widely accepted that people with a negative standard troponin test and a positive high-sensitivity troponin test (classified as false positives in the analysis) have an increased risk of reinfarction and mortality compared with people who have a negative result from both tests. The committee concluded that the secondary analysis was most appropriate for decision making.

All early rule-out test strategies in the model are cost effective compared with standard troponin testing at 0 hours and 12 hours

4.13 Compared with standard troponin testing, high-sensitivity troponin test strategies resulted in incremental cost-effectiveness ratios (ICERs) of less than £7,000 per quality-adjusted life year (QALY) gained. These ICERs are below £20,000 per QALY gained, which NICE would typically consider to be cost effective. The committee noted that there were only small differences in costs and QALYs between the different test strategies included in the economic model, and recalled its previous conclusion that it was not possible to indirectly compare the tests and early rule-out strategies. The committee concluded that it was not possible to differentiate between the different test strategies, and that all early rule-out strategies had the potential to be recommended for clinical practice, provided that each test used with them had enough diagnostic accuracy data.

The results of the economic model are robust to changes in the input parameter values

4.14 The model results were robust to changes in the input parameter values, for example, the number of admissions based on the specificity of the test strategy and the prevalence of NSTEMI. Early rule-out strategies with lower specificities would likely result in fewer people being discharged from hospital, but this does not have a substantial effect on the cost-effectiveness results. In addition, clinical experts noted that people having standard troponin testing and who get a negative test result would probably have a hospital length of stay of 24 hours

rather than the 14 hours assumed in the economic model. So the benefits of using early rule-out strategies may have been underestimated. The external assessment group (EAG) commented that changing this assumption would be unlikely to affect the model results.

Recommending a range of different high-sensitivity troponin tests gives greater flexibility to NHS trusts

4.15 Some of the tests had lower levels of clinical evidence than others. But the diagnostic performance and costs of all the tests used in the modelling were comparable (except for the test cost for TriageTrue). There was no strong evidence to differentiate one test over another (see section 4.3), and when used in the early rule-out strategies all were cost effective compared with the standard troponin test (see section 4.13). The committee noted that recommending a range of tests would benefit hospitals by enabling them to operate within existing equipment contracts or investments in a particular platform. It concluded that recommending a range of high-sensitivity troponin tests gives greater flexibility to NHS trusts and enables them to work with any local restrictions or equipment contracts.

Recommending a range of early rule-out strategies means hospitals can use one that works for their emergency department

4.16 The original NICE diagnostics guidance on troponin tests for myocardial infarction recommended strategies that test at 0 hours and 3 hours, report absolute values and use an upper reference limit at the 99th percentile. The committee noted that much more evidence is now available on different early rule-out strategies. The committee considered the different strategies included in the model:

- single-sample strategies using a threshold at or near to the limit of detection
- multiple sample strategies in which all patients would be tested at baseline and again at 1 to 3 hours after the initial test
- multiple sample strategies in which people only had a second test (1 hour to 3 hours after the initial test) if the first test result could not be used to rule

out acute myocardial infarction.

The multiple sample strategies incorporated different thresholds, including those at or close to the limit of detection, the general (mixed) population 99th percentile, and sex-specific 99th percentiles. The committee recalled that all single-sample strategies and multiple sample strategies included in the model were highly sensitive, that is, they had a low false negative rate (see sections 4.4 and 4.5). It considered that strategies in which people could be safely discharged after the first test could be beneficial because fewer people would have to remain in the emergency department for a second test. The committee noted further that all strategies were cost effective compared with a standard troponin test strategy (see section 4.13). The committee concluded that recommending a range of early rule-out strategies would enable hospitals to use strategies that worked with the set up of their emergency department.

Further diagnostic accuracy evidence is needed before the TriageTrue test can be recommended for routine clinical use

4.17 The TriageTrue point-of-care test, when used in the European Society of Cardiology 0/1-hour pathway, was cost effective compared with a standard troponin test strategy, with an ICER of less than £5,000 per QALY gained. The committee considered that the potential benefits associated with the rapid turnaround times of point-of-care tests (see section 4.9) may not have been fully captured in the economic model. But the committee was concerned about the evidence used to provide the diagnostic accuracy inputs in the model, so concluded that further research was needed on the TriageTrue test before it could be recommended for routine clinical use.

Research considerations

Further research to understand the 99th percentile in population subgroups would be useful

4.18 Some evidence supported using sex-specific 99th percentile thresholds in clinical practice in men and women but overall their value in early rule-out is unclear (see section 4.7). The clinical experts said that there are much less data on the 99th percentile in other subgroups, such as older or younger people, people with or without renal disease and black, Asian and minority ethnic groups. The committee considered that it would be helpful to have a better understanding of differences in the 99th percentile between these subgroups.

5 What research is needed

5.1 Further research is recommended on the diagnostic performance of the TriageTrue high-sensitivity troponin test using samples at point of care.

5.2 Further research is recommended on how using sex-specific 99th percentile thresholds affects treatment decisions and clinical outcomes for men and women.

6 Implementation

NICE will support this guidance through a range of activities to promote the recommendations for further research. The research proposed will be considered by the NICE Medical Technologies Evaluation Programme research facilitation team for developing specific research study protocols as appropriate. NICE will also incorporate the research recommendations in section 5 into its guidance research recommendations database and highlight these recommendations to public research bodies.

7 Diagnostics advisory committee members and NICE project team

Committee members

This topic was considered by the diagnostics advisory committee, which is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the test to be assessed. If it is considered there is a conflict of interest, the member is excluded from participating further in that assessment.

The minutes of each committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Additional specialist committee members took part in the discussions for this topic:

Specialist committee members

Professor Richard Body
Clinical Professor of Emergency Medicine, University of Manchester

Mr Antony Chuter
Lay specialist

Professor Paul Collinson
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NICE project team

Each diagnostics assessment is assigned to a team consisting of a technical analyst (who acts as the topic lead), a technical adviser and a project manager.

Simon Webster
Topic lead

Frances Nixon
Technical adviser

Donna Barnes
Project manager

Update information

Minor changes since publication

December 2025: Diagnostics guidance 40 has been migrated to HealthTech guidance 552. The recommendations and accompanying content remain unchanged.

ISBN: 978-1-4731-7381-1