

Myocardial infarction (acute): Early rule out using high-sensitivity troponin tests (Elecsys Troponin T high-sensitive, ARCHITECT STAT High Sensitive Troponin-I and AccuTnl+3 assays)

Diagnostics guidance

Published: 1 October 2014

[nice.org.uk/guidance/dg15](https://www.nice.org.uk/guidance/dg15)

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1 Recommendations

This guidance considers high-sensitivity troponin tests to be those that have a coefficient of variation of 10% or less at the 99th percentile (the upper limit of the reference population), and are able to detect cardiac troponin in at least 50% of the reference population. These recommendations refer to the use of these tests with early rule-out protocols.

NICE is aware that there is a wide range of non-high-sensitivity troponin tests available to the NHS which are used to rule-out non-ST-segment-elevation myocardial infarction (NSTEMI). The evidence for these tests has not been assessed in this guidance, and the recommendations, therefore, do not relate to the use of non-high-sensitivity troponin tests.

- 1.1 The Elecsys Troponin T high-sensitive assay and ARCHITECT STAT High Sensitive Troponin-I assay 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.
- 1.2 The assays are recommended for use with 'early rule-out protocols', which typically include a blood sample for cardiac troponin I or T taken at initial assessment in an emergency department and a second blood sample taken after 3 hours. Laboratories should report absolute values and the upper reference limit should be set at the 99th percentile. Results should be interpreted along with clinical judgement and the results of clinical assessment. Healthcare professionals should take into account the pre-test probability of NSTEMI, the length of time since the suspected acute coronary syndrome, the possibility of chronically elevated troponin levels in some patients and that 99th percentile thresholds for troponin I and T may differ between sexes. When NSTEMI is not ruled out using an 'early rule-out protocol', further clinical assessment is required to determine whether a diagnosis of NSTEMI is appropriate.
- 1.3 The AccuTnI+3 assay is only recommended for use in clinical research, for early rule out of NSTEMI in people presenting to an emergency department with chest pain and suspected acute coronary syndrome (see [section 7.1](#)).
- 1.4 Healthcare professionals using 'early rule-out protocols' including the Elecsys Troponin T high-sensitive or the ARCHITECT STAT High Sensitive Troponin-I assays should collect further information on the time taken to rule out NSTEMI in clinical practice and on the clinical outcomes of people presenting to an

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emergency department with chest pain and suspected acute coronary syndrome (see [section 7.2](#)).

2 The technologies

- 2.1 Three high-sensitivity troponin assays were identified during scoping as being relevant to the assessment. All of the assays are CE-marked and intended for use in a clinical laboratory setting. For the purposes of the assessment, a high-sensitivity troponin assay was defined as an assay that has a coefficient of variation of 10% or less at the 99th percentile (the upper limit of the reference population), and which is able to detect cardiac troponin in at least 50% of the reference population. Additional details of the high-sensitivity troponin assays included in the guidance are provided in [section 4](#).

3 Clinical need and practice

The problem addressed

- 3.1 Cardiac troponin I and cardiac troponin T are biological markers of cardiac muscle death (cardiomyocyte necrosis). They are released into the circulation when damage to cardiac muscle has occurred. Troponins C, I and T form the troponin-tropomyosin complex which is responsible for regulating cardiac muscle contraction. Troponins I and T are the recommended biomarkers for diagnosing myocardial infarction (MI) in [Chest pain of recent onset](#) (NICE clinical guideline 95), when a rise and fall in troponin levels can signify that myocardial damage has occurred. The optimum sensitivity of non-high-sensitivity troponin assays (hereafter referred to as standard troponin assays) for acute MI occurs 10–12 hours after the onset of symptoms. For many people, this results in the need for hospital admission and observation while serial troponin testing is carried out. To overcome this, high-sensitivity troponin assays have been developed. These are able to detect lower levels of troponin in the blood earlier than older standard assays, leading to improved early detection of acute MI.
- 3.2 Using these high-sensitivity assays enables earlier detection of changes in troponin levels. This allows non-ST-segment elevation myocardial infarction (NSTEMI) to be ruled out within 4 hours, if test results are available within 3 hours of presentation to the emergency department. The increased sensitivity of these assays could mean a shorter inpatient hospital stay for people without raised levels of troponin and earlier intervention for those with a confirmed NSTEMI. As with older standard troponin assays, the high-sensitivity assays are intended to be used with clinical history taking and the electrocardiogram to diagnose NSTEMI because, despite being highly specific for cardiomyocyte necrosis, troponin may also be raised in people who do not have underlying evidence of ischaemic heart disease. Conditions other than acute MI that may cause troponin levels to be raised include myocarditis, congestive heart failure, severe infections, musculoskeletal conditions and renal disease.
- 3.3 The purpose of this assessment is to evaluate the clinical and cost effectiveness of the Elecsys Troponin T high-sensitive, ARCHITECT STAT High Sensitive Troponin-I and the AccuTnI+3 assays for early rule out or diagnosis of acute MI (without ST-segment elevation). In this assessment, the timing of testing is

within 4 hours of people presenting to an emergency department with acute chest pain.

The condition

- 3.4 Acute MI is part of a group of conditions collectively known as acute coronary syndrome, which includes ST-segment-elevation myocardial infarction (STEMI), NSTEMI, and unstable angina. These conditions are associated with common symptoms but have different underlying pathologies. STEMI is usually associated with a relatively large amount of damage to the myocardium (heart muscle) caused by a major blockage in the coronary artery, and can be detected from ST-elevation on an electrocardiogram (ECG) trace. By comparison, NSTEMI is often associated with relatively less damage to the myocardium, caused by either partial blockage of the coronary artery or blockage of a smaller artery, and does not produce ST-elevation on ECG. Angina occurs because of narrowing of the coronary arteries, and a consequent reduction in blood flow to the heart. Angina may be considered unstable when chest pain is not relieved by rest or medications used for stable angina.
- 3.5 Acute coronary syndromes arise when blood flow is restricted in the coronary arteries, usually caused by atherosclerosis, a build-up of plaque. When blood flow to the heart is reduced or blocked for a significant length of time (around 30–60 minutes), damage to cardiomyocytes (heart muscle cells) occurs resulting in the release of cardiac troponin. This is a pathological change and the consequent rise and/or fall in troponin levels can distinguish an acute MI from unstable angina.
- 3.6 People with acute coronary syndrome generally present with chest pain, a symptom that is responsible for around 700,000 emergency department attendances per year in England and Wales, and 253,765 emergency admissions per year. During 2011/12, the Myocardial Ischaemia National Audit Project reported 79,433 admissions with acute MI recorded in England and Wales, 32,439 (41%) of which were categorised as STEMI and 46,994 (59%) of which were categorised as NSTEMI. The incidence of acute MI increases with age, with the average age of first STEMI being 65 years, and of first NSTEMI 70 years. The incidence of acute MI is also reported to be greater among men than women.

The diagnostic and care pathways

- 3.7 People with acute coronary syndrome often present with acute chest pain and other symptoms such as nausea, vomiting, dyspnoea, sweating and indigestion. These symptoms, including acute chest pain, are common to many other conditions such as anxiety, gastro-oesophageal reflux disease and muscle strain. If clinical assessment suggests a significant probability of acute coronary syndrome then investigations are carried out as described in [NICE clinical guideline 95](#). Initial assessment comprises:
- taking a resting 12-lead ECG along with a clinical history, a physical examination and biochemical marker analysis
 - managing people in whom regional ST-segment elevation or presumed new left branch bundle block is observed on ECG according to [Myocardial infarction with ST-segment elevation](#) (NICE clinical guideline 167).
- 3.8 People without persistent ST-elevation changes on ECG are given a working diagnosis of a suspected non-ST-segment-elevation acute coronary syndrome, and need further testing with biochemical marker analysis to distinguish NSTEMI from unstable angina, conditions that need different treatment. [NICE clinical guideline 95](#) makes the following recommendations on the use of biochemical markers and refers to the use of troponin tests during a 10–12 hour period:
- Take a blood sample for troponin I or troponin T on initial assessment in hospital. These are the preferred biochemical markers to diagnose acute MI.
 - Take a second blood sample for troponin I or T measurement 10–12 hours after the onset of symptoms.
 - Do not use biochemical markers such as natriuretic peptides and high sensitivity C-reactive protein to diagnose acute coronary syndrome.
 - Do not use biochemical markers of myocardial ischaemia (such as ischaemia modified albumin) as opposed to markers of necrosis when assessing people with acute chest pain.
 - Take into account the clinical presentation, the time from onset of symptoms and the resting 12-lead ECG findings, when interpreting troponin measurements.

- 3.9 [Guidelines from the European Society of Cardiology on the management of people with a suspected non-ST-segment elevation acute coronary syndrome](#) acknowledge the use of high-sensitivity troponin assays and make recommendations on the use of a fast-track rule-out protocol. The guidelines state that high-sensitivity troponin assays have a negative predictive value of greater than 95% for acute MI on admission; including a second test at 3 hours can increase this to 100%.
- 3.10 It is recommended that a diagnosis of NSTEMI should be made using the universal definition of MI. [The third universal definition of myocardial infarction](#) defines acute MI as "the detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99th percentile upper reference limit and with at least 1 of the following: symptoms of ischaemia; new or presumed new significant ST-segment-T wave changes or new left branch bundle block; development of pathological Q waves in the ECG; imaging evidence of new loss of viable myocardium or new regional wall motion abnormality; or identification of an intracoronary thrombus by angiography or autopsy."
- 3.11 The management of people with a suspected NSTEMI or unstable angina is described in [Unstable angina and NSTEMI](#) (NICE clinical guideline 94). Initial treatment includes a combination of antiplatelet (aspirin, clopidogrel and glycoprotein IIb/IIIa inhibitors) and antithrombin therapy, taking into account contraindications, risk factors and the likelihood of percutaneous coronary intervention.
- 3.12 People with a suspected non-ST-segment elevation acute coronary syndrome are often transferred out of the emergency department to a range of clinical areas depending on the likelihood of complications and adverse outcomes. Established risk scores, such as the GRACE score or the TIMI risk score, that predict 6-month mortality can be used in combination with ECG findings and initial cardiac biomarker analysis to stratify people with a suspected non-ST-segment elevation acute coronary syndrome. The care settings available vary between hospitals, but are likely to include coronary care, acute medical, chest pain and clinical decision units. People in whom a raised troponin level is not observed may be discharged for further follow up according to clinical judgement and, in some cases, the results of ischaemia testing.

- 3.13 It is recommended that people who have a diagnosis of NSTEMI, and who are assessed as being at low risk of future complications, have conservative treatment with aspirin and/or clopidogrel, or aspirin plus ticagrelor. Ischaemia testing is also recommended to identify people who may need further intervention. In addition, people at a higher risk of future complications may also have coronary angiography (within 96 hours of admission) with subsequent coronary revascularisation by percutaneous coronary intervention or coronary artery bypass grafting when indicated ([NICE clinical guideline 94](#)).
- 3.14 Longer-term follow up of people who have had an acute MI (including both STEMI and NSTEMI) is described in full in [Myocardial infarction: secondary prevention](#) (NICE clinical guideline 172). This includes recommendations on lifestyle changes, cardiac rehabilitation programmes, drug therapy (including a combination of angiotensin converting enzyme inhibitors, aspirin, beta-blockers and statins), and further cardiological assessment to determine whether coronary revascularisation is needed.

4 The diagnostic tests

The intervention(s)

Elecsys Troponin T high-sensitive assay

- 4.1 The Elecsys Troponin T high-sensitive assay (Roche Diagnostics) is designed for use in a laboratory setting and can be used on the Roche Elecsys 2010 analyser and the cobas Modular Analytics e-series immunoassay analysers. The Elecsys test is a sandwich electrochemiluminescence immunoassay, and is intended for the in vitro quantitative determination of troponin T in serum and plasma samples. The Elecsys Troponin T high-sensitive assay has an estimated turnaround time of 18 minutes. The manufacturer states that the Elecsys assay can detect troponin T in 61% of the reference population and has a recommended 99th percentile cut off of 14 nanograms/litre, with a coefficient of variation or imprecision of less than 10%. The assay is CE-marked and available to the NHS. The Elecsys Troponin T high-sensitive assay is also available as a STAT version, which has a shorter turnaround time of 9 minutes.

ARCHITECT STAT High Sensitive Troponin-I assay

- 4.2 The ARCHITECT STAT High Sensitive Troponin-I assay (Abbott Diagnostics) is designed for use in a laboratory setting and can be used with the Abbott ARCHITECT i2000SR and i1000SR analysers. The assay is a chemiluminescent microparticle immunoassay and is intended for the in vitro quantitative determination of cardiac troponin I in serum and plasma samples. Results are available within 16 minutes. The manufacturer states that the ARCHITECT STAT High Sensitive Troponin-I assay can detect troponin I in 96% of the reference population, and has a recommended 99th percentile cut-off of 26.2 nanograms/litre, with a coefficient of variation of 4%. The manufacturer's instructions for use also states a 99th percentile cut-off of 34.2 nanograms/litre for men and 15.6 nanograms/litre for women. The assay is CE-marked and available to the NHS.

AccuTnl+3 troponin I assay

- 4.3 The AccuTnl+3 troponin I assay (Beckman Coulter) is designed for use in a laboratory setting with the Beckman Coulter Access II and UniCel Dxl analysers. The AccuTnl+3 assay is a paramagnetic particle chemiluminescent

immunoassay, and is intended for the in vitro quantitative determination of cardiac troponin I in serum and plasma samples. The assay is designed to be run as a STAT test and results are available within 13 minutes. The manufacturer states that the AccuTnI+3 troponin I assay has a recommended 99th percentile cut-off of 40 nanograms/litre, with a coefficient of variation of 10%. Details of the performance of the assay in the reference population are currently considered as academic in confidence information by the manufacturer. The assay is CE-marked and available to the NHS.

The comparator: standard troponin

- 4.4 The comparator used in this assessment is standard troponin testing over 10–12 hours.

5 Outcomes

The Diagnostics Advisory Committee ([section 11](#)) considered evidence from a number of sources ([section 12](#)).

How outcomes were assessed

- 5.1 The assessment consisted of a systematic review of the evidence on test performance and clinical-effectiveness data for the Elecsys Troponin T high-sensitive, ARCHITECT STAT High Sensitive Troponin-I and AccuTnI+3 assays.

Clinical effectiveness

- 5.2 The External Assessment Group conducted a systematic review of the evidence on the clinical effectiveness of high-sensitivity troponin testing for early rule out or diagnosis of acute myocardial infarction (MI) within 4 hours of people presenting with acute chest pain at an emergency department. Studies were considered for inclusion based on criteria developed for each of the clinical-effectiveness questions defined in the review protocol.
- 5.3 In total, 18 studies reported in 38 publications were included in the review. Of these, 15 studies (reported in 34 publications) reported accuracy data for the Elecsys Troponin T high-sensitive assay and 4 studies (reported in 5 publications) reported accuracy data for the ARCHITECT STAT High Sensitive Troponin-I assay. No published studies for the AccuTnI+3 assay were identified. The External Assessment Group identified 2 studies (reported in 3 publications) reporting accuracy data for an assay described as a prototype Access high-sensitivity troponin I assay. Some studies included more than 1 high-sensitivity troponin assay. The External Assessment group indicated that it was not clear from the studies whether this prototype was designed as a previous version of the AccuTnI+3 assay. The data for this prototype were included by the External Assessment Group in the diagnostics assessment report because the assay was developed by Beckman Coulter and its characteristics met the criteria used for defining high-sensitivity in the scope. All 18 studies were classed as diagnostic cohort studies; no randomised controlled trials or controlled clinical trials were identified. Of the 18 identified studies, 13 were conducted in Europe (of which 2 were UK-based), 4 were

conducted in Australia and New Zealand, and 1 was conducted in the USA. In addition, data submitted to the FDA relating to the AccuTnl+3 assay were provided by Beckman Coulter. The manufacturer considered these data to be commercial in confidence at the time of publication of the guidance.

- 5.4 Critical appraisal of the identified studies was done using the QUADAS-2 tool. The main potential sources of bias in the included studies related to patient spectrum and patient flow, which were of particular concern in studies that excluded people presenting out of hours or that stopped recruitment when workload was high. There were concerns about applicability of the patient population; 7 studies excluded people with STEMI and 1 study reported data separately for people in whom STEMI was excluded. The remaining studies included in the assessment reported data from a mixed population; that is, for which the target condition was either NSTEMI or STEMI (any acute MI). There were also concerns about the applicability of the reference standard due to the review criteria stating that an appropriate reference standard was standard troponin measurement at baseline and at 10–12 hours in 80% of the study population (only 5 studies met this criterion).

Evidence on diagnostic accuracy

- 5.5 For meta-analyses including 4 or more studies, the External Assessment Group used the bivariate/hierarchical summary receiver operator characteristic model to estimate summary sensitivity and specificity with 95% confidence intervals and prediction regions. For meta-analyses involving fewer than 4 studies, the External Assessment Group calculated separate pooled estimates of sensitivity and specificity using random-effects logistic regression. Analyses were performed separately for each high-sensitivity troponin assay, and were stratified according to whether the study reported the prediction of acute MI or major adverse cardiac events, timing of the collection of the blood sample for troponin testing, and the threshold used to derive a positive high-sensitivity troponin result. Where possible, data were reported for all studies, studies excluding people with STEMI and studies in which the target condition was any acute MI.
- 5.6 The External Assessment Group presented the results of its analyses according to whether the studies reported results from samples taken at the time the patient presented to the emergency department (presentation samples),

samples taken between 1 and 3 hours after the patient presented to the emergency department (subsequent samples), and diagnostic strategies that involved multiple samples (multiple samples).

Diagnostic accuracy of the Elecsys Troponin T high-sensitive assay

- 5.7 Fourteen studies assessed the accuracy of the Elecsys Troponin T high-sensitive assay for the detection of acute MI.

Presentation samples

- 5.8 All 14 studies reported accuracy for the detection of acute MI on single samples taken at presentation. All but one of the studies reported data on presentation samples using the 99th percentile as the diagnostic threshold, providing a summary estimate of sensitivity of 89% (95% confidence interval [CI] 85% to 92%) and specificity of 82% (95% CI 77% to 86%). The positive likelihood ratio (LR+) – how many more times likely it is that a person with the target condition will receive a positive test result compared with a person without the condition – was 4.96 (95% CI 3.84 to 6.39). The negative likelihood ratio (LR-) (how many more times likely it is that a person with the target condition will receive a negative test result compared with a person without the condition) was 0.14 (95% CI 0.10 to 0.19). When this analysis was restricted to studies that excluded people with STEMI (6 studies), similar summary estimates were obtained: sensitivity 88% (95% CI 78% to 93%), specificity 84% (95% CI 74% to 90%), LR+ 5.41 (95% CI 3.40 to 8.63) and LR- 0.15 (95% CI 0.08 to 0.26). The External Assessment Group also repeated this analysis when restricted to studies with a mixed population, that is when the target condition was any acute MI (8 studies), and similar summary estimates were obtained: sensitivity 89% (95% CI 86% to 91%), specificity 81% (95% CI 76% to 85%), LR+ 4.64 (95% CI 3.73 to 5.76) and LR- 0.14 (95% CI 0.11 to 0.17). The External Assessment Group considered that the analysis which excluded people with STEMI was the most applicable to the population defined in the scope and this was used to inform the cost-effectiveness analysis.
- 5.9 Data on presentation samples using diagnostic thresholds equivalent to the limit of detection (5 nanograms/litre) or limit of blank (3 nanograms/litre) were reported in 5 studies. Three studies reported data for the limit of detection, 1 of

which was excluded from analyses because the limit of detection data were only reported for people over 70 years of age. The summary estimates for presentation samples at the limit of detection were sensitivity 95% (95% CI 92% to 97%), specificity 54% (95% CI 51% to 58%), LR+ 2.06 (95% CI 1.40 to 2.64) and LR- 0.09 (95% CI 0.07 to 0.17). One study reported these data excluding people with STEMI: sensitivity 93% (95% CI 89% to 96%), specificity 58% (95% CI 55% to 62%), LR+ 2.20 (95% CI 2.00 to 2.50) and LR- 0.11 (95% CI 0.07 to 0.19). Three studies reported data for the limit of blank: summary estimates were sensitivity 98% (95% CI 95% to 99%), specificity 40% (95% CI 38% to 43%), LR+ 1.63 (95% CI 1.24 to 1.86) and LR- 0.05 (95% CI 0.02 to 0.21). One study reported the limit of blank in a population that excluded people with STEMI and was used to inform the cost-effectiveness modelling; the results were sensitivity 95% (95% CI 92% to 98%), specificity 48% (95% CI 44% to 51%), LR+ 1.83 (95% CI 1.70 to 1.97) and LR- 0.10 (95% CI 0.05 to 0.18).

- 5.10 The External Assessment Group identified limited data on clinically relevant subgroups, including people aged less than 70 years compared with those aged 70 years or over, no pre-existing coronary artery disease compared with pre-existing coronary artery disease, and high pre-test probability compared with low-to-moderate pre-test probability. All of the studies that reported subgroup data were in a mixed population, and did not exclude people with STEMI. The External Assessment Group concluded that the results of subgroup analyses suggest that high-sensitivity troponin testing, using the 99th percentile diagnostic threshold on a sample taken at presentation, could be adequate for rule out of acute MI in people aged 70 years or older (LR- 0.05 for people aged 70 years or older compared with LR- 0.14 for people aged less than 70 years), people who do not have pre-existing coronary artery disease (LR- 0.07 for people without pre-existing coronary artery disease compared with LR- 0.12 for people with pre-existing coronary artery disease) and people who are classified as having a high pre-test probability of acute MI (LR- 0.09 for high pre-test probability compared with LR- 0.13 for low-to-moderate pre-test probability).
- 5.11 The External Assessment Group noted that the time between onset of chest pain and presentation at the emergency department was inconsistently reported in the included studies. In studies that did report time from chest pain onset, the median time ranged from 2.7 to 8.25 hours. Two studies, conducted in

a mixed population, stratified patients as presenting either before or after 3 hours since the onset of chest pain, and in addition, either before or after 6 hours since the onset of chest pain. The results of this analysis suggested that the Elecsys Troponin T high-sensitive assay, with the 99th percentile as the diagnostic threshold on a sample taken at presentation, had a higher sensitivity (94% [95% CI 92% to 96%]) and lower specificity (77% [95% CI 75% to 79%]) for any acute MI in people presenting more than 3 hours after the onset of chest pain compared with people presenting within 3 hours; sensitivity 78% (95% CI 71% to 83%) and specificity 84% (95% CI 81% to 86%). When the analysis was repeated using 6 hours as the threshold, the results were similar.

Subsequent samples

- 5.12 Of the 14 studies reporting accuracy of the Elecsys Troponin T high-sensitive assay for the detection of acute MI, 2 reported data on samples taken 1 to 3 hours after presentation. Both studies used the 99th percentile as the diagnostic threshold and excluded people with STEMI. Summary estimates were sensitivity 95% (95% CI 92% to 97%), specificity 80% (95% CI 77% to 82%), LR+ 4.75 (95% CI 3.98 to 5.23) and LR- 0.06 (95% CI 0.00 to 0.63).

Multiple samples

- 5.13 Of the 14 studies reporting accuracy of the Elecsys Troponin T high-sensitive assay for the detection of acute MI, 6 reported data on the performance of diagnostic strategies involving multiple samples. The most commonly reported strategies were those involving a combination of a peak troponin T value above the 99th percentile diagnostic threshold, and a 20% change in high-sensitivity troponin T over 2 to 3 hours after presentation; 1 study reported these data in a population that excluded people with STEMI, and consequently was used in the cost-effectiveness modelling. The results of this analysis suggested that a test strategy defining a positive result as a peak value above the 99th percentile diagnostic threshold and a delta change in troponin T levels (that is a change from baseline) of greater than 20% over 2 hours provided the optimal rule-in performance (LR+ of 8.42, 95% CI 6.11 to 11.60). Conversely, a test strategy defining a negative result as no value above the 99th percentile diagnostic threshold and a delta change of less than 20% over 2 hours provided the optimal rule-out performance (LR- 0.04, 95% CI 0.02 to 0.10).

Elecsys Troponin T high-sensitive assay test pathways

- 5.14 The External Assessment Group constructed an optimal test pathway for multiple sampling on which the cost-effectiveness modelling was based. This test pathway was based on the optimal diagnostic accuracy reported in the External Assessment Group's clinical effectiveness analysis, and included data only from studies that excluded people with STEMI. For the Elecsys Troponin T high-sensitive assay, this test pathway comprised a rule-out step of a presentation sample with the limit of blank (3 nanograms/litre) as the diagnostic threshold. This was followed by a second sample at 2 hours with the 99th percentile threshold and delta change of more or less than 20% as the diagnostic threshold, in which a peak value less than the 99th percentile, in combination with a delta change of less than 20%, was used as a second rule-out step. In addition, the results could also be combined when a peak value over the 99th percentile and a delta change of greater than 20% may have provided optimum rule-in performance. Combining the results of tests over 2 hours could also create a third category, in addition to the optimal rule-in and rule-out categories, which included people with either a peak value above the 99th percentile diagnostic threshold or a delta change of greater than 20% who needed further investigations to determine whether they were experiencing an acute MI. To construct the test pathway used in the economic modelling, the External Assessment Group assumed that the diagnostic performance of the second sample taken at 2 hours was the same for people in whom NSTEMI was not ruled out by the presentation sample reported at the limit of blank, as for the initial population presenting to the emergency department.
- 5.15 When the External Assessment Group applied this test pathway to a hypothetical cohort of 1000 people presenting with a suspected non-ST-segment elevation acute coronary syndrome, with an estimated prevalence of NSTEMI of 17%, the first step of the strategy could result in the discharge of 407 (40.7%) people, 9 (0.9%) of whom would have been discharged in error. The second stage of the strategy could lead to the discharge of a further 286 (28.6%) people, 5 (0.5%) of whom would have been discharged in error. The External Assessment Group also applied the hypothetical cohort to the Elecsys Troponin T high-sensitive 99th percentile presentation sample test strategy, and the number of people potentially discharged in error was 20 (2%).

Diagnostic accuracy of the ARCHITECT STAT High Sensitive Troponin-I assay

- 5.16 Of the 4 diagnostic cohort studies reporting data on the ARCHITECT STAT High Sensitive Troponin-I assay, 3 assessed the accuracy of the assay for the detection of acute MI. All 3 studies were conducted in a mixed population (any acute MI), and did not exclude people with STEMI.

Presentation samples

- 5.17 All 3 studies reporting accuracy of the ARCHITECT STAT High Sensitive Troponin-I assay for the detection of acute MI reported data for single samples taken at presentation. Summary estimates based on the 99th percentile as the diagnostic threshold were sensitivity 80% (95% CI 77% to 83%), specificity 93% (95% CI 92% to 94%), LR+ 11.47 (95% CI 9.04 to 16.19) and LR- 0.22 (95% CI 0.16 to 0.27).
- 5.18 One study also reported the accuracy of the ARCHITECT STAT High Sensitive Troponin-I assay based on the limit of detection as the diagnostic threshold. The results were sensitivity 100% (95% CI 98% to 100%), specificity 35% (95% CI 32% to 38%), LR+ 1.54 (95% CI 1.47 to 1.62) and LR- 0.01 (95% CI 0.00 to 0.08).

Subsequent samples

- 5.19 Of the 3 studies reporting accuracy of the of the ARCHITECT STAT High Sensitive Troponin-I assay for the detection of acute MI, 1 reported data on samples taken 3 hours after presentation. The study reported accuracy based on the 99th percentile as the diagnostic threshold; the results were sensitivity 98% (95% CI 96% to 99%), specificity 90% (95% CI 88% to 92%), LR+ 10.16 (95% CI 8.38 to 12.31), LR- 0.02 (95% CI 0.01 to 0.08).

Multiple samples

- 5.20 Of the 3 studies reporting accuracy of the ARCHITECT STAT High Sensitive Troponin-I assay for the detection of acute MI, 2 reported data on the performance of diagnostic strategies involving multiple samples. One study reported the accuracy of a sample taken at presentation and at 2 to 3 hours with a peak troponin I value over the 99th percentile. The second study reported the

accuracy of a sample taken on admission with the limit of detection as the threshold and a delta change of 20% at 3 hours, and the accuracy of a sample taken on presentation, and at 3 hours, with a delta change of 20%. The results of these studies suggested that the sensitivity and specificity of multiple sampling strategies could range from 77% to 91% and from 26% to 93% respectively, depending on the timing of sampling and the diagnostic threshold applied.

ARCHITECT STAT High Sensitive Troponin-I assay test pathways

- 5.21 The External Assessment Group constructed an optimal test pathway for multiple sampling on which the cost-effectiveness modelling was based. This test pathway was derived from the results of the External Assessment Group's clinical-effectiveness review, and included estimates taken from studies reporting diagnostic accuracy in a mixed population. For the ARCHITECT STAT High Sensitive Troponin-I assay this test pathway comprised a presentation sample with the limit of detection as the diagnostic threshold as an initial rule-out step, followed by a second sample at 3 hours with the 99th percentile as the diagnostic threshold. To construct the test pathway used in the economic modelling the External Assessment Group assumed that the diagnostic performance of the second sample taken at 3 hours was the same for people in whom NSTEMI was not ruled out by the presentation sample reported at the limit of detection, as for the initial population presenting to the emergency department.
- 5.22 The External Assessment Group applied this test pathway to a hypothetical cohort of 1000 people presenting with a suspected non-ST-segment elevation acute coronary syndrome and an estimated prevalence of NSTEMI of 17%. The first step of the strategy could result in the discharge of 291 (29.1%) people, none of whom would have been discharged in error. The second stage of the strategy could lead to the discharge of a further 486 (48.6%) people, 3 (0.3%) of whom would have been discharged in error. This cohort was also applied to the ARCHITECT STAT High Sensitive Troponin-I 99th percentile presentation test strategy and led to 34 (3.4%) people potentially being discharged in error.

Diagnostic accuracy of the AccuTnl+3 troponin I assay

- 5.23 Both of the diagnostic cohort studies reporting data on the prototype Access high-sensitivity troponin I assay assessed the accuracy of the assay for the

detection of acute MI. Both studies were conducted in a mixed population (any acute MI), and did not exclude people with STEMI. It should be noted that each of these studies report the performance of a prototype assay, with test characteristics that differ from those provided by the manufacturer for the AccuTnI+3 assay. These data were included by the External Assessment Group in their report because this prototype assay was developed by Beckman Coulter and the assay's characteristics met the criteria used for defining high-sensitivity in the scope and, therefore, it may be considered relevant by the Committee.

Presentation samples

- 5.24 Both studies reporting the accuracy of the prototype Access high-sensitivity troponin I assay for the detection of acute MI reported data on single samples taken at presentation. One study reported the diagnostic accuracy of a sample taken on presentation using the 99th percentile as the diagnostic threshold (note that this was 9 nanograms/litre for the assay used in this study, described as an investigational prototype). The results of the study were sensitivity 92% (95% CI 88% to 95%), specificity 75% (95% CI 72% to 78%), LR+ 3.67 (95% CI 3.26 to 4.13) and LR- 0.11 (95% CI 0.07 to 0.17). When the results of this study were combined with the second study, which reported presentation samples at a diagnostic threshold of 18 nanograms/litre, the summary estimates of accuracy were sensitivity 92% (95% CI 88% to 95%), specificity 75% (95% CI 72% to 77%), LR+ 3.68 (95% CI 2.46 to 4.48) and LR- 0.11 (95% CI 0.07 to 0.16).

Subsequent samples

- 5.25 None of the studies reporting data on the prototype Access high-sensitivity troponin I assay provided information on subsequent samples.

Multiple samples

- 5.26 Of the 2 studies reporting accuracy for the detection of acute MI, 1 reported data on the diagnostic performance of a 27% or greater change in troponin I levels between presentation and 1 hour. The results were sensitivity 63% (95% CI 53% to 71%), specificity 66% (95% CI 63% to 69%), LR+ 1.85 (95% CI 1.55 to 2.21) and LR- 0.56 (95% CI 0.44 to 0.72).

AccuTnl+3 troponin I test pathways

5.27 For the AccuTnl+3 assay economic modelling, the External Assessment Group included a single test strategy which comprised a presentation sample using the prototype Access high-sensitivity troponin I assay with the 99th percentile (9 nanograms/litre) as the diagnostic threshold, and was based on a study that did not exclude people with STEMI. When this test pathway was applied to a hypothetical cohort of 1000 people presenting with a suspected non-ST-segment elevation acute coronary syndrome and an estimated prevalence of NSTEMI of 17%, the number of people with acute MI potentially discharged in error on the basis of a negative high-sensitivity troponin I result was 14 (1.4%). The External Assessment Group did not construct a test pathway with a second sample because of the limited data available on this assay.

Comparative accuracy of the high-sensitivity troponin assays

5.28 The External Assessment Group derived summary estimates from analyses with common time points and cut-off thresholds to compare the accuracy of the 3 high-sensitivity troponin assays. In addition, 1 study provided a direct comparison of all 3 assays in the same population. This study reported data on presentation samples using the 99th percentile as the diagnostic threshold. The study reported a sensitivity of 90% for the Elecsys Troponin T high-sensitive assay, 77% for the ARCHITECT STAT High Sensitive Troponin-I assay and 92% for the Access high-sensitivity troponin I assay. Corresponding values for specificity were 78%, 93% and 75% for each assay respectively. Summary estimates derived from the indirect analysis were similar.

Evidence on prognostic accuracy

Prognostic accuracy of the Elecsys Troponin T high-sensitive assay

5.29 Of the 15 diagnostic cohort studies reporting data on the Elecsys Troponin T high-sensitive assay, 1 assessed the accuracy of the assay for the prediction of major adverse cardiac events within 30 days of presentation. The final scope for this assessment defined major adverse cardiac events as death, non-fatal acute MI, revascularisation or hospitalisation for myocardial ischaemia. The study, which excluded people with STEMI, reported the prognostic accuracy of a presentation sample using the limit of blank (3 nanograms/litre) as the threshold. The study reported a sensitivity of 85% (95% CI 74% to 92%),

specificity 46% (95% CI 41% to 51%), LR+ 1.58 (95% CI 1.37 to 1.81) and LR- 0.33 (95% CI 0.18 to 0.59).

Prognostic accuracy of the ARCHITECT STAT High Sensitive Troponin-I assay

5.30 Of the 3 diagnostic cohort studies reporting data on the ARCHITECT STAT High Sensitive Troponin-I assay, 1 assessed the accuracy of the assay for the prediction of major adverse cardiac events within 30 days of presentation. The study, in a mixed population (any acute MI), reported the prognostic accuracy of a presentation sample using the 99th percentile as the threshold. The study reported a sensitivity of 88% (95% CI 85% to 91%), specificity 93% (95% CI 91% to 94%), LR+ 12.57 (95% CI 8.88 to 15.35) and LR- 0.13 (95% CI 0.06 to 0.28).

Prognostic accuracy of the AccuTnl+3 troponin I assay

5.31 Neither of the 2 diagnostic cohort studies reporting data on the prototype Access high-sensitivity troponin I assay assessed the accuracy of the assay for the prediction of major adverse cardiac events within 30 days of presentation.

Costs and cost effectiveness

5.32 The External Assessment Group conducted a systematic review to identify existing studies investigating the cost effectiveness of diagnostic strategies for acute coronary syndrome which incorporated high-sensitivity troponin testing. Studies reporting a full economic analysis relating to the cost-effectiveness of either high-sensitivity troponin or standard troponin testing, which included survival or quality-adjusted life years (QALYs) as an outcome measure were eligible for inclusion.

5.33 The External Assessment Group also constructed a de novo economic model designed to assess the cost effectiveness of the Elecsys Troponin T high-sensitive assay, the ARCHITECT STAT High Sensitive Troponin-I assay and the AccuTnl+3 troponin I assay used singly or in series up to 4 hours from the onset of chest pain or presentation to an emergency department.

Systematic review of cost effectiveness

- 5.34 The systematic review identified 5 studies, reported in 7 publications. The included studies evaluated a range of diagnostic strategies for acute MI, including the use of both high-sensitivity troponin and standard troponin testing. The diagnostic strategies included using high-sensitivity troponin testing alone, combining high-sensitivity troponin testing with heart-fatty acid binding protein, panels of cardiac biomarkers and point of care cardiac biomarker panel testing. The timing of tests varied both within and between the included studies.
- 5.35 The results of the studies included in the systematic review varied widely, and the External Assessment Group concluded that the review demonstrated uncertainty about the cost effectiveness of diagnostic strategies incorporating high-sensitivity troponin testing. The External Assessment Group 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.

Economic analysis

- 5.36 The External Assessment Group developed a de novo economic model designed to assess the cost effectiveness of 5 high-sensitivity troponin test strategies using 3 high-sensitivity assays: the Elecsys Troponin T high-sensitive assay, the ARCHITECT STAT High Sensitive Troponin-I assay and the AccuTnl+3 troponin I assay. The population included in the economic model was people presenting to the emergency department with a suspected non-ST-segment elevation acute coronary syndrome (with STEMI ruled out), who had no major comorbidities needing hospital admission, such as heart failure or arrhythmia. Expected costs, life years and QALYs were calculated for each of the diagnostic strategies included in the model; discount rates of 3.5% and a half-cycle correction were applied for both costs and effects.
- 5.37 The following high-sensitivity troponin test strategies were included in the model:
- Single test strategies

- Elecsys Troponin T high-sensitive assay presentation sample with the 99th percentile as the diagnostic threshold
 - ARCHITECT STAT High Sensitive Troponin-I assay presentation sample with the 99th percentile as the diagnostic threshold
 - AccuTnI+3 troponin I presentation sample (using data from the prototype Access high-sensitivity troponin I assay with the 99th percentile [9 nanograms/litre] as the diagnostic threshold).
- Sequential test strategies
 - Elecsys Troponin T high-sensitive assay optimal test strategy (see section 5.14)
 - ARCHITECT STAT High Sensitive Troponin-I assay optimal test strategy (see section 5.21)

Model structure

- 5.38 The model structure was based upon a previous cost-effectiveness model reported in [Goodacre et al. \(2013\)](#). The model was adapted to fit the scope of this assessment.
- 5.39 The model comprised a decision tree to model the short-term (30 days) outcomes after presentation and a long-term Markov model. The decision tree modelled the results of high-sensitivity troponin or standard troponin testing and the resulting treatment decision, be it hospital admission and acute MI treatment or discharge from the emergency department. The outcomes included in the short-term model were 'no acute coronary syndrome, no unstable angina', 'unstable angina', 'untreated non-fatal acute MI', 'treated non-fatal acute MI' and 'death'. The long-term outcomes, based on a 60-year lifetime time horizon, were estimated using a Markov cohort model with a 1-year cycle time. The following health states were included in the model: 'no acute coronary syndrome, no unstable angina', 'unstable angina', 'post-acute MI (treated and untreated)', 'post-acute MI with re-infarction' and 'death'. People entered the Markov model based on their short-term outcome from the decision tree; consequently, in the first cycle, the model made a distinction between treated and untreated acute MI.

Model inputs

- 5.40 The model was populated using data from the published literature including previous economic evaluations and literature retrieved to inform key parameters (such as acute MI prevalence), routine sources of cost data and, when necessary, through consultation with experts for unpublished data. The test accuracy estimates used in the model were derived from the External Assessment Group's clinical effectiveness review. The diagnostic strategies included in the model were selected based upon optimal diagnostic performance derived from the External Assessment Group's clinical effectiveness review and, when possible, data were restricted to studies that excluded people with STEMI. Estimates of test accuracy for the ARCHITECT STAT High Sensitive Troponin-I and prototype Access high-sensitivity troponin I assays were based on studies that did not exclude people with STEMI.

Costs

- 5.41 Data on costs and resource use associated with the diagnostic strategies were estimated using previous economic evaluations, routinely available data on resource use and event costs, information provided by manufacturers and, when necessary, input from experts. Estimates of test-specific resource use were informed by the results of the External Assessment Group's clinical effectiveness review. It was assumed that acute MI treatment may include aspirin, statins, and angiotensin-converting enzyme inhibitors with consideration of coronary revascularisation for people considered as being at high-risk of major adverse cardiac events. It was also assumed that starting acute MI treatment for people with NSTEMI would reduce the probability of major adverse cardiac events, including cardiac death and re-infarction. The model also assumed that the average cost of a troponin test (high-sensitivity or standard) to the NHS is £20 ([Goodacre et al, 2013](#)). This estimate includes the cost of the assay reagents, the cost of the analyser and maintenance, and costs associated with calibration and quality control.

Health-state utilities

- 5.42 Health-state utility scores were obtained from the published literature. Age-dependent utility scores, based on the UK general population, were calculated for people in the 'no acute coronary syndrome, no unstable angina' health state based on a linear regression model. The disutility for age was

estimated to be 0.004. To calculate utility scores for the 'post-MI' health states, age-dependent utility scores from the general population were combined with age-dependent disutilities for acute MI. Utility scores for the 'unstable angina' health state were then based upon the 'post-MI' utilities, with a utility increment of 0.010.

Base-case analysis

5.43 The assumptions applied in the base-case analysis included the following:

- The comparator, serial troponin testing over 10–12 hours, has perfect diagnostic accuracy (sensitivity 1.0 and specificity 1.0).
- For the Elecsys Troponin T high-sensitive assay and ARCHITECT STAT High Sensitive Troponin-I optimal testing strategies, the sensitivity and specificity for the subpopulation not discharged after the presentation test is equal to the sensitivity and specificity for the initial group presenting at the emergency department.
- The life expectancy, quality of life and costs for people with false-positive results (that is those who are positive by the high-sensitivity troponin test strategy but negative by standard troponin testing) is equal to the life expectancy, quality of life and costs of people with true-negative results (this assumption was amended in the secondary analysis).
- In contrast with acute MIs occurring in the decision tree period, all acute MIs occurring in the Markov trace are correctly diagnosed and subsequently treated.
- Unstable angina is always correctly diagnosed and subsequently treated.
- The re-infarction probability for the 'post-MI with re-infarction' health state is equal to the re-infarction probability for the 'post-MI' health state.
- The increased post-MI re-infarction and mortality probabilities for untreated acute MI were assumed to last 1 year; after 1 year a relative risk of 1.0 was applied (for untreated compared with treated acute MI).
- There is no additional benefit of starting treatment early, so treatment effect for high-sensitivity troponin testing strategies is equal to treatment effect for standard troponin testing strategies.

- All deaths within 30 days of presentation at the emergency department are caused by fatal acute MI events and receive the associated costs.
- Doctors are available on demand to make management decisions based on test results.
- A total delay of 3 hours is assumed, which includes a delay between the patient presenting and the blood sample being taken, and a second delay between the sample being taken and the results becoming available.
- No additional treatment costs are applied to people with unstable angina in year 1.

5.44 Probabilistic results were presented for the base case (based on 10,000 simulations) and were used to construct cost-effectiveness acceptability curves and cost-effectiveness acceptability frontiers.

Base-case results

5.45 The base-case analysis included 6 test strategies: 5 high-sensitivity troponin test strategies and the comparator, standard troponin testing over 10–12 hours. The results of the base-case analysis suggested that standard troponin testing was the most effective (15.101 life years, 11.730 QALYs) and most expensive (£2697) test strategy. In contrast, the ARCHITECT STAT High Sensitive Troponin-I 99th percentile presentation sample was the least effective (15.076 life years, 11.712 QALYs) and least expensive (£2,253). The incremental cost-effectiveness ratios (ICERs) for the high-sensitivity troponin test strategies ranged from £24,019 to £90,725 saved per QALY lost compared with standard troponin.

Base-case deterministic sensitivity analyses

5.46 The External Assessment Group also presented the results of a deterministic base-case analysis. In this analysis, the ICERs for the high-sensitivity troponin testing ranged from £28,870 to £124,391 saved per QALY lost. The External Assessment Group performed a number of one-way sensitivity analyses to assess the impact of both model assumptions and input parameters on the estimated ICERs. The External Assessment Group concluded that the results of the sensitivity analyses showed that, in general, there were no major changes to relative cost effectiveness. When it was assumed that the increased re-infarction and mortality risk for treated versus untreated acute MI lasted for a lifetime, rather than just the first year, all high-sensitivity troponin testing

strategies had ICERs under £30,000 saved per QALY lost when compared with standard troponin. In all analyses where the waiting time for a doctor on a general ward is added (1–3 hours), the test cost was increased to £40, or the acute MI treatment cost was assumed to be £4295, all high-sensitivity troponin testing strategies had ICERs over £30,000 saved per QALY lost when compared with standard troponin. The assumption which had the most noticeable impact on the ICERs was applying acute MI treatment costs to people who received a false positive test result.

5.47 The External Assessment Group noted that input parameters which had a noticeable impact on the ICERs were as follows:

- 30-day mortality for treated acute MI – ICERs for high-sensitivity troponin testing compared with standard troponin testing ranged from £41,819 to £182,781 saved per QALY lost when the 30-day mortality was assumed to be 0.120, and from £22,206 to £94,345 saved per QALY lost when the 30-day mortality was assumed to be 0.074.
- 30-day mortality for untreated acute MI – ICERs for high-sensitivity troponin testing compared with standard troponin testing ranged from £11,153 to £45,686 saved per QALY lost when mortality was assumed to be 0.240, and when mortality was assumed to be 0.000 all 5 high-sensitivity troponin test strategies dominated standard troponin (that is standard troponin is more expensive and less effective), although the External Assessment Group noted that a scenario where the 30-day mortality is worse for treated than for untreated acute MI is unlikely.
- Relative risk for mortality for treated versus untreated acute MI – ICERs for high-sensitivity troponin testing compared with standard troponin testing ranged from £11,771 to £48,054 saved per QALY lost when the relative risk was assumed to be 3.908, and from £128,875 to £570,869 saved per QALY lost when the relative risk was assumed to be 0.901.

Base-case subgroup analyses

5.48 The External Assessment Group performed the following subgroup analyses: sex (stratified by age), history of previous STEMI, and acute MI prevalence based on clinically relevant subgroups defined in the scope. With the exception of acute MI prevalence, the subgroups were defined on the basis that these characteristics may be associated with physiological differences in peak troponin levels. No data were found for ethnicity and people with renal disease.

The subgroup analysis for MI prevalence varied from 1% to 30% and included a no-testing strategy as a comparator to reflect the assumption that troponin testing may not be needed when clinical judgement determines that the pre-test probability of acute MI is low.

- 5.49 For women, the ICERs increase with age, and by age 75 years, ICERs for all the high-sensitivity troponin testing strategies compared with standard troponin testing were over £30,000 saved per QALY lost, with the ARCHITECT STAT High Sensitive Troponin-I 99th percentile presentation test strategy having the lowest ICER (£32,776). The same effect of age was seen for men. However, by age 55 years, ICERs for all the high-sensitivity troponin testing strategies compared with standard troponin testing were over £30,000 saved per QALY lost, with the ARCHITECT STAT High Sensitive Troponin-I 99th percentile presentation test strategy having the lowest ICER (£30,338). The External Assessment Group also conducted a subgroup analysis of acute MI prevalence which suggested that when acute MI prevalence is 1% (compared with 17% in the base-case analysis), the no-testing strategy had an ICER of £96,456 saved per QALY lost. These subgroup analyses were performed with non-subgroup-specific accuracy data, and on this basis it is likely that there is substantial uncertainty surrounding the cost effectiveness of the high-sensitivity troponin testing strategies in the reported subgroups.
- 5.50 Subgroup analyses were also undertaken based on test accuracy and acute MI prevalence derived from the External Assessment Group's clinical effectiveness review. The following subgroups were considered in these analyses: aged 70 years or under and aged over 70 years, people with and without pre-existing coronary artery disease and symptom onset less than 3 hours before presentation or more than 3 hours before presentation. These analyses could only be performed for the Elecsys Troponin T high-sensitive 99th percentile presentation strategy because of the availability of subgroup data in the clinical-effectiveness review. In all subgroups the Elecsys Troponin T high-sensitive assay was less costly and less effective than standard troponin testing, but greater cost savings were reported for people aged younger than 70 years, people with pre-existing coronary artery disease, and people presenting within 3 hours of symptom onset. The limited availability of subgroup specific accuracy data means that it is likely that there is substantial uncertainty surrounding the cost effectiveness of the high-sensitivity troponin testing strategies in the reported subgroups.

Secondary analysis

- 5.51 The External Assessment Group also conducted a secondary analysis, which adjusted the risk of re-infarction and mortality for people with a false-positive test result (that is, those with a positive high-sensitivity troponin test result but negative standard troponin test result). This assumption is based on data that suggest that people who have a false-positive high-sensitivity troponin test result have an increased risk of re-infarction and mortality compared with people with a true negative test result. The secondary analysis assumed that the prevalence of this higher-risk subgroup was equal to the lowest proportion of people with false-positive results for all high-sensitivity troponin test strategies. The higher-risk subgroup was assumed to be treated in all high-sensitivity troponin test strategies, accruing the same relative treatment benefit as people with a true positive test result, but remained untreated for the standard troponin test. The post-MI utility and health state costs were also applied to the higher-risk subgroup.
- 5.52 For the secondary analysis, probabilistic results based on 10,000 simulations were presented, and used to construct cost-effectiveness acceptability curves and cost-effectiveness acceptability frontiers.

Secondary analysis results

- 5.53 The secondary analysis included the same test strategies as those reported in the base-case analysis. The results of the secondary analysis suggested that standard troponin testing was the least effective (14.785 life years, 11.464 QALYs) and most expensive (£3058) test strategy, and was dominated by all 5 high-sensitivity troponin test strategies. The ARCHITECT STAT High Sensitive Troponin-I 99th percentile threshold presentation sample test strategy was the least effective of the 5 high-sensitivity troponin testing strategies (14.833 life years, 11.501 QALYs), but was the overall least expensive test strategy (£2781). The ARCHITECT STAT High Sensitive Troponin-I optimal test strategy was the most effective (14.855 life years, 11.518 QALYs) test strategy, and also the most expensive (£3018).

Secondary analysis deterministic sensitivity analyses

- 5.54 The External Assessment Group also conducted a deterministic secondary analysis. As with the probabilistic secondary analysis, all high-sensitivity

troponin test strategies dominated standard troponin testing. The External Assessment Group did a number of one-way sensitivity analyses to assess the impact of both model assumptions and input parameters on the estimated ICERs. In most sensitivity analyses, the 5 high-sensitivity troponin testing strategies dominated standard troponin testing. The External Assessment Group concluded that the results of the sensitivity analyses showed that, in general, there were no major changes to relative cost effectiveness.

- 5.55 When the waiting time to see a doctor was increased to 3 hours, the ARCHITECT STAT High Sensitive Troponin-I optimum strategy no longer dominated standard troponin, with an ICER of £390 per QALY gained compared with standard troponin testing. This assumption did not affect the dominance of the other high-sensitivity troponin test strategies. When acute MI treatment costs were added for people with false-positive results, the 2 ARCHITECT STAT High Sensitive Troponin-I test strategies dominated standard troponin testing, Elecsys Troponin T high-sensitive 99th percentile presentation strategy had an ICER of £2065 per QALY gained, the Elecsys Troponin T high-sensitive optimal strategy had an ICER of £6360 per QALY gained and the AccuTnI+3 troponin I 99th percentile presentation strategy had an ICER of £9142 per QALY gained compared with standard troponin testing.
- 5.56 The External Assessment Group noted that the following input parameters had a noticeable impact on the estimated cost effectiveness of the secondary analysis: increased test cost (£40 per test), 30-day mortality for both treated and untreated acute MI in the decision tree, and the relative risk of mortality for treated compared with untreated acute MI in the Markov trace, although high-sensitivity troponin testing did remain dominant compared with standard troponin testing in each of these sensitivity analyses.

Secondary analysis subgroup analyses

- 5.57 The subgroups included in the secondary analysis were the same as those included in the base-case subgroup analyses. In both the sex and age subgroup analyses, high-sensitivity troponin testing dominated standard troponin testing. However, the External Assessment Group noted that ICERs were slightly higher for men and appeared to increase with age. There did not appear to be a substantial difference in cost effectiveness between acute MI prevalence subgroups. However, at a 1% prevalence of acute MI, the ICER for the no-testing

strategy was £96,456 saved per QALY lost when compared with standard troponin testing. These subgroup analyses were done with non-subgroup specific accuracy data and, on this basis, it is likely that there is substantial uncertainty surrounding the cost effectiveness of the high-sensitivity troponin testing strategies in the reported subgroups.

- 5.58 Subgroup analyses were also done based on test accuracy and acute MI prevalence for the Elecsys Troponin T high-sensitive 99th percentile presentation strategy derived from the External Assessment Group's clinical-effectiveness review. The subgroups included in the secondary analysis were the same as those included in the corresponding base-case subgroup analyses. In all subgroups, the Elecsys Troponin T high-sensitive assay dominated standard troponin testing, but higher savings per QALY gained were reported for people aged 70 years or younger, people with pre-existing coronary artery disease, and people presenting within 3 hours of symptom onset. The limited availability of subgroup-specific accuracy data makes it likely that there is substantial uncertainty surrounding the cost effectiveness of the high-sensitivity troponin testing strategies in the reported subgroups.

6 Considerations

- 6.1 The Diagnostics Advisory Committee reviewed the evidence available on the clinical and cost effectiveness of the Elecsys Troponin T high-sensitive, ARCHITECT STAT High Sensitive Troponin-I and AccuTnI+3 troponin I assays for the early rule out or diagnosis of acute myocardial infarction (MI) in people presenting to emergency departments with a suspected acute coronary syndrome. The Committee noted that the cost-effectiveness analysis included both a base-case analysis, in which it was assumed that people with a false-positive high-sensitivity troponin test result had no treatment and have a risk of mortality and re-infarction equivalent to people with true negative results, and a secondary analysis, in which it was assumed that a proportion of people with a false-positive high-sensitivity troponin test result have an increased risk of mortality and adverse events and are treated accordingly.
- 6.2 The Committee considered the diagnostic accuracy data for each of the high-sensitivity troponin assays. It noted that 34 publications reported data for the Elecsys Troponin T high-sensitive assay, 5 reported data for the ARCHITECT STAT High Sensitive Troponin-I assay and 3 reported data for a test described as a prototype Access high-sensitivity troponin I assay, which was included because the reported assay characteristics met the definition of high-sensitivity specified in the scope for the assessment and the prototype assay was developed by Beckman Coulter. The Committee also considered data submitted to the FDA relating to the AccuTnI+3 assay which were provided in confidence by the manufacturer. The Committee considered that the 99th percentile value reported for the prototype assay (9 nanograms/litre) and the commercially available AccuTnI+3 assay (40 nanograms/litre) were substantially different and heard from both clinical specialists and the manufacturer that the prototype assay had not been commercialised. The Committee concluded that the data on the prototype assay could not be considered applicable to the AccuTnI+3 assay. Furthermore, the Committee considered that the data available for the AccuTnI+3 assay itself could not be considered sufficient to determine its diagnostic accuracy.
- 6.3 The Committee questioned the assumption that serial troponin testing over 10–12 hours with standard troponin assays has perfect accuracy: that is, 100% sensitivity and 100% specificity. The Committee heard from clinical specialists that there is likely to be uncertainty around the accuracy of the high-sensitivity

troponin assays in the clinical-effectiveness analysis. The Committee heard from clinical specialists that it is plausible that the high-sensitivity troponin assays may pick up additional people (classified as having false-positive results in the analysis) who need treatment compared with standard troponin assays, and consequently the accuracy of the high-sensitivity troponin assays may have been underestimated. The Committee concluded that there is uncertainty around the accuracy of the high-sensitivity troponin assays in the clinical-effectiveness analysis, but that it is likely that the Elecsys Troponin T high-sensitive and ARCHITECT STAT High Sensitive Troponin-I assay are sufficiently sensitive to allow the early rule out of acute MI in practice.

- 6.4 The Committee questioned the applicability of the 99th percentile cut-offs derived from healthy reference populations to populations seen in emergency departments in UK practice. The Committee heard from clinical specialists that there is a wide variability in the composition of reference populations included in validation studies, and that this can impact upon the interpretation of the 99th percentile in routine practice. The Committee discussed the alternative of using receiver-operator characteristic curve-derived cut-offs for the high-sensitivity troponin assays, but noted that the clinical utility of adopting such strategies is unknown and that the evidence base for this is rapidly developing. The Committee concluded that the instructions for use for each of the assays should be consulted for guidance on the assay specific 99th percentile cut-off values, and calibrating the high-sensitivity troponin assays in clinical practice.
- 6.5 The Committee considered the risk of a false-positive result in people who have a positive result with a high-sensitivity troponin assay. The Committee heard from a clinical specialist that treatment for acute MI is not without risk, and heard from a patient expert that incorrect diagnosis of acute MI can have a negative and long-lasting impact on various aspects of a person's quality of life, including ability to get insurance cover. The Committee heard from clinical specialists that raised troponin levels can be caused by conditions such as heart failure, chronic obstructive pulmonary disease, renal failure and skeletal muscle disease, in which there is no evidence of underlying ischaemic heart disease, and that this would be differentiated from acute coronary syndromes during subsequent clinical investigations. The Committee was advised by clinical specialists that this group of people were likely to have underlying health problems that would need hospital admission regardless of a diagnosis of non-ST-segment elevation myocardial infarction (NSTEMI) being confirmed.

However, the Committee noted that caution should be advised in interpreting the results of high-sensitivity troponin tests when they are used outside the suspected acute coronary syndrome clinical setting.

- 6.6 The Committee considered the impact of a positive troponin test result on clinical decision making and questioned whether it could rule-in a NSTEMI diagnosis. The Committee noted that there was limited evidence on the use of high-sensitivity troponin assays to rule-in NSTEMI within 4 hours of arrival at an emergency department. The Committee concluded that there was insufficient evidence to support the routine use of the high-sensitivity troponin assays for early rule-in of NSTEMI and that people in whom NSTEMI could not be ruled-out within 4 hours should receive further clinical assessment to determine the cause of the suspected acute coronary syndrome.
- 6.7 The Committee noted that each of the modelled high-sensitivity troponin test strategies could result in people having a false-negative result, and being discharged incorrectly. In the modelling the proportion of people incorrectly discharged varied from 1.4% to 3.4% with the single test strategies, and from 0.3% to 1.4% with the sequential test strategies. The Committee heard from clinical specialists that current practice may result in around 2% of people with acute MI being incorrectly discharged and that people who have experienced a very small acute MI might not have elevated troponin levels. On this basis, the Committee considered that the introduction of 'early rule-out high-sensitivity troponin test protocols' was unlikely to result in an increased rate of incorrect discharges.
- 6.8 The Committee considered the applicability of studies included the External Assessment Group's analyses that were done in a mixed population; that is, they included people with any acute MI (both STEMI and NSTEMI). The Committee noted that data restricted to a NSTEMI population were only available for the Elecsys Troponin T high-sensitive assay, but noted that similar summary estimates were obtained in both the mixed population and the NSTEMI only population analyses, for the 99th percentile presentation test strategies (sensitivity 89% and 88% respectively, specificity 82% and 84%). The Committee concluded that the use of mixed population data for the ARCHITECT STAT High Sensitive Troponin-I and AccuTnI+3 analyses was unlikely to have a significant impact on results. The Committee also heard from a clinical specialist that the mixed population data, derived from studies where

people are most likely to have had a NSTEMI, could be considered applicable to current practice.

- 6.9 The Committee deliberated about the use and clinical applicability of the 99th percentile presentation and optimal test strategies that were modelled by the External Assessment Group. The Committee noted that the 99th percentile presentation tests strategies were cost effective in both the base-case and the secondary analysis but questioned the clinical effectiveness of the strategies. The Committee concluded that, on balance, the sensitivity of the modelled Elecsys Troponin T high-sensitive and ARCHITECT STAT High Sensitive Troponin-I 99th percentile presentation strategies (88% and 80%) was insufficient to recommend single test strategies for early rule out. The Committee further considered that the sequential test strategies, which included a sample taken at presentation with a repeat sample at 3 hours, showed merit as early rule-out test strategies, and agreed that the inclusion of a second sample improved the sensitivity of the strategies sufficiently to recommend the use of two-step early rule-out test strategies in clinical practice. The Committee concluded that although the results of the External Assessment Group's modelling supported both the clinical and cost effectiveness of two-step early rule-out test strategies, there was insufficient evidence to recommend a specific test strategy and agreed that 'early rule-out protocols' should be chosen according to local preference.
- 6.10 The Committee considered that the implementation of two-step early rule-out strategies would allow the use of delta values to improve the specificity through consideration of the change in high-sensitivity troponin levels at each step. However, the Committee acknowledged that the use of absolute delta values in the context of early rule-out was not widely understood and had not been considered in the economic modelling. The Committee concluded that the decision to include delta values in 'early rule-out protocols' should be made at a local level in conjunction with clinical and laboratory specialists.
- 6.11 The Committee discussed the use of the limit of blank and limit of detection in the high-sensitivity troponin optimal test strategies that were modelled by the External Assessment Group. The Committee heard from both clinical specialists and manufacturers that the precision of an assay is generally lower at the lower end of the assay's measuring range, and that consequently cut-offs employing the limit of blank or limit of detection may be less reproducible in practice. The

Committee considered that because of lower precision and reproducibility, the quality assurance of assays using the limit of blank and limit of detection could be problematic, and would need the development of additional quality-control materials for use in external quality assurance schemes. The Committee also heard from clinical specialists that the limit of blank and limit of detection may become increasingly lower as assays develop, which would have an impact on the use of these thresholds to rule out acute MI. The Committee concluded that, on balance, 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 are currently uncertain.

- 6.12 The Committee considered the cost-effectiveness analyses carried out by the External Assessment Group. The Committee noted that, based on the level of clinical evidence available, the Elecsys Troponin T high-sensitive assay and ARCHITECT STAT High Sensitive Troponin-I assay were cost effective in both the base-case and the secondary analysis, but the cost-effectiveness analysis for the AccuTnI+3 assay was not robust. After consideration of the assumptions applied in each analysis, 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. The Committee also noted that the true effect of clinical judgement on the interpretation of the high-sensitivity troponin test results was not fully captured in the model. It heard from clinical specialists that, in practice, a clinical assessment of a person's prior probability of acute MI (that is, whether they are at a low or high risk) is likely to influence the interpretation of high-sensitivity troponin test results and determine the diagnosis and management recommendations. The Committee concluded that, in routine practice, clinical judgement is likely to reduce the impact of both false-positive and false-negative results.
- 6.13 The Committee considered the subgroup analyses and concluded that there is insufficient evidence to make specific recommendations on the use of the high-sensitivity troponin tests in any subgroups. The Committee heard from clinical specialists that there is a developing body of evidence that suggests the 99th percentile cut-off values of high-sensitivity troponin assays may vary between men and women, which clinicians may need to take into account when interpreting the results of high-sensitivity troponin tests. The Committee also

considered the External Assessment Group's subgroup analyses of acute MI prevalence and noted that when the acute MI prevalence was reduced to 1%, in both the base-case and the secondary analysis, the no-testing strategy had an incremental cost-effectiveness ratio (ICER) of £96,456 saved per QALY lost compared with standard troponin testing. The Committee heard from clinical specialists that inappropriate use of troponin tests in people with acute chest pain and a very low pre-test probability of acute MI is a significant problem in emergency departments. The Committee concluded that clinicians should assess pre-test probability of acute MI to determine whether troponin testing is clinically appropriate.

- 6.14 The Committee considered the logistical barriers to achieving early rule out of acute MI and discharge of patients in routine clinical practice. The Committee considered that the External Assessment Group's base-case and secondary analysis allowed for a 3-hour delay between presentation and test results being available. The Committee heard from clinical specialists that the implementation of 'early rule-out protocols' would need consideration of laboratory turn-around times, for reporting the results of high-sensitivity troponin tests. An early rule-out protocol would also depend on the availability of clinicians within an emergency department to agree patient management options. The Committee concluded that the implementation of protocols that allow earlier rule out of acute MI and consequent earlier discharges should be encouraged.

7 Recommendations for further research

- 7.1 The Committee recommended that robust evidence be generated to show the clinical effectiveness of the AccuTnI+3 assay for the early rule out of non-ST-segment elevation myocardial infarction (NSTEMI) in people presenting to an emergency department with acute chest pain. Where possible the accuracy of the AccuTnI+3 assay and its resulting clinical outcomes should be compared with both high-sensitivity troponin assays recommended in [section 1.1](#) and standard troponin assays.
- 7.2 The Committee recommended the collection of further outcome data through clinical audit in centres adopting 'early rule-out protocols' with high-sensitivity troponin testing (see recommendation 1.4). The data collected through audit should be sufficient to allow analysis of the optimal timing of samples taken after presentation to an emergency department and the optimal high-sensitivity troponin test cut-offs for both ruling out and ruling in NSTEMI.
- 7.3 The Committee recommended further research comparing the clinical effectiveness of different early rule-out test protocols using high-sensitivity assays which meet the criteria applied for this assessment. The Committee recommended that future studies should include consideration of the clinical effectiveness of different test strategies including those employing low diagnostic thresholds, and the impact of different test strategies on both clinician behaviour and the health system, with a view to reducing uncertainty in the economic model. Future studies should also investigate the role of sex and age-specific 99th percentile thresholds in the assessment of suspected acute coronary syndrome. The Committee also considered that it would be appropriate to include adjudication with high-sensitivity troponin assays at time points earlier than 10–12 hours as the reference standard in future studies.
- 7.4 The Committee recommended further research to understand the underlying biological causes and the clinical implications of chronically elevated troponin levels in older people, and people with conditions known to cause troponin elevation in the absence of ischaemia.

8 Implementation

NICE intends to develop tools, in association with relevant stakeholders, to help organisations put this guidance into practice.

Laboratories using high-sensitivity troponin assays should be able to show compliance with an accredited external quality assurance scheme. The use of the early rule-out protocols recommended in [section 1](#) are conditional on laboratories meeting agreed turnaround times for high-sensitivity troponin tests and clinicians being available so that a management decision can be made within the 4-hour target for emergency departments.

9 Related NICE guidance

Published

- [Myocardial infarction – secondary prevention](#). NICE clinical guideline 172 (2013).
- [Myocardial infarction with ST-segment elevation](#). NICE clinical guideline 167 (2013).
- [BRAHMS copeptin assay to rule out myocardial infarction in patients with acute chest pain](#). Medical technologies guidance 4 (2011).
- [Unstable angina and NSTEMI](#). NICE clinical guideline 94 (2010).
- [Chest pain of recent onset](#). NICE clinical guideline 95 (2009).

Under development

NICE is developing the following guidance (details available from [the NICE website](#)):

- Acute coronary syndromes (including myocardial infarction). NICE quality standard. Publication expected September 2014.

10 Review

NICE updates the literature search at least every 3 years to ensure that relevant new evidence is identified. NICE will contact product sponsors and other stakeholders about issues that may affect the value of the diagnostic technology. NICE may review and update the guidance at any time if significant new evidence becomes available.

Andrew Dillon
Chief Executive
October 2014

11 Diagnostics Advisory Committee members and NICE project team

Diagnostics Advisory Committee

The Diagnostics Advisory Committee is an independent committee consisting of 22 standing members and additional specialist members. A list of the Committee members who participated in this assessment appears below.

Standing Committee members

Professor Ron Akehurst

Professor in Health Economics, School of Health and Related Research (SCHARR), University of Sheffield

Dr Paul Collinson

Consultant Chemical Pathologist & Professor of Cardiovascular Biomarkers, St George's Hospital

Dr Sue Crawford

General Practitioner (GP) Principal, Chillington Health Centre

Professor Ian A Cree

Senior Clinical Advisor, NIHR Evaluation Trials and Studies Coordinating Centre, University of Southampton

Professor Erika Denton

National Clinical Director for Diagnostics, NHS England, Honorary Professor of Radiology, University of East Anglia and Norfolk and Norwich University Hospital

Dr Steve Edwards

Head of Health Technology Assessment, BMJ Evidence Centre

Mr David Evans

Lay member

Dr Simon Fleming

Consultant in Clinical Biochemistry and Metabolic Medicine, Royal Cornwall Hospital

Professor Chris Hyde

Professor of Public Health and Clinical Epidemiology, Peninsula Technology Assessment Group (PenTAG)

Dr Mark Kroese

Vice Chair, Diagnostics Advisory Committee and Consultant in Public Health Medicine, PHG Foundation, Cambridge and UK Genetic Testing Network

Mr Matthew Lowry

Director of Finance and Infrastructure, Doncaster and Bassetlaw Hospitals NHS Foundation Trust

Dr Michael Messenger

Deputy Director and Scientific Manager NIHR Diagnostic Evidence Co-operative, Leeds

Dr Peter Naylor

General Practitioner (GP), Chair Wirral Health Commissioning Consortia

Dr Dermot Neely

Consultant in Clinical Biochemistry and Metabolic Medicine, Newcastle upon Tyne Hospitals NHS Foundation Trust

Professor Adrian Newland

Chair, Diagnostics Advisory Committee

Dr Richard Nicholas

Consultant Neurologist; Honorary Senior Lecturer, Heatherwood and Wexham Park Hospitals

Dr Gail Norbury

Consultant Clinical Scientist, Guys Hospital

Dr Diego Ossa

Director of Market Access Europe, Novartis Molecular Diagnostics

Dr Steve Thomas

Consultant Vascular and Cardiac Radiologist at Sheffield Teaching Hospitals Foundation Trust

Mr Paul Weinberger

CEO, DiaSolve Ltd, London

Specialist Committee members

Dr Rick Body

Consultant in Emergency Medicine and Honorary Lecturer in Cardiovascular Medicine, University of Manchester

Dr Nicholas Mills

Reader and Consultant Cardiologist, University of Edinburgh

Professor Steve Goodacre

Professor of Emergency Medicine, University of Sheffield

Professor Adam Timmis

Professor of Clinical Cardiology, Queen Mary University of London

Mr Alan Reid

UKNEQAS Cardiac Biomarkers Scheme Organiser and Principal Clinical Scientist, Southern General Hospital, Glasgow

Mr Thomas James

Advanced Nurse Practitioner, Wirral University Teaching Hospital NHS Trust

Mrs Liz Clark

Lay member

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.

Rebecca Albrow

Topic Lead

Dr Sarah Byron

Technical Adviser

Robert Fernley

Project Manager

12 Sources of evidence considered by the Committee

The diagnostics assessment report was prepared by Kleijnen Systematic Reviews Ltd.

- Westwood ME, van Asselt ADI, Ramaekers BLT et al. (2014) High-sensitivity troponin assays for the early rule-out or diagnosis of acute myocardial infarction in people with acute chest pain.

Registered stakeholders

The following organisations accepted the invitation to participate in this assessment as registered stakeholders. They were invited to attend the scoping workshop and to comment on the diagnostics assessment report and the diagnostics consultation document.

Manufacturers of technologies included in the final scope:

- Abbott Diagnostics UK
- Beckman Coulter UK Ltd.
- Roche Diagnostics Ltd

Other commercial organisations:

- Alere Ltd
- Juniper Consulting Group
- Randox
- Siemens
- Singulex
- Thermo Fisher Scientific

Professional groups and patient/carers groups:

- Association for Clinical Biochemistry and Laboratory Medicine
- British Cardiovascular Intervention Society
- British Society for Cardiovascular Research

- Royal College of Nursing
- South Asian Health Foundation

Research groups:

None

Associated guideline groups:

None

Others:

- Department of Health
- Healthcare Improvement Scotland
- NHS England
- Welsh Government

About this guidance

NICE diagnostics technologies guidance is designed to help the NHS adopt efficient and cost-effective medical diagnostic technologies more rapidly and consistently.

The programme concentrates on pathological tests, imaging, endoscopy and physiological measurement, since these represent most of the investigations performed on patients. The types of products that might be included are medical diagnostic technologies that give greater independence to patients, and diagnostic devices or tests used to detect or monitor medical conditions. Diagnostic technologies may be used for various purposes: diagnosis, clinical monitoring, screening, treatment triage, assessing stages of disease progression, and risk stratification.

This guidance was developed using the NICE [diagnostic technologies guidance](#) process.

We have produced a [summary for patients and carers](#). Tools to help you put the guidance into practice and information about the evidence it is based on are also [available](#).

Your responsibility

This guidance represents the view of NICE, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

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ISBN: 978-1-4731-0776-2