Diagnostics Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Care Excellence – Protocol

Title of project

High sensitivity troponin assays for the early rule-out of acute myocardial infarction (AMI) in people with acute chest pain

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1 Plain English Summary

Heart disease is a leading cause of death in the UK, with myocardial infarction (MI) (heart attack) accounting for approximately 4% of all deaths recorded in 2018. Many people attend hospital with chest pain and suspected MI; chest pain has been reported as the most common cause of hospital admissions in the UK and 2017-2018 statistics showed that it accounted for approximately 5% of all emergency admissions. It is important to diagnose people who are suspected of having an MI as early as possible in order to ensure quick and effective treatment. However, only around 20% of emergency admissions for chest pain will actually have an MI and there are many other possible causes of chest pain (e.g. gastro-oesophageal disorders, muscle pain, anxiety, or stable ischaemic heart disease). Tests which can quickly tell which patients do not have MI could therefore avoid unnecessary hospital admissions and anxiety for many people.

Some types of MI can be easily and quickly diagnosed using an electrocardiogram (ECG). Others are not apparent on ECG and are currently diagnosed based on levels of certain proteins in the blood (cardiac biomarkers) such as troponins, which go up when heart muscle is damaged. However, because it takes time for levels to increase to amounts which can be measured, people who have not had an MI can sometimes have to stay in hospital for up to 12 hours after the first chest pain before this can be confirmed. Methods have been developed which can detect lower levels of troponins in the blood (high sensitivity troponin tests). The use of these methods may help to achieve earlier rule-out of MI.

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

2 Decision problem

2.1 Population

The primary indication for this assessment is the early rule-out of acute myocardial infarction (AMI) and consequent early discharge in people presenting with acute chest pain and suspected, but not confirmed, non-ST segment elevation myocardial infarction (NSTEMI).

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

Acute coronary syndrome usually presents as chest pain and chest pain has been reported as the most common cause of hospital admissions in the UK;[1] Hospital Episode Statistics (HES) for 2017-2018 show 226,393 emergency admissions for chest pain, accounting for approximately 5% of all emergency admissions.[2] However, many people presenting with acute chest pain will have non-cardiac underlying causes, such as gastro-oesophageal disorders, muscle pain, anxiety, or stable ischaemic heart disease. A 2003 study on the impact of cardiology guidelines on the diagnostic classification of people with ACS in the UK reported that the majority people admitted to hospital with chest pain have either no ischaemic heart disease or stable ischaemic heart disease.[3] Hospital Episode Statistics (HES) for 2017-2018 remain consistent with this observation, showing diagnoses of AMI in 45,163 emergency admissions and unstable angina in 13,056 admissions; this represents approximately 20% and 6% of emergency admissions with chest pain, respectively.[2] Accurate and prompt differentiation of ACS (in particular AMI), stable CAD and other causes of chest pain is therefore vital to ensure appropriate and timely intervention where required and to avoid unnecessary hospital admissions.

STEMI can usually be diagnosed on presentation by electrocardiogram, hence the main diagnostic challenge in the investigation of suspected ACS is the detection or rule-out of NSTEMI. Investigation of ACS can also involve identification of people

with unstable angina (CAD with worsening symptoms, but no evidence of myocardial necrosis).

Since the development of protein biomarkers of myocardial damage in the 1980s, the number of biomarker assays available has proliferated, cardiac specificity has increased, and the role of biomarkers in the diagnostic work-up of acute chest pain has expanded. The most recent Hospital Episode Statistics show that the number of Emergency Department attendances where the first recorded investigation was a cardiac biomarker has risen substantially from the 13,743 in 2010-2011 to 28,379 in 2011-2012,[4] recorded in our original report for DG15,[5] to 36,907 in 2017-2018.[6] Cardiac troponins I and T (cTnI and cTnT), together with cardiac troponin C, form the troponin-tropomyosin complex which is responsible for regulating cardiac muscle contraction. cTnI and cTnT are used clinically as markers of cardiomyocyte necrosis, indicative of AMI. Troponin assays are intended for use in conjunction with clinical history taking and electrocardiography (ECG) monitoring as, although specificity is high, troponins may also be elevated in many other conditions including myocarditis, congestive heart failure, severe infections, renal disease and chronic inflammatory conditions of the muscle or skin. Standard biochemical diagnosis of NSTEMI is based on elevation of the cardiac biomarker troponin above the 99th percentile of the reference range for the normal population.[7] However, the optimal sensitivity of standard troponin assays for MI occurs several hours after the onset of symptoms[8] and, historically, this has been reflected in clinical guidelines, which recommended standard cTnI or cTnT testing at initial hospital assessment and again 10-12 hours after the onset of symptoms.[9, 10] Since the majority of people presenting with chest pain do not have NSTEMI, where presentation is within a few hours of symptom onset, delayed biomarker measurement may result in unnecessary periods of extended observation or hospitalisation and associated costs. DG15 recommended the use of some high-sensitivity cardiac troponin (hs-cTn) assays (Elecsys Troponin T high-sensitive assay and ARCHITECT STAT High Sensitive Troponin-I assay) as options for the early rule-out of NSTEMI in people presenting to an emergency department with chest pain and suspected ACS.[11] This recommendation was incorporated in the 2016 update to the NICE clinical guideline, “Chest pain of recent onset: assessment and diagnosis,”(CG95).[12] High-sensitivity troponin assays are now also included in Scottish Intercollegiate Guidelines Network (SIGN 148) guidance on the management of ACS.[13] This updated assessment is being undertaken in order to ensure that guidance is based on current evidence (including new hs-cTn assays developed and marketed since the publication of DG15) and, where possible, to facilitate the provision of more detailed, evidence-based recommendations on how to use hs-cTn assays (e.g. timing of testing and use of tests in series).

2.2 Intervention technologies

High-sensitivity cTn (hs-cTn) assays are now available, which are able to detect lower levels of troponin in the blood. Current generations of commercially available assays have analytical sensitivities up to 100 times greater than was the case for early troponin assays (1 ng/L versus 100 ng/L).[14] Use of these high-sensitivity assays enable the detection of small changes in cTn levels, and may enable NSTEMI to be ruled out at an earlier time after the onset of acute chest pain. Use of the hs-cTn assays has the potential to facilitate earlier discharge for people with normal cTn levels. The recommended definition of an hs-cTn assay uses two criteria:[14, 15]

- The total imprecision, co-efficient of variation (CV), of the assay should be ≤10% at the 99th percentile value for the healthy reference population.
- The limit of detection (LoD) of the assay should be such as to allow measurable concentrations to be attainable for at least 50% (ideally >95%) of healthy individuals.

A number of high-sensitivity cTnI and cTnT (hs-cTnI and hs-cTnT) assays are currently available for use in the NHS in England and Wales. All but one, Quidel Cardiovascular, are designed for use in clinical laboratory settings; the Quidel Cardiovascular is designed for the near-patient setting, but can be used in the laboratory. Details of the assays to be evaluated in this review are provided below:

Troponin I assays

Access hsTnI assay (Beckman Coulter)

The Access hsTnI is designed for use in a laboratory setting with the Beckman Coulter Access 2 and DxI/DxC analysers. It is a paramagnetic particle chemiluminescent immunoassay, and is intended for the in-vitro quantitative determination of troponin I in serum and plasma samples. The turnaround time of the assay is 17 minutes. It has a recommended 99th percentile cut-off of 17.5 ng/L for the whole population, 11.6 ng/L for females and 19.8 ng/L for males. Each 99th percentile has a CV of less than 10%. The assay can detect troponin I in >97% of the reference population. The assay is CE marked and available to the NHS. The company states that the performance of the assay does not differ by analyser.

ARCHITECT high-sensitivity troponin I assay (Abbott Diagnostics)

The ARCHITECT high-sensitivity troponin I STAT assay 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 troponin I in serum and plasma samples. Results are available within 18 minutes. The ARCHITECT high-sensitivity troponin I STAT assay can detect troponin I in 96% of the reference population, and has a recommended 99th percentile cut-off of 26.2ng/L with a CV of 4%. Sex specific 99th percentile cut offs of 15.6 ng/L for females (CV of 5.3%) and 34.2 ng/L for males (CV of 3.5%) are also provided. The assay is CE marked and available to the NHS.

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

The Alinity i STAT High Sensitive Troponin-I assay is designed for use in a laboratory setting and can be used with the Alinity i analyser. It is a chemiluminescent microparticle immunoassay used for the quantitative determination of troponin I in plasma and serum samples. Results are available within 18 minutes. The Alinity i STAT High Sensitive Troponin-I assay has a recommended 99th percentile cut-off of 26.2 ng/L with a CV of 4.6%. Sex specific 99th percentile cut offs of 15.6 ng/L for females (CV of 5.0%) and 34.2 ng/L for males (CV of 4.5%) are also provided. The assay is CE marked and available to the NHS.

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

The ADVIA Centaur high-sensitivity troponin I assay is designed for use in a laboratory setting with the Siemens ADVIA Centaur XP and ADVIA Centaur XPT analysers. It is a magnetic latex particle chemiluminescent immunoassay, and is intended for the in-vitro quantitative determination of troponin I in serum and plasma samples. Test results are available in 18 minutes. It has a recommended 99th percentile cut-off of 47.34 ng/L for the whole population in lithium heparin and of 46.47 ng/l in serum. Sex specific 99th percentile cut offs of 36.99 ng/L for females and 57.27 ng/L for males in lithium heparin and 39.59 ng/L for females and 58.05 ng/L for males in serum are also provided. Each 99th percentile has a CV of less than 10%. The assay can detect troponin I in more than 50% of the reference population. The assay is CE marked and available to the NHS.

Atellica IM High-sensitivity troponin I assay (Siemens Healthineers)

The Atellica IM high-sensitivity troponin I assay is designed for use in a laboratory setting with the Siemens Atellica IM analyser. It is a magnetic latex particle chemiluminescent immunoassay, and is intended for the in-vitro quantitative determination of troponin I in serum and plasma samples. Test results are available in 10 minutes. It has a recommended 99th percentile cut-off of 45.2 ng/L for lithium heparin and 45.43 ng/L for serum. Sex specific 99th percentile cut offs of 34.11 ng/L for females and 53.48 ng/L for males in lithium heparin and 38.64 ng/L for females and 53.53 ng/L for males in serum are provided. Each 99th percentile has a CV of less

than 10%. The assay can detect troponin I in more than 50% of the reference population. The assay is CE marked and available to the NHS.

Dimension EXL High-sensitivity troponin I assay (Siemens Healthineers)

The Dimenson EXL high-sensitivity troponin I assay is designed for use in a laboratory setting with the Siemens Dimension EXL analyser. It is a magnetic latex particle chemiluminescent immunoassay, and is intended for the in-vitro quantitative determination of troponin I in serum and plasma samples. Test results are available in 18 minutes. It has a recommended 99th percentile cut-off of 60.4 ng/L for lithium heparin and 58.2 ng/L for serum. Sex-specific 99th percentile cut offs of 51.4 ng/L for females and 76.2 ng/L for males in lithium heparin and 47.8 ng/L for females and 71.8 ng/L for males in serum are provided. Each 99th percentile has a CV of less than 10%. The assay can detect troponin I in more than 50% of the reference population. The assay is CE marked and available to the NHS.

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

The Dimension Vista high-sensitivity troponin I assay is designed for use in a laboratory setting with the Siemens Dimension Vista analysers. It is a magnetic latex particle chemiluminescent immunoassay, and is intended for the in-vitro quantitative determination of troponin I in serum and plasma samples. Test results are available in 10 minutes. It has a recommended 99th percentile cut-off of 58.9 ng/L for lithium heparin and 57.9% for serum. Sex specific 99th percentile cut offs of 53.77 ng/L for females and 78.5 ng/L for males in lithium heparin and 51.1 ng/L for females and 74.9 ng/L for males in serum are provided. Each 99th percentile has a CV of less than 10%. The assay can detect troponin I in more than 50% of the reference population. The assay is CE marked and available to the NHS.

TriageTrue High Sensitivity Troponin I Test (Quidel Cardiovascular)

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

VITROS High Sensitivity Troponin I Assay (Ortho Clinical Diagnostics)

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

VIDAS High sensitive Troponin I assay (Biomérieux)

The VIDAS High sensitive Troponin I assay is designed for use in a laboratory setting on the following analysers: VIDAS, MINI VIDAS and VIDAS 3. It is intended for the in-vitro quantitative determination of troponin I in serum and plasma (lithium heparin) samples. Test results are available in 20 minutes. It has a recommended 99th percentile cut-off of 19 ng/L. Sex specific 99th percentile cut offs of 11 ng/L for females and 25 ng/L for males are provided. The assay is CE marked and available to the NHS.

Troponin T assays

The Elecsys troponin T high-sensitive assay (Roche)

The Elecsys troponin T high-sensitive assay and the Elecsys troponin T high-sensitive STAT assay are designed for use in a laboratory setting. The Elecsys troponin T high-sensitive assay (200 test pack) and Elecsys troponin T high-sensitive STAT assay (100 test pack) can be used on the Roche cobas e411, e 601, and e602 analysers. The company state that the performance characteristics are equivalent when used on these analysers. The assay can also be run on the cobas e801 analyser which is designed for very high throughput as both a standard and STAT assay. This requires the test to be purchased as a 300 test pack, the reagents are the same as the 100 and 200 test packs but the application on the cobas e801 analyser results in a lower limit of detection (see table 1) 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. Results are available within 18 minutes with the standard assay and within 9 minutes if the STAT assay is used. The Elecsys assays can detect troponin T in 57% of the reference population and have a recommended 99th percentile cut-off of 14 ng/L with a CV of less than 10%. Sex specific 99th percentile cut offs of 9 ng/L for females and 16.8 ng/L for males are also provided. The assays are CE marked and available to the NHS.

A summary of the product properties of hs-cTnI and hs-cTnT assays available as single tests or cardiac biomarker panels in the NHS in England and Wales is provided in Table 1.

This assessment will consider hs-cTn assays used singly or in series, up to three hours after the onset of chest pain or up to three hours after presentation (as reported); for serial troponin measurements, both data on relative and absolute change in troponin levels and peak troponin will be considered (as reported).

Table 1: Summary of key high-sensitivity troponin I and troponin T assay characteristics

Manufacturer	System and compatible analysers	Assay	99th percentile (ng/L)	CV at 99th percentile	% of reference population cTn detected in	Turn-around time	LoD	LOQ
Abbott Diagnostics	ARCHITECT i1000sr and i2000sr	ARCHITECT HsTnI	Overall: 26.2 ng/L Female: 15.6 ng/L Male: 34.2 ng/L	Overall: 4.0% Female: 5.3% Male: 3.5%	96% (Apple et al. 2012)	18 minutes	1.9 ng/L	4.7 ng/L (10% CV); 1.3 ng/L (20% CV)
Abbott Diagnostics	Alinity i	Alinity hsTnI	Overall: 26.2 ng/L Female: 15.6 ng/L Male: 34.2 ng/L	Overall: 4.6% Female: 5.0% Male: 4.5%	96% (Apple et al. 2012)	18 minutes	1.6 ng/L	3.7 ng/L (10% CV); 2.1 ng/L (20% CV)
Beckman Coulter	Access 2, DxI 600/ 800, DxC 600i/880i /860i/680i/660i	Access hsTnI	Overall: 17.5 ng/L Female: 11.6 ng/L Male: 19.8 ng/L	Overall: 3.7% Female: 4.2% Male: 3.6%	97.1% to >99%	17 minutes	2.3 ng/L	2.3ng/L
Roche	200 test pack: cobas e411, e601, e602 300 test pack cobas: e801	Elecsys TnT-hs	Overall: 14 ng/L Female: 9 ng/L Male: 16.8 ng/L	<10%	57%	18 minutes	5 ng/L (3ng/L on Cobas e801)	13 ng/L
Roche	100 test pack: cobas e411, e601, e602, 300 test pack: cobas e801	Elecsys TnT-hs STAT	Overall: 14 ng/L Female: 9 ng/L Male: 16.8 ng/L	<10%	57%	9 minutes	5ng/L (3ng/L on Cobas e801)	13 ng/L
Siemens Healthineers	Atellica	Atellica IM High-sensitivity troponin I	Lithium heparin: Overall: 45.2 ng/L Female: 34.11 ng/L Male: 53.48 ng/L Serum:	<4%	75%	10 minutes to first result	1.6 ng/L	2.5 ng/L

Manufacturer	System and compatible analysers	Assay	99th percentile (ng/L)	CV at 99th percentile	% of reference population cTn detected in	Turn-around time	LoD	LOQ
			Overall: 45.43 ng/L Female: 38.64 ng/L Male: 53.53 ng/L					
Siemens Healthineers	Dimension EXL	Dimension EXL High-sensitivity troponin I	Lithium heparin: Overall: 60.4 ng/L Female: 51.4 ng/L Male: 76.2 ng/L	<5%	>50%	10 minutes to first result	2.7 ng/L	4.0 ng/L
			Serum: Overall: 58.2 ng/L Female: 47.8 ng/L Male: 71.8 ng/L					
Siemens Healthineers	Dimension Vista	Dimension Vista high-sensitivity troponin I	Lithium heparin: Overall: 58.9 ng/L Female: 53.7 ng/L Male: 78.5 ng/L	<5%	>50%	10 minutes to first result	2.0 ng/L	3.0 ng/L
			Serum: Overall: 57.9 ng/L Female: 51.1 ng/L Male: 74.9 ng/L					
Siemens Healthineers	ADVIA Centaur XP and ADVIA Centaur XPT	ADVIA Centaur high-sensitivity troponin I	Lithium heparin: Overall: 47.34 ng/L Female: 36.99 ng/L Male: 57.27 ng/L	<4.9%	63%	18 minutes to first result	1.6 ng/L	2.5 ng/L

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2.3 Care pathway

Diagnostic assessment

The assessment of patients with suspected ACS is described in NICE clinical guideline 95 (CG95) "Chest pain of recent onset: assessment and diagnosis" has been updated since the publication of DG15[16] to include recommendations on the use of high sensitivity troponin assays.[12] The guideline specifies that initial assessment should include a resting 12-lead ECG along with a clinical history, a physical examination and biochemical marker analysis. For people in whom a regional ST-segment elevation or presumed new left branch bundle block is seen on ECG, management should follow NICE clinical guideline 167 (CG167) "The acute management of myocardial infarction with ST-segment elevation."[17] People without persistent ST-elevation changes on ECG, i.e. with suspected non-ST-segment-elevation ACS (NSTE-ACS), should receive further investigation using cardiac biomarkers with the aim of distinguishing NSTEMI from unstable angina. NICE CG95 makes the following recommendations on the use of cardiac biomarkers:[12]

- Do not use high-sensitivity troponin tests for people in whom ACS is not suspected.
- For people at high or moderate risk of MI (as indicated by a validated tool), perform high-sensitivity troponin tests as recommended in the NICE diagnostics guidance on myocardial infarction (DG15).
- For people at low risk of MI (as indicated by a validated tool):
    - perform a second high-sensitivity troponin test as recommended in the NICE diagnostics guidance on myocardial infarction (DG15) if the first troponin test at presentation is positive.
- consider performing a single high-sensitivity troponin test only at presentation to rule out NSTEMI if the first troponin test is below the lower limit of detection (negative).
- Ensure that patients understand that a detectable troponin on the first high-sensitivity test does not necessarily indicate that they have had an MI. Do not use biochemical markers such as natriuretic peptides and high-sensitivity C-reactive protein to diagnose an ACS.
- Do not use biochemical markers of myocardial ischaemia (such as ischaemia-modified albumin) as opposed to markers of necrosis when assessing people with acute chest pain.
- When interpreting high-sensitivity troponin measurements, take into account:

- the clinical presentation
- the time from onset of symptoms
- the resting 12-lead ECG findings
- the pre-test probability of NSTEMI
- the length of time since the suspected ACS
- the probability of chronically elevated troponin levels in some people
- that 99th percentile thresholds for troponin I and T may differ between sexes.

CG95 recommends that a diagnosis of NSTEMI should be made using the universal definition of myocardial infarction, which states that AMI is defined as "The detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99th percentile upper reference limit and with at least one of the following: symptoms of ischaemia, new or presumed new significant ST-segment-T wave changes or new left branch bundle block, development of pathological Q waves in the ECG, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, or identification of an intracoronary thrombus by angiography or autopsy." [18]

The Scottish Intercollegiate Guidelines Network guideline 148 (SIGN 148), "Acute coronary syndrome," provides that the following recommendations in relation to cardiac troponins:[13]

- In patients with suspected acute coronary syndrome, serum troponin concentration should be measured at presentation to guide appropriate management and treatment.
- Serum troponin concentration should be measured 12 hours from the onset of symptoms to establish a diagnosis of myocardial infarction.
- In patients with suspected acute coronary syndrome, measurement of cardiac troponin at presentation and at three hours after presentation with a high-sensitivity assay should be considered as an alternative to serial measurement over 10–12 hours with a standard troponin assay to rule out myocardial infarction.
- Sex-specific thresholds of cardiac troponin should be used for the diagnosis of myocardial infarction in men and women.

Guidelines from the European Society of Cardiology, on the management of ACS in patients presenting without persistent ST-segment elevation, recommend "measurement of cardiac

troponins with sensitive or high-sensitivity assays to obtain results within 60 minutes." The guideline also describes 0/1 hour and 0/3 hour rule out algorithms, which incorporate both high-sensitivity troponin assays and clinical risk scores. For the 0/1 hour algorithm, additional troponin testing, after 3-6 hours, is recommended if the first two measurements are inconclusive and the clinical condition is still suggestive of ACS.[19]

Guidelines from the American College of Cardiology/American Heart Association (ACC/AHA), on the management of patients with non-ST-elevation ACS, do not include any specific recommendations about the use of high-sensitivity troponin assays.[20] However, the guideline does state that: "The TIMI risk index is useful in predicting 30-day and 1-year mortality in patients with NSTE-ACS. For patients with a TIMI risk score of 0 and normal high-sensitivity cardiac troponin 2 hours after presentation, accelerated diagnostic protocols have been developed that predict a very low rate of 30-day MACE."[20]

The 2017 publication "Asia-Pacific consensus statement on the optimal use of high-sensitivity troponin assays in acute coronary syndromes diagnosis: focus on hs-TnI" makes 9 recommendations:[21]

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

The rapidly expanding evidence base on high-sensitivity cardiac troponins, together with their increasing uptake and inclusion in clinical guidelines, means that an up-date to NICE

diagnostics guidance on early rule out of acute myocardial infarction using high-sensitivity troponin tests (DG15), published in October 2014,[16] is now considered necessary.

3 Objectives

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

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

- What is the diagnostic performance of hs-cTn assays (used singly or in series) for the early rule-out of NSTEMI in adults with acute chest pain? Is there evidence to recommended the use of specific early rule-out testing protocols within one and within three hours.

- Should different cut-offs be used for subgroups defined by:
    - Sex
    - People with chronically elevated troponin levels (e.g older people and those with renal disease)
    - People with low and high pre-test probabilities for NSTEMI (e.g. based on time since symptom onset and history of previous MI)
- Can the limit of detection of the assay be used as a threshold in an early rule-out testing protocol?

- What is the cost-effectiveness of using hs-cTn assays (used singly or in series, such that results are available within 3 hours of presentation) compared with the current standard of serial troponin T and/or I testing on admission and at 10-12 hours post-admission?

4 Methods for assessing clinical effectiveness

Systematic review methods will follow the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care,[22] NICE Diagnostics

Assessment Programme manual[23] and the Cochrane Handbook for Diagnostic Test Accuracy Reviews.[24] All data for studies included in the original Diagnostic Assessment Report (DAR),[5] conducted to support the development of DG15,[16] will be taken directly from that report.

4.1 Inclusion and exclusion criteria

Separate inclusion criteria were developed for each of the clinical effectiveness questions. These are summarised in Table 2.

Table 2: Inclusion criteria

Question	**What is the diagnostic preformance of hs-cTn assays (used singly or in series, such that results are available within 3 hours of presentation) for the early rule-out of NSTEMI in adults with acute chest pain?**	**What is the effectiveness of hs-cTn assays (used singly or in series) compared with conventional diagnostic assessment, for achieving successful early discharge of adults with acute chest pain within 4 hours of presentation?**
Participants:	Adults (≥18 yrs) presenting with acute 'pain, discomfort or pressure in the chest, epigastrium, neck, jaw, or upper limb without an apparent non-cardiac source'[20] due to a suspected, but not proven, AMI	
Setting:	Secondary or tertiary care	
Interventions (index test):	Any hs-cTnT or hs-cTnI test*, listed in Table 1 , hs-cTn assays (used singly or in series**, such that results are available within 3 hours of presentation)	
Comparators:	Any other hs-cTn test or testing sequence, as specified above, or no comparator	Troponin T or I measurement on presentation and 10-12 hours after the onset of symptoms
Reference standard:	Third universal definition of AMI,[18] including measurement of troponin T or I (using any method) on presentation and 3-6 hours later **or** occurrence of MACE (any definition used in identified studies) during 30 day follow-up	Not applicable
Outcomes$:	Test accuracy (the numbers of true positive, false negative, false positive and true negative test results)	Early discharge (≤4 hrs after initial presentation) without MACE during follow-up, incidence of MACE during follow-up, re-attendance at or re-admission to hospital during follow-up, time to discharge, patient anxiety, patient satisfaction or health-related quality of life (HRQoL) measures
Study design:	Diagnostic cohort studies	RCTs (CCTs will be considered if no RCTs are identified)

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

** For serial troponin assays, both data on relative or absolute change in troponin levels and peak troponin values will be considered

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

4.2 Search strategy

Search strategies utilised in the original report [5] will be updated with any new interventions identified in the NICE Scope. Search strategies will be based on intervention (high-sensitivity troponin assays) and target condition, as recommended in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care[22] and the Cochrane Handbook for Diagnostic Test Accuracy Reviews.[24] Additional supplementary searches will be carried out as necessary.

Search strategies will be developed specifically for each database and the keywords associated with high sensitivity troponin T/I will be adapted according to the configuration of each database.

The following databases will be searched for relevant studies from 2013 to the present:

- MEDLINE (Ovid)
- MEDLINE In-Process Citations, Daily Update and Epub Ahead of Print (Ovid)
- EMBASE (Ovid)
- Cochrane Database of Systematic Reviews (CDSR) (Wiley)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley)
- Database of Abstracts of Reviews of Effects (DARE) (CRD)
- Health Technology Assessment Database (HTA) (CRD)
- Science Citation Index (SCI) (Web of Science)
- LILACS (Latin American and Caribbean Health Sciences Literature) (Internet) http://regional.bvsalud.org/php/index.php?lang=en
- NIHR Health Technology Assessment Programme (Internet)
- PROSPERO (International Prospective Register of Systematic Reviews) (Internet) http://www.crd.york.ac.uk/prospero/

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

- NIH ClinicalTrials.gov (http://www.clinicaltrials.gov/)
- WHO International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/)

References in retrieved articles and relevant systematic reviews will be checked.

Searches will take into account generic and other product names for the intervention. An example search strategy is presented in Appendix 1; these will be adapted as necessary following consultation with clinical experts. The main Embase strategy for each search will be independently peer reviewed by a second Information Specialist, using the CADTH Peer

Review checklist.[25] Identified references will be downloaded in Endnote X4 software for further assessment and handling. References in retrieved articles will be checked for additional studies.

4.3 Review methods

Two reviewers will independently screen titles and abstracts of all reports identified by the searches and discrepancies will be discussed. Full copies of all studies deemed potentially relevant, after discussion, will be obtained and two reviewers will independently assess these for inclusion; any disagreements will be resolved by consensus or discussion with a third reviewer.

Where available, data will be extracted on the following: study design/details, participant characteristics (e.g. demographic characteristics and cardiac risk factors, etc.), details of the hs-cTnT or hs-cTnI test (manufacturer, timing, baseline (onset of symptoms or presentation), definition of diagnostic threshold, etc.), details of comparator cardiac biomarker tests (manufacturer, timing, definition of diagnostic threshold, etc.), details of reference standard (manufacturer, timing and diagnostic threshold for conventional troponin T or I testing), clinical outcomes (number of participants discharged early (up to 4 hrs after initial presentation), incidence of MACE during follow-up, re-attendance at or re-admission to hospital during follow-up, time to discharge, any patient satisfaction or HRQoL measures), and test performance outcome measures. Data will be extracted by one reviewer, using the data extraction forms used for the original systematic review[5] conducted to support the development of DG15[16] (edited as necessary). A second reviewer will check data extraction and any disagreements will be resolved by consensus or discussion with a third reviewer.

4.4 Quality assessment

The methodological quality of included RCTs will be assessed using the revised Cochrane Risk of Bias Tool for RandomizedTrials (RoB 2).[26] Diagnostic accuracy studies will be assessed using QUADAS-2.[27] The results of the quality assessment will be used for descriptive purposes to provide an evaluation of the overall quality of the included studies and to provide a transparent method of recommendation for design of any future studies. Where sufficient data are available the results of quality assessment may be used to inform stratified meta-analyses in order to explore the impact if individual components of study quality upon the findings of the review. Quality assessment will be undertaken by one reviewer and checked by a second reviewer, any disagreements will be resolved by consensus or discussion with a third reviewer.

4.5 Data synthesis

If available data allow, summary estimates of the sensitivity and specificity together with 95% confidence intervals (CIs) and prediction regions of hs-cTnT and hs-cTnI, used singly or in series, up to three hours from the onset of chest pain/presentation will be calculated. We will use the bivariate/hierarchical summary receiver operating characteristic (HSROC) random effects model to generate summary estimates and an SROC curve.[28-30] If more than one RCT evaluates the same clinical outcome in patients assessed with the same intervention (hs-cTnT or hs-cTnI assay method) and comparator (standard diagnostic assessment), then data will be pooled on treatment effect (e.g. hazard ratio, odds ratio, relative risk, weighted mean difference). The DerSimonian and Laird random effects model will be used to generate summary estimates together with 95% CIs. Any estimates of the relative accuracy/effectiveness of different hs-cTnT or hs-cTnI tests, used singly or in series, will be derived from direct, within study comparisons. Where sufficient data are available, clinically relevant subgroup analysis will be considered (e.g. gender, NSTEMI population versus mixed population, age, previous MI, renal function, risk stratification/pre-test probability).

Where meta-analysis is considered unsuitable for some or all of the data identified (e.g. due to the heterogeneity and/or small numbers of studies), we will employ a narrative synthesis. Typically, this will involve the use of text and tables to summarise data. These will allow the reader to consider any outcomes in the light of differences in study designs and potential sources of bias for each of the studies being reviewed. Studies will be organised by research question addressed and by hs-cTnT or hs-cTnI assay, and mode of application (single or serial testing). A detailed commentary on the major methodological problems or biases that affected the studies will also be included, together with a description of how this may have affected the individual study results. Recommendations for further research will be made based on any gaps in the evidence or methodological flaws.

The structure of our report will be based on that of the original Diagnostic Assessment Report (DAR),[5] conducted to support the development of DG15[16]; new studies, added during the update process, will be clearly identified.

5 Methods for synthesising evidence of cost-effectiveness

5.1 Identifying and reviewing published cost-effectiveness studies

Search strategy

Targeted searches for input parameters in the economic model will be performed if deemed necessary (on an ad-hoc basis).

5.2 Evaluation of costs, quality of life and cost-effectiveness

Decision analytic modelling will be undertaken to determine the cost-effectiveness of hs-cTn assays (used singly or in series, up to four hours from the onset of chest pain/presentation) compared with the current standard of serial troponin T and/or I testing on admission and at 10-12 hours post-admission for the early rule out of acute myocardial infarction in people with acute chest pain.

Diagnosis and treatment strategies

The analysis will consider the long term consequences of clinical validity and diagnostic performance (early rule-out of NSTEMI) of the different tests. For tests for which clinical validity and/or prognostic value is unclear, when feasible, assumptions will be made to provide some indication of the (range) of cost-effectiveness outcomes.

Subgroup analyses will be used to examine the effect of varying the NSTEMI prevalence (i.e. the pretest-probability) of MI (0% to a clinically relevant upper limit, e.g. 20%); the main analysis will use a prevalence of 17%, which is consistent with the original Diagnostic Assessment Report (DAR),[5] conducted to support the development of DG15[16]. In addition, if allowed by the data, subgroup analyses will be preformed based on sex, age and people with and without a history of previous NSTEMI.

Model structure

In order to be consistent with earlier related assessments, the economic model used the original Diagnostic Assessment Report (DAR),[5] conducted to support the development of DG15[16] will be used as a starting point. This diagnostic model compares various testing strategies (i.e. a troponin test on arrival, a 10-hour troponin test, and a biomarker + troponin strategy) and calculates long-term costs and QALYs for each of these strategies.
Issues relevant to analyses:

- Longer term costs and consequences will be discounted using the UK discount rates of 3.5% of both costs and effects.
- Probabilistic sensitivity analyses will be performed using parameter distributions instead of fixed values.
- Decision uncertainty regarding mutually exclusive alternatives will be reflected using cost-effectiveness planes and cost-effectiveness acceptability curves.

A simple draft model structure is presented (Appendix 3); this may be developed/expanded as indicated and as available data allow.

Health outcomes

Utility values, based on literature or other sources, will be incorporated in the economic model. QALYs will be calculated from the economic modelling.

Costs

Resource utilisation will be estimated for the diagnostic tests and treatments. Data for the cost analyses will be drawn from routine NHS sources (e.g. NHS reference costs, Personal Social Services Research Unit (PSSRU), British National Formulary (BNF)), discussions with individual hospitals and with the manufacturers of the comparators.

Updating of the original Diagnostic Assessment Report

The updating of the original assessment will focus on incorporating the updated accuracy (i.e. sensitivity and specificity data) as well as the inclusion of new assays which have become available to the NHS since publication of DG15. The costs used in the economic model will also be updated.

6 Handling of information from the companies

All data submitted by the manufacturers/sponsors will be considered if received by the EAG no later than 15/12/2019. Data arriving after this date will not be considered. If the data meet the inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol.

Any 'commercial in confidence' data provided by manufacturers, and specified as such, will be highlighted in blue and underlined in the assessment report (followed by company name in parentheses). Any 'academic in confidence' data provided by manufacturers, and specified as such, will be highlighted in yellow and underlined in the assessment report. Any confidential data used in the cost-effectiveness models will also be highlighted.

7 Competing interests of authors

None

8 Timetable/milestones

Milestones	Completion data
Draft protocol	7/08/2019
Final protocol	10/09/2019
Final assessment report	25/02/2020
DAC 1	02/04/2020
DAC 2	03/06/2020

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Appendix 1: Clinical effectiveness search

Embase (Ovid): 1974 to 2019/09/04
Searched 5.9.19

1 "high sensitivity cardiac troponin T"/ or high sensitivity troponin t assay/ (89)
2 "high sensitivity cardiac troponin I"/ or high sensitivity troponin i assay/ (44)
3 (Hstnt or hs-tnt or hsctnt or hs-ctnt or tnt-hs or tnths or ctnths or ctnt-hs).ti,ab,ot. (2920)
4 (Hstni or hs-tni or hsctni or hs-ctni or tni-hs or tnihs or ctnihs or ctni-hs or ctni-ultra).ti,ab,ot. (1188)
5 ((troponin t or tnt or ctnt or tropt or trop t) adj2 (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive)).ti,ab,ot,hw. (4179)
6 ((troponin I or tni or ctni or tropI or trop I) adj2 (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive)).ti,ab,ot,hw. (2405)
7 (troponin$ adj2 (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive)).ti,ab,ot,hw. (6566)
8 (troponin$ adj5 (architect or elecsys or access or unicel or centaur or vidas or vitros or dimension or vista or triagetrue or triage-true or atellica or alinity or advia)).ti,ab,hw,ot. (398)
9 ("dimension exl" or "atellica IM" or atellica-im or "alinity i" or alinity-i or "advia centaur" or "dimension vista").ti,ab,hw,ot. (1298)
10 troponin$.mv,my. (63)
11 (elecsys$ or architect$ or unicel$ or centaur or vidas or vitros or atellica or alinity).dv. (2900)
12 (advia or advia120 or advia1800 or advia2120i or advia2400 or adviacentaur).dv. (969)
13 or/1-12 (12130)
14 troponin t/ or troponin I/ or (60304-72-5 or 77108-40-8).rn. (37883)
15 (sensitiv$ or hs or early or initial or rapid or present$ or ultra or high performance or ultrasensitive).ti,ab,ot,hw. (9791619)
16 14 and 15 (21545)
17 13 or 16 (27742)
18 thorax pain/ (83801)
19 ((chest or thorax or thoracic) adj2 (pain$ or discomfort or tight$ or pressure)).ti,ab,ot,hw. (109892)
20 acute coronary syndrome/ (53939)
21 (acute adj2 coronary adj2 syndrome$).ti,ab,ot,hw. (67355)
22 exp heart muscle ischemia/ (91308)
23 exp heart infarction/ (363585)
24 exp Unstable-Angina-Pectoris/ (23528)
25 (preinfarc$ Angina$ or pre infarc$ Angina$).ti,ab,ot,hw. (409)
26 Unstable angina$.ti,ab,ot. (19163)
27 ((heart$ or myocardi$ or cardiac or coronary) adj2 (preinfarc$ or infarc$ or attack$ or arrest$ or occlusion$ or isch?emia$)).ti,ab,ot,hw. (552181)
28 (MI or ACS or STEMI or NSTE-ACS or NSTEACS or nonSTEMI or NSTEMI or AMI or UAP or OMI).ti,ab,ot,hw. (163187)
29 or/18-28 (716481)

30 17 and 29 (14208)
31 animal/ (1427724)
32 animal experiment/ (2426931)
33 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (6552498)
34 or/31-33 (6552498)
35 exp human/ (20114671)
36 human experiment/ (465906)
37 or/35-36 (20116097)
38 34 not (34 and 37) (5056906)
39 30 not 38 (13441)
40 limit 39 to yr="2013 -Current" (8121)

Appendix 2: Related NICE guidance

MI – Secondary prevention: Secondary prevention in primary and secondary for patients following a myocardial infarction: NICE Clinical Guideline CG48 (2007) Available from http://guidance.nice.org.uk/CG48 Update expected November 2013.

Chest pain of recent onset: Assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin: NICE Clinical Guideline CG95 (2009) Available from: http://www.nice.org.uk/guidance/CG95 Date for review: 2012.

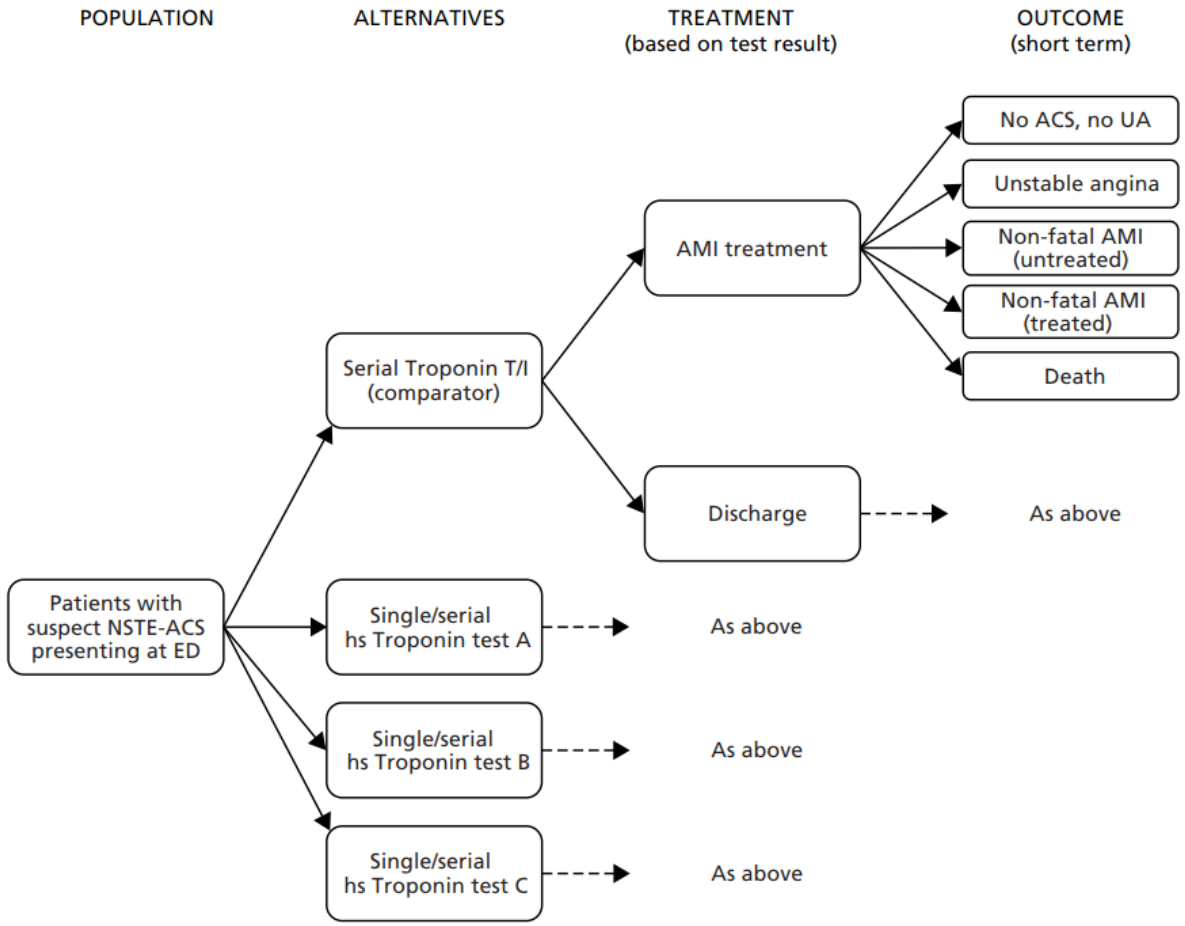
Unstable angina and NSTEMI: The early management of unstable angina and non-ST-segment-elevation myocardial infarction. Clinical Guideline CG94 (2010) Available from: http://www.nice.org.uk/guidance/CG94 Date for review: 2013.

BRAHMS copeptin assay to rule out myocardial infarction in patients with acute chest pain: Medical technologies guidance MTG4 (2011). Available from: http://guidance.nice.org.uk/MTG4 Date for review: not stated.

Myocardial Infarction with ST-segment elevation: The acute management of myocardial infarction with ST-segment elevation. NICE Clinical Guideline CG167 (2013) Available from http://guidance.nice.org.uk/CG167 Date for review: not stated.

Appendix 3: Draft model structure

Decision tree (short term; approximately 30 days)



State transition model (long term)