

High-sensitivity troponin assays for early rule-out of acute myocardial infarction in people with acute chest pain: a systematic review and economic evaluation

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Scientific summary

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Scientific summary

Background

Coronary artery disease and myocardial infarction are a significant health burden in the UK. Many people attend hospital with chest pain and suspected myocardial infarction, with statistics showing that chest pain accounted for approximately 5% of emergency admissions in 2017–18. It is important to diagnose people suspected of having an myocardial infarction as early as possible to ensure quick and effective treatment. However, only around 20% of emergency admissions for chest pain will have an myocardial infarction and there are many other causes of chest pain. Tests that can quickly tell which patients do not have myocardial infarction could avoid unnecessary hospital admissions, waiting time and anxiety.

Cardiac troponins I and T are used as markers of acute myocardial infarction. They are intended for use in conjunction with clinical history and electrocardiography. ST segment elevation myocardial infarction can usually be diagnosed on presentation by electrocardiogram and therefore the main diagnostic challenge is the detection or rule out of non-ST segment elevation myocardial infarction. High-sensitivity cardiac troponin assays can detect lower levels of troponin in the blood than conventional assays and may enable non-ST segment elevation myocardial infarction to be ruled out at an earlier time after the onset of acute chest pain. National Institute for Health and Care Excellence guidance currently recommends the use of some high-sensitivity cardiac troponin assays [e.g. the Elecsys® Troponin-T high sensitive (Roche, Basel, Switzerland) and the ARCHITECT STAT High Sensitive Troponin-I (Abbott Laboratories, Abbott Park, IL, USA)] as options for the early rule out of non-ST segment elevation myocardial infarction in people presenting to an emergency department with chest pain and suspected acute coronary syndrome.

This update assessment was undertaken to ensure that guidance is based on current evidence (including new high-sensitivity cardiac troponin assays developed and marketed since the publication of National Institute for Health and Care Excellence guidance) and to facilitate the provision of more detailed, evidence-based recommendations on how to use high-sensitivity cardiac troponin assays (e.g. timing of testing and use of sequential testing strategies).

Objectives

This assessment aimed to assess the clinical effectiveness and cost-effectiveness of high sensitivity troponin tests, used as single tests or repeated over a short time, for the early (i.e. < 4 hours) rule out of myocardial infarction (and consequent early discharge) in people who present to hospital with chest pain.

Methods

This report contains reference to confidential information provided as part of the NICE appraisal process. This information has been removed from the report and the results, discussions and conclusions of the report do not include the confidential information. These sections are clearly marked in the report.

Assessment of clinical effectiveness

Sixteen databases, including MEDLINE, EMBASE, research registers and conference proceedings, were searched for relevant studies from 2013 (date of the previous assessment) to September 2019. Search results were screened for relevance independently by two reviewers. Full copies of all studies deemed potentially relevant were obtained and assessed independently by two reviewers. Any disagreements were resolved by consensus. Data extraction and quality assessment were conducted by one reviewer, and checked by a second. The methodological quality of included randomised controlled trials was assessed using the revised Cochrane Risk-of-Bias tool for Randomised Trials. The methodological quality of included diagnostic test accuracy studies was assessed using QUADAS-2 (for studies assessing a single high-sensitivity cardiac troponin assay) or QUADAS-2C (for studies comparing two or more high-sensitivity cardiac troponin assays).

The hierarchical summary receiver operating characteristic model was used to estimate summary sensitivity and specificity with 95% confidence intervals (CIs) and prediction regions around the summary points, and to derive hierarchical summary receiver operating characteristic curves for meta-analyses involving four or more studies. For meta-analyses with fewer than four studies, we estimated separate pooled estimates of sensitivity and specificity using random-effects logistic regression. Analyses were conducted separately for each high-sensitivity cardiac troponin assay. Analyses were stratified according to target condition (i.e. non-ST segment elevation myocardial infarction, any acute myocardial infarction or 30-day major adverse cardiac event), timing of collection of blood sample for testing and the threshold used to define a positive high-sensitivity cardiac troponin result.

Assessment of cost-effectiveness

We considered the long-term costs and quality-adjusted life-years associated with different troponin testing methods to diagnose or rule out non-ST segment elevation myocardial infarction for patients presenting at the emergency department with suspected non-ST segment elevation acute coronary syndrome. The de novo model consisted of a decision tree and a state-transition cohort model. The decision tree was used to model the 30-day outcomes after presentation, based on test results and the accompanying treatment decision. The long-term consequences in terms of costs and quality-adjusted life-years were estimated using a state-transition cohort model with a lifetime time horizon (i.e. 60 years). For the economic analyses, based on expert opinion, only high-sensitivity troponin tests that had a sensitivity of $\geq 97\%$ were selected. A total of 22 unique testing strategies were included in the main economic analysis.

In the base case, it was assumed that standard troponin testing had perfect sensitivity and specificity (reference case) for diagnosing acute myocardial infarction, and that only those patients testing positive with the reference standard (standard troponin) were at increased risk for adverse events (myocardial infarction and mortality) and would benefit from immediate treatment. In a secondary analysis, a proportion of patients testing positive with a high-sensitivity cardiac troponin test and not testing positive with standard troponin (i.e. false positives) were assumed to be at increased risk of myocardial infarction and mortality. These patients were assumed to be treated for the high-sensitivity cardiac troponin assays and left untreated for the standard troponin test.

Results

Assessment of clinical effectiveness

Thirty-seven studies (123 publications) were included in the review. Thirty studies reported accuracy data for the Roche Elecsys Troponin-T high sensitive assay, nine studies reported accuracy data for the Abbott ARCHITECT STAT High Sensitive Troponin-I assay, two studies reported accuracy data for the Atellica[®] IM High-Sensitivity Troponin I (Siemens Healthcare, Erlangen, Germany), three studies reported accuracy data for the ADVIA Centaur[®] High-Sensitivity Troponin I (Siemens Healthcare, Erlangen, Germany), two studies reported accuracy data for the Access High Sensitivity Troponin I

(Beckman Coulter, Brea, CA, USA) and one study reported accuracy data for each of the Dimension Vista® High-Sensitivity Troponin I (Siemens Healthcare, Erlangen, Germany), VITROS® High Sensitivity Troponin I Assay (Ortho Clinical Diagnostics, Marlow, UK), VIDAS® High sensitive Troponin I (bioMérieux SA, Marcy l'Etoile, France) and TriageTrue High Sensitivity Troponin I Test (Quidel, San Diego, CA, USA). Seven studies reported accuracy data for more than one assay. We did not identify any studies of the Alinity i STAT high-sensitivity troponin I (Abbott Laboratories, Abbott Park, IL, USA) or Dimension® EXL™ hs-cTnI (Siemens Healthcare, Erlangen, Germany) that met the inclusion criteria for this review.

The high-sensitivity cardiac troponin test strategies evaluated by included studies are defined by the combination of four factors (i.e. assay, number and timing of tests, and threshold concentration), resulting in a large number of possible combinations. Clinical opinion, provided by the specialist committee members, indicated a minimum clinically acceptable sensitivity of 97%.

When considering single test strategies, only those using a threshold at or near to the limit of detection for the assay, in a sample taken at presentation, met the minimum clinically acceptable sensitivity criterion. The summary estimates of sensitivity and specificity for the target condition (i.e. non-ST segment elevation myocardial infarction) using the Roche Elecsys Troponin-T high sensitive assay (5 ng/l) were 99% (95% CI 97% to 100%) and 35% (95% CI 25% to 46%), respectively (six studies). The summary sensitivity and specificity estimates for the Abbott ARCHITECT STAT High Sensitive Troponin-I assay (2 ng/l) were 100% (95% CI 99% to 100%) and 21% (95% CI 16% to 26%), respectively (four studies). Of the remaining high-sensitivity cardiac troponin assays, only the Atellica IM High-Sensitivity Troponin I and ADVIA Centaur High-Sensitivity Troponin I assays were evaluated using a single presentation sample rule-out strategy, with a threshold at or near to the limit of detection for the assay. The limit of detection for both of these assays is 1.6 ng/l. Using a rule-out threshold of 2 ng/l, the sensitivity and specificity estimates were 100% (95% CI 99% to 100%) and 23% (95% CI 21% to 25%), respectively, for the ADVIA Centaur High-Sensitivity Troponin I, and 100% (95% CI 98% to 100%) and 26% (95% CI 24% to 28%), respectively, for the Atellica IM High-Sensitivity Troponin I assay.

The majority of the multiple test strategies meeting the minimum clinically acceptable sensitivity comprised an initial rule-out step, based on high-sensitivity cardiac troponin levels in a sample taken on presentation and a minimum symptom duration, and a second stage for patients not meeting the initial rule-out criteria, based on presentation levels of high-sensitivity cardiac troponin and absolute change in high-sensitivity cardiac troponin between presentation and a second sample taken after 1, 2 or 3 hours. The 2015 European Society of Cardiology guidelines for the management of acute coronary syndromes in patients presenting without persistent ST segment elevation included a 0/1-hour algorithm, which incorporates a rule-out pathway following this structure. Versions of the European Society of Cardiology 0/1-hour rule-out pathway have been evaluated using the following assays: Roche Elecsys Troponin-T high sensitive (sensitivity 99%, 95% CI 98% to 100%; specificity 68%, 95% CI 67% to 70%); Abbott ARCHITECT STAT High Sensitive Troponin-I assay (sensitivity 99%, 95% CI 98% to 100%; specificity 57%, 95% CI 56% to 59%) (summary estimate from two studies); Access High Sensitivity Troponin I (sensitivity 99%, 95% CI 94% to 100%; specificity 70%, 95% CI 66% to 74%); VITROS High Sensitivity Troponin I Assay (sensitivity 100%, 95% CI 95% to 100%; specificity 60%, 95% CI 55% to 64%); TriageTrue High Sensitivity Troponin I Test (sensitivity 100%, 95% CI 97% to 100%; specificity 66%, 95% CI 62% to 70%); ADVIA Centaur High-Sensitivity Troponin I (sensitivity 99%, 95% CI 95% to 100%; specificity 67%, 95% CI 61% to 72%). The High-Sensitivity Troponin in the Evaluation of Patients With Acute Coronary Syndrome (High-STEACS) pathway, which uses a later (3-hour) second sample, offers the potential to increase overall specificity and hence the proportion of patients in whom non-ST segment elevation myocardial infarction can be ruled out, without loss of sensitivity. Sensitivity and specificity estimates for the High-STEACS pathway were 99% (95% CI 97% to 100%) and 76% (95% CI 73% to 78%), respectively, using the Abbott ARCHITECT STAT High Sensitive Troponin-I assay, and 98% (95% CI 95% to 100%) and 74% (95% CI 72% to 76%), respectively, using the Atellica IM High-Sensitivity Troponin I assay.

Two randomised trials were included in the review. High-STEACS evaluated the implementation of an early rule-out pathway in hospitals in Scotland, which assessed rates of reclassification of patients, and subsequent incidence of myocardial infarction and cardiovascular death when high-sensitivity cardiac troponin I results were made available for patients previously classified using conventional cardiac troponin I results. The High-Sensitivity Cardiac Troponin On Presentation to Rule Out Myocardial Infarction (HiSTORIC) trial (confidential information has been removed) also evaluated the implementation of an early rule-out pathway in hospitals in Scotland. The primary outcomes were length of stay and myocardial infarction or cardiac death after discharge (at 30 days). In the High-STEACS study, the median length of stay was 7 (interquartile range 3–24) hours in the implementation phase and 4 (interquartile range 3–20) hours in the validation phase. In the HiSTORIC trial (confidential information has been removed). Both studies reported that the implementation of an early rule-out pathway was not associated with any increase in myocardial infarction or cardiac death after discharge, at 30 days or 1 year.

Assessment of cost-effectiveness

Base-case analysis

In the base-case analysis, standard troponin testing (at presentation and after 10–12 hours) was the most effective (probabilistic: 15.5331 life-years and 12.0825 quality adjusted life-years) and the most expensive strategy (£38,871). However, other testing strategies with a sensitivity of 100% (subject to uncertainty) were almost equally effective, resulting in the same life-year and quality-adjusted life-year gain at up to four decimal places. Comparisons based on the next best alternative showed that for willingness-to-pay values < £8455 per quality adjusted life-year, the Access High Sensitivity Troponin I [(symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 5 at 0 to 2 hours)] would be cost-effective. For thresholds between £8455 and £20,190 per quality-adjusted life-year, the Elecsys Troponin-T high sensitive (< 12 ng/l at 0 hours AND Δ < 3 ng/l at 0 to 1 hours) would be cost-effective. For a threshold > £20,190 per quality-adjusted life-year, the Dimension Vista High-Sensitivity Troponin I (< 5 ng/l at 0 hours AND Δ < 2 ng/l at 0 to 1 hours) would be cost-effective.

Secondary analysis

In the secondary analysis, which assumed that a proportion of false positives in the high-sensitivity cardiac troponin testing strategies had an increased risk of adverse events (i.e. myocardial infarction and mortality), standard troponin (at presentation and after 10–12 hours) was the cheapest (£37,517) and least effective (11.334 quality-adjusted life-years) testing strategy (probabilistic analysis). The Access High Sensitivity Troponin I [European Society of Cardiology 0/1-hour pathway: (symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 4 ng/l at 0 to 1 hours)] was the most effective testing strategy (11.4725 quality-adjusted life-years) at higher costs (£38,077). All other strategies were (extendedly) dominated. The incremental cost-effectiveness ratio of the Access High Sensitivity Troponin I [European Society of Cardiology 0/1-hour pathway: (symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND Δ < 4 ng/l at 0 to 1 hours)] compared with standard troponin (at presentation and after 10–12 hours) was £4043 per quality-adjusted life-year gained.

Sensitivity and scenario analyses

The following input parameters had a notable impact on the estimated cost-effectiveness: the 30-day mortality for untreated acute myocardial infarction, mortality 1 year after treated and untreated acute myocardial infarction, the discount rate used for outcomes, and the relative mortality for patients who tested true positive compared with those who tested false positive. Moreover, only scenario analysis 1 (i.e. increasing the costs for false positives) had a substantial impact on the cost-effectiveness.

Conclusions

There is evidence to indicate that high-sensitivity troponin assays can be used to rule out non-ST segment elevation myocardial infarction in adults presenting with acute chest pain, within the 4-hour NHS emergency department target. Test strategies that comprise an initial rule-out step, based on low high-sensitivity cardiac troponin levels in a sample taken on presentation and a minimum symptom duration, and a second stage for patients not meeting the initial rule-out criteria, based on low presentation levels of high-sensitivity cardiac troponin and small absolute change in high-sensitivity cardiac troponin between presentation and a second sample taken after 1, 2 or 3 hours, are likely to produce the highest rule-out rates while maintaining clinically acceptable sensitivity (i.e. very low rates of missed non-ST segment elevation myocardial infarction).

From a cost-effectiveness perspective, the Elecsys Troponin-T high sensitive (< 12 ng/l at 0 hours AND $\Delta < 3$ ng/l at 0 to 1 hours) and the Dimension Vista High-Sensitivity Troponin I (< 5 ng/l at 0 hours AND $\Delta < 2$ ng/l at 0 to 1 hours) might be cost-effective for thresholds of £20,000 and £30,000 per quality-adjusted life-year gained, respectively (base case). For the secondary analysis, the Access High Sensitivity Troponin I [(symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND $\Delta < 5$ ng/l at 0 to 2 hours)] was considered cost-effective for these thresholds. The cost-effectiveness results should, however, be interpreted while noting that the differences between the strategies in both costs and quality-adjusted life-years were very small. Given these minimal differences in cost-effectiveness, it might be worthwhile to consider other aspects not captured in the economic assessment. Therefore, it is worth noting that the high-sensitivity test strategies with the highest true negatives (i.e. $\geq 65\%$) involve high-sensitivity tests strategies with a second test 2–3 hours after the initial test {i.e. Atellica IM High-Sensitivity Troponin I (High-STEACS pathway), ARCHITECT STAT High Sensitive Troponin-I assay (High-STEACS pathway), Elecsys Troponin-T high sensitive (99th centile) and Access High Sensitivity Troponin I [(symptoms > 3 hours AND < 4 ng/l at 0 hours) OR (< 5 ng/l AND $\Delta < 5$ ng/l at 0 to 2 hours)]}.

Study registration

This study is registered as PROSPERO CRD42019154716.

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This report

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