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REVIEW

Performance of the European Society of Cardiology 0/1-Hour, 0/2-Hour, and 0/3-Hour Algorithms for Rapid Triage of Acute Myocardial Infarction

An International Collaborative Meta-analysis

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Background: The 2020 European Society of Cardiology (ESC) guidelines recommend using the 0/1-hour and 0/2-hour algorithms over the 0/3-hour algorithm as the first and second choices of high-sensitivity cardiac troponin (hs-cTn)–based strategies for triage of patients with suspected acute myocardial infarction (AMI).

Purpose: To evaluate the diagnostic accuracies of the ESC 0/1-hour, 0/2-hour, and 0/3-hour algorithms.

Data Sources: PubMed, Embase, Cochrane Central Register of Controlled Trials, Web of Science, and Scopus from 1 January 2011 to 31 December 2020. (PROSPERO: CRD42020216479)

Study Selection: Prospective studies that evaluated the ESC 0/1-hour, 0/2-hour, or 0/3-hour algorithms in adult patients presenting with suspected AMI.

Data Extraction: The primary outcome was index AMI. Twenty unique cohorts were identified. Primary data were obtained from investigators of 16 cohorts and aggregate data were extracted from 4 cohorts. Two independent authors assessed each study for methodological quality.

Data Synthesis: A total of 32 studies (20 cohorts) with 30 066 patients were analyzed. The 0/1-hour algorithm had a pooled sensitivity of 99.1% (95% CI, 98.5% to 99.5%) and negative predictive value (NPV) of 99.8% (CI, 99.6% to 99.9%) for ruling out AMI. The 0/2-hour algorithm had a pooled sensitivity of 98.6% (CI, 97.2% to 99.3%) and NPV of 99.6% (CI, 99.4% to 99.8%). The 0/3-hour algorithm had a pooled sensitivity of 93.7% (CI, 87.4% to 97.0%) and NPV of 98.7% (CI, 97.7% to 99.3%). Sensitivity of the 0/3-hour algorithm was attenuated in studies that did not use clinical criteria (GRACE score <140 and pain-free) compared with studies that used clinical criteria (90.2% [CI, 82.9 to 94.6] vs. 98.4% [CI, 88.6 to 99.8]). All 3 algorithms had similar specificities and positive predictive values for ruling in AMI, but heterogeneity across studies was substantial. Diagnostic performance was similar across the hs-cTnT (Elecsys; Roche), hs-cTnI (Architect; Abbott), and hs-cTnI (Centaur/Atellica; Siemens) assays.

Limitation: Diagnostic accuracy, inclusion and exclusion criteria, and cardiac troponin sampling time varied among studies.

Conclusion: The ESC 0/1-hour and 0/2-hour algorithms have higher sensitivities and NPVs than the 0/3-hour algorithm for index AMI.

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Chest pain of suspected cardiac origin is common in the emergency department (ED), but only 10% to 20% of these cases are eventually diagnosed as acute myocardial infarction (AMI) (1). Rapid rule-out of patients at low risk for AMI not only reduces ED overcrowding (2) but also mitigates the potential risks for prolonged hospitalization (3). Accordingly, recent development of accelerated diagnostic protocols based on high-sensitivity cardiac troponin (hs-cTn) tests has allowed earlier ED discharge and detection of non–ST-segment elevation myocardial infarction (NSTEMI), leading to improved patient outcomes (4, 5).

The European Society of Cardiology (ESC) diagnostic protocols for ruling out or ruling in AMI have been adopted by many institutions worldwide. One of the earliest and most commonly used protocols is the ESC 0/3-hour algorithm (6). This algorithm applies a cardiac troponin threshold at the 99th percentile of a normal reference population at presentation and 3 hours, in conjunction with clinical criteria, to rule out or rule in myocardial infarction (7, 8).

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Whereas an earlier study reported a sensitivity and negative predictive value (NPV) greater than 99% for this algorithm (9), recent studies reported only a modest sensitivity of 90% to 95% (10–12). Consequently, the 0/3-hour algorithm is now recommended only as an alternative to the other ESC algorithms in the 2020 guidelines (13).

In the latest ESC recommendations, the 0/1-hour and 0/2-hour algorithms are featured as the first and second choices for hs-cTn–based accelerated diagnostic protocols for the triage of NSTEMI (13). The 0/1-hour and 0/2-hour algorithms apply assay-specific cardiac troponin thresholds lower than the 99th percentile of a normal reference population at presentation, combined with absolute changes within the first or second hour, to triage patients into rule-out, observation, and rule-in groups. The 0/1-hour algorithm was first featured in the 2015 guidelines and was shown to have high diagnostic accuracy across multiple cohorts and subpopulations of patients (8, 14–18). On the other hand, the 0/2-hour algorithm is a newly introduced protocol and has been validated in only a few prospective studies (19–21).

A 1% miss rate for AMI is generally considered acceptable among emergency physicians, with some advocating for a 1% miss rate for major adverse cardiac events at 30 days as an acceptable benchmark (22). To examine the performance of hs-cTn–based diagnostic protocols, we aimed to summarize and compare the diagnostic accuracies and triage efficacies of the ESC 0/1-hour, 0/2-hour, and 0/3-hour algorithms, with consideration of study- and population-level differences.

METHODS

This meta-analysis was conducted according to the PRISMA-DTA (Preferred Reporting Items for Systematic reviews and Meta-analyses of Diagnostic Test Accuracy studies) (23) and MOOSE (Meta-analysis Of Observational Studies in Epidemiology) guidelines (24). The review protocol is registered with PROSPERO (CRD42020216479).

Data Sources and Searches

We conducted a comprehensive literature search through PubMed, Embase, Cochrane Central Register of Controlled Trials, Web of Science, and Scopus without any language restrictions, using a strategy that incorporated the keywords *myocardial infarction*, *troponin*, *0/1-hour algorithm*, *0/2-hour algorithm,* and *0/3-hour algorithm* (**Appendix Table 1**, available at Annals.org). Studies published between 1 January 2011 (the year in which the 0/3-hour algorithm was first recommended) and 31 December 2020 were considered for inclusion. References of original and review articles were searched manually to capture additional relevant studies. Articles published in languages other than English were interpreted by using Google Translate.

Study Selection

Two reviewers (Cho-Han Chiang and Cho-Hung Chiang) independently screened titles and abstracts and retrieved full texts of potential studies for further review. A third reviewer (C.C. Lee) decided on the inclusion or exclusion of studies. Studies eligible for inclusion were randomized controlled trials, prospective cohort studies, or implementation studies that evaluated the diagnostic accuracy of the ESC 0/1-hour, 0/2-hour, or 0/3-hour algorithm in adult patients presenting to the ED or chest pain unit with suspected NSTEMI or acute coronary syndrome. We focused on studies that evaluated the 3 ESC algorithms using the Elecsys hs-cTnT (Roche), Architect hs-cTnI (Abbott), and Centaur/Atellica hs-cTnI (Siemens) assays because they are the predominant hs-cTn assays used by EDs. Analytic characteristics of each assay are shown in **Supplement Table 1** (available at Annals.org). We contacted principal investigators and lead authors for each eligible study by e-mail for additional aggregate data based on a predesigned template (**Supplement Tables 2** and **3**, available at Annals.org). We excluded articles if they did not contain sufficient information on the outcomes of interest and when the authors could not be contacted or declined to participate (**Appendix Table 2**, available at Annals.org). We excluded case–control studies, clinical guidelines, editorials, review articles, and case reports.

The triage strategy of the ESC 0/1-hour, 0/2-hour, and 0/3-hour algorithms is shown in **Supplement Figures 1** and **2** (available at Annals.org). The diagnosis of myocardial infarction was adjudicated according to the Third or Fourth Global Task Force Universal Definition of Myocardial Infarction (25, 26) (**Supplement Table 4**, available at Annals.org). Studies that included patients with an initial diagnosis of ST-segment elevation myocardial infarction (STEMI) were excluded because the algorithms were designed for detecting NSTEMI. We used thresholds recommended in the 2015 ESC guidelines for the Architect hs-cTnI assay–based 0/1-hour algorithm because this work preceded the 2020 ESC guidelines and more studies using the 2015 thresholds were available. We evaluated a commonly utilized rule-in strategy for the 0/3-hour algorithm because the ESC guidelines did not specify the exact rule-in thresholds (27). This strategy rules in patients for myocardial infarction if they had a change in hs-cTn greater than 50% of the 99th percentile of a normal reference population at 3 hours when the initial concentration was in the 99th percentile or less, or more than 20% of the initial concentration when the initial concentration was above the 99th percentile.

Data Extraction and Quality Assessment

Two reviewers (Cho-Han Chiang and Cho-Hung Chiang) independently extracted data on study demographic characteristics and on the primary and secondary end points. The primary outcome was diagnostic accuracy (sensitivity, specificity, NPV, positive predictive value [PPV]) with index admission AMI (type 1 or type 2 MI). Type 1 MI is caused by atherothrombotic coronary artery disease, and type 2 MI is caused by a mismatch between oxygen supply and demand (26). The secondary outcomes were 30-day mortality and proportion of patients triaged toward rule-out, observation, or rule-in. We extracted information from studies on such variables as sample size, study setting, prevalence of AMI, hs-cTn assay used, and proportion of patients in different triage groups. We also extracted outcomes for subgroups with

early versus late onset of chest pain (≤3 hours or >3 hours) from aggregate data provided by primary investigators.

Two reviewers (Cho-Han Chiang and Cho-Hung Chiang) independently evaluated the methodological quality of included studies by using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2) tool (**Supplement Table 5**, available at Annals.org). In cases of disagreement, consensus was reached by discussion with a third reviewer (C.C. Lee).

Data Synthesis and Analysis

We pooled diagnostic accuracy estimates by using the bivariate random-effects regression model to evaluate performance of the algorithms across different cohorts (28). Diagnostic accuracy was defined as the sensitivity and NPV for ruling out MI or specificity and PPV for ruling in MI. The negative likelihood ratio for the rule-out group and the positive likelihood ratio for the rule-in group were calculated directly according to the pooled sensitivity and specificity estimates. For the rule-out group, we excluded studies that used only serial sampling without the 0-hour rule-out strategy.

We calculated the inconsistency index (I^2) statistic to measure interstudy variation with point estimates attributable to heterogeneity between studies; I^2 values of 25%, 50%, and 75% represent low, moderate, and high heterogeneity, respectively (29). We explored potential sources of heterogeneity by adding covariates of interest to a bivariate regression model. We considered geographic location (Europe vs. non-Europe) as a potential source of heterogeneity because the ESC algorithms were developed in European cohorts and may perform differently outside of these settings. We considered prevalence of AMI (≤10% vs. >10%) and proportion of patients who presented with chest pain (100% vs. <100%) as potential sources of heterogeneity because these factors influence the number of patients at risk for the target condition (AMI) and can directly influence diagnostic performance. We considered risk of bias (low risk vs. high risk of bias across different domains in QUADAS), study design (observational cohort vs. quasi-experimental vs. randomized controlled trial), sample size (<500 participants vs. ≥500 participants), and method of adjudication of AMI (using the same or a different cardiac troponin assay as the index test for adjudication) as potential sources of heterogeneity because these factors may overestimate or underestimate the diagnostic accuracies of the ESC algorithms.

Because many studies used the same hs-cTn assay for evaluation of the 3 algorithms and adjudication of AMI, there were concerns about incorporation bias. Incorporation bias may occur if the index test is used as part of the gold standard for diagnosing AMI. To address this issue, we performed latent class analysis using a latent class bivariate model (LCBM) to adjust for conditional dependence (30–32). We did not assess publication bias because standard tests are not recommended in meta-analysis of diagnostic accuracy studies (33). We conducted meta-analyses of proportions to calculate mortality rates and proportions of patients in different triage groups. We conducted sensitivity analyses by including studies that made head-to-head comparisons between the 0/1-hour, 0/2-hour, and 0/3-hour algorithms by pooling cohorts that evaluated at least 2 of the 3 algorithms. Continuous variables are presented as means (95% CIs) or medians (interquartile ranges) and categorical variables as numbers and percentages. *P* values less than 0.05 were considered statistically significant. Meta-analysis was performed using the midas, metatrim, metaprop, and metadta packages in Stata, version 14.0, or the Mada package in R software, version 3.5.3. Latent class analysis was performed by using Latent GOLD 6.0 software.

Role of the Funding Source

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RESULTS

The initial search identified 1010 articles, of which 100 studies had full-text review. A total of 32 studies (20 unique cohorts) with 30 066 patients and 4246 cases of index AMI were included in the final analysis (**Figure 1**) (9–12, 15, 19–21, 34–57). We obtained primary data from the principal investigators for 16 cohorts and extracted aggregate data from published articles for 4 cohorts.

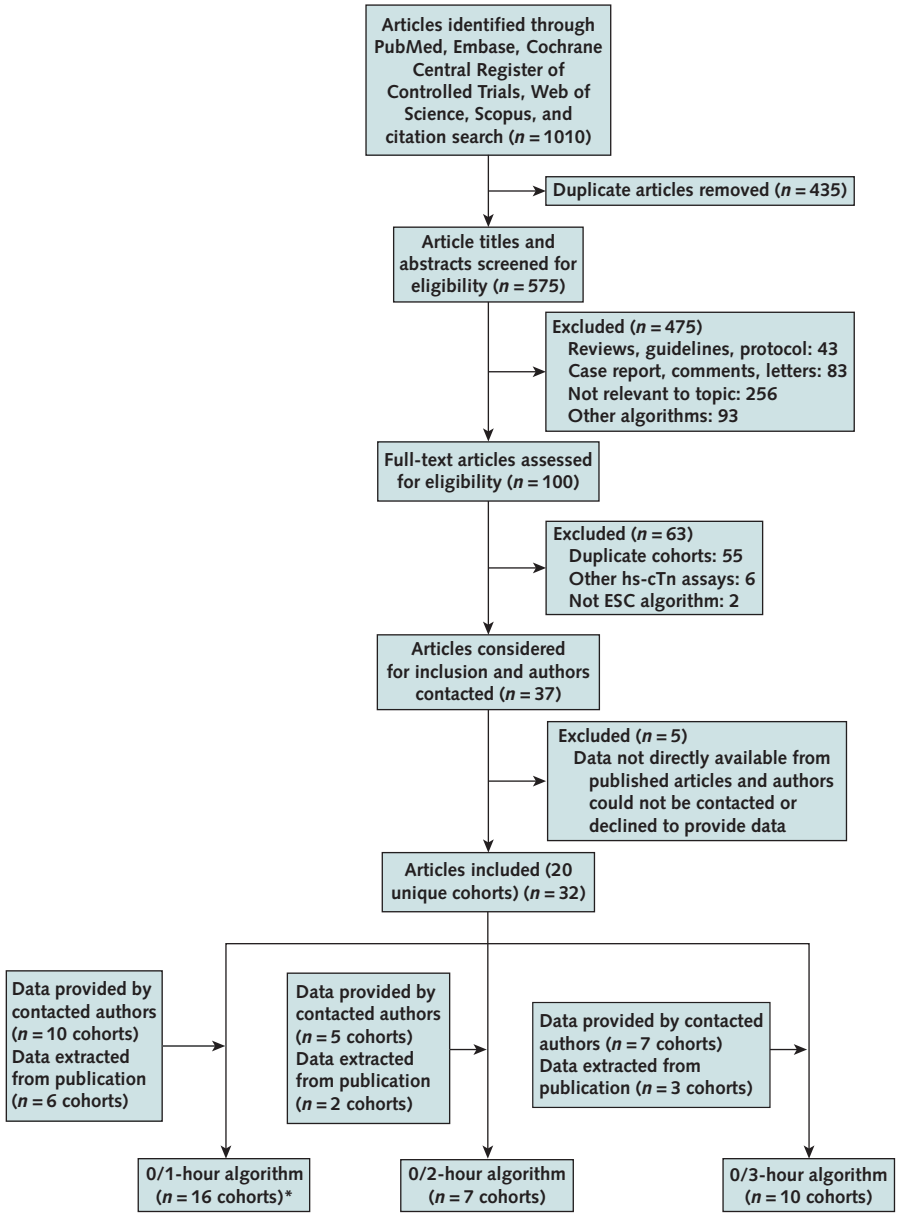
Study Characteristics

The included studies comprised patients from Europe, Australasia, North America, and Asia (**Appendix Table 3**, available at Annals.org). The prevalence of AMI ranged from 4% to 37% across studies. For studies that reported on the timing of sample collection, the median time from ED presentation to first sample collection ranged from 0 minutes to 136 minutes; the median time from first to second sample collection ranged from 60 minutes to 103 minutes for the 0/1-hour algorithm, 90 minutes to 138 minutes for the 0/2-hour algorithm, and 175 minutes to 215 minutes for the 0/3-hour algorithm. **Supplement Tables 6** and **7** (available at Annals.org) show detailed characteristics of all studies.

Quality Assessment

All studies prospectively recruited patients presenting to the ED or chest pain unit with symptoms suggestive of AMI. Most studies had low risk of selection bias because they enrolled patients consecutively or by random sampling and excluded patients with STEMI on electrocardiography at presentation. Most studies used prespecified thresholds as recommended in the ESC guidelines to rule out or rule in patients. However, 4 studies derived the thresholds for the 0/1-hour and 0/2-hour algorithms (20, 34, 35, 37) and 6 studies did not use the clinical criteria (Global Registry of Acute Coronary Events [GRACE] score and pain-free) for the 0/3-hour algorithm recommended in the guidelines (12, 47–49, 53, 55); as a result, these studies were considered as high risk of bias or applicability concerns for the index test. In most studies, AMI was adjudicated independently by at least 2 physicians as defined by the Global Task

Figure 1. Evidence search and selection.



ESC = European Society of Cardiology; hs-cTn = high-sensitivity cardiac troponin.
* The number of cohorts for the rule-out group is only 14 because 2 cohorts only assessed serial sampling without the 0-hour strategy stipulated by the ESC 0/1-hour algorithm.

Force (25, 26). Some studies used a contemporary cardiac troponin assay or a different hs-cTn assay for adjudication of AMI and were considered at high risk of bias for the reference standard (12, 15, 21, 35, 41–45, 57). In most studies, samples for serial cardiac troponin measurement were collected at the timing stipulated by the algorithms. The overall risk of bias summary for each included study is shown in the Appendix Figure (available at Annals.org) and Appendix Tables 4 and 5 (available at Annals.org).

Meta-estimate of Rule-Out Performance

Overall, the 0/1-hour algorithm classified 54% (95% CI, 45% to 62%) of patients to the rule-out category, with a pooled sensitivity of 99.1% (CI, 98.5% to 99.5%; I^2 = 0%) and NPV of 99.8% (CI, 99.6% to 99.9%) (Table 1 and Figure 2). The 0/2-hour algorithm classified 61% (CI, 52% to 69%) of patients to the rule-out category, with a pooled sensitivity of 98.6% (CI, 97.2% to 99.3%; I^2 = 20%) and NPV of 99.6% (CI, 99.4% to 99.8%). The 0/3-hour algorithm classified 66% (CI, 52% to 79%) of

patients to the rule-out category, with a pooled sensitivity of 93.7% (CI, 87.4% to 97.0%; I^2, 84%) and NPV of 98.7% (CI, 97.7% to 99.3%). All 3 algorithms had comparable 30-day mortality rates for patients in the rule-out category (**Appendix Table 6**, available at Annals.org).

When stratified by assay, all 3 algorithms showed similar sensitivities and NPVs for the Elecsys hs-cTnT, Architect hs-cTnI, and Centaur/Atellica hs-cTnI assays (**Table 1** and **Figure 2**). All 3 algorithms showed similar sensitivities between early and late presenters (onset of chest pain ≤3 hours vs. >3 hours, respectively). However, the 0/3-hour algorithm in early presenters had reduced sensitivity compared with the 0/1-hour and 0/2-hour algorithms (**Appendix Table 7**, available at Annals.org). Sensitivity of the 0/3-hour algorithm was lower in studies that did not apply a GRACE score less than 140 and pain-free as the clinical criteria versus studies that applied these criteria (90.2% [CI, 82.9% to 94.6%] vs. 98.4% [CI, 88.6% to 99.8%]) (**Table 1** and **Appendix Table 8**, available at Annals.org; risk of bias for index test). In meta-regression analysis, sensitivity was reduced for studies that had high risk of bias by the reference standard. Most of these studies did not use the same hs-cTn assay for AMI adjudication. Sensitivities of the 3 algorithms did not appear to vary with geographic location, AMI prevalence, proportion of patients who presented with chest pain, study design, and sample size (**Appendix Tables 8** to **10**, available at Annals.org).

Meta-estimate of Rule-In Performance

Overall, the 0/1-hour algorithm classified 17% (CI, 12% to 23%) of patients to the rule-in category, with a pooled specificity of 94.0% (CI, 90.7% to 96.2%; I^2 = 98%) and PPV of 65.1% (CI, 56.3% to 73.0%) (**Table 2** and **Figure 3**). The 0/2-hour algorithm classified 15% (CI, 9% to 22%) of patients to the rule-in category, with a pooled specificity of 96.1% (CI, 92.9% to 97.9%; I^2 = 98%) and PPV of 75.9% (CI, 66.3% to 83.5%). The 0/3-hour algorithm classified 19% (CI, 12% to 28%) of patients to the rule-in category, with a pooled specificity of 93.2% (CI, 86.9% to 96.6%; I^2 = 98%) and PPV of 64.4% (CI, 47.4% to 78.3%).

When stratified by assay, all 3 algorithms showed similar specificities and PPVs for the Elecsys hs-cTnT, Architect hs-cTnI, and Centaur/Atellica hs-cTnI assays (**Table 2** and **Figure 3**). In meta-regression analysis, specificity appeared to be lower in studies with AMI prevalence greater than 10% and a proportion of patients with chest pain of less than 100%. Specificities of the 3 algorithms did not seem to vary with geographic location, sample size, and risk of bias by the index test and reference standard (**Appendix Tables 7 to 9**).

Sensitivity Analysis

In head-to-head comparison analysis, the 0/1-hour algorithm had a rule-out sensitivity and NPV and a rule-in specificity and PPV similar to those of the 0/2-hour algorithm (**Table 3**). Compared with the 0/3-hour algorithm, the 0/1-hour and 0/2-hour algorithms had higher sensitivity and NPV and similar specificity and PPV. These trends were similar to those in the overall estimates shown in **Tables 1** and **2**.

Latent Class Analysis

Latent class analysis identified 2 clusters of studies with different sensitivity and specificity (**Appendix Table**

Table 1. Pooled Accuracy and Efficacy Estimates Across Different Stratification Subgroups for Ruling Out Acute Myocardial Infarction

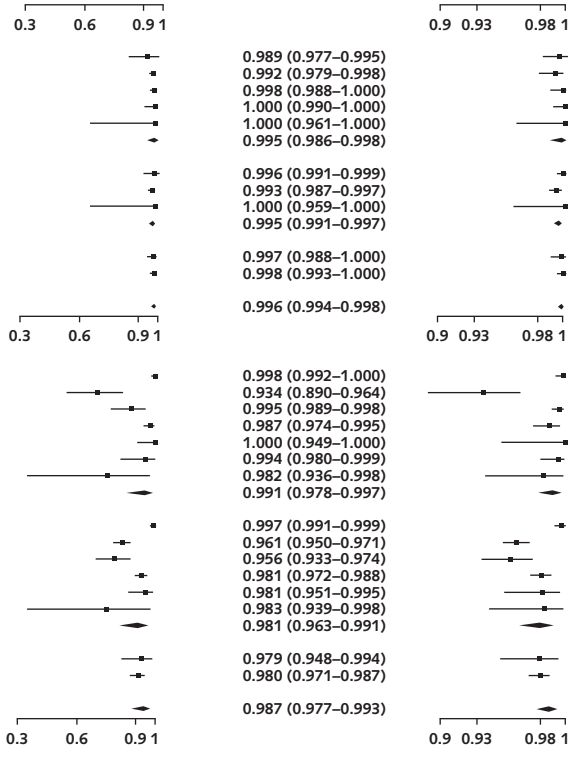
Algorithm and Stratification	Cohorts, *n*	Cohort Size, *n*	Sensitivity (95% CI)	NPV (95% CI)	NLR (95% CI)	Proportion Ruled Out (95% CI)	I^2, %
0/1-hour algorithm							
Overall	14	13 899	0.991 (0.985–0.995)	0.998 (0.996–0.999)	0.01 (0.01–0.02)	0.54 (0.45–0.62)	0
By assay*							
Elecsys hs-cTnT	12	13 899	0.992 (0.985–0.996)	0.998 (0.996–0.999)	0.01 (0.00–0.02)	0.53 (0.44–0.63)	6
Architect hs-cTnI	4	4929	0.993 (0.984–0.997)	0.998 (0.995–0.999)	0.01 (0.00–0.04)	0.55 (0.43–0.66)	0
Centaur/Atellica hs-cTnI	3	3866	0.986 (0.971–0.993)	0.996 (0.992–0.998)	0.03 (0.01–0.11)	0.53 (0.45–0.62)	58
0/2-hour algorithm							
Overall	7	6079	0.986 (0.972–0.993)	0.996 (0.994–0.998)	0.02 (0.01–0.04)	0.61 (0.52–0.69)	20
By assay*							
Elecsys hs-cTnT	5	2488	0.990 (0.945–0.997)	0.995 (0.986–0.998)	0.03 (0.01–0.08)	0.58 (0.41–0.74)	72
Architect hs-cTnI	3	2165	0.974 (0.957–0.985)	0.995 (0.991–0.997)	0.03 (0.02–0.06)	0.66 (0.50–0.81)	0
Centaur/Atellica hs-cTnI	2	2949	NA	NA	NA	NA	NA
0/3-hour algorithm							
Overall	10	10 237	0.937 (0.874–0.970)	0.987 (0.977–0.993)	0.09 (0.05–0.15)	0.66 (0.52–0.79)	84
By assay*							
Elecsys hs-cTnT	7	5544	0.950 (0.849–0.985)	0.991 (0.978–0.997)	0.06 (0.03–0.17)	0.68 (0.49–0.88)	87
Architect hs-cTnI	6	6758	0.914 (0.814–0.963)	0.981 (0.963–0.991)	0.11 (0.06–0.21)	0.69 (0.56–0.81)	88
Centaur/Atellica hs-cTnI	2	2269	NA	NA	NA	NA	NA
Clinical criteria							
Yes	3	4136	0.984 (0.886–0.998)	0.994 (0.971–0.999)	0.01 (0.00–0.16)	0.44 (0.25–0.64)	85
No	7	6101	0.902 (0.829–0.946)	0.984 (0.970–0.992)	0.11 (0.06–0.18)	0.76 (0.61–0.89)	81

hs-cTnI = high-sensitivity cardiac troponin I; hs-cTnT = high-sensitivity cardiac troponin T; NA = not available; NLR = negative likelihood ratio; NPV = negative predictive value.

* Manufacturers of the Elecsys hs-cTnT, Architect hs-cTnI, and Centaur/Atellica hs-cTnI assays are Roche, Abbott, and Siemens, respectively.

Figure 2. Forest plot summarizing the rule-out performance of the European Society of Cardiology 0/1-hour, 0/2-hour, and 0/3-hour algorithms.

Study	Prevalence, %	TP, *n*	FN, *n*	FP, *n*	TN, *n*	Sensitivity	NPV
0/1-hour algorithm							
hs-cTnT (Elecsys*)							
APACE (38)	16	443	3	652	1761	0.993 (0.980–0.999)	0.998 (0.995–1.000)
BACC (38)	19	287	2	478	742	0.993 (0.975–0.999)	0.997 (0.990–1.000)
Christchurch (41)	21	117	4	100	354	0.967 (0.918–0.991)	0.989 (0.972–0.997)
RAPID-TnT (47)	4	57	2	387	1185	0.966 (0.883–0.996)	0.998 (0.994–1.000)
RAPID-CPU (48)	20	228	3	399	516	0.987 (0.963–0.997)	0.994 (0.983–0.999)
Tokyo and Taipei (50)	11	198	0	835	700	1.000 (0.982–1.000)	1.000 (0.995–1.000)
FAST-MI (52)	37	485	1	434	397	0.998 (0.989–1.000)	0.997 (0.986–1.000)
Bangkok (54)	14	48	0	158	144	1.000 (0.926–1.000)	1.000 (0.975–1.000)
OUT-ACS (51)	4	60	1	340	1310	0.984 (0.912–1.000)	0.999 (0.996–1.000)
Lund (46)	8	76	2	274	686	0.974 (0.910–0.997)	0.997 (0.990–1.000)
Brighton and Sussex (53)	9	44	0	125	322	1.000 (0.920–1.000)	1.000 (0.989–1.000)
Shanghai (56)	18	106	0	323	148	1.000 (0.966–1.000)	1.000 (0.975–1.000)
Subtotal						0.992 (0.985–0.996)	0.998 (0.996–0.999)
hs-cTnI (Architect*†)							
APACE (38)	14	286	2	733	1038	0.993 (0.975–0.999)	0.998 (0.993–1.000)
BACC (49)	18	337	3	830	749	0.991 (0.974–0.998)	0.996 (0.988–0.999)
Christchurch (41)	16	86	0	147	312	1.000 (0.958–1.000)	1.000 (0.988–1.000)
HighSTEACS (10)	8	33	0	83	290	1.000 (0.894–1.000)	1.000 (0.987–1.000)
Subtotal						0.993 (0.984–0.997)	0.998 (0.995–0.999)
hs-cTnI (Centaur/Atellica*†)							
APACE (20)	18	236	2	494	615	0.992 (0.970–0.999)	0.997 (0.988–1.000)
HighSTEACS (11)	8	29	2	115	260	0.935 (0.786–0.992)	0.992 (0.973–0.999)
HIGH-US (21)	11	228	3	820	1062	0.987 (0.963–0.997)	0.997 (0.992–0.999)
Subtotal						0.986 (0.971–0.993)	0.996 (0.992–0.998)
Total						0.991 (0.985–0.995)	0.998 (0.996–0.999)
0/2-hour algorithm							
hs-cTnT (Elecsys*)							
Brisbane (35)	10	71	7	111	616	0.910 (0.824–0.963)	0.989 (0.977–0.995)
Christchurch (43)	22	300	4	593	483	0.987 (0.967–0.996)	0.992 (0.979–0.998)
RAPID-CPU (48)	22	212	1	293	459	0.995 (0.974–1.000)	0.998 (0.988–1.000)
Calgary (19)	11	63	0	137	350	1.000 (0.943–1.000)	1.000 (0.990–1.000)
RING (12,57)	6	9	0	41	93	1.000 (0.664–1.000)	1.000 (0.961–1.000)
Subtotal						0.988 (0.945–0.997)	0.995 (0.986–0.998)
hs-cTnI (Architect*†)							
Brisbane (35)	7	134	6	296	1469	0.957 (0.909–0.984)	0.996 (0.991–0.999)
Christchurch (42–45)	19	385	8	473	1156	0.980 (0.960–0.991)	0.993 (0.987–0.997)
RING (12, 57)	6	9	0	45	89	1.000 (0.664–1.000)	1.000 (0.959–1.000)
Subtotal						0.974 (0.957–0.985)	0.995 (0.991–0.997)
hs-cTnI (Centaur/Atelllca*†)							
APACE (20)	16	165	2	289	577	0.988 (0.957–0.999)	0.997 (0.988–1.000)
HIGH-US (21)	12	219	2	631	1064	0.991 (0.968–0.999)	0.998 (0.993–1.000)
Total						0.986 (0.972–0.993)	0.996 (0.994–0.998)
0/3-hour algorithm							
hs-cTnT (Elecsys*)							
APACE (9)	16	311	2	746	849	0.994 (0.977–0.999)	0.998 (0.992–1.000)
Christchurch (12)	19	31	13	1	184	0.705 (0.548–0.832)	0.934 (0.890–0.964)
RAPIO-TnT (47)	4	57	8	82	1485	0.877 (0.772–0.945)	0.995 (0.989–0.998)
RAPID-CPU (48)	25	234	7	164	543	0.971 (0.941–0.988)	0.987 (0.974–0.995)
Nuremberg (40)	12	38	0	199	71	1.000 (0.907–1.000)	1.000 (0.949–1.000)
Brighton and Sussex (53)	10	36	2	3	350	0.947 (0.823–0.994)	0.994 (0.980–0.999)
RING (12, 57)	6	6	2	12	108	0.750 (0.349–0.968)	0.982 (0.936–0.998)
Subtotal						0.950 (0.849–0.985)	0.991 (0.978–0.997)
hs-cTnI (Architect*†)							
APACE (9)	15	267	3	519	953	0.989 (0.968–0.998)	0.997 (0.991–0.999)
BACC (49)	18	278	57	146	1423	0.830 (0.785–0.869)	0.961 (0.950–0.971)
Christchurch (12)	18	72	19	9	416	0.791 (0.693–0.869)	0.956 (0.933–0.974)
HighSTEACS (10)	18	318	25	240	1303	0.927 (0.894–0.952)	0.981 (0.972–0.988)
UTROPIA (55)	12	66	4	310	202	0.943 (0.860–0.984)	0.981 (0.951–0.995)
RING (12, 57)	6	6	2	6	114	0.750 (0.349–0.968)	0.983 (0.939–0.998)
Subtotal						0.914 (0.814–0.963)	0.981 (0.963–0.991)
hs-cTnI (Centaur/Atellica*†)							
APACE (20)	16	51	4	106	188	0.927 (0.824–0.980)	0.979 (0.948–0.994)
HighSTEACS (11)	14	252	25	420	1223	0.910 (0.870–0.941)	0.980 (0.971–0.987)
Total						0.937 (0.874–0.970)	0.987 (0.977–0.993)



AMI = acute myocardial infarction; APACE = Advantageous Predictors of Acute Coronary Syndromes Evaluation; BACC = Biomarkers in Acute Cardiac Care; FAST-MI = FAST detection of Myocardial Infarction; HighSTEACS = High-sensitivity Troponin in the Evaluation of Patients with Acute Coronary Syndrome; HIGH-US = High-Sensitivity Cardiac Troponin I in the United States; hs-cTnI = high sensitivity cardiac troponin I; hs-cTnT = high sensitivity cardiac troponin T; NPV = negative predictive value; OUT-ACS = One-hoUr Troponin in a low-prevalence population of Acute Coronary Syndrome; RAPID-CPU = Rule-out Protocols in Patients Admitted With Chest Pain to a Crowded Chest Pain Unit; RAPID-TnT = Rapid Assessment of Possible Acute Coronary Syndrome in the Emergency Department With High-Sensitivity Troponin T; RING = Reducing the time Interval for identifying New Guidelines; TP = true positive; TN = true negative; FP = false positive; FN = false negative; TRAPID-AMI = The High Sensitivity Cardiac Troponin T Assay for Rapid Rule-out of Acute Myocardial Infarction; UTROPIA = Use of Abbott high-sensitivity TROPonin I assay In Acute coronary syndromes.

* Manufacturers of the Elecsys hs-cTnT, Architect hs-cTnI, and Centaur/Atellica hs-cTnI assays are Roche, Abbott, and Siemens, respectively.

† Performance of the 0/2-hour and 0/3-hour algorithm based on the Centaur/Atellica hs-cTnI assay could not be pooled owing to an insufficient number of studies.

11, available at Annals.org). Studies that adjudicated AMI by using a different cardiac troponin assay from the rapid algorithm were mostly classified in the first latent class (68%), and LCBM analysis showed estimated sensitivity and specificity of 97.1% (CI, 95.6% to 98.6%) and 89.0% (CI, 86.5% to 91.6%), respectively (**Appendix Table 12**, available at Annals.org). Studies that adjudicated AMI by using the same cardiac troponin assay as the rapid algorithm were mostly classified in the second latent class (97%), and LCBM analysis showed estimated sensitivity and specificity of 95.7% (CI, 92.6% to 98.7%) and 91.9% (CI, 90.2% to 93.5%), respectively.

Discussion

In this collaborative meta-analysis, we included 20 unique cohorts to evaluate the comparative performances of the ESC 0/1-hour, 0/2-hour, and 0/3-hour algorithms. The pooled sensitivities for the 0/1-hour, 0/2-hour, and 0/3-hour algorithms were 99.1% (CI, 98.5% to 99.5%), 98.6% (CI, 97.2% to 99.3%), and 93.7% (CI, 87.4% to 97.0%), respectively. Given a pretest probability of 12% (median prevalence of AMI across the studies), 120 of 1000 tested patients would receive a final diagnosis of AMI; of these 120 patients, we can be confident that no more than 3 (lower bound of CI) may test false-negative according to the 0/1-hour and 0/2-hour algorithms and up to 15 (lower bound of CI) may test false-negative according to the 0/3-hour algorithm. The pooled specificities for the 0/1-hour, 0/2-hour, and 0/3-hour algorithm were 94.0% (CI, 90.7% to 96.2%), 96.1% (CI, 92.9% to 97.9%), and 93.2% (CI, 86.9% to 96.6%), respectively. This implies that of the 880 of 1000 patients without AMI, approximately 18 to 115 patients may test false-positive (lower and upper bound of CI) using the ESC algorithms.

The 0/1-hour and 0/2-hour algorithms had consistently high sensitivities and NPV across different population demographic characteristics. The NPVs for all studies, regardless of AMI prevalence, were close to or above 99%, which approximates to safety estimates proposed by other investigators (22, 58). By contrast, the 0/3-hour algorithm had a lower sensitivity and NPV than the 0/1-hour and 0/2-hour algorithms. In particular, many studies reported an NPV of only 95% to 98% for the 0/3-hour algorithm, indicating a 2% to 5% miss rate for AMI. This finding may be counterintuitive because the 0/3-hour algorithm has additional triage time for monitoring cardiac troponin elevation and AMI progression. This could be because the 0/1-hour and 0/2-hour algorithms use a much lower threshold of cardiac troponin concentration to rule out AMI at presentation and a low delta change between the first and second sample, which had been shown to have very good safety (59–62).

The 99th percentile threshold used in the ESC 0/3-hour algorithm may result in a considerably high number of false-negative results and has been challenged by several studies (10, 11). In contrast, an alternative 0/3-hour pathway, HighSTEACS, which uses thresholds much lower than the 99th percentile, was demonstrated to have higher sensitivity and NPV than the ESC 0/3-hour algorithm (10, 11, 55). There was high heterogeneity in sensitivities across studies, most likely owing to differences in implementation of the 0/3-hour algorithm. In the RAPID-TnT trial, physicians were masked to hs-cTnT

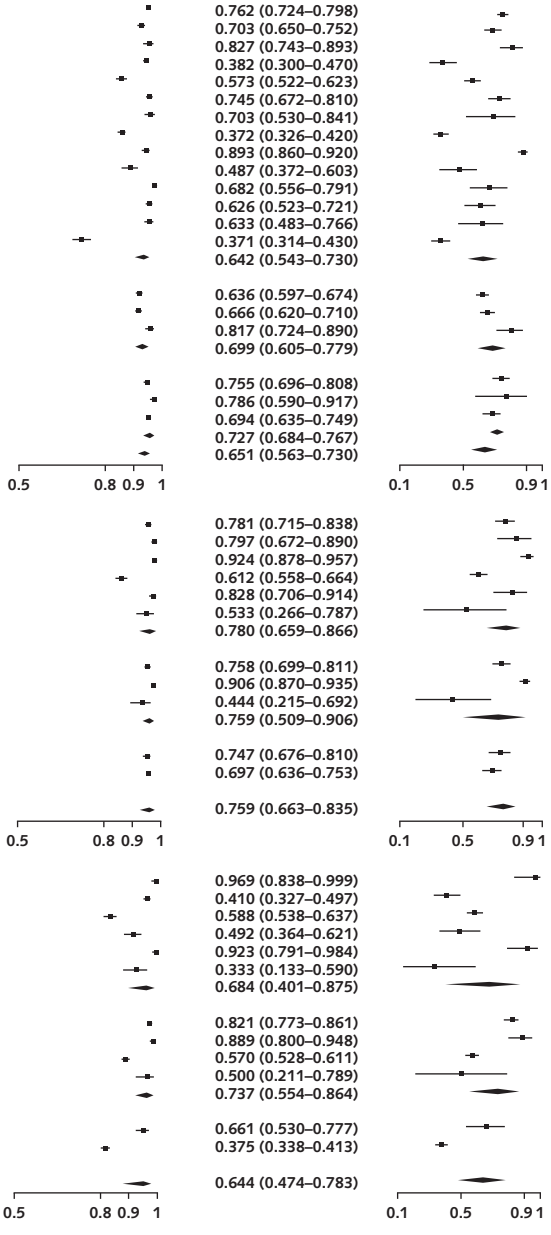
Table 2. Pooled Accuracy and Efficacy Estimates Across Different Stratification Subgroups for Ruling In Acute Myocardial Infarction

Algorithm and Stratification	Cohorts, *n*	Patients, *n*	Specificity (95% CI)	PPV (95% CI)	PLR (95% CI)	Proportion Ruled In (95% CI)	I^2, %
0/1-hour algorithm							
Overall	16	19 913	0.940 (0.907–0.962)	0.651 (0.563–0.730)	13.5 (9.1–19.9)	0.17 (0.12–0.23)	98
By assay*							
Elecsys hs-cTnT	14	16 984	0.934 (0.895–0.959)	0.642 (0.543–0.730)	12.3 (8.1–18.5)	0.18 (0.13–0.25)	98
Architect hs-cTnI	3	5429	0.929 (0.891–0.954)	0.699 (0.605–0.779)	12 (6.9–22)	0.20 (0.18–0.23)	86
Centaur/Atellica hs-cTnI	3	3866	0.964 (0.933–0.981)	0.727 (0.684–0.767)	21 (12–39)	0.12 (0.07–0.18)	88
0/2-hour algorithm							
Overall	7	8936	0.961 (0.929–0.979)	0.759 (0.663–0.835)	21.1 (12.7–35.3)	0.15 (0.09–0.22)	98
By assay*							
Elecsys hs-cTnT	6	4991	0.965 (0.926–0.983)	0.780 (0.659–0.866)	21.4 (11.3–36.9)	0.15 (0.08–0.23)	98
Architect hs-cTnI	4	5505	0.969 (0.943–0.984)	0.772 (0.601–0.883)	24.9 (13.5–45.7)	0.13 (0.07–0.20)	93
Centaur/Atellica hs-cTnI	2	2949	NA	NA	NA	NA	NA
0/3-hour algorithm							
Overall	9	8096	0.932 (0.869–0.966)	0.644 (0.474–0.783)	12.7 (6.7–23.8)	0.19 (0.12–0.28)	98
By assay*							
Elecsys hs-cTnT	6	3636	0.951 (0.860–0.984)	0.684 (0.401–0.875)	17 (5.9–50)	0.18 (0.07–0.29)	97
Architect hs-cTnI	4	4434	0.949 (0.891–0.977)	0.737 (0.554–0.864)	16 (8.4–30)	0.18 (0.10–0.26)	98
Centaur/Atellica hs-cTnI	2	2269	NA	NA	NA	NA	NA
Clinical criteria							
Yes	3	2577	0.865 (0.758–0.930)	0.498 (0.361–0.636)	6.2 (3.6–10.6)	0.24 (0.13–0.37)	97
No	6	5519	0.953 (0.891–0.980)	0.709 (0.486–0.863)	18 (8.4–40)	0.17 (0.08–0.27)	98

hs-cTnI = high-sensitivity cardiac troponin I; hs-cTnT = high-sensitivity cardiac troponin T; NA = not available; NLR = positive likelihood ratio; NPV = positive predictive value.
* Manufacturers of the Elecsys hs-cTnT, Architect hs-cTnI, and Centaur/Atellica hs-cTnI assays are Roche, Abbott, and Siemens, respectively.

Figure 3. Forest plot summarizing the rule-in performance of the European Society of Cardiology 0/1-hour, 0/2-hour and 0/3-hour algorithm.

Study	Prevalence, %	TP, *n*	FN, *n*	FP, *n*	TN, *n*	Specificity	PPV
0/1-hour algorithm							
hs-cTnT (Elecsys*)							
APACE (34, 38)	16	398	123	124	2650	0.955 (0.947–0.963)	0.762 (0.724–0.798)
BACC (38)	19	227	62	96	1124	0.921 (0.905–0.936)	0.703 (0.650–0.752)
Christchurch (41)	21	91	30	19	435	0.958 (0.935–0.975)	0.827 (0.743–0.893)
RAPID-TnT (47)	4	52	7	84	1488	0.947 (0.934–0.957)	0.382 (0.300–0.470)
RAPID-CPU (48)	20	219	12	163	752	0.822 (0.796–0.846)	0.573 (0.522–0.623)
TRAPID-AMI (15)	15	123	69	42	1027	0.961 (0.947–0.972)	0.745 (0.672–0.810)
Calgary (19)	11	26	11	11	302	0.965 (0.938–0.982)	0.703 (0.530–0.841)
Tokyo and Taipei (50)	11	160	38	270	1265	0.824 (0.804–0.843)	0.372 (0.326–0.420)
FAST-MI (52)	37	400	86	48	783	0.942 (0.924–0.957)	0.893 (0.860–0.920)
Bangkok (54)	14	38	10	40	262	0.868 (0.824–0.904)	0.487 (0.372–0.603)
OUT-ACS (51)	4	45	16	21	1629	0.987 (0.981–0.992)	0.682 (0.556–0.791)
Lund (46)	8	62	16	37	923	0.961 (0.947–0.973)	0.626 (0.523–0.721)
Brighton and Sussex (53)	9	31	13	18	429	0.960 (0.937–0.976)	0.633 (0.483–0.766)
Shanghai (56)	18	103	3	175	296	0.628 (0.583–0.672)	0.371 (0.314–0.430)
Subtotal						0.934 (0.895–0.959)	0.642 (0.543–0.730)
hs-cTnI (Architect*†)							
APACE (36, 38)	16	390	86	223	2266	0.910 (0.899–0.921)	0.636 (0.597–0.674)
BACC (49)	18	291	49	146	1433	0.908 (0.892–0.921)	0.666 (0.620–0.710)
Christchurch (12)	16	76	10	17	442	0.963 (0.941–0.978)	0.817 (0.724–0.890)
Subtotal						0.929 (0.891–0.954)	0.699 (0.605–0.779)
hs-cTnI (Centaur/Atellica*†)							
APACE (20)	18	182	56	59	1050	0.947 (0.932–0.959)	0.755 (0.696–0.808)
HighSTEACS (11)	8	22	9	6	368	0.984 (0.965–0.993)	0.786 (0.590–0.917)
HIGH-US (21)	11	184	47	81	1801	0.957 (0.947–0.965)	0.694 (0.635–0.749)
Subtotal						0.964 (0.933–0.981)	0.727 (0.684–0.767)
Total						0.940 (0.907–0.962)	0.651 (0.563–0.730)
0/2-hour algorithm							
hs-cTnT (Elecsys*)							
APACE (35)	16	146	41	41	920	0.957 (0.943–0.969)	0.781 (0.715–0.838)
Brisbane (35)	10	47	31	12	715	0.983 (0.971–0.991)	0.797 (0.672–0.890)
Christchurch (43)	22	183	121	15	1061	0.986 (0.977–0.992)	0.924 (0.878–0.957)
RAPID-CPU (47)	22	208	5	132	620	0.824 (0.795–0.851)	0.612 (0.558–0.664)
Calgary (19)	11	48	15	10	477	0.979 (0.963–0.990)	0.828 (0.706–0.914)
RING (12,57)	6	8	1	7	127	0.948 (0.895–0.979)	0.533 (0.266–0.787)
Subtotal						0.965 (0.926–0.983)	0.780 (0.659–0.866)
hs-cTnI (Architect*†)							
APACE (37)	17	182	57	58	1138	0.952 (0.938–0.963)	0.758 (0.699–0.811)
Christchurch (42–45)	19	308	85	32	1597	0.980 (0.972–0.987)	0.906 (0.870–0.935)
RING (12, 57)	6	8	1	10	124	0.925 (0.867–0.964)	0.444 (0.215–0.692)
Subtotal						0.961 (0.928–0.979)	0.759 (0.509–0.906)
hs-cTnI (Centaur/Atelllca*†)							
APACE (20)	16	130	37	44	822	0.949 (0.932–0.963)	0.747 (0.676–0.810)
HIGH-US (21)	12	177	44	77	1618	0.955 (0.944–0.964)	0.697 (0.636–0.753)
Total						0.961 (0.929–0.979)	0.759 (0.663–0.835)
0/3-hour algorithm							
hs-cTnT (Elecsys*)							
Christchurch (12)	19	31	13	1	184	0.995 (0.970–1.000)	0.969 (0.838–0.999)
RAPIO-TnT (47)	4	57	8	82	1485	0.948 (0.935–0.958)	0.410 (0.327–0.497)
RAPID-CPU (48)	25	234	7	164	543	0.768 (0.735–0.799)	0.588 (0.538–0.637)
Nuremberg (40)	12	31	7	32	238	0.881 (0.837–0.918)	0.492 (0.364–0.621)
Brighton and Sussex (53)	10	36	2	3	350	0.992 (0.975–0.998)	0.923 (0.791–0.984)
RING (12, 57)	6	6	2	12	108	0.900 (0.832–0.947)	0.333 (0.133–0.590)
Subtotal						0.951 (0.860–0.984)	0.684 (0.401–0.875)
hs-cTnI (Architect*†)							
BACC (49)	18	256	79	56	1513	0.964 (0.954–0.973)	0.821 (0.773–0.861)
Christchurch (12)	18	72	19	9	416	0.979 (0.960–0.990)	0.889 (0.800–0.948)
HighSTEACS (10)	18	318	25	240	1303	0.844 (0.825–0.862)	0.570 (0.528–0.611)
RING (12, 57)	6	6	2	6	114	0.950 (0.894–0.981)	0.500 (0.211–0.789)
Subtotal						0.949 (0.891–0.977)	0.737 (0.554–0.864)
hs-cTnI (Centaur/Atellica*†)							
APACE (20)	16	51	14	21	273	0.929 (0.893–0.955)	0.661 (0.530–0.777)
HighSTEACS (11)	14	252	25	420	1223	0.744 (0.723–0.765)	0.375 (0.338–0.413)
Total						0.932 (0.859–0.969)	0.644 (0.474–0.783)



AMI = acute myocardial infarction; APACE = Advantageous Predictors of Acute Coronary Syndromes Evaluation; BACC = Biomarkers in Acute Cardiac Care; FAST-MI = FAST detection of Myocardial Infarction; HighSTEACS = High-sensitivity Troponin in the Evaluation of Patients with Acute Coronary Syndrome; HIGH-US = High-Sensitivity Cardiac Troponin I in the United States; hs-cTnI = high sensitivity cardiac troponin I; hs-cTnT = high sensitivity cardiac troponin T; NPV = negative predictive value; OUT-ACS = One-hoUr Troponin in a low-prevalence population of Acute Coronary Syndrome; RAPID-CPU = Rule-out Protocols in Patients Admitted With Chest Pain to a Crowded Chest Pain Unit; RAPID-TnT = Rapid Assessment of Possible Acute Coronary Syndrome in the Emergency Department With High-Sensitivity Troponin T; RING = Reducing the time Interval for identifying New Guidelines; TP = true positive; TN = true negative; FP = false positive; FN = false negative; TRAPID-AMI = The High Sensitivity Cardiac Troponin T Assay for Rapid Rule-out of Acute Myocardial Infarction; UTROPIA = Use of Abbott high-sensitivity TROPonin I assay In Acute coronary syndromes.

* Manufacturers of the Elecsys hs-cTnT, Architect hs-cTnI, and Centaur/Atellica hs-cTnI assays are Roche, Abbott, and Siemens, respectively.

† Performance of the 0/2-hour and 0/3-hour algorithm based on the Centaur/Atellica hs-cTnI assay could not be pooled owing to an insufficient number of studies.

concentrations less than 29 ng/L and were unable to apply the full 0/3-hour algorithm (47). In many studies, the clinical criteria of GRACE score and pain-free recommended in the ESC guidelines were not used. This may in part reflect the difficulty in implementing clinical risk scores in a busy ED setting. In our analysis, omission of these clinical criteria lowers the sensitivity of the ESC 0/3-hour algorithm (18). When used with clinical criteria, the 0/3-hour algorithm had similar performance to that of the 0/1-hour and 0/2-hour algorithms. The high heterogeneity could also be due to miscalibration of the Elecsys hs-cTnT lots used in 2010–2012 worldwide. This low-end shift affected almost exclusively hs-cTnT levels below the 99th percentile, leading to misclassification of patients with adjudicated AMI to the rule-out category and compromising sensitivity and NPV (63).

All 3 ESC algorithms had high pooled specificities, but with substantial heterogeneity across studies. The reason for this is probably multifactorial. Our meta-regression analysis showed that specificity varied with AMI prevalence, in which studies with AMI prevalence more than 10% had lower specificity than studies with AMI prevalence of 10% or less. This may seem surprising because specificity does not usually vary with pretest probability or prevalence of the target condition (64). Nevertheless, this could be because in populations with a higher prevalence of AMI, there may also be a higher prevalence of other non-MI conditions (such as myocarditis or other causes of myocardial injury) that cause cardiac troponin elevations, resulting in higher rates of false-positive cases (56, 65). Another reason for the observed disparities could be different inclusion and exclusion criteria used in the studies. In our systematic review, studies that included only patients who presented with chest pain appeared to have higher specificities than studies that included patients with other cardiac and atypical symptoms. Two cohorts (RAPID-CPU and HighSTEACS) did not exclude patients with chronic kidney disease or those undergoing renal dialysis (who tend to have elevated hs-cTn levels) and reported a specificity of only 80% (10, 11, 48, 50). Furthermore, there were methodological discrepancies among studies. Some studies used a hs-cTn assay for central adjudication that differed from that used in the rapid algorithm (12, 15, 41). Because there are infrequent but well-described discrepancies between hs-cTnT and hs-cTnI, using a hs-cTnI–based reference standard for a hs-cTnT–based rapid algorithm may underestimate the true accuracy of hs-cTnT–based algorithms (12, 15, 41). Some studies used samples that were collected differently from the timing stipulated in the ESC guidelines (21, 53); the HIGH-US cohort had a 0-2/3 hour blood draw after baseline sampling instead of a 0/2 or 0/3-hour blood draw (21). Samples collected after the recommended timing may overestimate the true accuracy of the ESC algorithms, whereas samples collected before the recommended timing may underestimate the true accuracy.

To increase the specificities of the ESC algorithms, it may be possible to adjust the rule-in threshold at presentation or the change between the first and second cardiac troponin test, but this may increase the number of patients in the observation or rule-out group. Furthermore, elevations in cardiac troponin levels are associated with higher risk for AMI or death, and further evaluation is often required (17). Given this and the substantial heterogeneity across studies, the rule-in strategy should be used along

Table 3. Head-to-Head Comparison of the European Society of Cardiology Algorithms

Algorithm Comparison	Sensitivity (95% CI)	NPV (95% CI)	Proportion Ruled Out (95% CI)	Specificity (95% CI)	PPV (95% CI)	Proportion Ruled In (95% CI)
0/1-hour vs. 0/2-hour*						
0/1-hour	0.990 (0.980–0.995)	0.997 (0.994–0.998)	0.49 (0.45–0.54)	0.943 (0.900–0.968)	0.709 (0.627–0.779)	0.18 (0.11–0.26)
0/2-hour	0.987 (0.978–0.992)	0.996 (0.993–0.998)	0.54 (0.50–0.58)	0.955 (0.908–0.978)	0.773 (0.659–0.858)	0.18 (0.12–0.25)
0/1-hour vs. 0/3-hour†						
0/1-hour	0.988 (0.980–0.993)	0.997 (0.994–0.999)	0.60 (0.49–0.70)	0.944 (0.907–0.966)	0.667 (0.553–0.764)	0.16 (0.10–0.23)
0/3-hour	0.932 (0.843–0.972)	0.987 (0.971–0.994)	0.76 (0.61–0.88)	0.949 (0.864–0.982)	0.725 (0.505–0.872)	0.19 (0.11–0.30)
0/2-hour vs. 0/3-hour‡						
0/2-hour	0.986 (0.975–0.992)	0.995 (0.991–0.997)	0.56 (0.50–0.61)	0.944 (0.877–0.976)	0.741 (0.563–0.864)	0.19 (0.11–0.29)
0/3-hour	0.906 (0.781–0.963)	0.977 (0.960–0.988)	0.72 (0.55–0.86)	0.920 (0.817–0.967)	0.655 (0.429–0.828)	0.22 (0.09–0.38)
0/1-hour vs. 0/2-hour vs. 0/3-hour§						
0/1-hour	0.991 (0.979–0.996)	0.997 (0.992–0.999)	0.49 (0.43–0.56)	0.927 (0.844–0.968)	0.719 (0.589–0.820)	0.22 (0.13–0.34)
0/2-hour	0.986 (0.974–0.992)	0.995 (0.991–0.997)	0.54 (0.48–0.60)	0.924 (0.844–0.980)	0.780 (0.601–0.893)	0.22 (0.13–0.34)
0/3-hour	0.923 (0.800–0.973)	0.977 (0.955–0.988)	0.67 (0.47–0.84)	0.925 (0.782–0.977)	0.730 (0.539–0.862)	0.24 (0.09–0.44)

NA = not available; NPV = negative predictive value; PPV = positive predictive value.
* Based on 4 cohorts for rule-out sensitivity and NPV and 5 cohorts for rule-in specificity and PPV.
† Based on 7 cohorts for rule-out sensitivity and NPV and 7 cohorts for rule-in specificity and PPV.
‡ Based on 4 cohorts for rule-out sensitivity and NPV and 4 cohorts for rule-in specificity and PPV.
§ Based on 3 cohorts for rule-out sensitivity and NPV and 3 cohorts for rule-in specificity and PPV.

with detailed clinical assessments by the attending physicians and cardiologists.

In the LCBM analysis, there was little difference between the diagnostic accuracy of studies that adjudicated AMI with the same cardiac troponin assay and that of studies that adjudicated AMI with a different cardiac troponin assay. These results suggest that use of the same cardiac troponin assay for adjudication of AMI might have only a minimal effect on the diagnostic accuracy estimates reported in our study. There were concerns that these studies posed risks of incorporation bias and might overestimate performance of the algorithms. Nevertheless, the rapid algorithms should be considered as proxies to the universal definition of MI, with the role of diagnosing AMI with similar safety in a shorter time. As such, using the same hs-cTn assay to validate the algorithms and adjudicate AMI should be considered methodologically appropriate. Conversely, using a different cardiac troponin assay for assessment of the algorithm and adjudication of AMI might underestimate the diagnostic accuracies of the algorithms.

We detected similar performances for all of the algorithms among different hs-cTn assays. This implies that institutions planning to implement hs-cTn–based algorithms may not need to introduce a new hs-cTn assay for measuring hs-cTn. Nevertheless, these results can be generalized only to the Elecsys hs-cTnT, Architect hs-cTnI, and Centaur/Atellica hs-cTnI assays. Other novel hs-cTn assays are recommended in the 2020 ESC guidelines for which few studies were available for analysis (13, 66). The latest guidelines also recommend a new threshold for the 0/1-hour algorithm using the Architect hs-cTnI assay. More studies are needed to evaluate the performance of these novel assays or thresholds.

Overall, our study supports the changes reflected in the latest ESC guidelines (13). Our previous meta-analysis cautioned that the 0/1-hour algorithm may not be universally safe, in part on the basis that 2 small, non–peer-reviewed studies reported only modest sensitivity and NPV (62). In this updated meta-analysis of high-quality studies, we found strong evidence that the 0/1-hour algorithm has high sensitivity and NPV for index AMI and can potentially be implemented across populations with different demographic characteristics. Nevertheless, it is important to recognize that the algorithm has not been validated in such regions as South Asia, the Middle East, and Africa. The 0/2-hour algorithm had a pooled sensitivity that was lower than 99%, a commonly regarded safety benchmark for ruling out AMI. However, evidence was insufficient to draw conclusions about its safety and efficacy because the algorithm was validated in a small number of cohorts. On the basis of robust evidence from 10 unique cohorts, the 0/3-hour algorithm only had a modest sensitivity and NPV for index AMI, particularly when used without the guideline-recommended clinical criteria. Additional studies are required to validate the performance of these algorithms in high-risk subgroups, such as patients with renal failure undergoing hemodialysis, who were often excluded from previous observational studies. The NPV and PPV estimates reported in this study may be used to guide clinical decision making, but these measures are prevalence dependent. Finally, all 3 algorithms should be used in conjunction with a detailed clinical assessment that includes focused history taking, electrocardiography, and adjunctive imaging.

Before this study, we performed 2 systematic reviews to investigate the performance of hs-cTn–based algorithms for the diagnosis of AMI. In a review that investigated the diagnostic accuracies of the 0-hour, 1-hour, 2-hour, and 0/1-hour algorithms (67), many of the included studies used thresholds that differed from those in the ESC guidelines to rule out or rule in AMI. As a result, the reported accuracy estimates were heterogenous and not reflective of the latest ESC recommendations. Furthermore, head-to-head comparison was lacking between different triage protocols within the same study cohort. In another review that focused on the 0/1-hour algorithm (62), most of the included studies were observational studies performed in Europe. Since the publication of these 2 reviews, several critical studies, including randomized controlled trials and quasi-experimental studies from both European and non-European countries, have been published (21, 47–52, 54). Of note, the 2 previous reviews were not designed to investigate the diagnostic accuracy of the broadly implemented 0/3-hour or the newly recommended 0/2-hour algorithm. Given these knowledge gaps, this systematic review was done to capture the individual and comparative diagnostic accuracies of the rapid triage algorithms endorsed by the 2020 ESC guidelines.

The main strength of our study was that it included investigator-provided primary data that have not been published previously. Reanalysis of these data allowed us to perform head-to-head comparisons between different ESC algorithms and investigate performance in subgroups of patients who presented with recent-onset chest pain. Despite differences in reporting outcomes in the included studies, we were able to standardize the primary outcome as index visit AMI. We also obtained the timing of sample collection for most studies; this is important because performance of the algorithms is highly dependent on this timing.

Our study has limitations. First, there was substantial heterogeneity in the diagnostic accuracy reported by the included studies. We attempted to address heterogeneity by using a bivariate random-effects meta-analysis and meta-regression including categorical variables that may contribute to interstudy heterogeneity. Although many covariates that we assessed in the meta-regression did not have a detectable effect on the diagnostic accuracy estimates, these analyses may not have had sufficient power to detect statistically significant differences between subgroups. Second, we could not acquire individual patient data and could not account for the patients who were falsely ruled out or ruled in by the ESC algorithms. Characterization of these patients will be valuable for the interpretation and clinical application of the algorithms. Third, inclusion and exclusion criteria varied across studies, which could have contributed to the heterogeneity in reported diagnostic

accuracies. Fourth, we included studies that analyzed cardiac troponin samples collected more than 30 minutes outside of the time stipulated by the ESC algorithms; this might have influenced the estimates described in our study. Nevertheless, this greater flexibility in cardiac troponin sampling may better reflect clinical performance of the algorithms in real-world settings. Fifth, a few studies did not use blinding during the adjudication process and may have conferred incorporation bias to the accuracy estimates. Nevertheless, the reported diagnostic accuracies were consistent across studies regardless of blinding status during adjudication. Sixth, in many studies, patient care was not dictated by the algorithms; therefore, patient outcomes could have been influenced by cardiac troponin levels and clinical management. Finally, accuracy estimates from this analysis may not be fully compatible with the newly updated fourth universal AMI definition because many studies used the third universal definition of AMI.

In conclusion, the ESC 0/1-hour and 0/2-hour algorithms have higher sensitivities and NPVs than the ESC 0/3-hour algorithm in ruling out patients for myocardial infarction. The ESC 0/3-hour algorithm should not be used without the clinical criteria recommended in the guidelines. Further studies, particularly on the 0/2-hour algorithm, are required to confirm the applicability and implementation of the ESC algorithms in real-world clinical settings.

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65. **Shiozaki M, Inoue K, Suwa S, et al.** Utility of the 0-hour/1-hour high-sensitivity cardiac troponin T algorithm in Asian patients with suspected non-ST elevation myocardial infarction. Int J Cardiol. 2017;249:32-35. [PMID: 28986063] doi:10.1016/j.ijcard.2017.09.009
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Appendix Table 1. Literature Search Strategy*

Search Set	PubMed	Embase	Scopus, Web of Science, Cochrane Database
1	MYOCARDIAL INFARCTION or ACUTE CORONARY SYNDROME or acute myocardial infarction or heart infarction	HEART INFARCTION or ACUTE CORONARY SYNDROME or ACUTE MYOCARDIAL INFARCTION or myocardial infarction	Myocardial infarction or acute coronary syndrome
2	TROPONIN or cardiac troponin or high-sensitivity troponin or high-sensitivity cardiac troponin	TROPONIN or cardiac troponin or high-sensitivity troponin or high-sensitivity cardiac troponin	Troponin or cardiac troponin or high-sensitivity troponin or high-sensitivity cardiac troponin
3	0/1-hour or 0-hour/1-hour or 1-hour or 0/2-hour or 0-hour/2-hour or 2-hour or 0/3-hour or 0-hour/3-hour or 3-hour or 0/1-hour algorithm or 0/1-hour protocol or 0/2-hour algorithm or 0/2-hour protocol or 0/3-hour algorithm or 0/3-hour protocol	0/1-hour or 0-hour/1-hour or 1-hour or 0/2-hour or 0-hour/2-hour or 2-hour or 0/3-hour or 0-hour/3-hour or 3-hour or 0/1-hour algorithm or 0/1-hour protocol or 0/2-hour algorithm or 0/2-hour protocol or 0/3-hour algorithm or 0/3-hour protocol	0/1-hour or 0-hour/1-hour or 1-hour or 0/2-hour or 0-hour/2-hour or 2-hour or 0/3-hour or 0-hour/3-hour or 3-hour or 0/1-hour algorithm or 0/1-hour protocol or 0/2-hour algorithm or 0/2-hour protocol or 0/3-hour algorithm or 0/3-hour protocol
Sets 1 to 3 are combined with “AND”			

* Capital letters indicate MeSH or Emtree terms. All-fields search was conducted by using PubMed and Embase, and title/abstract/keyword search was conducted by using Scopus, Web of Science, and the Cochrane database.

Appendix Table 2. Summary of Data Requested and Obtained From Authors*

Cohort (Reference)	Authors Contacted and Provided Data	Authors Contacted But Unable to Provide Data	Authors Contacted But Did Not Respond	Data Requested and Obtained From Authors				Data Extracted From Publication			
				Primary and Secondary Outcomes†			Demographics‡	Primary and Secondary Outcomes†			Demographics‡
				0/1-hour	0/2-hour	0/3-hour		0/1-hour	0/2-hour	0/3-hour	
APACE (9, 20, 34–39)	✓						✓	✓	✓	✓	✓
Brisbane (35)	✓				✓		✓				
Christchurch (12, 41–45)	✓			✓	✓	✓	✓				
RAPID-TnT (47)	✓			✓		✓	✓				
TRAPID-AMI (15)		✓						✓			✓
RAPID-CPU (48)	✓			✓	✓	✓	✓				
BACC (49)	✓			✓		✓	✓				✓
HighSTEACS (10, 11)			✓					✓		✓	✓
Brighton and Sussex (53)	✓			✓		✓	✓				
Calgary (19)	✓				✓			✓	✓		✓
Tokyo and Taipei (50)	✓			✓			✓				
FAST-MI (52)	✓			✓			✓				
Bangkok (54)	✓			✓			✓				
OUT-ACS (51)	✓			✓			✓				
Lund (46)	✓			✓			✓				
Shanghai (56)			✓					✓			✓
UTROPIA (55)			✓							✓	✓
HIGH-US (21)	✓						✓	✓	✓		✓
Nuremberg (40)	✓					✓	✓				
RING (12, 57)	✓				✓	✓	✓				
Excluded§											
Beijing		✓									
Buenos Aires			✓								
Manchester			✓								
Parkland			✓								
Fujita			✓								

* Data that were not requested from authors were extracted directly from published articles

† Includes number of patients, cases of index acute myocardial infarction, cases of 30-day mortality in rule-out, observe, and rule-in categories for all patients, and early (chest pain onset ≤3 hours) versus late presenters (chest pain onset >3 hours).

‡ Includes sample size, median age with 25th and 75th percentile, proportion of male sex, proportion of patients presenting with chest pain, median time from initial emergency department presentation to first sample collection in minutes, median time from first to second sample collection in minutes, proportion of hypertension, proportion of dyslipidemia, proportion of diabetes mellitus, proportion of smoker, proportion of family history of heart disease, proportion of prior myocardial infarction, proportion of prior stroke, proportion of prior coronary artery disease, proportion of prior percutaneous coronary intervention.

§ The following studies were not included because the authors could not be contacted for data or authors were unable to provide data, and the published data were insufficient for analysis and assessment of risk of bias:

Beijing: Lin Y, Zhang G, Feng G, et al. 1/3 hours rule in and rule out algorithm for NSTEMI using a high-sensitivity cardiac troponin I at emergency department in Chinese population. Clin Chem. 2018;64:S49.

Buenos Aires: Cortés M, Haseeb S, Lambardi F, et al. The HEART score in the era of the European Society of Cardiology 0/1-hour algorithm. Eur Heart J Acute Cardiovasc Care. 2020;9:30-38. [PMID: 31657616] doi:10.1177/2048872619883619

Manchester: Berg PVD, Collinson P, Morris N, et al. 020 Diagnostic accuracy of the Siemens TNIH assay with 0/3 hour rule out algorithms. Emergency Medicine Journal. 2019;36:784-5.

Parkland: Vigen R, Kutscher P, Fernandez F, et al. Evaluation of a novel rule-out myocardial infarction protocol incorporating high-sensitivity troponin T in a US hospital [Letter]. Circulation. 2018;138:2061-2063. [PMID: 30372140] doi:10.1161/CIRCULATIONAHA.118.033861

Fujita: Ohtake H, Ishii J, Nishimura H, et al. Prospective validation of 0-hour/1-hour algorithm using high-sensitivity cardiac troponin I in Japanese patients presenting to emergency department. Eur Heart J. 2020;41:ehaa946.1707. doi:10.1093/ehjci/ehaa946.1707

Appendix Table 3. Characteristics of Included Studies

Cohort (Reference)	Country	Sample Size, *n*	AMI Prevalence, %	Algorithm	Troponin Assay*	Study Type	MI Type	Chest Pain, %	Median Time From ED Presentation to First Sample Collection, *min*†	Median Time From First to Second Sample Collection, *min*†		
										1-Hour	2-Hour	3-Hour
APACE (9, 20, 34–39)	Switzerland, Spain, Poland, Italy, Czech Republic	3295	16	0/1-hour; 0/2-hour; 0/3-hour	Elecsys hs-cTnT; Architect hs-cTnI; Centaur hs-cTnI	Observational	1 and 2	100	NA	60 (59–68)	NA	NA
Brisbane (35)	Australia	1905	7	0/2-hour	Elecsys hs-cTnT; Architect hs-cTnI	Observational	1 and 2	100	24 (18–36)	–	138 (126–150)	–
Christchurch (12, 41–45)	New Zealand	2022	19	0/1-hour; 0/2-hour; 0/3-hour	Elecsys hs-cTnT; Architect hs-cTnI	Observational	1 and 2	100	NA	60 (60–65)	120 (120–125)	181 (176–190)
RAPID–TnT (47)	Australia	3263	4	0/1-hour; 0/3-hour	Elecsys hs-cTnT	Randomized controlled trial	1 and 2	61	NA	60 (60–72)	–	186 (174–210)
TRAPID–AMI (15)	Switzerland, Spain, Italy, Belgium, Germany, Sweden, United States, Australia, United Kingdom	1261	15	0/1-hour	Elecsys hs-cTnT	Observational	ND	NA	NA	60 (30–90)	–	–
RAPID–CPU (48)	Germany	3059	20	0/1-hour; 0/2-hour 0/3-hour	Elecsys hs-cTnT	Quasi-experimental	ND	46	25 (7–43)	72 (54–90)	110 (82–138)	183 (157–209)
BACC (49)	Germany	1919	18	0/1-hour 0/3-hour	Elecsys hs-cTnT; Architect hs-cTnI	Observational	1 and 2	85	22 (14–35)	60 (60–63)	–	180 (180–183)
HighSTEACS (10, 11)	United Kingdom	1920	14	0/1-hour 0/3-hour	Architect hs-cTnI; Atellica hs-cTnI	Observational	1 and 2	84	28 (15–46)	65 (60–73)	–	176 (146–205)
Brighton an d Sussex (53)	United Kingdom	882	9	0/1-hour 0/3-hour	Elecsys hs-cTnT	Observational	1 and 2	100	62	103	–	215
Calgary (19)	Canada	550	11	0/1-hour 0/2-hour	Elecsys hs-cTnT	Observational	1 and 2	100	NA	67	127	–
Tokyo and Taipei (50)	Japan, Taiwan	1733	11	0/1-hour	Elecsys hs-cTnT	Observational	1 and 2	100	171 (75–525)‡	NA	–	–
FAST–MI (52)	Germany	1317	37	0/1-hour	Elecsys hs-cTnT	Observational	1 and 2	60	0	60	–	–
Bangkok (54)	Thailand	350	14	0/1-hour	Elecsys hs-cTnT	Observational	ND	100	NA	NA	–	–
OUT–ACS (51)	Norway	1711	4	0/1-hour	Elecsys hs-cTnT	Observational	ND	87	136 (100–194)	65 (60–70)	–	–
Lund (46)	Sweden	1038	8	0/1-hour	Elecsys hs-cTnT	Observational	1 and 2	100	32 (19–54)	60 (60–60)	–	–
Shanghai (56)	China	577	18	0/1-hour	Elecsys hs-cTnT	Observational	ND	NA	NA	NA	–	–
UTROPIA (55)	United States	582	12	0/3-hour	Architect hs-cTnI	Observational	1 and 2	NA	NA	–	–	NA
HIGH–US (21)	United States	2113	11	0/1-hour; 0/2-3-hour§	Centaur hs-cTnI	Observational	1 and 2	NA	56 (SD, 49)	98 (SD, 53)	98 (SD, 53)	–
Nuremberg (40)	Germany	308		0/3-hour	Elecsys hs-cTnT	Observational	1 and 2	48	15 (14–48)	–	–	175 (154–192)
RING (12, 57)	Canada	143	6	0/2-hour; 0/3-hour	Elecsys hs-cTnT; Architect hs-cTnI	Observational	1 and 2	92	210	–	90 (90–90)	180 (180–182)

AMI = acute myocardial infarction; APACE = Advantageous Predictors of Acute Coronary Syndromes Evaluation; BACC = Biomarkers in Acute Cardiac Care; ESC-TROP = European Society of Cardiology 0-/1-h hs-cTnT; ED = emergency department; FAST-MI = FAST detection of Myocardial Infarction; HighSTEACS = High-sensitivity Troponin in the Evaluation of Patients with Acute Coronary Syndrome; HIGH-US = High-Sensitivity Cardiac Troponin I in the United States; hs-cTnI = high sensitivity cardiac troponin I; hs-cTnT = high sensitivity cardiac troponin T; NA = not available; ND = not differentiated; OUT-ACS = One-hoUr Troponin in a low-prevalence population of Acute Coronary Syndrome; RAPID-CPU = Rule-out Protocols in Patients Admitted With Chest Pain to a Crowded Chest Pain Unit; RAPID-TnT = Rapid Assessment of Possible Acute Coronary Syndrome in the Emergency Department With High-Sensitivity Troponin T; RING = Reducing the time Interval for identifying New Guideline Defined Myocardial Infarction in Patients with Suspected Acute Coronary Syndrome; TRAPID-AMI = The High Sensitivity Cardiac Troponin T Assay for Rapid Rule-out of Acute Myocardial Infarction; UTROPIA = Use of Abbott high-sensitivity TROPonin I assay In Acute coronary syndromes.

* Manufacturers of the Elecsys hs-cTnT, Architect hs-cTnI, and Centaur/Atellica hs-cTnI assays are Roche, Abbott, and Siemens, respectively.

† Unless otherwise indicated, values in parentheses are interquartile ranges.

‡ Data from onset of chest pain to first sample.

§ All samples were obtained between 2 and 3 hours after the baseline sample.

Appendix Table 4. Methodological Quality Assessment With the QUADAS-2 Tool

Cohort	Study, Year (Reference)	Risk of Bias				Applicability Concerns		
		Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
APACE	Wildi et al, 2019 (39)	Low	Low	Low	Unclear	Low	Low	Low
APACE	Twerenbold et al, 2018 (38)	Low	Low	Low	Low	Low	Low	Low
APACE	Reichlin et al, 2012 (34)	Low	High	Low	Unclear	Low	Low	Low
APACE	Rubini Giminez et al, 2015 (36)	Low	High	Low	Unclear	Low	Low	Low
APACE	Boeddinghaus et al, 2016 (37)	Low	High	Low	Unclear	Low	Low	Low
APACE	Boeddinghaus et al, 2018 (20)	Low	Low	Low	Low	Low	Low	Low
APACE	Reichlin et al, 2014 (35)	Unclear	High	Low	Unclear	Low	Low	Low
APACE	Wildi et al, 2016 (9)	Low	Low	Low	Unclear	Low	Low	Low
Brisbane	Reichlin et al, 2015 (35)	Unclear	Low	High	Unclear	Low	Low	Low
Christchurch	Pickering et al, 2016 (41)	Low	Low	High	Low	Low	Low	Low
Christchurch and RING	Pickering et al, 2016 (12)	Low	Low	High	Low	Low	High	Low
Christchurch	Than et al, 2012 (42)	Low	Low	High	Low	Low	Low	Low
Christchurch	Than et al, 2014 (43)	Low	Low	High	Low	Low	Low	Low
Christchurch	Than et al, 2016 (44)	Low	Low	High	Low	Low	Low	Low
Christchurch	Pickering et al, 2020 (45)	Low	Low	High	Low	Low	Low	Low
RING	Kavsak et al, 2013 (57)	Unclear	Low	High	Low	Low	High	Low
RAPID-TnT	Chew et al, 2019 (47)	Low	Low	Low	Low	Low	High	Low
TRAPID-AMI	Mueller et al, 2016 (15)	Low	Low	High	Low	Low	Low	Low
RAPID-CPU	Stoyanov et al, 2020 (48)	Low	Low	Low	Low	Low	High	Low
BACC	Haller et al, 2020 (49)	Unclear	Low	Low	Low	Low	High	Low
HighSTEACS	Chapman et al, 2018 (10)	Unclear	Low	Low	Low	Low	Low	Low
HighSTEACS	Chapman et al, 2019 (11)	Low	Low	Low	Low	Low	Low	Low
Brighton and Sussex	Buttinger et al, 2019 (53)	Low	Low	Low	Low	Low	High	Low
Calgary	Andruchow et al, 2020 (19)	Low	Low	Low	Low	Low	Low	Low
Tokyo and Taipei	Shiozaki et al, 2020 (50)	Unclear	Low	Low	Unclear	Low	Low	Low
FAST-MI	Amann et al, 2019 (52)	Low	Low	Low	Low	Low	Low	Low
Bangkok	Ruangsomboon et al, 2021 (54)	Low	Low	Low	Unclear	Low	Low	Low
OUT-ACS	Johannessen et al, 2020 (51)	Low	Low	Low	Low	Low	Low	Low
Lund	Mokhtari et al, 2016 (46)	Low	Low	Low	Low	Low	Low	Low
Shanghai	Dongxu et al, 2020 (56)	Low	Low	High	Unclear	Low	Low	Low

Continued on following page

Appendix Table 4–Continued

Cohort	Study, Year (Reference)	Risk of Bias				Applicability Concerns		
		Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
UTROPIA	Sandoval et al, 2020 (55)	Low	Low	Low	Unclear	Low	High	Low
HIGH-US	Nowak et al, 2020 (21)	Unclear	Low	High	Low	Low	Low	Low
Nuremberg	Bahrmann et al, 2013 (40)	Low	Low	Low	Low	Low	Low	Low

APACE = Advantageous Predictors of Acute Coronary Syndromes Evaluation; BACC = Biomarkers in Acute Cardiac Care; ESC-TROP = European Society of Cardiology 0-/1-h hs-cTnT; ED = emergency department; FAST-MI = FAST detection of Myocardial Infarction; HighSTEACS = High-sensitivity Troponin in the Evaluation of Patients with Acute Coronary Syndrome; HIGH-US = High-Sensitivity Cardiac Troponin I in the United States; OUT-ACS = One-hoUr Troponin in a low-prevalence population of Acute Coronary Syndrome; RAPID-CPU = Rule-out Protocols in Patients Admitted With Chest Pain to a Crowded Chest Pain Unit; RAPID-TnT = Rapid Assessment of Possible Acute Coronary Syndrome in the Emergency Department With High-Sensitivity Troponin T; RING = Reducing the time Interval for identifying New Guideline Defined Myocardial Infarction in Patients with Suspected Acute Coronary Syndrome; TRAPID-AMI = The High Sensitivity Cardiac Troponin T Assay for Rapid Rule-out of Acute Myocardial Infarction; UTROPIA = Use of Abbott high-sensitivity TROPonin I assay In Acute coronary syndromes.

Appendix Table 5. Methodological Quality Assessment With the QUADAS-2 Tool, by Individual Domains

Cohort	Study, Year (Reference)	Risk of Bias										Applicability Concerns		
		Patient Selection		Index Test		Reference Standard			Flow and Timing			Patient Selection	Index Test	Reference Standard
		Q1	Q2	Q1	Q2	Q1	Q2	Q3	Q1	Q2	Q3			
APACE	Wildi et al, 2019 (39)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
APACE	Twerenbold et al, 2018 (38)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
APACE	Reichlin et al, 2012 (34)	Yes	Yes	Yes	No	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
APACE	Rubini et al, 2015 (36)	Yes	Yes	Yes	No	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
APACE	Boeddinghaus et al, 2016 (37)	Yes	Yes	Yes	No	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
APACE	Boeddinghaus et al, 2018 (20)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
APACE	Reichlin et al, 2014 (35)	Unclear	Yes	Yes	No	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
APACE	Wildi et al, 2016 (9)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Brisbane	Reichlin et al, 2014 (35)	Unclear	Yes	Yes	Yes	No	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Christchurch	Pickering et al, 2016 (41)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Christchurch and RING	Pickering et al, 2016 (12)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Christchurch	Than et al, 2012 (42)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Christchurch	Than et al, 2014 (43)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Christchurch	Than et al, 2016 (44)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Christchurch	Pickering et al, 2020 (45)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
RING	Kavsak et al, 2013 (57)	Unclear	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
RAPID-TnT	Chew et al, 2019 (47)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
TRAPID-AMI	Mueller et al, 2016 (15)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
RAPID-CPU	Stoyanov et al, 2019 (48)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
BACC	Haller et al, 2020 (49)	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
HighSTEACS	Chapman et al, 2018 (10)	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
HighSTEACS	Chapman et al, 2019 (11)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Brighton and Sussex	Buttinger et al, 2019 (53)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Calgary	Andruchow et al, 2020 (19)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Tokyo and Taipei	Shiozakiet al, 2020 (50)	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
FAST-MI	Amann et al, 2019 (52)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bangkok	Ruangsomboon et al, 2020 (54)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
OUT-ACS	Johannessen et al, 2020 (51)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lund	Mokhtari et al, 2016 (46)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Shanghai	Dongxu et al, 2020 (56)	Unclear	Yes	Yes	Yes	Yes	Yes	No	Unclear	Yes	Yes	Yes	Yes	Yes
UTROPIA	Sandoval et al, 2020 (55)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No	Yes
HIGH-US	Nowak et al, 2020 (21)	Unclear	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Nuremberg	Bahrmann et al, 2013 (40)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

APACE = Advantageous Predictors of Acute Coronary Syndromes Evaluation; BACC = Biomarkers in Acute Cardiac Care; ESC-TROP = European Society of Cardiology 0-/1-h hs-cTnT; ED = emergency department; FAST-MI = FAST detection of Myocardial Infarction; HighSTEACS = High-sensitivity Troponin in the Evaluation of Patients with Acute Coronary Syndrome; HIGH-US = High-Sensitivity Cardiac Troponin I in the United States; OUT-ACS = One-hoUr Troponin in a low-prevalence population of Acute Coronary Syndrome; RAPID-CPU = Rule-out Protocols in Patients Admitted With Chest Pain to a Crowded Chest Pain Unit; RAPID-TnT = Rapid Assessment of Possible Acute Coronary Syndrome in the Emergency Department With High-Sensitivity Troponin T; RING = Reducing the time Interval for identifying New Guideline Defined Myocardial Infarction in Patients with Suspected Acute Coronary Syndrome; TRAPID-AMI = The High Sensitivity Cardiac Troponin T Assay for Rapid Rule-out of Acute Myocardial Infarction; UTROPIA = Use of Abbott high-sensitivity TROPonin I assay In Acute coronary syndromes.

Appendix Table 6. Pooled Incidence of 30-Day Mortality in the Rule-Out, Observation, and Rule-In Groups

Algorithm	Rule-Out Group		Observation Group		Rule-In Group	
	30-Day Mortality (95% CI)	Cases/Patients at Risk, *n/n*	30-Day Mortality (95% CI)	Cases/Patients at Risk, *n/n*	30-Day Mortality (95% CI)	Cases/Patients at Risk, *n/n*
0/1-hour	0.001 (0.000–0.002)	14/8783	0.01 (0.00–0.01)	9/4130	0.03 (0.01–0.04)	99/2978
0/2-hour	0.001 (0.000–0.002)	7/4511	0.01 (0.00–0.02)	40/4380	0.04 (0.01–0.08)	51/1116
0/3-hour	0.001 (0.000–0.002)	9/4310	NA	–	0.02 (0.00–0.06)	46/1060

NA = not applicable.

Appendix Table 7. Rule-Out Performance of the European Society of Cardiology Algorithms in Early Versus Late Presenters

Algorithm	Onset of Chest Pain	Patients, *n**	False Negative, *n*	True Negative, *n*	Sensitivity (95% CI)	NPV (95% CI)	Proportion Ruled Out (95% CI)
0/1-hour	≤3 h	5250	9	2875	0.988 (0.978–0.994)	0.997 (0.994–0.998)	0.55 (0.46–0.64)
0/1-hour	>3 h	10 235	8	5320	0.994 (0.988–0.997)	0.998 (0.997–0.999)	0.52 (0.42–0.62)
0/2-hour	≤3 h	3328	2	2222	0.998 (0.877–1.000)	1.000 (0.968–1.000)	0.63 (0.55–0.71)
0/2-hour	>3 h	5802	17	3527	0.981 (0.962–0.991)	0.995 (0.992–0.997)	0.62 (0.54–0.70)
0/3-hour	≤3 h	2585	19	1861	0.959 (0.842–0.990)	0.995 (0.981–0.999)	0.78 (0.59–0.93)
0/3-hour	>3 h	4737	76	3034	0.941 (0.835–0.981)	0.985 (0.964–0.994)	0.64 (0.43–0.82)

NPV = negative predictive value.
* Based on 11 cohorts for the 0/1-hour algorithm, 6 cohorts for the 0/2-hour algorithm, and 7 cohorts for the 0/3-hour algorithm.

Appendix Table 8. Meta-regression of Effects of Study Characteristics on Diagnostic Accuracy for the 0/3-Hour Algorithm*

Covariates	Studies, *n*	Relative Sensitivity (95% CI)	*P* Value	Studies, *n*	Relative Specificity (95% CI)	*P* Value
Geographic location			0.21			0.28
Europe	6	0.96 (0.90–0.98)		6	0.91 (0.81–0.95)	
Non-Europe	4	0.88 (0.70–0.96)		3	0.95 (0.87–0.98)	
AMI prevalence			0.45			0.120
>10%	7	0.95 (0.89–0.98)		6	0.90 (0.81–0.95)	
≤10%	3	0.90 (0.69–0.97)		3	0.96 (0.89–0.99)	
Study design			0.91			0.53
Observational	8	0.94 (0.86–0.97)		7	0.93 (0.87–0.97)	
RCT or quasi-experimental	2	0.94 (0.76–0.99)		2	0.89 (0.67–0.97)	
Sample size			0.38			0.43
<500	3	0.97 (0.83–0.99)		4	0.94 (0.86–0.98)	
≥500	7	0.93 (0.85–0.97)		5	0.91 (0.80–0.96)	
Proportion of patients with chest pain			0.71			<0.001
100%	3	0.95 (0.79–0.99)		3	0.97 (0.94–0.99)	
<100%	6	0.93 (0.81–0.98)		6	0.88 (0.80–0.93)	
Adjudication of AMI			0.27			0.35
Same hs-cTn	8	0.95 (0.90–0.98)		7	0.91 (0.83–0.96)	
Different hs-cTn or contemporary cardiac troponin	2	0.80 (0.47–0.95)		2	0.95 (0.83–0.99)	
Risk of bias and applicability concerns						
Index test			0.040			0.25
Low	3	0.98 (0.93–0.99)		3	0.87 (0.70–0.95)	
High	7	0.90 (0.81–0.95)		6	0.94 (0.89–0.97)	
Reference standard			0.27			0.35
Low	8	0.95 (0.90–0.98)		7	0.91 (0.83–0.96)	
High	2	0.80 (0.47–0.95)		2	0.95 (0.83–0.99)	

AMI = acute myocardial infarction; hs-cTn = high-sensitivity cardiac troponin; NA = not applicable; RCT = randomized controlled trial.
* Patient selection and flow and timing could not be analyzed because there were no studies with high risk of bias.

Appendix Table 9. Meta-regression of Effects of Study Characteristics on Diagnostic Accuracy for the 0/1-Hour Algorithm*

Covariates	Studies, *n*	Relative Sensitivity (95% CI)	*P* Value	Studies, *n*	Relative Specificity (95% CI)	*P* Value
Geographic location			0.83			0.140
Europe	8	0.99 (0.98–1.00)		9	0.96 (0.92–0.97)	
Non-Europe	6	0.99 (0.98–1.00)		7	0.91 (0.84–0.95)	
AMI prevalence			0.23			0.010
>10%	9	0.99 (0.99–1.00)		11	0.92 (0.87–0.95)	
≤10%	5	0.98 (0.95–0.99)		5	0.97 (0.94–0.99)	
Study design			0.34			0.48
Observational	12	0.99 (0.99–1.00)		14	0.94 (0.91–0.97)	
RCT or quasi-experimental	2	0.98 (0.93–0.99)		2	0.90 (0.72–0.97)	
Sample size			0.77			0.36
<500	3	0.99 (0.94–1.00)		4	0.96 (0.90–0.98)	
≥500	11	0.99 (0.98–0.99)		12	0.93 (0.89–0.96)	
Proportion of patients with chest pain			0.45			0.63
100%	6	0.99 (0.98–1.00)		7	0.94 (0.89–0.97)	
<100%	6	0.99 (0.97–0.99)		6	0.95 (0.91–0.97)	
Adjudication of AMI			0.25			0.35
Same hs-cTn	12	0.99 (0.99–1.00)		13	0.93 (0.90–0.96)	
Different hs-cTn or contemporary cardiac troponin	2	0.98 (0.94–0.99)		3	0.96 (0.89–0.99)	
Risk of bias and applicability concerns						
Index test			NA			0.69
Low	NA	NA		15	0.94 (0.90–0.96)	
High	NA	NA		1	0.96 (0.95–0.96)	
Reference standard			0.59			0.57
Low	11	0.99 (0.98–1.00)		12	0.94 (0.91–0.97)	
High	3	0.99 (0.97–1.00)		4	0.92 (0.83–0.97)	

AMI = acute myocardial infarction; hs-cTn = high-sensitivity cardiac troponin; NA = not applicable; RCT = randomized controlled trial.
* Patient selection and flow and timing could not be analyzed because there were no studies with high risk of bias.

Appendix Table 10. Meta-regression of Effects of Study Characteristics on Diagnostic Accuracy for the 0/2-Hour Algorithm*

Covariates	Studies, *n*	Relative Sensitivity (95% CI)	*P* Value	Studies, *n*	Relative Specificity (95% CI)	*P* Value
Geographic location			0.20			0.060
Europe	2	0.99 (0.97–1.00)		2	0.91 (0.82–0.95)	
Non-Europe	5	0.98 (0.97–0.99)		5	0.97 (0.96–0.98)	
AMI prevalence			0.48			0.35
>10%	5	0.99 (0.98–0.99)		5	0.95 (0.91–0.98)	
≤10%	2	0.98 (0.91–0.99)		2	0.97 (0.92–0.99)	
Study design			0.100			0.040
Observational	6	0.98 (0.97–0.99)		6	0.97 (0.96–0.98)	
RCT or quasi-experimental	1	1.00 (0.97–1.00)		1	0.82 (0.80–0.85)	
Sample size			0.45			0.79
<500	1	0.90 (0.55–1.00)		1	0.95 (0.90–0.98)	
≥500	6	0.99 (0.97–0.99)		6	0.96 (0.93–0.98)	
Proportion of patients with chest pain			0.130			0.040
100%	4	0.98 (0.96–0.99)		4	0.98 (0.96–0.99)	
<100%	2	0.99 (0.96–1.00)		2	0.89 (0.79–0.95)	
Adjudication of AMI			0.120			0.22
Same hs-cTn	3	0.99 (0.98–1.00)		3	0.94 (0.87–0.97)	
Different hs-cTn or contemporary cardiac troponin	4	0.98 (0.96–0.99)		4	0.97 (0.94–0.99)	
Risk of bias and applicability concerns						
Index test			0.81			0.80
Low	6	0.99 (0.97–0.99)		6	0.96 (0.93–0.98)	
High	1	0.99 (0.96–1.00)		1	0.95 (0.94–0.96)	
Reference standard			0.120			0.22
Low	3	0.99 (0.98–1.00)		3	0.94 (0.87–0.97)	
High	4	0.98 (0.96–0.99)		4	0.97 (0.94–0.99)	

AMI = acute myocardial infarction; hs-cTn = high-sensitivity cardiac troponin; NA = not applicable; RCT = randomized controlled trial.
* Patient selection and flow and timing could not be analyzed because there were no studies with high risk of bias.

Appendix Table 11. Diagnostic Accuracy and Classification Probabilities of the Studies in the Latent Classes

Latent Class	Sensitivity	Specificity
Cluster 1	0.990 (0.987–0.994)	0.779 (0.766–0.791)
Cluster 2	0.912 (0.891–0.932)	0.923 (0.915–0.930)

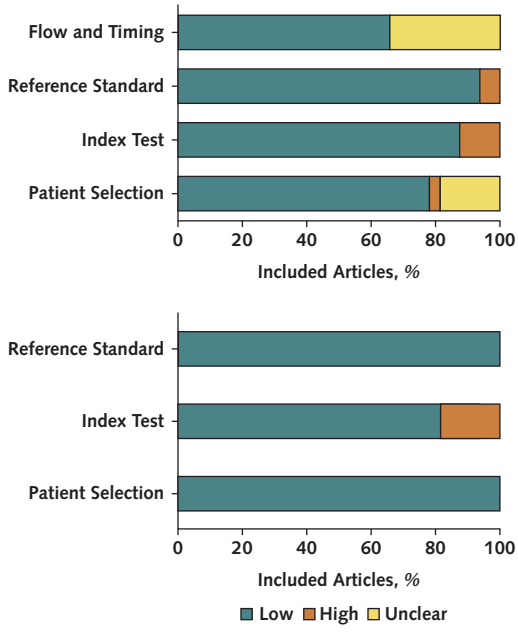
AMI = acute myocardial infarction.

Appendix Table 12. Latent Class Analysis for Studies That Used Different Methods of AMI Adjudication

Model and Variable	Same Cardiac Troponin Assay for AMI Adjudication	Different Cardiac Troponin Assay for AMI Adjudication
Bivariate model		
Sensitivity	0.958 (0.944–0.971)	0.983 (0.974–0.992)
Specificity	0.911 (0.899–0.922)	0.894 (0.889–0.899)
Latent class bivariate model		
Sensitivity	0.957 (0.926–0.987)	0.971 (0.956–0.986)
Specificity	0.919 (0.902–0.935)	0.890 (0.865–0.916)

AMI = acute myocardial infarction.

Appendix Figure. Risk and quality assessment of included studies.



The figure summarizes risk of bias (*top*) and applicability concerns (*bottom*) as judged by reviewers for each QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies 2) domain and by individual study.