# High-sensitivity troponin assays for the early rule-out or diagnosis of acute myocardial infarction in people with acute chest pain: a systematic review and cost-effectiveness analysis

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## Scientific summary

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# Scientific summary

## Background

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

Cardiac troponins (cTns) I and T are used as markers of AMI. They are intended for use in conjunction with clinical history-taking and electrocardiography monitoring. Elevated troponin (Tn) levels are associated with an increased risk of adverse cardiac outcomes. However, the optimal sensitivity of standard Tn assays for AMI occurs several (10–12) hours after the onset of symptoms. Two high-sensitivity cardiac troponin (hs-cTn) assays are currently available for use in the NHS in England and Wales: ARCHITECT high-sensitivity troponin I assay (Abbott Diagnostics, Chicago, IL, USA) and the Elecsys troponin T high-sensitive assay (Roche Diagnostics GmbH, Mannheim, Germany). One additional assay, AccuTnI+3 troponin I assay (Beckman Coulter, Brea, CA, USA), was included in the scope for this assessment pending CE marking; CE marking has now been confirmed. These assays are able to detect lower levels of Tn in the blood with analytical sensitivities up to 100 times greater than conventional Tn assays. Use of high-sensitivity assays enables the detection of small changes in Tn levels and may enable AMI to be ruled out at an earlier time after the onset of acute chest pain.

This assessment considers hs-cTn assays used singly or in series, up to 4 hours after the onset of chest pain or up to 4 hours after presentation; for serial Tn measurements, both data on change in Tn levels and peak Tn are considered.

## Objective

To assess the clinical effectiveness and cost-effectiveness of high-sensitivity Tn assays for the management of adults presenting with acute chest pain, in particular for the early (within 4 hours of presentation) rule-out of AMI.

## Methods

### *Assessment of clinical effectiveness*

Sixteen databases, including MEDLINE and EMBASE, research registers and conference proceedings, were searched to October 2013. Search results were screened for relevance independently by two reviewers. Full-text inclusion assessment, data extraction and quality assessment were conducted by one reviewer and checked by a second. Study quality was assessed using QUADAS-2. The bivariate/hierarchical summary receiver operating characteristic (HSROC) model was used to estimate summary sensitivity and specificity with 95% confidence intervals (CIs) and prediction regions around the summary points, and to derive HSROC 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. Summary positive likelihood ratios (LR+) and negative likelihood ratios (LR–) were derived from the summary estimates of sensitivity and specificity. Analyses were conducted separately for each of the three hs-cTn assays and were stratified according to whether or not the study evaluated the prediction of AMI or major adverse cardiac event (MACE), test timing, and the threshold used to define a positive hs-cTn result. Stratified analyses were used to investigate heterogeneity and the influence of risk of bias on summary estimates.

### *Assessment of cost-effectiveness*

We considered the long-term costs and quality-adjusted life-years (QALYs) associated with different Tn testing methods, to diagnose or rule out NSTEMI, for patients presenting at the emergency department (ED) with suspected non-ST segment elevation acute coronary syndrome (NSTE-ACS). The de novo model consisted of a decision tree and a Markov model. The decision tree was used to model the 30-day outcomes after presentation, based on test results and the accompanying treatment decision. The long-term consequences in terms of costs and QALYs were estimated using a Markov cohort model with a lifetime time horizon (60 years). The following strategies were included in the main economic analysis:

- standard Tn at presentation and at 10–12 hours (reference standard)
- Roche Elecsys hs-cTnT at presentation: 99th centile threshold
- Roche Elecsys hs-cTnT (optimal strategy): limit of blank (LoB) threshold at presentation followed by 99th centile threshold peak within 3 hours and/or Δ20% (compared with presentation test) at 1–3 hours
- Abbott ARCHITECT hs-cTnI at presentation: 99th centile threshold
- Abbott ARCHITECT hs-cTnI (optimal strategy): limit of detection (LoD) threshold at presentation, followed by 99th centile threshold at 3 hours
- Beckman Coulter hs-cTnI at presentation: 99th centile threshold.

In the base case, it was assumed that standard Tn testing had perfect sensitivity and specificity (reference case) for diagnosing AMI and that only patients testing positive on the reference standard (standard Tn) were at increased risk for adverse events and would benefit from immediate treatment. In a secondary analysis, a proportion of patients testing positive on a hs-cTn test were treated accordingly. These patients were assumed to be treated for the hs-cTn assays and left untreated for the standard Tn test and at increased risk for adverse events. In addition, a number of sensitivity and subgroup analyses were performed.

## Results

### *Assessment of clinical effectiveness*

Eighteen studies (38 publications) were included in the review. The main potential sources of bias in the included studies related to patient spectrum and patient flow. There were also concerns regarding the applicability of the patient population and the reference standard in some of the included studies.

#### Diagnostic accuracy of the Roche Elecsys high-sensitivity cardiac troponin T assay (15 studies)

The most commonly evaluated testing strategy was the 99th centile threshold in a blood sample taken on presentation. Studies ($n = 6$) that excluded patients with ST segment elevation myocardial infarction (STEMI) gave a summary LR+ of 5.41 (95% CI 3.40 to 8.63) and summary LR– of 0.15 (95% CI 0.08 to 0.26) for this strategy. Estimates were similar when derived from all studies ($n = 13$) that evaluated this strategy. The optimum strategy based on this assay appeared to be one based on the combination of a LoB threshold in a presentation sample, which could be used to rule out AMI (LR– 0.10, 95% CI 0.05 to 0.18) but has limited potential to rule in an AMI (LR+ 1.83, 95% CI 1.70 to 1.97). Patients testing positive could then have a further sample taken at 2 hours; a result above the 99th centile on either the presentation or 2-hour sample and a Δ of at least 20% has some potential for ruling in an AMI (LR+ 8.42, 95% CI 6.11 to 11.60), whereas a result below the 99th centile on both samples and a Δ of $< 20\%$ can be used to rule out an AMI (LR– 0.04, 95% CI 0.02 to 0.10).

### Diagnostic accuracy of the Abbott ARCHITECT high-sensitivity cardiac troponin I assay (four studies)

Three studies, all conducted in populations that included patients with STEMI, evaluated this assay at the 99th centile threshold in a blood sample taken on presentation. The summary LR+ was 11.47 (95% CI 9.04 to 16.19) and the summary LR– was 0.22 (95% CI 0.16 to 0.27). The optimum strategy appeared to be one based on the combination of a LoD threshold in a presentation sample, which could be used to rule out AMI (LR– 0.01, 95% CI 0.00 to 0.08) but has limited potential to rule in an AMI (LR+ 1.54, 95% CI 1.47 to 1.62). Patients testing positive could then have a further sample taken at 3 hours, a result above the 99th centile on this sample has some potential for ruling in an AMI (LR+ 10.16, 95% CI 8.38 to 12.31), whereas a result below the 99th centile can be used to rule out an AMI (LR– 0.02, 95% CI 0.01 to 0.05).

### Diagnostic accuracy of the Beckman Coulter Access high-sensitivity cardiac troponin I (two studies)

One study, conducted in a population that included patients with STEMI, evaluated this assay at the 99th centile threshold in a blood sample taken on presentation. The summary LR+ was 3.67 (95% CI 3.26 to 4.13) and the summary LR– was 0.11 (95% CI 0.07 to 0.17). Data were not reported for the LoB/LoD threshold. There were insufficient data to determine the optimum testing strategy for this assay.

## *Assessment of cost-effectiveness*

### Base-case analysis

In the base-case analysis, standard Tn testing was both most effective and most costly. Strategies considered cost-effective depending upon incremental cost-effectiveness ratio (ICER) thresholds were Abbott ARCHITECT hs-cTnI 99th centile (thresholds of < £6597), Beckman Coulter hs-cTnI 99th centile (thresholds between £6597 and £30,042), Abbott ARCHITECT hs-cTnI optimal strategy (LoD threshold at presentation, followed by 99th centile threshold at 3 hours) (thresholds between £30,042 and £103,194), and the standard Tn test (thresholds of > £103,194). The Roche Elecsys hs-cTnT 99th centile and the Roche Elecsys hs-cTnT optimal strategy [LoB threshold at presentation followed by 99th centile threshold and/or Δ20% (compared with presentation test) at 1–3 hours] were extendedly dominated in this analysis (one of the more effective strategies was better value, in that the ICER was lower).

### Secondary analysis

In the secondary analysis, which assumed that a proportion of false-positives (FPs) in the hs-cTn testing strategies had an increased risk of adverse events, standard Tn was least effective and most costly, and therefore a dominated strategy. The most effective strategy here was the Abbott ARCHITECT hs-cTnI optimal strategy. The Roche Elecsys hs-cTnT optimal strategy was extendedly dominated (one of the more effective strategies was better value in that the ICER was lower), as was the Beckman Coulter hs-cTnI 99th centile in this analysis. Strategies considered cost-effective were Abbott ARCHITECT hs-cTnI 99th centile (thresholds below £12,217), Roche Elecsys hs-cTnT 99th centile (thresholds between £12,217 and £14,992) and Abbott ARCHITECT hs-cTnI optimal strategy (thresholds over £14,992).

### Sensitivity and subgroup analyses

Sensitivity analyses showed that assumptions regarding the difference between treated and untreated patients (e.g. mortality rate, risk of re-infarction) had the largest impact on relative cost-effectiveness, as well as whether or not patients testing FP were assigned treatment costs. In general, the base-case analysis was affected more by varying these assumptions than the secondary analysis. Results from the subgroup analyses led to the conclusion that hs-cTn testing is likely to be more cost-effective in younger populations, in populations with pre-existing coronary artery disease (CAD), and for patients whose symptom onset was < 3 hours ago. A no-testing strategy can be considered cost-effective only in populations with a prevalence as low as 1%.

## Conclusions

### *Implications for service provision*

There is evidence to suggest that undetectable levels of Tns (below the LoB/LoD of the assay) on presentation, measured using the Roche Elecsys hs-cTnT assay or the Abbott ARCHITECT hs-cTnI assay, may be sufficient to rule out NSTEMI in people presenting with symptoms suggestive of acute coronary syndrome (ACS). There is also evidence to suggest that, for the Roche Elecsys hs-cTnT assay and the Abbott ARCHITECT hs-cTnI assay, a further rule-out step may be possible within the 4-hour NHS ED target. There is insufficient evidence to determine an optimum testing strategy for the Beckman Coulter hs-cTnI assay. There is some limited evidence to suggest that a Tn level below the 99th centile on presentation, measured using the Roche Elecsys hs-cTnT assay, may be sufficient to rule out NSTEMI in some groups (people > 70 years old, people without pre-existing CAD and people with a clinically determined high pre-test probability).

The economic model does not provide strong evidence to prefer one hs-cTn testing strategy over another. Results do, however, indicate that hs-cTn testing in general may be cost-effective compared with standard Tn testing given that hs-cTn testing leads to cost-saving at a QALY loss. This becomes more likely if one assumes that hs-cTn testing detects some patients who require treatment despite their testing negative with standard Tn, as shown in the secondary analysis hs-cTn testing. In particular, the Abbott ARCHITECT hs-cTnI optimal strategy, which involves multiple testing and varying cut-off levels, may be promising. The main issue, with regard to service provision, if implementation of a hs-cTn testing strategy is considered, is the balance between the likely reduction in cost and the risk of a reduction in effectiveness, albeit possibly small.

### *Suggested research priorities*

New studies are needed to evaluate fully the performance of our proposed optimal testing strategies in a clinical setting. Further research (diagnostic cohort studies or multivariable prediction modelling studies) is needed to explore fully possible variation in the performance of hs-cTn assays and the optimal testing strategies for these assays in relevant demographic and clinical subgroups (sex, age, ethnicity, renal function, previous CAD, previous AMI) and to investigate the effects of clinical judgement (assessment of pre-test probability) on test performance. As most of the uncertainties in the economic model were caused by assumptions relating to clinical effectiveness, this type of research would also facilitate economic analyses of hs-cTn testing.

## Study registration

The study is registered as PROSPERO CRD42013005939.

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