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Optimising the use of high-sensitivity troponin assays for the early rule-out of myocardial infarction in patients presenting with chest pain: A systematic review

Marie E Westwood[1], Nigel Armstrong[1], Gill Worthy[1], Debra Fayter[1], Bram LT Ramaekers[2], Sabine Grimm[2], Titas Buksnys[1], Janine Ross[1], Nicholas L Mills[3], Richard Body[4,5], Paul O Collinson[6], Adam Timmis[7], Jos Kleijnen[8,1]

[1]Kleijnen Systematic Reviews Ltd, Unit 6, Escrick Business Park, Riccall Road, Escrick, York YO19 6FD, UK

[2]Department of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Centre, P.O. Box 5800, 6202 AZ Maastricht, the Netherlands

[3] BHF/University Centre for Cardiovascular Science and Usher Institute, The University of Edinburgh, Edinburgh, EH16 4SU, United Kingdom

[4] Division of Cardiovascular Sciences, The University of Manchester, Manchester, M13 9PL, United Kingdom

[5] Emergency Department, Manchester Royal Infirmary, Manchester University NHS Foundation Trust, Manchester, M13 9WL, United Kingdom

[6] Departments of Clinical Blood Sciences and Cardiology, St George's University Hospitals NHS Foundation Trust and St George's University of London, UK

[7]Barts Heart Centre, Queen Mary University, London, UK.

[8]School for Public Health and Primary Care (CAPHRI), Maastricht University, Universiteitssingel 40, 6229 ER Maastricht, the Netherlands

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Corresponding author: Marie Westwood, marie@systematic-reviews.com; Kleijnen Systematic Reviews Ltd, Unit 6, Escrick Business Park, Riccall Road, Escrick, York YO19 6FD, United Kingdom

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Abstract

Aims

To assess the accuracy and clinical effectiveness of high-sensitivity cardiac troponin (hs-cTn) assays for early rule-out of non-ST-segment elevation myocardial infarction (NSTEMI), in adults presenting with acute chest pain.

Methods

Sixteen databases were searched to September 2019. Review methods followed published guidelines. The bivariate model was used to estimate summary sensitivity and specificity with 95% confidence intervals (CIs) for meta-analyses involving four or more studies, otherwise random-effects logistic regression was used.

Results

Thirty-seven studies (124 publications) were included in the review. The hs-cTn test strategies evaluated in the included studies are defined by the combination of four factors (assay, number of tests, timing of tests and threshold concentration or change in concentration between tests). Clinical opinion indicated a minimum acceptable sensitivity of 97%. A single test at presentation using a threshold at or near the assay limit of detection, can reliably rule-out NSTEMI for a range of hs-cTn assays. Serial testing strategies, which include an immediate rule-out step, increase the proportion ruled out without loss of sensitivity. Finally, serial testing strategies without an immediate rule-out step have excellent sensitivity and specificity, but at the expense of the option for immediate patient discharge.

Conclusion

Test strategies that comprise an initial rule-out step, based on low hs-cTn levels at presentation and a minimum symptom duration, and a second step for those not ruled-out that incorporates a small absolute change in hs-cTn at 1, 2 or 3 hours, produce the highest rule-out rates with a very low risk of missed NSTEMI.

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Introduction

Chest pain has been reported as the most common cause of emergency hospital admissions in the UK.*(1)* Hospital Episode Statistics (HES) for 2017-2018 show 226,393 emergency admissions for chest pain, approximately 5% of emergency admissions.*(2)* Many people presenting with acute chest pain have non-cardiac causes, such as gastro-oesophageal disorders, muscle pain, or anxiety. A 2003 UK study reported that the majority of people admitted to hospital with chest pain have no or stable ischaemic heart disease.*(3)* HES for 2017-2018 showed diagnoses of acute myocardial infarction (MI) in 45,163 emergency admissions and unstable angina in 13,056 admissions; 20% and 6% of emergency admissions with chest pain.*(2)* ST-segment elevation MI can usually be diagnosed by electrocardiogram, the main diagnostic challenge in the investigation of patients with suspected ACS lies in the detection or rule-out of non-ST-segment elevation MI (NSTEMI).

Authors of this article conducted the systematic review and cost-effectiveness analysis,*(4)* which informed the 2014 (DG15) and 2010 (CG95) guidance from the UK National Institute for Health and Care Excellence (NICE).*(5,6)* This article describes an updated systematic review, which was undertaken to inform new NICE guidance (DG40).*(7)*

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Methods

Sixteen databases, including MEDLINE and EMBASE, research registers and conference proceedings were searched from 2013 (date of our previous systematic review)*(4)* to September 2019. Full search strategies are provided in on-line Supplementary File 1. Studies were selected for inclusion using the criteria in Table 1. Search results were screened independently by two reviewers. Full text inclusion assessment, 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 (RoB 2.0).*(8)* The methodological quality of included diagnostic test accuracy (DTA) studies was assessed using QUADAS-2.*(9)* These are provided in on-line Supplementary File 6.

For diagnostic cohort studies, diagnostic accuracy data were extracted for each unique hs-cTn test strategy evaluated; a test strategy was defined by the combination of four factors: assay, number and timing of tests, and rule-out threshold. The 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.*(10-12)* For meta-analyses with fewer than four studies we calculated separate pooled estimates of sensitivity and specificity, using random-effects logistic regression.*(13)* Analyses were performed in Stata 13 (StataCorp LP, College Station, Texas, USA) and MetaDisc.*(14)*

Only those test strategies with a reported point estimate for sensitivity which reached the minimum acceptable value of ≥97% (defined by consensus between clinical co-authors RB, NM, PC and AT), and where the target condition was NSTEMI are included in this article. The minimum value was set on the basis that rule-out strategies with a sensitivity of <97%

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are very unlikely to be considered clinically relevant and is not intended to indicate that any test strategy with a sensitivity ≥97% should automatically be considered acceptable. Patients with STEMI were excluded from the study or analysis. Full results for these strategies are provided in Supplementary Files 3-5. All sensitivity and specificity estimates are for NSTEMI at the index presentation.

Results

The evidence base relating to the use of hs-cTn assays for early rule-out of acute myocardial infarction in people presenting with chest pain has expanded rapidly since the publication of 2014 NICE guidance.*(5)* Up-date searches, conducted for this systematic review, identified a total of 9,379 unique references, compared to the total of 6,766 identified for the nine-year period (2005 to October 2013) covered by the searches conducted for our previous systematic review.*(4)* A total of 124 publications of 37 studies (35 diagnostic cohort studies and two randomised controlled trials) were included in the current systematic review. Publications reporting new data were identified for three of the studies included in our previous systematic review;*(4)* ADAPT,*(15)* APACE*(16)* and QUART.*(17)* Studies are cited using the primary publication and, where this is different, the publication in which the referenced data were reported. Figure 1 illustrates the flow of studies through the review process. Supplementary File 2 provides an overview of the included studies and related publications.

Single sample test strategies

Only very low hs-cTn rule-out thresholds, using a sample taken on presentation, met the minimum acceptable sensitivity criterion. Using a rule-out threshold of 5 ng/L (the limit of detection for the assay) for the Roche Elecsys hs-TnT assay, the summary estimates of sensitivity and specificity for the target condition NSTEMI were 99% (95% CI: 97 to 100%) and 35% (95% CI: 25 to 46%), based on data from six studies. Figure 2 shows the SROC

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curve for these studies. The 5 ng/L rule-out threshold has also been validated for the Abbott ARCHITECT hs-cTnI, Siemens ADVIA Centaur hs-cTnI and Siemens Atellica hs-cTnI assays. The summary sensitivity and specificty estimates, for the Abbott ARCHITECT hs-cTn assay, were 97% (95% CI: 95 to 98%) and 58% (95% CI: 57 to 59%), three studies. The sensitivity estimate for the Siemens ADVIA Centaur hs-cTnI and Siemens Atellica hs-cTnI assays was 99% (95% CI: 97 to 100%) for both assays and the specificity estimates were 52% (95% CI: 50 to 54%) and 53% (95% CI: 51 to 55%), respectively, based on data from a single study.

The Abbott ARCHITECT hs-cTnI assay, using a rule-out threshold of 2 ng/L (the limit of detection for the assay) produced summary estimates of sensitivity and specificity of (100% (95% CI: 99 to 100) and 21% (95% CI: 16 to 26%), four studies. Of the remaining assays and platforms included in this systematic review, only the Siemens Atellica hs-cTnI assay and the Siemens ADVIA Centaur hs-cTnI assay were evaluated using a single presentation sample rule-out strategy, with a low rule-out threshold. The limit of detection for both of these assays is 1.6 ng/L and both were evaluated by one study, 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%) for the Siemens ADVIA Centaur hs-cTnI assay, and 100% (95% CI: 98 to 100%) and 26% (95% CI: 24 to 28%) for the Siemens Atellica hs-cTnI assay.

Multiple sample test strategies

Our systematic review identified a total of 37 distinct multiple sample strategies, evaluated in populations which excluded patients with STEMI (target condition NSTEMI). However, only 18 strategies met the minimum acceptable sensitivity criterion. The majority of strategies comprised an initial rule-out step, based on hs-cTn levels in a sample taken on presentation and a minimum symptom duration, and a second stage (for patients not meeting the initial

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rule-out criteria) based on presentation levels of hs-cTn and absolute change in hs-cTn between presentation and a second sample taken after 1, 2 or 3 hours, strategies using an 'OR' combination (Supplementary File 4).

Strategies based on the ESC 0/1 hour rule-out algorithm were the most commonly evaluated. The published ESC 0/1 hour algorithm specifies rule-out thresholds to be used with the Roche Elecsys hs-cTnT assay, the Abbott ARCHITECT hs-cTnI asay and the Siemens Dimension Vista hs-cTnI assay.*(18)* Subsequently, ESC 0/1 hour algorithm rule-out thresholds have been published for the Beckman Coulter Access hs-cTnI assay,*(19)* the Ortho VITROS hs-cTnI assay,*(20)* the Quidel TriageTrue hs-cTnI assay*(21)* and the Siemens ADVIA Centaur hs-cTnI assay.*(22)* Data on the rule-out performance of the ESC 0/1 hour algorithm were calculated by dichotomising at the rule-out threshold; study participants in the observe or the rule-in categories were classified as test positive.

The ESC 0/1 hour rule-out pathway, for the Roche Elecsys hs-cTnT assay had a sensitivity of 99% (95% CI: 98 to 100%) and a specificity of 68% (95% CI: 67 to 70%), with an overall rule-out rate of 57%, based on data from one study; it was uclear in what proportion of participants NSTEMI was ruled-out using the presentation sample alone. This strategy would miss 5/746 (0.67%) of people with NSTEMI. A further publication of the APACE study *(23)* reported data for the performance of the ESC 0/1 hour rule-out pathway for both the target condition NSTEMI and the target condition MACE at 30-day follow-up (including MI at index admission). Data from this publication indicated that, whilst the ESC 0/1 hour rule-out pathway did not miss any participants with NSTEMI at the index admission, 3/1420 (0.21%) of participants who met the rule-out criteria experienced MACE during 30-day follow-up.

For the Abbott ARCHITECT hs-cTnI assay the ESC 0/1 hour rule-out pathway sensitivity and specificity estimates were 99% (95% CI: 98 to 100%) and 57% (95% CI: 56 to 59%), 2

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studies; the overall rule-out rate was 71% and NSTEMI was ruled-out using the single presentation sample alone in 38% of participants.

The ESC 0/1 hour rule-out pathway for the Beckman Coulter Access hs-cTnI assay had a sensitivity of 99% (95% CI: 94 to 100%) and a specificity of 70% (95% CI: 66 to 74%). The overall rule-out rate was 60%, with NSTEMI being ruled out in 32% of participants based on the presentation sample alone. 1/96 (1.04%) participants with NSTEMI were missed using this strategy *(19)*.

For the Ortho VITROS hs-cTnI assay, the sensitivity and specificity estimates were 100% (95% CI: 95 to 100%) and 605 (95% CI: 55 to 64%). The overall rule-out was 53%, with NSTEMI being ruled out in 18% of patients based on the presentation sample alone (*20*). No patients with NSTEMI were missed.

The ESC 0/1 hour rule-out pathway for the Quidel TriageTrue hs-cTnI assay had sensitivity and specificity estimates of 100% (95% CI: 97 to 100%) and 66% (95% CI: 62 to 70%).The overall rule-out rate was 55%, with NSTEMI being ruled out in 45% of patients based on the presentation sample alone.*(21)*

For the Siemens ADVIA Centaur hs-cTnI assay, the sensitivity and specificity estimates were 99% (95% CI: 95 to 100%) and 56% (95% C: 52 to 60%);*(22)* the overall rule-out rate was 46%, with NSTEMI being ruled out in 16% of patients based on the presentation sample alone. Based on data from this study, use of the ESC 0/1 hour pathway would miss 1/114 (0.88%) of people with NSTEMI. For the Siemens Atellica hs-cTnI assay, the sensitivity and specificity estimates were 98% (95% CI: 96 to 99%) and 59% (95% CI: 57 to 61%), two studies.(*24,25*) The reported overall rule-out rates for this strategy were 65% and 50% with NSTEMI being ruled out in 24% and 34% of patients based on the presentation sample alone.

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The High-STEACS rule-out pathway, developed with the Abbott ARCHITECT hs-cTnI assay, appears to offer increased specificity, relative to the ESC 0/1 hour rule-out pathway. The sensitvity and specificity estimates were 99% (95% CI: 97 to 100%) and 76% (95% CI: 73 to 79%). The overall rule-out rate for this pathway was 65%, with 38% ruled-out using the presentation sample alone.*(26)* The High-STEACS pathway would miss 2/275 (0.73%) of patients with NSTEMI. A further 4/1244 (0.32%) participants who met the rule-out criteria, experienced MACE during 30-day follow-up.*(26)* Thresholds for the High-STEACS rule-out pathway have also been defined for the Siemens Atellica hs-cTnI assay.*(27)* The sensitivity and specificity estimates were 98% (95% CI: 95 to 99%) and 74% (95% CI: 72 to 76%). The overall rule-out rate for this strategy was 65% with NSTEMI ruled out in 30% of patients based on the presentation sample alone. Application this strategy missed 4/274 (1.45%) of patients with NSTEMI.

High sensitivity estimates for some strategies involving an 'AND' combination of initial hs-cTnT level and absolute change (Supplementary File 5) have been reported for the Roche hs cTnT and Siemens Dimension Vista hs-cTnI assay. For the Roche Elecsys hs-cTnT assay, this strategy is equivalent to the rule-out threshold used in the repeat testing component of the ESC 0/1 hour pathway. The very early rule-out step in the ESC 0/1 hour pathway does not appear to improve overall rule-out rates, but may facilitate earlier discharge for some patients.

Randomised controlled trials

In addition to the rapid expansion of the diagnostic accuracy evidence base, two major randomised controlled trials the High-STEACS trial*(28)* and the HiSTORIC trial*(29)* were identified. Both trials were stepped-wedge, cluster randomised controlled trials of hospitals in

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Scotland, evaluating implementation of a hs-cTnI assay and an early rule-out pathway (the High-STEACS pathway). Both trials used the Abbott ARCHITECT hs-cTnI assay.

The primary outcome for the High-STEACS trial was MI or cardiovascular death at one year. During the validation phase of the trial (6 to 12 months), results of the hs-cTnI assay were concealed from the attending clinician and a contemporary cardiac troponin assay was used to guide care. The high-sensitivity test was introduced after 6 months (early implementation) or 12 months (late implementation).*(28)* Of 1,771 patients reclassified by the hs-cTnI assay, 105 of 720 (15%) had a primary outcome event in the validation phase and 131 of 1,051 (12%) had an event in the implementation phase. The adjusted OR for implementation vs. validation was 1.10 (95% CI: 0.75 to 1.61). The High-STEACS investigators concluded that the implemention of hs-cTnI did not reduce future MI or cardiovascular death at one year, nor did it result in harm due to excess bleeding or non-cardiovascular death. Furthermore, implementation reduced median length of stay by 3 hours compared to contemporary troponin testing suggesting that the major benefit of hs-cTnI testing is to permit earlier rule-out of myocardial infarction.

In the HiSTORIC trial, hs-cTnI testing was performed at presentation and repeated 6 to 12 hours after the onset of symptoms in the validation phase, and the High-STEACS early rule-out pathway was introduced in the implementation phase.*(29)* At one year, 703 patients (2.2%) had an MI or cardiac death following discharge from hospital. Before and after implementation this occurred in 396 of 14,700 (2.7%) and 307 of 16,792 (1.8%) (adjusted OR 1.02 (95% CI: 0.74 to 1.40)). At 30 days, there were 57/14700 (0.4%) and 56/16792 (0.3%) events following discharge (adjusted OR 1.97 (95% CI: 0.95 to 4.08)).*(29)* In HiSTORIC, the mean length of stay was reduced from 10.1 (SD 4.1) to 6.8 (SD 3.9) hours

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(adjusted geometric mean ratio 0.78 (95% confidence interval 0.73 to 0.83) and the proportion of patients discharged directly from the Emergency Department without hospital admission increased from 50% to 71% (adjusted OR 1.59, 95% CI: 1.45 to 1.75).*(29)*

These studies represent direct, real world evidence about the effects of implementing an early rule-out strategy, based on high-sensitivity cardiac troponin testing.

Discussion

Statement of principal findings

The evidence base for the use of high-sensitivity cardiac troponin assays has expanded rapidly since the publication of our previous systematic review.*(4)* The main areas of change have been an increase in the number of hs-cTn assays available and a proliferation of studies considering how to operationalise hs-cTn assays in clinical practice. Previously, the majority of studies assessed the diagnostic accuracy of a single test.

There are three principal findings. First, single admission strategy rule-out can be reliably achieved across a range of high sensitivity troponin assays. Secondly, a combined strategy of admission measurement with immediate rule-out plus serial testing and a delta change has good diagnostic efficiency (increased rule-out rates compared to single admission strategies) with improvements in specificity. Finally, a strategy of serial testing alone has excellent sensitivity and specificity but lacks the option for immediate patient discharge.

With respect to single test strategies, our findings were consistent with those of our previous systematic review,*(4*) indicating that very low hs-cTn levels (below a threshold at or near the limit of detection for a given assay) in a single sample, taken on presentation, achieve the minimum acceptable sensitivity of ≥97% and hence may be considered adequate to rule-out

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NSTEMI. The results of a recent randomised controlled trial support the safety of this approach.*(30)*

Versions of the ESC 0/1 hour rule-out pathway,*(18)* adapted for use with different hs-cTn assays, were the most commonly evaluated multiple sample test strategies. For all of the hs-cTn assays, in which versions of the ESC 0/1 hour rule-out pathway have been evaluated, reported sensitivity estimates exceeded the minimum acceptable threshold of 97%.

Considering a hypothetical cohort of 1,000 patients and an NSTEMI prevalence of 12.2%, calculated by combining the UK Hospital Episode Statistics (HES) 2017-2018 prevalence of MI (19.9%) in people presenting to the ED with chest pain*(2)* and the proportion of all confirmed cases of MI that are NSTEMI (0.613) from the Myocardial Ischemia National Audit Project (MINAP) 2019,*(31)* application of the ESC 0/1 hour rule-out pathway would result in the discharge of between 500 and 615 patients (depending on the hs-cTn assay used) within 2 hours of presentation (allowing for a 1 hour assay turnaround time), with a maximum of 1 instance of NSTEMI missed per 1,000 patients.

Two-step rule-out strategies, such as the High-STEACS pathway,*(28,29)* which use a later (3 hours from presentation) second sample offer the potential to further increase overall specificity without loss of sensitivity. Based on the hypothetical cohort of 1,000 patients described, application of the High-STEACS rule-out pathway would result in the discharge of between 650 and 667 patients within 4 hours (allowing for a 1 hour assay turnaround time), with up to 2 patients with NSTEMI being erroneously discharged for every 1,000 presenting with chest pain. This calculation is consistent with the conclusions from a recently published large, individual patient-level analysis, which took data from 19 international patient cohorts (n = 22,457 patients).*(32)* Furthermore, data from these cohorts were subsequently pooled and a derivation-validation design used to assess multiple hs-cTn test strategies and inform

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the development of a risk assessment tool.*(33)* This study found that patients at low risk for myocardial infarction were likely to have very low concentrations of hs-cTn at presentation and small absolute changes on serial sampling, and that these patients were also at very low risk for myocardial infarction or death from any cause at 30 days.

There was a notable lack of evidence for the accuracy of serial sampling over 1-3 hours using the 99th percentile upper reference limit as a cut-off. Only the Roche hs-cTnT assay has published data to suggest that using the 99th percentile on arrival and 3 hours later (or 2 hours later in combination with a delta threshold of 4 ng/L) achieves a sensitivity >97% to rule out AMI. For all other assays, it would appear preferable to use the combination of a low cut-off on arrival and the absence of a delta change (Supplementary File 4) to rule out MI.

Strengths, limitations and uncertainties

Extensive literature searches were conducted in an attempt to maximise retrieval of relevant studies. Because of the known difficulties in identifying test accuracy studies using study design-related search terms,*(34)* search strategies were developed to maximise sensitivity at the expense of reduced specificity. Thus, large numbers of citations were identified and screened, relatively few of which met the inclusion criteria of the review.

Caution should be exercised in comparing different assays and drawing conclusions about overall diagnostic performance of one individual assay. None of the studies are sufficiently powered to detect differences in diagnostic efficiency and the populations studied are heterogeneous.

Our systematic review did not include studies evaluating the use of hs-cTn assays as part of or in combination with a clinical risk score. However, the High-STEACS study*(26)* reported data on the performance of the High-STEACS pathway, using the Abbott ARCHITECT hs-cTnI assay, alone and in combination validated clinical risk scores as did one where troponin

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levels were measured using the Siemens ADVIA Centaur hs-cTnI assay *(35)*. The addition of a clinical risk score did not improve the negative predictive value of the troponin based diagnostic strategies. These data provide an indication that the addition of clinical risk scores to the key hs-cTn multiple test strategies considered in this assessment would be likely to reduce the proportion of patients discharged within four hours (ruled-out), without improving safety.

A recent systematic review of sex-specific and overall 99th centiles of hs-cTnI and hs-cTnT derived from healthy reference populations*(36)* found that 14/16 (87.5%) of hs-cTnI studies and 11/18 (61.1%) of hs-cTnT studies reported lower female-specific thresholds than the overall threshold for the population, conversely, male-specific thresholds were reported as being "generally in line with currently used overall thresholds." Despite this, the clinical effectiveness of using sex-specific threshold for hs-cTn assay remains unclear. In this systematic review only the High-STEACS pathway utilises sex-specific thresholds. It remains unclear whether the use of sex-specific thresholds in the High-STEACS pathway offers any advantage over the use of a single general population threshold.

Conclusions

High-sensitivity troponin assays can be safely used for the rapid rule-out NSTEMI, in adults presenting with acute chest pain. Test strategies that comprise an initial rule-out step, based on low hs-cTn levels in a sample taken on presentation and a minimum symptom duration, and a second step (for patients not meeting the initial rule-out criteria) based on low presentation levels of hs-cTn and small absolute change between presentation and a second sample taken after 1, 2 or 3 hours, are likely to produce the highest rule-out rates whilst maintaining acceptable sensitivity and very low rates of missed NSTEMI.

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Table 1: Inclusion criteria.

Question	**What is the diagnostic performance 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'*(63)* due to a suspected, but not proven, AMI	
Setting:	Secondary or tertiary care	
Interventions (index	hs-cTn assays: Roche Elecsys hs-cTnT, Abbott ARCHITECT hs-cTnI, Abbott Alinity hs-cTnI, Beckman Coulter	

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test):	Access hs-cTnI, Biomérieux VIDAS hs-cTnI, Ortho VITROS hs-cTnI, Quidel TriageTrue hs-cTnI, Siemens ADVIA Centaur hs-cTnI, Siemens Atellica hs-cTnI, Siemens Dimension EXL hs-cTnI, Siemens Dimension Vista hs-cTnI), hs-cTn assays (used singly or in series[***], such that results were available within 3 hours of presentation)	
Comparators:	Any other hs-cTn test or test 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,*(64)* 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

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		follow-up, re-attendance at or re-admission to hospital during follow-up, time to discharge, patient satisfaction or health-related quality of life (HRQoL) measures
Study design:	Diagnostic cohort studies	Randomised controlled trials (RCTs) (controlled clinical trials (CCTs) will be considered if no RCTs are identified)

* UK waiting time target for hospital Accident and Emergency departments

** A high sensitivity assay is defined as one which has a CV ≤10% at the 99th centile 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 hs-cTn assays, data on relative or absolute change in cTn levels and peak cTn values were considered.

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Figure legends

Figure 1: Flow of studies through the review process.

Figure 2: SROC for the Roche Elecsys hs-cTnT assay using the LoD threshold and a presentation sample, target condition any NSTEMI (6 studies).

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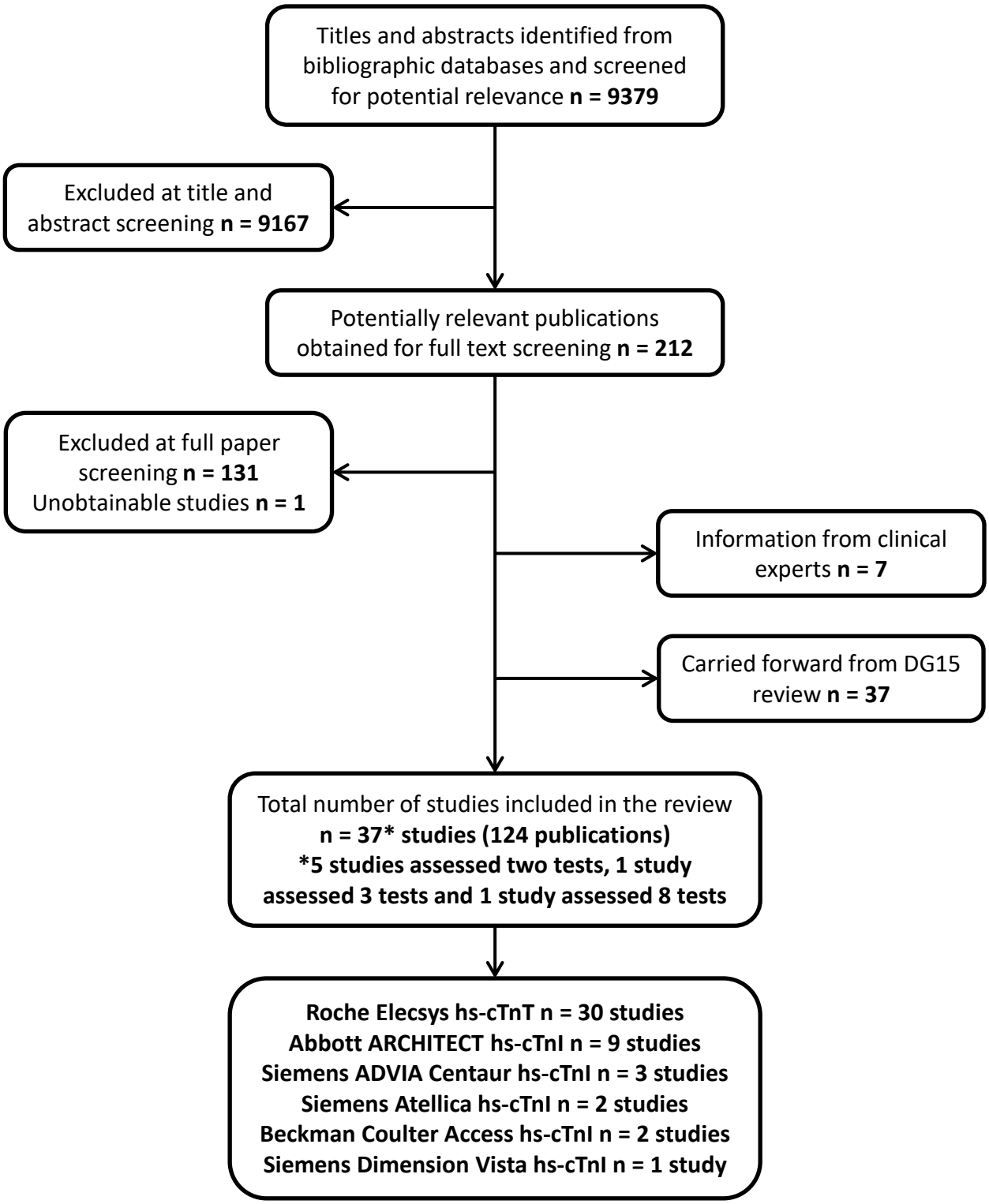

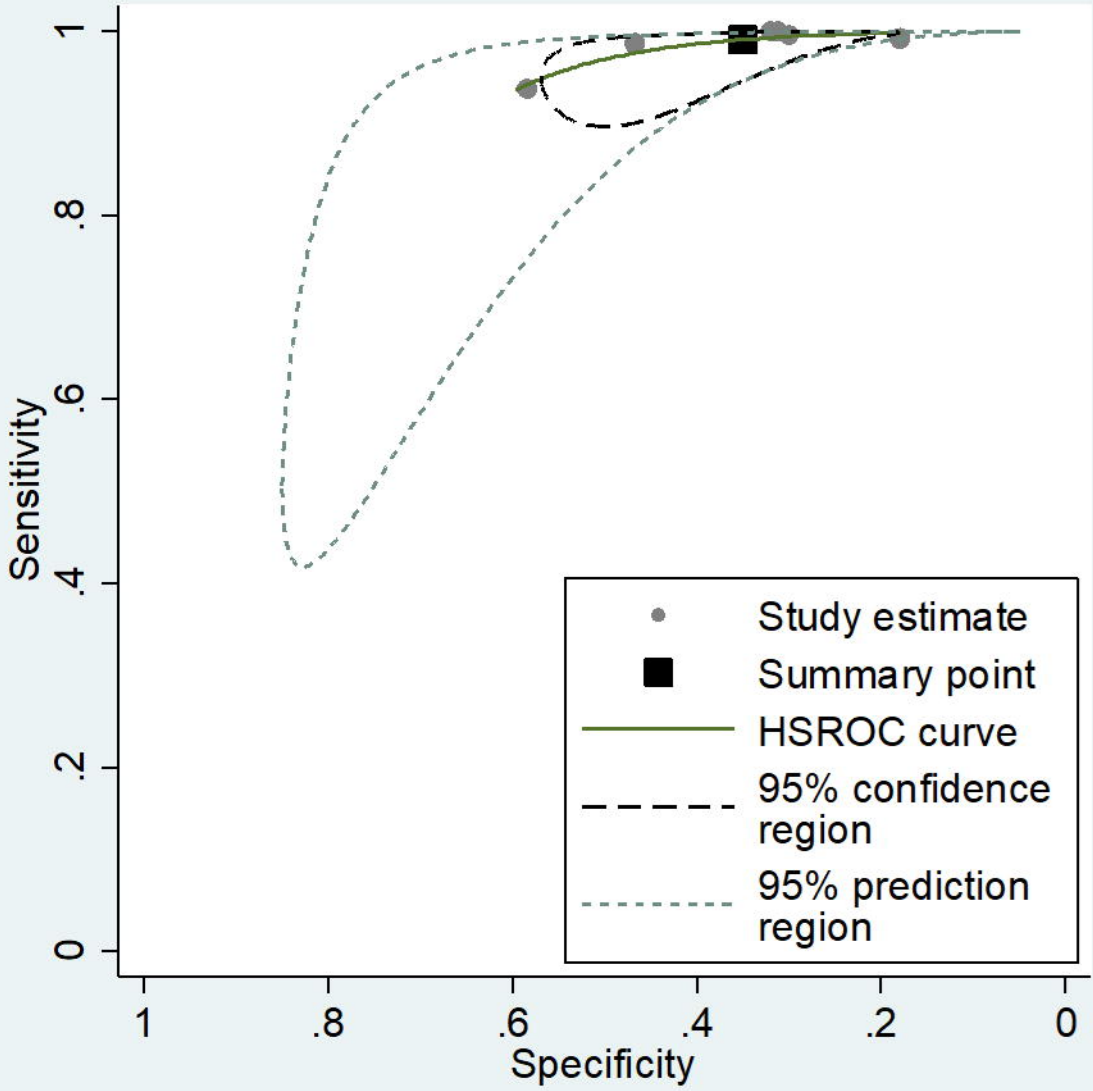
Sensitivity
0
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.6
.8
1
1
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0
Specificity
Study estimate
Summary point
HSROC curve
95% confidence region
95% prediction region