in collaboration with:

Maastricht University

ERRATUM TO

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

1. There was an error in the text describing cost-effectiveness results, in the executive summary (page 22) and in section 4.4.2 (page 133): "Beckman Coulter ACCESS hs-cTnI (ESC 0/1 hour pathway: (symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <4 at 0 to 1 h))" corrected to "Beckman Coulter ACCESS hs-cTnI ((symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h))."

   Corrected versions of pages 22 and 133 are copied below.

2. Some information was erroneously omitted from section 2.2.3, pages 28 -29 of the report.
   Missing statement: "The assay can detect troponin I in more than 50% of the reference population."
   Corrected statement: "The turnaround time of the assay is to be confirmed by the company."
   Corrected to: "The turnaround time of the assay is 17 minutes."

   Corrected versions of pages 28 and 29 are copied below.

3. Typographical error, page 31: "The assay has a recommended 99th centile cut-off of 58.9 ng/L for lithium heparin samples and 57.9% for serum samples"
   Corrected to: "The assay has a recommended 99th centile cut-off of 58.9 ng/L for lithium heparin samples and 57.9ng/L for serum samples."

   A corrected version of page 31 is copied below.

4. Some technical information about the Beckman Coulter hs-cTnI assay has been up-dated, in line with new information provided by the manufacturer LoD and LoQ changed from "2.0 ng/L" to "2.3 ng/L".

   A corrected version of the relevant section of Table 1, page 32, is copied below.

5. Some technical information about the Roche Elecsys hs-cTnT assay has been up-dated, in line with new information provided by the manufacturer LoQ changed from "13 ng/L" to "2.97 ng/L to 6.60 ng/L".

   A corrected version of the relevant section of Table 1, page 33, is copied below.

6. There was an error in the reporting of the inclusions criteria for the systematic review, with respect to the reference standard used in diagnostic accuracy studies. The report specifies the third universal definition of AMI; it should have specified minimum third universal definition of AMI (i.e. third or fourth universal definition of AMI).

   Corrected versions of Table 2 page 42 and Appendix 4 page 312 are copied below.

7. An error was identified in Table 25 (page 119): The PPV for strategy 17, Beckman Coulter ACCESS hs-cTnI (ESC pathway), was reported as "0.00", corrected to "0.31".

   A corrected version of the relevant section of Table 25, page 119 is copied below.

8. Typographical errors: Misspelling, “Beckmann” (pages 127, 139 and 140) corrected to “Beckman.”

   Corrected versions of pages 127, 139 and 140 are copied below.

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(£38,871). However, other testing strategies with a sensitivity of 100% (subject to uncertainty) were almost equally effective, resulting in the same LY and QALY gain in up to four decimal places. Comparisons based on the next best alternative showed that for willingness to pay values below £8,455 per QALY, the Beckman Coulter ACCESS hsTnI ((symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h)) would be cost-effective. For thresholds between £8,455 and £20,190 per QALY, the Roche Elecsys hsTnT (<12 ng/L at 0 h AND Δ <3 ng/L at 0 to 1 h) was cost-effective; above £20,190 per QALY Siemens Dimension Vista hsTnI (<5 ng/L at 0 h AND Δ <2 ng/L at 0 to 1 h) would be cost-effective.

Secondary analysis

In the secondary analysis, which assumed that a proportion of false positives in the hs-cTn testing strategies had an increased risk of adverse events (MI and mortality), standard troponin (at presentation and after 10-12 hours) was the cheapest (£37,517) and the least effective (11.334 QALYs) testing strategy (probabilistic analysis). Beckman Coulter ACCESS hs-cTnI ((symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h)) was the most effective testing strategy (11.4725 QALYs) at higher costs (£38,077). All other strategies were (extendedly) dominated. The ICER of Beckman Coulter ACCESS hs-cTnI ((symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h)) versus Standard troponin (at presentation and after 10-12 hours) was £4,043 per QALY gained.

Sensitivity and scenario analyses

The following input parameters had a noticeable impact on the estimated cost-effectiveness the parameters with notable impact on the estimated cost-effectiveness were: the 30 day mortality for untreated AMI, the mortality one year after treated and untreated AMI, the discount rate used for outcomes, and the relative mortality for patients tested true positive versus those that tested false positive. Moreover, only scenario analysis one, increasing the costs for false positives had a substantial impact on the cost-effectiveness.

Conclusions

There is evidence to indicate that high sensitivity troponin assays can be used to rule-out NSTEMI, in adults presenting with acute chest pain, within the four-hour NHS emergency department target. 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 stage (for patients not meeting the initial rule-out criteria) based on low presentation levels of hs-cTn and small absolute change in hs-cTn between presentation and a second sample taken after 1, 2 or 3 hours, are likely to produce the

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2.2 Intervention technologies

High-sensitivity cTn (hs-cTn) assays are now available, which are able to detect lower levels of troponin in the blood. Current generations of commercially available assays have analytical sensitivities up to 100 times greater than was the case for early troponin assays (1 ng/L versus 100 ng/L).[15] Use of these high-sensitivity assays enable the detection of small changes in cTn levels, and may enable NSTEMI to be ruled out at an earlier time after the onset of acute chest pain. Use of the hs-cTn assays has the potential to facilitate earlier discharge for people with normal cTn levels. The recommended definition of an hs-cTn assay uses two criteria:[15, 16]

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

A number of high-sensitivity cTnI and cTnT (hs-cTnI and hs-cTnT) assays are currently available for use in the NHS in England and Wales; all are designed for use in clinical laboratory settings.

2.2.1 Abbott ARCHITECT high-sensitivity troponin I assay (Abbott Diagnostics)

The ARCHITECT hs-cTnI STAT assay can be used with the Abbott ARCHITECT i2000SR and i1000SR analysers. The assay is a quantitative, chemiluminescent micro particle immunoassay (CMIA) for serum or plasma samples. Results are available within 16 minutes. The ARCHITECT hs-cTnI STAT assay can detect cTnI in 96% of the reference population, and has a recommended 99th centile cut-off of 26.2ng/L with a CV of 4%.[17] The assay is CE marked and available to the NHS.

2.2.2 Alinity i STAT high-sensitivity troponin I assay (Abbott Diagnostics)

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

2.2.3 Access high-sensitivity troponin I assay (Beckman-Coulter)

The Access hs-cTnI assay can be used with both the Beckman Coulter Access 2 and DxI/DxC analysers. The assay is a quantitative, paramagnetic particle chemiluminescent immunoassay for serum or plasma samples. The turnaround time of the assay is 17 minutes. The Access hs-cTnI assay

has a recommended 99th centile cut-off of 17.5ng/L for the whole population, 11.6 ng/L for females and 19.8 ng/L for males, with a CV of <10%.[19] The assay can detect troponin I in more than 50% of the reference population. The assay is CE marked and available to the NHS.

2.2.4 VIDAS high sensitive Troponin I assay (Biomérieux)

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

2.2.5 VITROS high Sensitivity Troponin I Assay (Ortho Clinical Diagnostics)

The VITROS High Sensitivity Troponin I assay is designed for use in a laboratory setting on the following analysers: VITROS ECi/ECiQ/3600 Immunodiagnostic Systems and the VITROS 5600/XT 7600 Integrated System. It is an immunometric immunoassay and is intended for the in-vitro quantitative determination of troponin I in serum and plasma samples. Test results are available in 15 minutes. It has a recommended 99th centile cut-off of 11 ng/L for both lithium heparin and serum samples. Sex specific 99th centile cut offs of 9 ng/L (in lithium heparin and serum) for females and 13 ng/L (in lithium heparin) and 12 ng/L (in serum) for males are provided.[21] The assay can detect troponin I in more than 50% of the reference population. The assay is CE marked and available to the NHS.

2.2.6 TriageTrue high Sensitivity Troponin I Test (Quidel Cardiovascular)

The TriageTrue High Sensitivity Troponin I test can be used in a near patient setting (point-of-care [PoC]) or in a laboratory with the Triage MeterPro analyser. It is a fluorescence immunoassay and is intended for the in-vitro quantitative determination of troponin I in ethylenediaminetetraacetic acid (EDTA) anticoagulated whole blood and plasma samples. Test results are available in less than 20 minutes. It has a recommended 99th centile cut-off of 20.5 ng/L with a CV of less than 10%. Sex specific 99th centile cut offs of 14.4 ng/L for females and 25.7 ng/L for males are provided.[22] The test can detect troponin I in more than 50% of the reference population. The test is CE marked and available to the NHS.

2.2.7 Elecsys high-sensitive troponin T assay (Roche diagnostics)

The Elecsys cTnT-hs and Elecsys cTnT-hs STAT assays can be used on the Roche cobas e411, e601, e602 and e801 analysers. The assay is a quantitative, sandwich electrochemiluminescence immunoassay (ECLIA) for serum and plasma samples. Results are available within 18 minutes with

immunoassay, and is intended for the in-vitro quantitative determination of cTnI in serum and plasma samples. Test results are available within 10 minutes. The assay has a recommended 99th centile cut-off of 58.9 ng/L for lithium heparin samples and 57.9ng/L for serum samples.[29] Sex specific 99th centile cut-offs of 53.77 ng/L for females and 78.5 ng/L for males are also recommended.[29] Each 99th centile has a CV of <10%. The assay can detect cTnI in more than 50% of the reference population. The assay is CE marked and available to the NHS.

A summary of the product properties of hs-cTnI and hs-cTnT assays available as in the NHS in England and Wales is provided in Table 1.

This assessment considers hs-cTn assays used singly or in series, up to three hours after the onset of chest pain or up to three hours after presentation (as reported); for serial Tn measurements. Data for both relative and absolute change in Tn levels and peak Tn are presented.

Table 1: Overview of cardiac biomarkers

Manufacturer	System and compatible analysers	Assay	99th centile (ng/L)	CV at 99th centile (%)	Proportion of reference population in which cTn is detected (%)	Turn-around time (mins)	LoD (ng/L)	LoQ (ng/L)
Abbott Diagnostics	ARCHITECT i1000sr and i2000sr	ARCHITECT hs-cTnI [17]	Overall: 26.2 Female: 15.6 Male: 34.2	Overall: 4.0 Female: 5.3 Male: 3.5	96[30]	18*	1.9	4.7 (10% CV) 1.3 (20% CV)
Abbott Diagnostics	Alinity i	Alinity hs-cTnI [18]	Overall: 26.2 Female: 15.6 Male: 34.2	Overall: 4.6 Female: 5.0 Male: 4.5	96[30]	18*	1.6	3.7 (10% CV) 2.1 (20% CV)
Beckman Coulter	Access 2, DxI 600/ 800, DxC 600i/880i /860i/680i/660i	Access hs-cTnI [19]	Lithium heparin: Overall: 17.5 Female: 11.6 Male: 19.8	Lithium heparin Overall: 3.7 Female: 4.2 Male: 3.6	>50	17*	2.3*	2.3*
			Serum: Overall: 18.2 Female: 11.8 Male: 19.7	Serum: Overall: 6.0 Female: 6.9 Male: 5.8				
Biomérieux	VIDAS, MINI VIDAS, VIDAS 3	VIDAS hs-cTnI *	Overall: 19 Female: 11 Male: 25			20		
Ortho Clinical Diagnostics	VITROS ECi/ECiQ/3600 Immunodiagnostic Systems and the VITROS 5600/XT 7600 Integrated System	VITROS hs-cTnI [21]	Lithium heparin: Overall: 11 Female: 9	≤10*	>50	15*	0.39 to 0.86	1.23

Manufacturer	System and compatible analysers	Assay	99th centile (ng/L)	CV at 99th centile (%)	Proportion of reference population in which cTn is detected (%)	Turn-around time (mins)	LoD (ng/L)	LoQ (ng/L)
			Male: 13					

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VITROS ECi/ECiQ/3600 Immunodiagnostic Systems and the VITROS 5600/XT 7600 Integrated System	VITROS hs-cTnI [21]	Lithium heparin: Overall: 11 Female: 9 Male: 13 Serum: Overall: 11 Female: 9 Male: 12	≤10*	>50	15*	0.39 to 0.86	1.23
Triage MeterPro	TriageTrue hs-cTnI [22]	Overall: 20.5 Female: 14.4 Male: 25.7	Overall: <10	>50	<20*	Plasma: 1.6 Whole blood: 1.9	Plasma: 8.4 (10% CV) 3.6 (20% CV) Whole blood: 6.2 (10% CV) 2.8 (20% CV)
200 test pack: cobas e411, e601, e602 300 test pack cobas: e801	Elecsys hs-cTnT [23, 24]	Overall: 14 Female: 9 Male: 16.8	<10	57	18	3 (cobas e801) 5 (all others)	2.97 to 6.60
100 test pack: cobas e411, e601, e602, 300 test pack: cobas e801	Elecsys hs TnT STAT[25]	Overall: 14 Female: 9 Male: 16.8	<10	57	9	3 (cobas e801) 5 (all others)	
Atellica	Atellica IM hs-cTnI [27]	Lithium heparin: Overall: 45.2 Female: 34.11 Male: 53.48	<4	75	10	1.6	2.5

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Table 2: 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'[35] due to a suspected, but not proven, AMI	
Setting:	Secondary or tertiary care	
Interventions (index test):	Any hs-cTnT or hs-cTnI test[*], listed in Table 1, hs-cTn assays (used singly or in series[**], such that results 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 or fourth universal definition of AMI,[33] including measurement of troponin T or I (using any method) on presentation and 3-6 hours later **or** occurrence of MACE (any definition used in identified studies) during 30-day follow-up	Not applicable
Outcomes[$]:	Test accuracy (the numbers of true positive, false negative, false positive and true negative test results)	Early discharge (≤4 hrs after initial presentation) without MACE during follow-up, incidence of MACE during follow-up, re-attendance at or re-admission to hospital during follow-up, time to discharge, patient 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)

[*] 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, both data on relative or absolute change in Tn levels and peak Tn values were considered

[$] Any estimates of the relative accuracy/effectiveness of different hs-cTnT or hs-cTnI tests, were derived from direct, within study comparisons

7 Abbott ARCHITECT hs-cTnI (LoD)	0.12	0.69	0.00	0.18	0.15	1.00
8 Abbott ARCHITECT hs-cTnI (ESC pathway)	0.12	0.38	0.00	0.50	0.24	1.00
9 Abbott ARCHITECT hs-cTnI (High-STEACS pathway)	0.12	0.21	0.00	0.67	0.36	1.00
10 Abbott ARCHITECT hs-cTnI (<4 ng/L at 0 h)	0.12	0.44	0.00	0.44	0.22	1.00
11 Siemens ADVIA Centaur hs-cTnI (<2 ng/L at 0 h)	0.12	0.68	0.00	0.20	0.15	1.00
12 Siemens ADVIA Centaur hs-cTnI (<3 ng/L at 0 h OR (<8 ng/L at 0 h AND Δ <7 ng/L at 0 to 2 h))	0.12	0.29	0.00	0.59	0.30	1.00
13 Siemens ADVIA Centaur hs-cTnI (ESC pathway)	0.12	0.39	0.00	0.49	0.24	1.00
14 Siemens ADVIA Centaur hs-cTnI (<5 ng/L at 0 h)	0.12	0.42	0.00	0.46	0.22	1.00
15 Siemens Atellica hs-cTnI (<2 ng/L at 0 h)	0.12	0.65	0.00	0.23	0.16	1.00
16 Siemens Atellica hs-cTnI (High-STEACS pathway)	0.12	0.23	0.00	0.65	0.34	1.00
17 Beckman Coulter ACCESS hs-cTnI (ESC pathway)	0.12	0.26	0.00	0.61	0.31	1.00
18 Beckman Coulter ACCESS hs-cTnI ((symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h))	0.12	0.15	0.00	0.73	0.45	1.00
19 Ortho VITROS hs-cTnI (ESC pathway)	0.12	0.35	0.00	0.53	0.26	1.00
20 bioMérieux VIDAS hs-cTnI (<2 ng/L at 0 h OR (<6 ng/l at 0 AND 2 h))	0.12	0.32	0.00	0.56	0.27	1.00
21 Quidel TriageTrue hs-cTnI (ESC pathway)	0.12	0.30	0.00	0.58	0.29	1.00

After treatment, TP patients in the decision tree were allocated to 'Non-fatal AMI (treated)' and FP patients were further subdivided between 'no ACS, no UA' and 'UA' (based on the proportion of UA among non-NSTEMI patients; Table 23). After being discharged, TN patients were also subdivided between 'no ACS, no UA' and 'UA', whereas FN patients were allocated to 'Non-fatal AMI (untreated)'. The proportions of FN's, reported in Table 25, can be considered as the proportions of AMIs that would have been missed when assuming that standard troponin testing had perfect accuracy. Finally, to calculate the total number of deaths in the decision tree, the probability of 30-day mortality was assigned based on above mentioned subdivision (Table 23). It was assumed that UA was always correctly diagnosed, hence the mortality probability for treated UA was used.

State-transition model

The age-dependent AMI incidence in the UK[206] was used to model the occurrence of AMI for patients in the health states 'no ACS,' and 'UA'. It was assumed that all AMIs in the state-transition model were diagnosed correctly and thus received treatment. For patients in the 'Post-MI' health state, the probability of re-infarction after treated AMI was retrieved from a UK record linkage study,

outcomes between these strategies, some of these appear to be on the cost effectiveness frontier, even when they are not.

Beckman Coulter ACCESS hs-cTnI (symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h), the test strategy with the highest specificity (of 83; CI 81, 86), was the cheapest (probabilistic analysis: £38,625), but it was also amongst the least effective (15.5254 LYs and 12.0768 QALYs), owing to a sensitivity of 98 (CI 92, 100). Compared to standard troponin testing, hs-cTn testing resulted in probabilistic ICERs ranging between £34,307 and £36,842,603 savings per QALY lost.

Comparisons based on the next best alternative showed that for willingness to pay values below £8,455 per QALY, the Beckman Coulter ACCESS hsTnI ((symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h)) would be cost-effective. For thresholds between £8,455 and £20,190 per QALY, the Roche Elecsys hsTnT (<12 ng/L at 0 h AND Δ <3 ng/L at 0 to 1 h) was cost-effective; above £20,190 per QALY Siemens Dimension Vista hsTnI (<5 ng/L at 0 h AND Δ <2 ng/L at 0 to 1 h) would be cost-effective (Table 30).

At a willingness to pay threshold of £20,000 and £30,000 per QALY, the Beckman Coulter ACCESS hs-cTnI (ESC 0/1 hour pathway: (symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <4 at 0 to 1 h)) had a probability of being cost-effective of 41% and 36% respectively. At these thresholds, the Siemens Dimension Vista hs-cTnI (<5 ng/L at 0 h AND Δ <2 ng/L at 0 to 1 h) had a probability of being cost-effective of 13% and 22% respectively.

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4.4.2 Secondary analysis

The secondary analysis includes the same test strategies. This analysis assumed that in a proportion of patients with a false positive hs-cTn test (i.e. positive hs-cTn test and a negative standard troponin test), there is prognostic significance (i.e. it is associated with an increased risk of adverse events (mortality and MI), which can be reduced by testing positive using the hs-cTn test (Tables 31 and 32). In the secondary analysis, Standard troponin (at presentation and after 10-12 hours) was the cheapest (£37,517) and the least effective (11.334 QALYs) testing strategy (probabilistic analysis). Beckman Coulter ACCESS hs-cTnI ((symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h)) was the most effective testing strategy (11.4725 QALYs) at higher costs (£38,077). All other strategies were (extendedly) dominated. The ICER of Beckman Coulter ACCESS hs-cTnI ((symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h)) versus Standard troponin (at presentation and after 10-12 hours) was £4,043 per QALY gained.

At a willingness to pay threshold of £20,000 and £30,000 per QALY, the Beckman Coulter ACCESS hs-cTnI ((symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h)) had a probability of being cost-effective of 67% and 64% respectively (see Figure 15).

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4.4.3 Scenario analyses

Three scenario analyses were performed deterministically and conditional on both the base-case and the secondary analysis. Results are shown in Appendix 6. Scenario 1 assumed that patients who tested false positive would receive treatment and a treatment cost would be incurred for these patients. In this scenario conditional on the base-case, Beckman Coulter ACCESS hs-cTnI (symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h), the test strategy with the highest specificity (of 83; CI 81, 86), was the cheapest. Roche Elecsys hs-cTnT (99th centile threshold (<14 ng/L at 0 h AND 3 h)) was cost-effective for thresholds over £57,659 per QALY gained and Standard troponin (at presentation and after 10-12 hours) would be cost-effective at thresholds over £157,505,897 per QALY gained.

Scenario 1 conditional on the secondary analysis resulted in Standard troponin (at presentation and after 10-12 hours) being the cheapest strategy. Beckman Coulter ACCESS hs-cTnI (symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h) was cost-effective at and above a threshold of £4,869 per QALY gained and all other test strategies were more costly and not more effective.

Scenario 2 assumed a lifetime relative risk of higher mortality and reinfarction rate for those that tested false negative (instead of only an increased one-year risk). Conditional on the base-case, Beckman Coulter ACCESS hs-cTnI (symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h), remained the cheapest, and Beckman Coulter ACCESS hs-cTnI (ESC 0/1 hour pathway: (symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <4 at 0 to 1 h)) and Siemens Dimension Vista hs-cTnI (<5 ng/L at 0 h AND Δ <2 ng/L at 0 to 1 h) were cost-effective at thresholds above £6,962 and £7,874 per QALY gained respectively. Standard troponin (at presentation and after 10-12 hours) would be cost-effective thereafter, only over thresholds of almost £70 million.

Scenario 2 conditional on the secondary analysis resulted in Standard troponin (at presentation and after 10-12 hours) testing being the cheapest strategy. Beckman Coulter ACCESS hs-cTnI (symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h) was cost-effective above a threshold of £3,362 per QALY gained and all other test strategies were less effective and therefore dominated or extendedly dominated.

Scenario 3 assumed differential test costs for all tests, based on information provided by the manufacturers. Conditional on the base-case, Beckman Coulter ACCESS hs-cTnI (symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h), remained the cheapest, and Beckman Coulter ACCESS hs-cTnI (ESC 0/1 hour pathway: (symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L

and Δ <4 at 0 to 1 h)) and Siemens Dimension Vista hs-cTnI (<5 ng/L at 0 h AND Δ <2 ng/L at 0 to 1 h) were cost-effective over thresholds of £22,200 and £23,949 per QALY gained. Standard troponin (at presentation and after 10-12 hours) would only be cost-effective thereafter, above thresholds of approximately £330 million.

In scenario 3 conditional on the secondary analysis, Standard troponin (at presentation and after 10-12 hours) testing remained the cheapest strategy. Beckman Coulter ACCESS hs-cTnI (symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h) was cost-effective up to a threshold of £4,281 per QALY gained and all other test strategies were less effective and therefore dominated or extendedly dominated.

4.4.4 Sensitivity analyses

The following input parameters had a noticeable impact on the estimated cost-effectiveness in the base-case analysis: the 30-day mortality for untreated and treated AMI (decision tree) and the mortality one year after treated and untreated AMI (Markov trace). Varying the remaining parameters did not have a substantial impact on the results in the comparisons between Siemens Dimension Vista hs-cTnI (<5 ng/L at 0 h AND Δ <2 ng/L at 0 to 1 h), Roche Elecsys hs-cTnT (ESC 0/1 hour pathway: (symptoms >3 hours AND <5 ng/L at 0 h) OR (<12 ng/L at 0 h AND Δ <3 ng/L at 0 to 1 h)) and Beckman Coulter ACCESS hs-cTnI ((symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <5 at 0 to 2 h)). In the comparison between Siemens Dimension Vista hs-cTnI (<5 ng/L at 0 h AND Δ <2 ng/L at 0 to 1 h) and Standard troponin (at presentation and after 10-12 hours), in addition to parameters in the other comparisons, parameters with the most impact on results were the proportions of AMI in emergency admissions and of NSTEMI with patients with heart attack (Appendix 7).

In the secondary analysis, the parameters with notable impact on the estimated cost-effectiveness were: the 30 day mortality for untreated AMI, the mortality one year after treated and untreated AMI, the discount rate used for outcomes, and the relative mortality for patients tested true positive versus those that tested false positive (comparison of Beckman Coulter ACCESS hs-cTnI (ESC 0/1 hour pathway: (symptoms >3 hours AND <4 ng/L at 0 h) OR (<5 ng/L and Δ <4 at 0 to 1 h)) versus Standard troponin (at presentation and after 10-12 hours) testing) (Appendix 7).

4.4.5 Incremental analyses per assay

Base-case analysis

The per assay analyses (Table 33) indicate that at willingness to pay thresholds of £20,000 and £30,000 per QALY gain the following test strategies would be the most cost-effective use of the

APPENDIX 4: DETAILS OF EXCLUDED STUDIES WITH RATIONALE

To be included in the review studies had to fulfil the following criteria:

Population: 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' due to a suspected, but not proven, AMI

Setting: Secondary or tertiary care

Index Test: Abbott ARCHITECT hs-cTnI; Abbott Alinity hs-cTnI; Beckman Coulter Access hs-cTnI; Biomérieux VIDAS hs-cTnI; Ortho VITROS hs-cTnI; Quidel Triage True hs-cTnI Roche Elecsys (cTnT-hs or cTnT-hs STAT); Siemens Atellica hs-cTnI, Siemens Dimension EXL hs-cTnI; Siemens Dimension Vista hs-cTnI; Siemens ADVIA Centaur hs-cTnI; results available within 3 hours

Reference Standard: Third or fourth universal definition of AMI,[33] 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

Outcome: Sufficient data to construct 2x2 table of test performance

The table below summarises studies which were screened for inclusion based on full text publication but did not fulfil one or more of the above criteria. Studies were assessed sequentially against criteria; as soon as a study had failed based on one of the criteria it was not assessed against subsequent criteria. The table shows which of the criteria each study fulfilled ("Y") and on which item it failed ("N") or was unclear.

Study Details	Study Design	Setting	Population	Index Test	Reference Standard	Outcome
Aguirre, 2014[232]	Y	Y	Y	Y	Y	N
Ambavane, 2017[192]	Y	Y	Y	Y	Unclear	N
Badertscher, 2018[233]	Y	Y	Unclear	Unclear	Unclear	Y
Bandstein, 2014[234]	Y	Y	Y	Unclear	Y	N
Biener, 2013[235]	Y	Y	Y	N		
Borna, 2014[236]	Y	N				
Burgio, 2018[237]					N	
Burgio, 201[238]	Y	Y	Y	N		
Canadian Institutes of Health Research McMaster University, 2017[239]	N					
Chew, 2019[216]	Y	Y	Y	Y	Y	N