

RESEARCH

Diagnostic accuracy of single baseline measurement of Elecsys Troponin T high-sensitive assay for diagnosis of acute myocardial infarction in emergency department: systematic review and meta-analysis

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Abstract

Objective To obtain summary estimates of the accuracy of a single baseline measurement of the Elecsys Troponin T high-sensitive assay (Roche Diagnostics) for the diagnosis of acute myocardial infarction in patients presenting to the emergency department.

Design Systematic review and meta-analysis of diagnostic test accuracy studies.

Data sources Medline, Embase, and other relevant electronic databases were searched for papers published between January 2006 and December 2013.

Study selection Studies were included if they evaluated the diagnostic accuracy of a single baseline measurement of Elecsys Troponin T high-sensitive assay for the diagnosis of acute myocardial infarction in patients presenting to the emergency department with suspected acute coronary syndrome.

Study appraisal and data synthesis The first author screened all titles and abstracts identified through the searches and selected all potentially relevant papers. The screening of the full texts, the data extraction, and the methodological quality assessment, using the adapted QUADAS-2 tool, were conducted independently by two reviewers with disagreements being resolved through discussion or arbitration. If appropriate, meta-analysis was conducted using the hierarchical bivariate model.

Results Twenty three studies reported the performance of the evaluated assay at presentation. The results for 14 ng/L and 3-5 ng/L cut-off values were pooled separately. At 14 ng/L (20 papers), the summary sensitivity was 89.5% (95% confidence interval 86.3% to 92.1%) and the summary

specificity was 77.1% (68.7% to 83.7%). At 3-5 ng/L (six papers), the summary sensitivity was 97.4% (94.9% to 98.7%) and the summary specificity was 42.4% (31.2% to 54.5%). This means that if 21 of 100 consecutive patients have the target condition (21%, the median prevalence across the studies), 2 (95% confidence interval 2 to 3) of 21 patients with acute myocardial infarction will be missed (false negatives) if 14 ng/L is used as a cut-off value and 18 (13 to 25) of 79 patients without acute myocardial infarction will test positive (false positives). If the 3-5 ng/L cut-off value is used, <1 (0 to 1) patient with acute myocardial infarction will be missed and 46 (36 to 54) patients without acute myocardial infarction will test positive.

Conclusions The results indicate that a single baseline measurement of the Elecsys Troponin T high-sensitive assay could be used to rule out acute myocardial infarction if lower cut-off values such as 3 ng/L or 5 ng/L are used. However, this method should be part of a comprehensive triage strategy and may not be appropriate for patients who present less than three hours after symptom onset. Care must also be exercised because of the higher imprecision of the evaluated assay and the greater effect of lot-to-lot reagent variation at low troponin concentrations.

Systematic review registration PROSPERO registration number CRD42013003926.

Introduction

Emergency physicians commonly encounter chest pain and other symptoms suggestive of acute coronary syndrome, which account for approximately 5% to 10% of all visits to the

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emergency department.^{1 2} Timely diagnosis of such patients, especially ruling in or out of acute myocardial infarction, is of paramount importance. Delays in confirming the diagnosis may increase the risk of complications, and missing it may have fatal consequences for the patient.^{3 4} Until recently, the triage tools used by emergency physicians—clinical symptoms, history, 12 lead electrocardiogram, and standard troponin assays—did not allow early exclusion of evolving acute myocardial infarction. To avoid inadvertent discharge home, approximately 80% of all patients with chest pain were admitted to hospital for clinical observation and further testing, despite the fact that only a small proportion of them (approximately 25%) were eventually diagnosed as having myocardial infarction.⁵

The need to triage patients with chest pain more effectively and efficiently—to avoid unnecessary hospital admissions and to speed up the diagnostic process—has driven the development of the so called high sensitivity cardiac troponin assays. To be classified as high sensitivity, a cardiac troponin assay should meet two criteria: firstly, its total imprecision (coefficient of variation) at the 99th centile of the healthy reference population should be 10% or less; secondly, measureable concentrations above the limit of detection and below the 99th centile should be attainable for at least 50% of the reference population.⁶ Over the past few years in the United Kingdom, standard troponin assays have gradually been replaced with high sensitivity ones. Although authoritative data on how and to what extent they are used in different National Health Service trusts are unavailable, anecdotal evidence strongly suggests both that standard troponin assay use remains common and that where used high sensitivity assays are being used in the same manner as standard troponin assays, not capitalising on their greater sensitivity.

To improve this situation, the National Institute for Health and Care Excellence (NICE) has recently published guidance on the clinical application of high sensitivity troponin assays in the early rule-out of acute myocardial infarction. The guidance recommends the Elecsys Troponin T high-sensitive assay (Roche Diagnostics) and the ARCHITECT^{STAT} high sensitive troponin I (Abbott Laboratories) for use with early rule-out protocols that include blood samples taken at the patient's presentation to the emergency department and a second sample three hours later. A third assay, the AccuTnI+3 (Beckman Coulter) has also been evaluated, but owing to insufficient evidence it is recommended only for use in clinical research.⁷ The guidance recommends the use of the 99th centile as a cut-off value when deciding whether to rule out acute myocardial infarction or to refer the patient for further investigations. Given the high negative predictive value of high sensitivity troponin assays and the fact that patients who present with very low cardiac troponin concentrations also have a very low risk of myocardial infarction, a rule-out strategy based on a single sample at presentation and lower decision thresholds, such as the assay's limit of detection or limit of blank, has also been proposed.⁵ The limit of blank is the highest apparent analyte concentration (analytical noise) expected to be found when replicates of a blank sample containing no analyte are tested. The limit of detection, on the other hand, is the lowest analyte concentration likely to be reliably distinguished from the limit of blank and at which detection is feasible.⁸ Using these cut-off values may provide the means to identify patients at very low risk in whom acute myocardial infarction could be excluded without a second troponin measurement. The effectiveness and feasibility of such a strategy, however, will depend on a range of factors, including the diagnostic sensitivity and the precision of the assay at such low threshold values.

We did a systematic review and meta-analyses of studies evaluating the diagnostic accuracy of the Elecsys Troponin T high-sensitive assay (hereinafter referred to as the high sensitivity troponin T assay) for early diagnosis of acute myocardial infarction in patients presenting to the emergency department with chest pain and other symptoms suggestive of acute coronary syndrome. The review protocol was registered on the PROSPERO database (registration number CRD42013003926). Here we report the results pertaining to the hypothesis that a single use of the high sensitivity troponin T assay at presentation is sensitive enough to allow the safe exclusion of acute myocardial infarction. The accuracy estimates obtained for serial measurements and change in troponin concentration (the other objective stated in our review protocol) will be reported in a separate publication.

The high sensitivity troponin T assay is a modification of Roche's fourth generation standard troponin T assay. The specifications provided by the manufacturer are as follows. The assay's limit of blank is 3 ng/L, the limit of detection is 5 ng/L, and the limit of quantification (the lowest analyte concentration that can be reproducibly measured with coefficient of variation of 10% or less) is 13 ng/L. The 99th centile of a healthy reference population recommended as a positivity threshold for the diagnosis of acute myocardial infarction is 14 ng/L, and the estimated turnaround time is 18 minutes. The assay is also available as a short turnaround time version with an estimated turnaround time of nine minutes.⁹ It is commercially available and in clinical use worldwide with the exception of the United States, where it is used for research but has not yet obtained clearance from the US Food and Drug Administration.⁶

Methods

We followed the recommendations of the Cochrane Collaboration's Diagnostic Test Accuracy Group.¹⁰ We searched the following databases: Ovid Medline and Medline in-process, Ovid Embase, Science Citation Index, Medion database, Database of Abstracts of Reviews of Effects (DARE), Cochrane Database of Systematic Reviews (CDSR), Research Portfolio Online Reporting Tools (RePORT, formally CRISP), and International Network of Agencies for Health Technology Assessment (INAHTA). The search strategies for Embase and Medline are provided in web appendix 1. The initial validation study of the high sensitivity troponin T assay was reported in 2010.¹¹ To capture earlier studies using the pre-commercial version of the assay, we extended the search period back to January 2006 and hand searched the reference lists of all relevant publications including systematic reviews and relevant opinion papers.

The first author (ZZ) did the initial selection on the basis of titles and abstracts. Full text copies of potentially relevant publications were obtained and screened independently by two reviewers (ZZ, HC, TJH), with all discrepancies resolved through discussion or arbitration by a third reviewer (CH). We used the reference management software EndNote X7 for the selection process. We selected studies for inclusion in the review if they met the following pre-specified criteria: diagnostic cohort studies, evaluating the diagnostic accuracy of the Roche high sensitivity troponin T assay for the diagnosis of acute myocardial infarction, in patients presenting to the emergency department with suspected acute coronary syndrome, against a reference standard based on the contemporary universal definition of acute myocardial infarction,¹² and published in peer reviewed journals. We included in the meta-analyses reported here only those studies reporting the diagnostic accuracy of the high sensitivity

troponin T assay at the patient's presentation to the emergency department and using pre-specified positivity thresholds. Two reviewers (ZZ, EY) used a standardised data extraction form to independently abstract relevant details on the publication, the study methods, and the results. We included publications reporting results from the same study or studies based on overlapping samples only if they complemented each other in terms of reported results (for instance, if they reported results for different cut-off values); we took care to avoid double counting. We excluded studies if they failed to meet the inclusion criteria or essential information was missing and could not be obtained from the authors.

Two reviewers (ZZ, EY) independently assessed the methodological quality of the included studies by using a modified version of the QUADAS-2 tool (web appendix 2).¹³ Any disagreements were resolved through discussion and, if necessary, arbitration by another reviewer (CH).

We constructed two-by-two tables, calculated sensitivity and specificity with 95% confidence intervals, and created coupled forest plots for each subset of data. We used random effects bivariate models to do separate meta-analyses for different pre-specified cut-off values.¹⁴ We explored heterogeneity in the first instance through visual examination of the forest plot and the receiver operating characteristics plot for each set of raw data. We considered the following sources of heterogeneity and, if appropriate, added them to a bivariate regression model: target condition, reference test, patients' characteristics, and QUADAS-2 items. We did sensitivity analysis to check the robustness of the results. We used Cook's distance to identify particularly influential studies and created a scatter plot of the standardised predicted random effects (standardised level 2 residuals) to check for outliers.¹⁵ Then we refitted the model leaving out any outliers and very influential studies, one at a time, to check the robustness of the results. As standard funnel plots and tests for publication bias are not recommended in meta-analysis of diagnostic accuracy studies, we did not investigate publication bias.¹⁰ All data processing and statistical analyses were done using Review Manager 5.2 and STATA version 13 including the user written commands *metandi* and *midas*.^{13 15-17}

Results

The electronic searches identified 3071 records, of which 141 full text articles were assessed for eligibility. Thirty nine of them met the criteria for inclusion in the review, and one additional paper was included from the hand search.^{5 18-56} Twenty studies (23 papers) were included in the meta-analyses reported here (fig 1).^{5 19-23 28-32 34-37 39 41 42 45 53-56} Table 1 shows their main characteristics, and additional details are provided in supplementary tables A-C.

Two of the 23 included papers reported results from the ongoing multicentre study Advantageous Predictors of Acute Coronary Syndromes Evaluation (APACE),^{35 53} and four reported results from two other studies.¹⁹⁻²² The total number of patients in the included studies was 9428, ranging from 137²⁸ to 2072^{35 53} (median 350, interquartile range 221-491). The reported mean or median age of the included patients ranged from 54²⁹ to 71 years⁴¹ (with the exception of the study by Bahrmann et al,²³ which included only patients aged 70 years or over), and the proportion of men ranged from 49%²³ to 83%.³⁹ One study included only patients with coronary artery disease,³⁹ and another included unselected patients aged 70 or over presenting to the emergency department with a non-surgical condition.²³ Ten studies defined specific time from onset of symptoms to

presentation as an inclusion criterion, which ranged from four hours³⁹ to 24 hours.⁵ Most of the patients presented to the emergency department within 12 hours of symptom onset, with study medians ranging from 3.5 hours⁵ to 6.3 hours,^{21 22} but the average time was reported inconsistently. In 11 papers, the results for non-ST elevation myocardial infarction were reported separately or patients with ST elevation on the initial electrocardiogram were excluded from the study. The median prevalence of acute myocardial infarction was 21.4% (interquartile range 13.3-34.7%) and ranged from 8.0%²⁹ to 56.2%.⁴²

All included studies used a composite reference standard based on the contemporary universal definition of myocardial infarction.¹² In terms of reference assays used to diagnose myocardial necrosis, eight studies used serial high sensitivity troponin T assay; 13 studies used standard troponin T or I assays, or a combination of them; one study used a combination of either standard troponin T or I (local assays) and high sensitivity troponin I assays (central laboratory)³⁹; one study used a combination of standard and high sensitivity troponin T assays⁴¹; and the reference assay in one study was unclear³⁶ (in some studies the accuracies according to different reference assays were reported separately).

Twenty studies reported the performance of high sensitivity troponin T at the manufacturer's recommended cut-off value of 14 ng/L, which represents the 99th centile of a healthy reference population^{5 20 21 23 28-32 34-37 39 41 42 45 54-56}; four studies reported the performance of the test at 3 ng/L (limit of blank)^{5 22 28 43} and four at 5 ng/L (limit of detection)^{19 22 34 53}; results for receiver operating characteristics optimised or other cut-off values were also reported in some papers (table 1 and supplementary table C).

Table 2 and supplementary table D show the results from the assessment of the methodological quality of the included studies. In approximately half of the studies, patients with ST elevation myocardial infarction were not excluded. As cardiac markers play no role in the diagnosis of this condition, which is made primarily on the results from the electrocardiogram, including patients with this diagnosis may compromise the applicability of the results.³² The use of high sensitivity troponin T as part of the reference standard may lead to incorporation bias, thus inflating the accuracy estimates, whereas using a standard troponin assay as a reference test may result in patients with minor myocardial infarctions being misclassified as false positives. We investigated the effect of using different generations of reference assays in the meta-regression.

To obtain clinically relevant estimates of the performance of a single baseline measurement of the high sensitivity troponin T assay, we conducted, as far as the data permitted, separate meta-analyses for the different pre-specified cut-off values reported in the papers. The results from these meta-analyses are presented below.

Performance of assay at 14 ng/L cut-off value

We pooled the results from 20 studies to obtain summary estimates of the sensitivity and specificity at the 14 ng/L cut-off value. When a study reported separately the results for non-ST elevation myocardial infarction and acute myocardial infarction (that is, both patients with ST and non-ST elevation myocardial infarction were included in the study cohort), we included only those for non-ST elevation myocardial infarction, which are clinically more relevant. In a similar way, when both standard troponin and high sensitivity troponin assays were used as reference tests, we included only the results obtained with high

sensitivity assays because, being more sensitive, they are able to identify patients with small myocardial infarctions that would be missed by the standard assays. The target condition was acute myocardial infarction in 10 studies and non-ST elevation myocardial infarction in the remaining 10 studies; the reference test was a standard troponin assay in nine studies, high sensitivity troponin assay in eight, either standard or high sensitivity in one, both standard and high sensitivity in one, and unclear in one study. Figure 2 shows a forest plot of the coupled sensitivity and specificity with 95% confidence intervals for each study included in this meta-analysis.

Pooling the results produced the following summary estimates: sensitivity 89.5% (95% confidence interval 86.3% to 92.1%), specificity 77.1% (68.7% to 83.7%), positive likelihood ratio 3.9 (2.8 to 5.4), and negative likelihood ratio 0.14 (0.10 to 0.18). The summary receiver operating characteristics plot (fig 3) shows the summary sensitivity and specificity (the solid blue spot in the middle) and the 95% confidence and prediction regions (the inner and outer ellipses, respectively).

As shown in figures 2 and 3, a significant level of heterogeneity was apparent in the results, greater in specificity than in sensitivity. We investigated the effect of the target condition (acute myocardial infarction versus non-ST elevation myocardial infarction) and the reference test (standard versus high sensitivity troponin assay) on the summary estimates of sensitivity and specificity by adding them as covariates to a bivariate regression model (one covariate at a time) and used a likelihood ratio test to determine the statistical significance of the results. As in two studies a combination of standard and high sensitivity assays were used as a reference test,^{29 41} and the type of the reference assay was unclear in another study,³⁶ we excluded those three studies from the meta-regression. Without them, the likelihood ratio test showed that the use of different reference standards accounts for some of the variability in the sensitivity ($P=0.008$) but not in the specificity ($P=0.66$) (fig 4). A model that allowed for sensitivity and its variance to vary between studies using different reference tests (standard versus high sensitivity assays) produced the following summary estimates: sensitivity (standard reference assay) 87.7% (82.6% to 89.9%), sensitivity (high sensitivity reference assay) 93.4% (89.8% to 95.7%), specificity 74.7% (73.6% to 75.8%), positive likelihood ratio (standard reference assay) 3.43 (3.08 to 3.82), positive likelihood ratio (high sensitivity reference assay) 3.69 (3.13 to 4.36), negative likelihood ratio (standard reference assay) 0.18 (0.14 to 0.23), negative likelihood ratio (high sensitivity reference assay) 0.09 (0.06 to 0.14). The target condition, on the other hand, had no effect on the results ($P=0.79$).

On the basis of the Cook's distance, we found the following studies to be the most influential in the meta-analysis (in descending order): Khan et al,³⁹ Melki et al,⁴² Invernizzi et al,³⁷ and Collinson et al²⁹ (fig 5). Of these, only Khan et al was identified as an outlier having the highest standardised residuals for specificity (fig 6). After refitting the model and leaving this study out, we observed no change in sensitivity (89.5% v 89.7%) but specificity decreased from 77.1% to 74.9%. This could be explained by the fact that this study excluded patients without coronary artery disease, thus reducing the probability of false positive results.

Performance of assay when either 3 ng/L (limit of blank) or 5 ng/L (limit of detection) was used as cut-off value

Seven papers reported the results for 3 ng/L and/or 5 ng/L cut-off values at presentation.^{5 19 22 28 34 43 53} Given the small number of studies, pooling the data for each cut-off value separately would have produced unreliable results. Instead, we decided to obtain more precise and reliable summary estimates by including in the meta-analysis all independent 3 ng/L and 5 ng/L data.^{5 19 22 28 34 53} Two studies reported the results for both cut-off values.^{22 43 53} As in this analysis we were interested mainly in the sensitivity of the test (its accuracy for ruling out acute myocardial infarction), we decided to include the results for 5 ng/L as the performance at a higher cut-off value would produce a lower sensitivity estimate thus representing the worse case scenario. Owing to the inverse correlation between sensitivity and specificity, we could assume that using even lower cut-off values would further increase the sensitivity of the assay and its ability to rule out the target condition. Thus, from the APACE trial we excluded the results reported by Meune et al,⁴³ included those reported by Rubini Gimenez et al,⁵³ and included only the 5 ng/L data reported by Aldous et al.²² Also, Christ et al reported two different sets of 3 ng/L results, obtained using standard troponin T and high sensitivity troponin T as reference assays.²⁸ As in the previous analysis, we included the results obtained by using high sensitivity troponin T as a reference assay, which is more sensitive and, therefore, more likely to capture small myocardial infarctions. Figure 7 shows a forest plot of the sensitivities and specificities of the included studies. Pooling the results from the six studies produced the following summary estimates: sensitivity 97.4% (94.9% to 98.7%), specificity 42.4% (31.2% to 54.5%), positive likelihood ratio 1.69 (1.40 to 2.05), and negative likelihood ratio 0.06 (0.04 to 0.10) (fig 8).

Discussion

In the meta-analyses reported here, we included 20 studies (23 papers) evaluating the diagnostic accuracy of a single baseline determination of the Elecsys Troponin T high-sensitive assay at pre-specified cut-off values in patients presenting to the emergency department with suspected acute coronary syndrome. We pooled data separately for 14 ng/L and for the combined 3 and 5 ng/L cut-off values. At 14 ng/L, the 99th centile of a healthy reference population as reported by the manufacturer, the summary sensitivity and specificity were 89.5% (95% confidence interval 86.3% to 92.1%) and 77.1% (68.7% to 83.7%). This means that if the pre-test probability is 21% (the median prevalence of the target condition across the studies), then 21 of 100 tested patients will have a final diagnosis of acute myocardial infarction; of them, between 18 and 19 will test positive (true positives) and two or three will test negative (false negatives). Of the 79 without the target condition, between 54 and 66 will test negative (true negatives) and between 13 and 25 will test positive (false positives).

Pooling all independent data for 3 ng/L and 5 ng/L cut-off values produced a summary sensitivity of 97.4% (94.9% to 98.7%) and a summary specificity of 42.4% (31.2% to 54.5%). This means that of 21 patients with acute myocardial infarction, between 20 and 21 will test positive (true positives) and between none and one will be missed (false negatives). Of the 79 without the target condition, between 25 and 43 will test negative (true negatives) and between 36 and 54 will test positive (false positives). Given the presence of a clear threshold effect—sensitivity increases at the expense of specificity when

a lower threshold is used—we can anticipate that in patients with high sensitivity troponin T concentrations below 3 ng/L the sensitivity will be even higher and no patients with myocardial infarction will be missed. On the other hand, using lower cut-off values will inevitably result in more false positives.

Strengths and limitations of study

These results should be treated with caution. They apply only to a specific assay, the Elecsys Troponin T high-sensitive assay (Roche Diagnostics), and may not generalise to other high sensitivity assays by other manufacturers. The sensitivity of a baseline measurement depends on the time between symptom onset and blood draw. Although we were unable to investigate this here, the results reported in the primary studies indicate that in patients who present within three hours of symptom onset the probability of false negatives is higher and a second measurement may be needed to avoid the inadvertent discharge of patients with an evolving acute myocardial infarction.^{5 18 53}

One unexpected result in our review was the effect of the reference assay on the summary estimates. The meta-regression at a 14 ng/L cut-off value showed that the sensitivity estimate was higher when serial high sensitivity troponin assay was used as a reference test and lower when the reference test was a standard troponin assay. Using a high sensitivity rather than a standard troponin assay as a reference test would normally result in fewer false positives. This is because patients with borderline troponin concentrations that fall below the positivity threshold of the standard assay but above that of the high sensitivity one would be reclassified from false positives to true positives.²⁰

Although this would affect the specificity of the test, it would have little effect on its sensitivity. It is entirely possible that the higher sensitivity obtained by using high sensitivity assay as a reference test is a result of incorporation bias rather than a reflection of a real effect. If this is the case, it is unlikely to have affected the summary estimates obtained for the 3-5 ng/L cut-off value, as in this meta-analysis all but one study used a standard assay as the reference test.

We were unable to investigate the effect of some characteristics of patients that are known to affect the accuracy of high sensitivity troponin assays, such as age and comorbidities, as such analysis would have required data from individual patients.¹⁰ Most of these factors, however, affect the specificity of the test owing to the increased number of false positives in older patients or patients with other cardiac or non-cardiac conditions and, therefore, are of little relevance to the question we tried to answer here—namely, whether the evaluated test has high enough sensitivity to allow exclusion of acute myocardial infarction with a single baseline measurement.

A further threat to the validity of our results, especially those related to 3-5 ng/L cut-off values, comes from the downward shift observed in the Elecsys Troponin T high-sensitive assay at low concentrations of the measurement interval.⁵⁷ The shift has caused as much as 88% of the samples from healthy people to be measured with values below the limit of blank rather than the 50% or less in the initial evaluation study.^{58 59} Recently, the manufacturer Roche Diagnostics has made adjustments to return the assay to its original specifications.^{57 58} As a consequence, great care would need to be taken with the way the test is carried out in practice to ensure that the test's accuracy at low thresholds achieved in the research reviewed is maintained consistently in the long term. This need for care is reinforced by the assay's total imprecision being much higher at the low end of the measurement interval compared with the required coefficient of variation 10% or less at the 99th centile.

With these provisos, the results from the meta-analyses suggest that although single measurement of high sensitivity troponin T at presentation may result in unacceptably high number of patients with acute myocardial infarction being missed if the 99th centile (14 ng/L) is used as a cut-off value, lowering the decision threshold to the limit of blank or limit of detection could increase the negative predictive value of the assay to a point at which no patients with the target condition will be missed.

To appreciate the significance of this result, we need to know what proportion of patients actually present with baseline concentrations below the assay's limit of blank and limit of detection. Two of the included studies reported such data. In the study by Body et al, 195 (27.7%) of the included 703 patients had undetectable (<3 ng/L) high sensitivity troponin T concentrations at presentation and none of them was diagnosed as having myocardial infarction. Of the 296 (42.1%) patients who had concentrations between 3 ng/L and 14 ng/L, 19 (6.4%) patients developed acute myocardial infarction.⁵ In the APACE trial, as reported by Rubini Gimenez et al,⁵³ of the 2245 patients included in the analysis, 550 (25%) had values below 5 ng/L at presentation and eight (1.5%) of them were diagnosed as having myocardial infarction. These studies show that a significant proportion of the patients who undergo troponin testing in emergency setting present with high sensitivity troponin T concentrations below the limit of detection, and only a very small proportion of them are later diagnosed as having acute myocardial infarction. A diagnostic strategy that incorporates a baseline measurement with the Elecsys Troponin T high-sensitive assay and uses a low cut-off value, such as the limit of blank or limit of detection, to rule out myocardial infarction may help to reduce the number of patients who undergo unnecessary further testing (often associated with potentially harmful effects) and may save resources and relieve pressure on overcrowded emergency departments. Patients with troponin concentrations above this low rule-out threshold could undergo the usual second sample testing before a decision about discharge or admission for further investigations is made.

A recently published study by Body et al suggests that an alternative to the low threshold rule-out strategy discussed above might be available.⁶⁰ In this study, the performance of the 99th centile of the Elecsys Troponin T high-sensitive assay at presentation was evaluated not as a standalone test but in conjunction with the emergency physicians' clinical judgment (based on the patient's history and clinical examination) and the results from the initial electrocardiogram. When combined, the diagnostic information from these three sources had 100% (95.4% to 100%) sensitivity and 100% (95.7% to 100%) negative predictive value. These findings suggest that the summary estimates obtained from our meta-analyses may underestimate the sensitivity of the assay and that using the 99th centile cut-off value in a single measurement at presentation, especially in patients who present more than three hours after symptom onset, may be sufficient to rule out acute myocardial infarction. As Body et al point out, however, such a strategy needs to be prospectively validated in independent populations before clinical implementation.

Comparison with other studies

As far as we are aware, the only other systematic review that has investigated the performance of the Elecsys Troponin T high-sensitive assay is the one by Westwood et al,⁶¹ which underpins the National Institute for Health and Care Excellence's recent guidance on high sensitivity troponin assays.⁷ Our findings are consistent with the NICE guidance to consider two

of the high sensitivity troponin assays, including the one evaluated in this study, as options for the early rule-out of non-ST elevation myocardial infarction in people presenting to an emergency department with chest pain and suspected acute coronary syndrome. The NICE guidance was, however, more cautious about using low cut-off values, expressing concern about “the clinical and practical implications of introducing limit of blank and limit of detection cut-off thresholds into practice.”¹⁷

Conclusions and policy implications

In conclusion, when used with blood samples drawn at the patient’s presentation to the emergency department and given a pre-test probability of 21%, the Elecsys Troponin T high-sensitivity assay will miss two or three patients with acute myocardial infarction if the 99th centile is used as a cut-off value and no patients or one patient if 5 ng/L is used. Using 3 ng/L is likely to reduce even further the proportion of patients with the target condition that would be missed. In patients presenting within three hours of symptom onset, the proportion of missed patients with acute myocardial infarction might be higher. The above results suggest that if low cut-off values are used a single measurement of high sensitivity troponin T at presentation might be sufficient to rule out acute myocardial infarction. Such a strategy would, however, need to be carefully implemented owing to the high imprecision of the assay and greater effect of lot-to-lot reagent variation at low troponin concentrations. In clinical practice, the 99th centile of the index assay used with samples taken at presentation might be able to exclude acute myocardial infarction with sufficient accuracy when combined with the results from the patient’s history, clinical examination, and the initial electrocardiogram. This, however, needs to be prospectively validated in independent cohorts before implementation.

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Contributors: ZZ, CH, SF, and TS drafted the protocol. MR developed the search strategy and did the electronic searches. ZZ, HC, TJ-H, and EY screened the titles and abstracts and selected studies for inclusion. ZZ and EY carried out the data extraction and methodological quality assessment. CH, SF, and TS provided advice and arbitration on the selection process, data extraction, and methodological quality assessment. ZZ and VN did the statistical analysis. ZZ wrote the original draft, and the other authors revised the draft critically for important intellectual content and approved the final version of the paper. ZZ and CH are the guarantors.

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Transparency declaration: The lead author (ZZ) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data sharing: No additional data available.

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What is already known on this topic

Only a small proportion of patients admitted to hospital with chest pain are diagnosed as having acute myocardial infarction

High sensitivity cardiac troponin assays may help emergency physicians to rule out this condition early in the triage, thus avoiding unnecessary additional tests and hospital admissions

What this study adds

A single measurement of the Elecsys Troponin T high-sensitive assay at the patient's presentation to the emergency department will miss two or three patients who have acute myocardial infarction if 14 ng/L is used as a cut-off value

Less than one patient will be missed if 3 ng/L or 5 ng/L is used as a cut-off value; acute myocardial infarction could be ruled out in patients who present with high sensitivity troponin T concentrations below these values

This method should be considered as part of a comprehensive triage strategy and may not be appropriate for patients presenting within three hours after symptom onset

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Tables

Table 1 | Characteristics of included studies

Publication	Study type and location	Target condition	Reference assay	Index test cut-offs (ng/L)	Total No included	Prevalence of target condition (%)	Median (IQR) or mean (SD) age	Sex (% male)	Median (IQR) time to presentation
Aldous 2011 ¹⁹	Single centre, New Zealand	AMI	cTnl	5, 13, 14, 15 (ROC optimised)	332	33.1	64 (53-74)	60.2	4.0 (2.0-8.6) h
Aldous 2011 ²¹	Single centre, New Zealand	NSTEMI	cTnl	14	939	21.3	65 (56-76)	59.7	6.3 (3.3-13.3) h
Aldous 2012 ²⁰	Single centre, New Zealand	AMI	hs-cTnT	14	322	39.0	64 (53-74)	60.2	4.0 (2.0-8.6) h
Aldous 2012 ²²	Single centre, New Zealand	NSTEMI	cTnl	3, 5, 14, 17 (ROC optimised)	939	21.8	65 (56-76)	59.7	6.3 (3.3-13.3) h
Bahrman 2013 ²³	Single centre, Germany	NSTEMI	hs-cTnT	14	306	12.4	81 (6)	49.0	0-3 h: 79 (26%); 3-6 h: 42 (14%); 6-12 h: 25 (8%); >12 h: 161 (52%)
Body 2011 ⁵	Single centre, UK	AMI	cTnT	5, 14	703	18.5	59 (14)	61.2	3.5 h
Christ 2010 ²⁸	Single centre, Germany	AMI	cTnT, hs-cTnT	3, 14	137	15.0 (cTnT), 25.5 (hs-cTnT)	66 (16)	64.0	Within 2 h: 36%; 2-6 h: 22%; 6-24 h: 33%; >24 h: 20%
Collinson 2013 ²⁹	Multicentre, UK	NSTEMI	cTnT, cTnl, hs-cTnl	14	833	8.04	54 (44-64)	60.0	8.25 (5.17-12.30) h
Eggers 2012 ³⁰	Multicentre, Sweden	NSTEMI	cTnl	14	360	35.6	67 (58-76)	65.6	<4 h: 143 (39.7%)
Freund 2011 ³¹	Multicentre, France	AMI	cTnl	14	317	14.2	57 (17)	65.0	NA
Giannitsis 2011 ³²	Single centre, Germany	AMI	hs-cTnT	14	503	27.0	63 (16)	63.0	0-3 h: 45.5%; 3-6 h: 19.5%; 6-12 h: 17.3%; >12 h: 15.1%; missing data: 2.6%
Hammerer-Lercher 2013 ³⁴	Single centre, Austria	AMI	cTnT	5, 14, 20 (ROC optimised), 30, 45 (optimised for LR+ and LR- respectively)	2384 (all), 440 (chest pain)	9.1	60 (21) (all patients); 56 (20) (chest pain patients only)	47.8 (all), 52.3 (chest pain)	AMI: 2 (1-8) h; other cardiac diseases: 3 (2-8) h; other diseases: 3 (2-10) h
Hoeller 2013 ³⁵	Multicentre (APACE), Switzerland, Italy, Spain	AMI	cTnT, cTnl	14	2072	21.4	62 (50-75)	68.8	<3 h: 24.4%; ≥3 h: 75.6%
Inoue 2011 ³⁶	Multicentre, Japan	NSTEMI	Unclear	14	209	35.9	67 (59-75)	73.0	NA
Invernizzi 2013 ³⁷	Single centre, Italy	AMI	cTnT	14	386	8.3	68 (17)	58.0	NA
Khan 2011 ³⁹	Single centre, Pakistan	AMI	hs-cTnT	12, 14, 17	180	33.9	58 (10)	83.0	358 (152-929.3) min
Lotze 2011 ⁴¹	Single centre, Germany	AMI	cTnT, hs-cTnT	14	142	9.2	71 (14)	76.0	NA
Melki 2011 ⁴²	Single centre, Sweden	NSTEMI	cTnT, cTnl, hs-cTnT	14	233	56.2	65 (55-76)	67.0	5.3 (3.3-7.5) h
Normann 2012 ⁴⁵	Single centre, Germany	NSTEMI	hs-cTnT	14, 27 (ROC optimised)	342	48.2	81 (78-85) (in patients ≥75 years); 66 (56-71) (in patients <75 years)	52.5 (≥75 years); 71.5 (<75 years)	NA
Rubini Gimenez 2013 ⁵³	Multicentre (APACE), Switzerland, Italy, Spain	AMI	cTnT, cTnl	5	2072	21.4	62 (50-75)	68.8	<3 h: 24.4%; ≥3 h: 75.6%

Table 1 (continued)

Publication	Study type and location	Target condition	Reference assay	Index test cut-offs (ng/L)	Total No included	Prevalence of target condition (%)	Median (IQR) or mean (SD) age	Sex (% male)	Median (IQR) time to presentation
Santaló 2013 ⁵⁴	Multicentre, Spain	NSTEMI	cTnT	14; 12.2, 25 (ROC optimised)	358	22.1	69 (27-93)	67.9	<3 h: 46.2%
Sebbane 2013 ⁵⁵	Single centre, France	NSTEMI	cTnI	14, 18 (ROC optimised)	167	15.0	61 (48-75)	63.4	NSTEMI: 3.65 (2.75-12) h; UA: 3.76 (2.32-6.50) h; AP: 2.82 (2.63-4.5) h; NCAD: 5.32 (3.05-9.68)
Theelin 2013 ⁵⁶	Single centre, Sweden	NSTEMI	hs-cTnT	14	478	14.6	66 (55-76)	63.0	Unclear

AMI=acute myocardial infarction; AP=angina pectoris; cTnI=cardiac troponin I; cTnT=cardiac troponin T; hs=high sensitivity; IQR=interquartile range; LR=likelihood ratio; NA=not available; NCAD=non-coronary artery disease; NSTEMI=non-ST segment myocardial infarction; ROC=receiver operating characteristics; UA=unstable angina.

Table 2 | Methodological quality assessment of included studies

Study	Patient selection		Index text		Reference standard		Time and flow
	Risk of bias	Concerns about applicability	Risk of bias	Concerns about applicability	Risk of bias	Concerns about applicability	Risk of bias
Aldous 2011 ¹⁹	Low	High	Low	Low	Low	High	High
Aldous 2012 ²⁰	Low	High	Low	Low	High	High	Low
Aldous 2012 ²¹	Low	Low	Low	Low	Low	Low	Low
Aldous 2012 ²²	High	Low	Low	Low	Low	Low	Low
Bahrman 2013 ²³	Low	High	Low	Low	High	Low	Low
Body 2011 ⁵	Unclear	High	Low	Low	Low	High	Low
Christ 2010 ²⁸	Low	High	Low	Low	High	High	Low
Collinson 2013 ²⁹	Low	Low	Low	Low	Low	Low	High
Eggers 2012 ³⁰	Unclear	High	Low	Low	Unclear	Low	High
Freund 2011 ³¹	Low	High	Low	Low	Low	High	Low
Giannitsis 2011 ³²	Unclear	High	Low	Low	High	High	Low
Hammerer-Lercher 2013 ³⁴	Low	High	Low	Low	Yes	High	Low
Hoeller 2013 ³⁵	Low	High	Low	Low	Low	High	Low
Inoue 2011 ³⁶	Unclear	Low	Low	Low	Unclear	Low	Low
Invernizzi 2013 ³⁷	Low	High	Low	Low	Unclear	High	Low
Khan 2011 ³⁹	High	High	Low	Low	High	High	Low
Lotze 2011 ⁴¹	Low	High	Low	Low	High	High	Low
Melki 2011 ⁴²	High	High	Low	Low	Low	Low	Low
Normann 2012 ⁴⁵	Low	Low	Low	Low	High	Low	Low
Rubini Gimenez 2013 ⁵³	Low	High	Low	Low	Low	High	Low
Santaló 2013 ⁵⁴	Low	Low	Low	Low	Unclear	Low	Low
Sebbane 2013 ⁵⁵	Unclear	Low	Low	Low	Low	Low	High
Theilin 2013 ⁵⁶	Low	Low	Low	Low	High	Low	Low

Figures

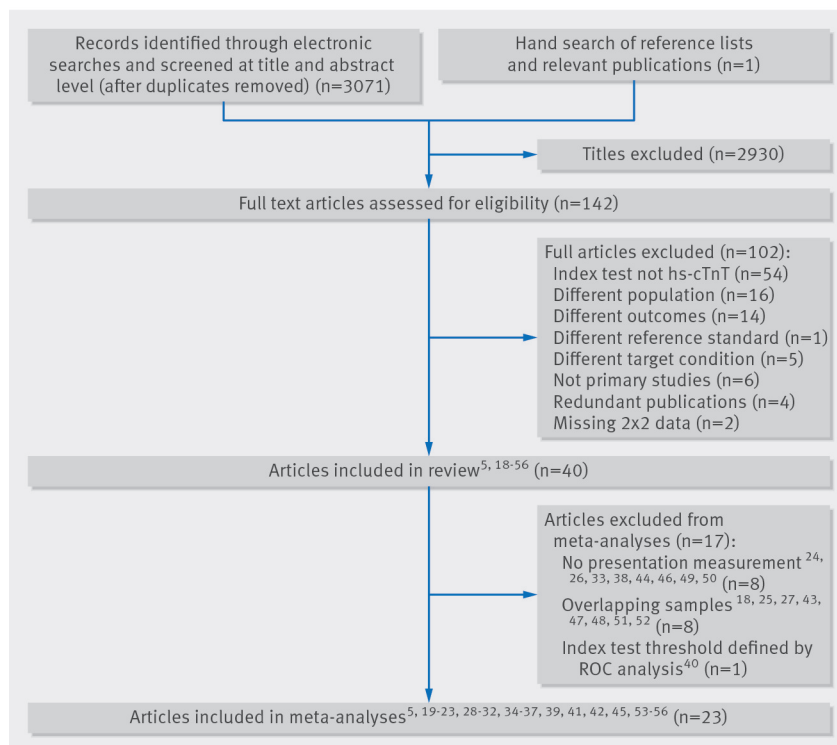


Fig 1 Flow chart of selection process. hs-cTnT=high sensitivity cardiac troponin T; ROC=receiver operating characteristics

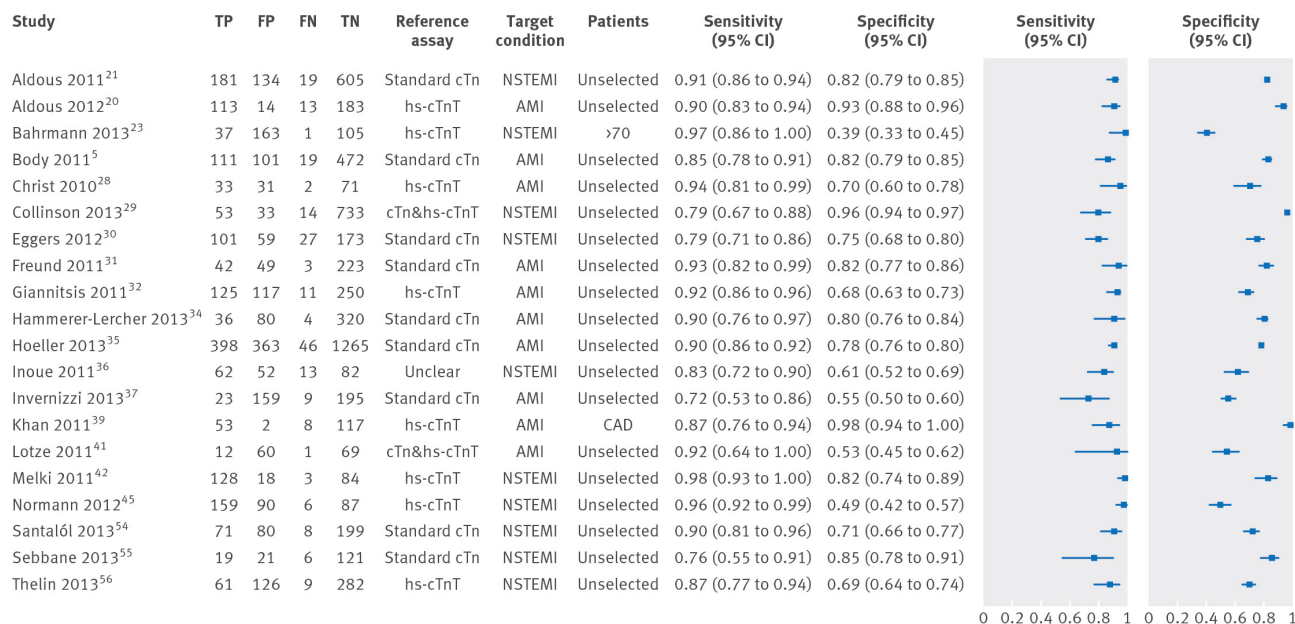
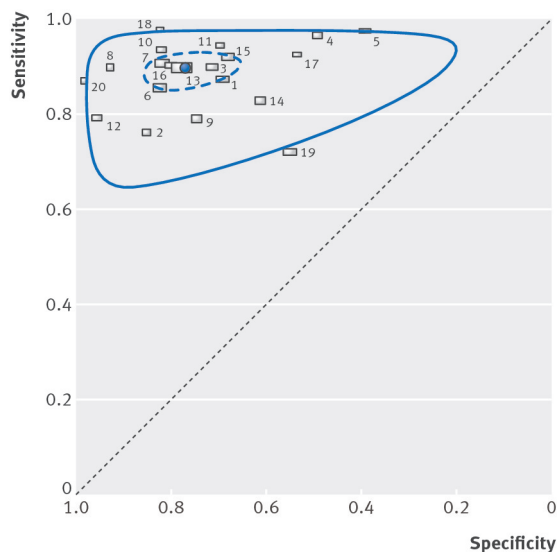


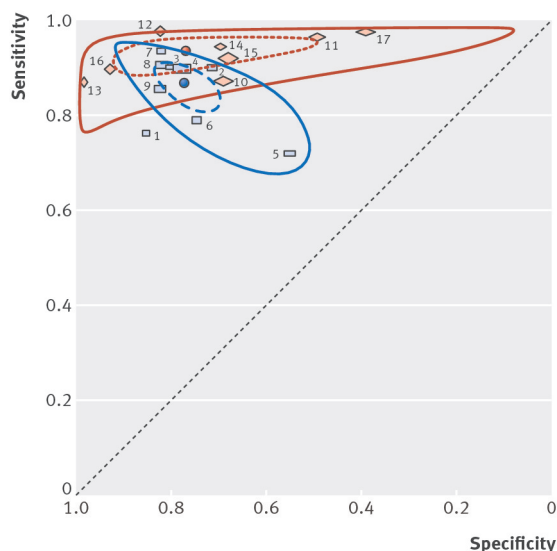
Fig 2 Forest plots of coupled sensitivity and specificity at 14 ng/L (99th centile). FN=false negative; FP=false positive; TN=true negative; TP=true positive. See footnote to table 1 for other abbreviations



Key

- 14 ng/L
- 1 Thelin 2013⁵⁶ 8 Aldous 2012²⁰ 15 Giannitsis 2011³²
- 2 Sebbane 2013⁵⁵ 9 Eggers 2012³⁰ 16 Hammerer-Lercher 2013³⁴
- 3 Santalo 2013⁵⁴ 10 Freund 2011³¹ 17 Lotze 2011⁴¹
- 4 Normann 2012⁴⁵ 11 Christ 2010²⁸ 18 Melki 2011⁴²
- 5 Bahmann 2013²³ 12 Collinson 2013²⁹ 19 Invernizzi 2013³⁷
- 6 Body 2011⁵ 13 Hoeller 2013³⁵ 20 Khan 2011³⁹
- 7 Aldous 2011²¹ 14 Inoue 2011³⁶

Fig 3 Summary receiver operating characteristics plot of sensitivity and specificity at 14 ng/L cut-off value. Each rectangle represents an individual study; size of symbol reflects inverse standard error of specificity (width) and sensitivity (height) estimates; solid spot in middle is summary sensitivity and specificity; inner ellipse represents 95% confidence region, and outer ellipse represents 95% prediction region



Key

- reference assay: standard cTn
- ◇ reference assay: hs-cTnT
- 1 Sebbane 2013⁵⁵ 10 Thelin 2013⁵⁶
- 2 Santalo 2013⁵⁴ 11 Normann 2012⁴⁵
- 3 Hammerer-Lercher 2013³⁴ 12 Melki 2011⁴²
- 4 Hoeller 2013³⁵ 13 Khan 2011³⁹
- 5 Invernizzi 2013³⁷ 14 Christ 2010²⁸
- 6 Eggers 2012³⁰ 15 Giannitsis 2011³²
- 7 Freund 2011³¹ 16 Aldous 2012²⁰
- 8 Aldous 2011²¹ 17 Bahmann 2013²³
- 9 Body 2011⁵

Fig 4 Summary receiver operating characteristics plot comparing effect of different reference tests (standard troponin assay v high sensitivity troponin assay) on summary estimates of sensitivity and specificity (Inoue 2011,³⁶ Lotze 2011,⁴¹ and Collinson 2013²⁹ were

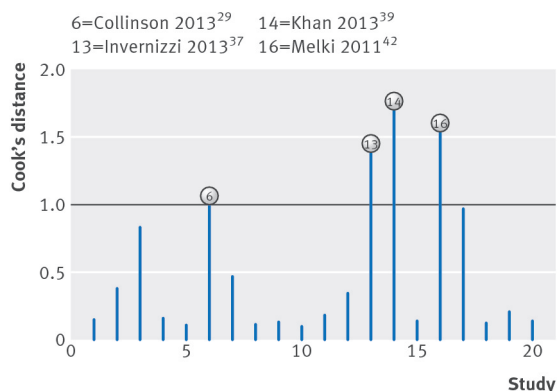
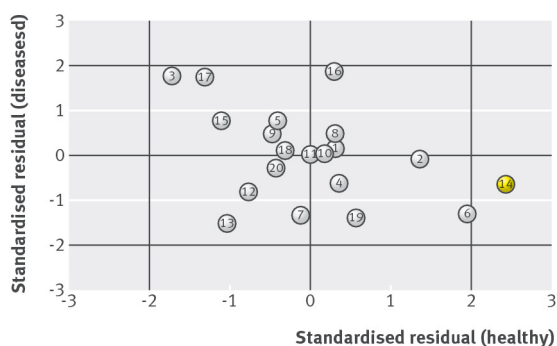


Fig 5 Influence analysis



- 1=Aldous 2011²¹
- 2=Aldous 2012²⁰
- 3=Bahrman 2013²³
- 4=Body 2011⁵
- 5=Christ 2010²⁸
- 6=Collinson 2013²⁹
- 7=Eggers 2012³⁰
- 8=Freund 2011³¹
- 9=Giannitsis 2011³²
- 10=Hammerer-Lercher 2013³⁴
- 11=Hoeller 2013³⁵
- 12=Inoue 2011³⁶
- 13=Invernizzi 2013³⁷
- 14=Khan 2011³⁹
- 15=Lotze 2011⁴¹
- 16=Melki 2011⁴²
- 17=Normann 2012⁴⁵
- 18=Santaló 2013⁵⁴
- 19=Sebbane 2013⁵⁵
- 20=Thelin 2013⁵⁶

Fig 6 Outlier detection

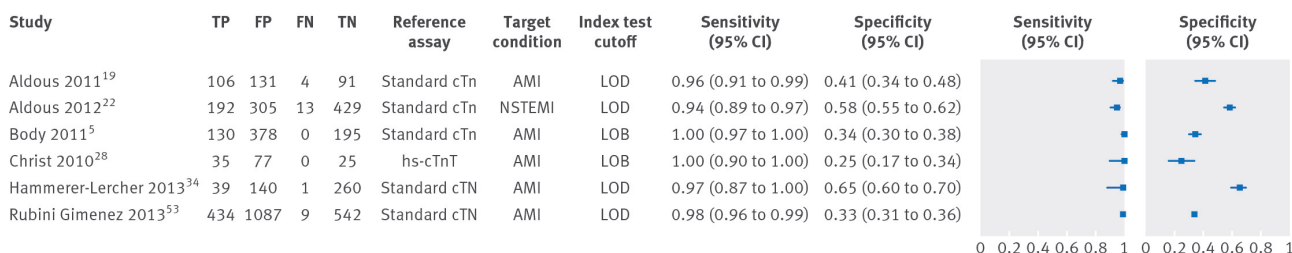
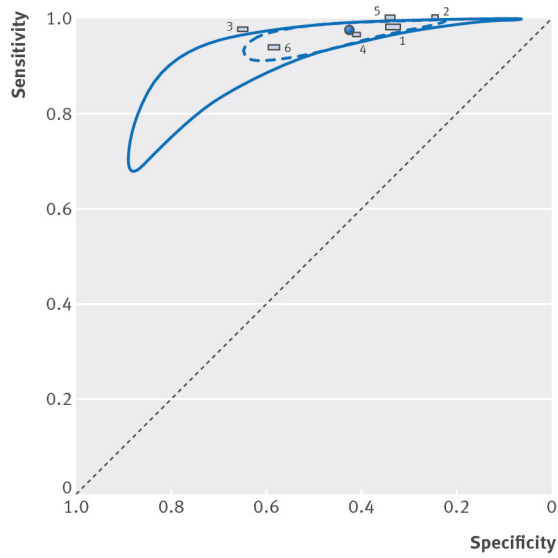


Fig 7 Forest plot of studies included in meta-analysis of combined 3 ng/L and 5 ng/L. FN=false negative; FP=false positive; TN=true negative; TP=true positive. See footnote to table 1 for other abbreviations



Key

- | | |
|---------------------------------------|-----------------------------|
| 1 Rubini Gimenez 2013 ⁵³ | 4 Aldous 2011 ¹⁹ |
| 2 Christ 2010 ²⁸ | 5 Body 2011 ⁵ |
| 3 Hammerer-Lercher 2013 ³⁴ | 6 Aldous 2012 ²² |

- Study estimate
 Summary point
--- 95% confidence region
 — 95% prediction region

Fig 8 Summary receiver operating characteristics plot of sensitivity and specificity for cut-off value of either 3 ng/L or 5 ng/L