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Comparison of conventional and high-sensitivity troponin in patients with chest pain: A collaborative meta-analysis

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Background Multiple studies have evaluated the diagnostic and prognostic performance of conventional troponin (cTn) and high-sensitivity troponin (hs-cTn). We performed a collaborative meta-analysis comparing cTn and hs-cTn for diagnosis of acute myocardial infarction (AMI) and assessment of prognosis in patients with chest pain.

Methods MEDLINE/PubMed, Cochrane CENTRAL, and EMBASE were searched for studies assessing both cTn and hs-cTn in patients with chest pain. Study authors were contacted and many provided previously unpublished data.

Results From 17 included studies, there were 8,644 patients. Compared with baseline cTn, baseline hs-cTn had significantly greater sensitivity (0.884 vs 0.749, $P < .001$) and negative predictive value (NPV; 0.964 vs 0.935, $P < .001$), whereas specificity (0.816 vs 0.938, $P < .001$) and positive predictive value (0.558 vs 0.759, $P < .001$) were significantly reduced. Based on summary receiver operating characteristic curves, test performance for the diagnosis of AMI was not significantly different between baseline cTn and hs-cTn [0.90 [95% CI 0.85-0.95] vs 0.92 [95% CI 0.90-0.94]]. In a subanalysis of 6 studies that alternatively defined AMI based on hs-cTn, cTn had lower sensitivity (0.666, $P < .001$) and NPV (0.906, $P < .001$). Elevation of baseline hs-cTn, but negative baseline cTn, was associated with increased risk of death or nonfatal myocardial infarction during follow-up ($P < .001$) compared with both negative.

Conclusion High-sensitivity troponin has significantly greater early sensitivity and NPV for the diagnosis of AMI at the cost of specificity and positive predictive value, which may enable early rule in/out of AMI in patients with chest pain. Baseline hs-cTn elevation in the setting of negative cTn is also associated with increased nonfatal myocardial infarction or death during follow-up.

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More than 7 million patients present annually to the emergency department (ED) with chest pain,¹ and >1 million patients are hospitalized each year in the United States with acute myocardial infarction (AMI).² The ability to rapidly exclude AMI through high-sensitivity troponin (hs-cTn) in combination with clinical evaluation may reduce ED length of stay, reduce financial cost, and improve outcomes in these challenging patients. Evidence suggests that even minimal elevations of conventional troponin (cTn) are associated with worse clinical outcome and that these patients may benefit from initiation of appropriate medical intervention.^{3,4} Furthermore, use of a very low cut-point for hs-cTn has been suggested as a tool to rule out AMI due to the resulting high negative predictive value (NPV).⁵ However, the introduction of hs-cTn may significantly decrease specificity and can prompt a costly cardiovascular workup in patients in which cTn is elevated due to nonischemic causes for cTn release. Although multiple studies have compared the diagnostic and prognostic test characteristics of cTn and hs-cTn, the results of these data are mixed. Therefore, we performed a diagnostic and prognostic collaborative meta-analysis to assess cTn values and hs-cTn values in patients with chest pain.

Methods

Data sources and searches

Two independent reviewers (M.J.L. and N.C.B.) systematically searched (November 2013) Cochrane CENTRAL, EMBASE, and MEDLINE/PubMed for studies that assessed both cTn and hs-cTn in patients with nontraumatic chest pain. Search criteria included “high sensitivity troponin” AND (“chest pain” OR “acute coronary syndromes” [ACS] OR “myocardial infarction”). We limited our search to studies published in peer-reviewed journals; trials presented in abstract-only form were excluded. Our meta-analysis was performed in accordance with the Meta-Analysis Of Observational Studies in Epidemiology guidelines.⁶ After obtaining full reports, eligibility was assessed from the full-text articles with divergences resolved after consensus. No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

Study selection

Prespecified inclusion and exclusion criteria were established at study onset. We included any study that (a) assessed patients with nontraumatic chest pain and (b) measured both cTn and hs-cTn levels. We excluded any study that (a) limited patients to only those with myocardial infarction (MI) or a specific subgroup of patients, (b) excluded patients with a baseline positive troponin, and (c) used a case-control format. We included studies regardless of whether patients with ST-segment elevation MI (STEMI) were included or excluded, whether the criterion standard diagnosis was

made centrally or locally, and regardless of the cTn criteria used for diagnosis of AMI.

Data extraction and quality assessment

Data were abstracted by the same 2 investigators (M.J.L. and N.C.B.). An attempt was made to contact the corresponding authors of included studies to obtain complete data. Study quality was appraised in accordance with QUality Assessment of Diagnostic Accuracy Studies (QUADAS)-2.⁷ We accepted the authors' definitions of conventional and hs-cTn.

Data synthesis and analysis

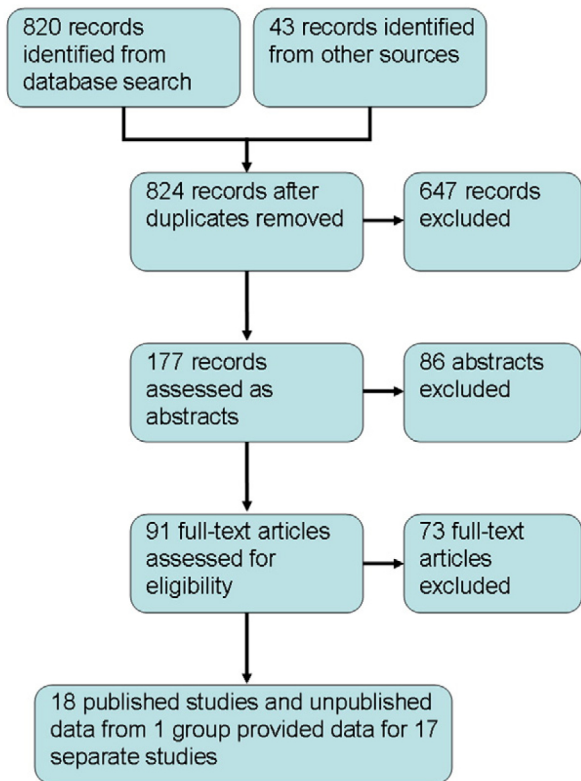
Dichotomous variables are reported as proportions (percentages), whereas continuous variables are reported as mean (SD) or median. Sensitivity, specificity, positive predictive values (PPV), NPVs, positive and negative likelihood ratios (LRs), and diagnostic odds ratios (ORs) were computed. Pooling was performed using random-effects methods. Measures of test performance are reported as point estimates (with 95% CIs). These were calculated for the baseline cTn at presentation, baseline hs-cTn at presentation, cTn at the second serial sampling (second cTn), and hs-cTn at the second serial sampling (second hs-cTn). Adjudication of AMI was typically defined by cTn. Given that authors used their own cut-points and delta changes in troponin with different times for sampling, we were unable to assess for value of serial sampling in this meta-analysis.

We generated weighted symmetric summary receiver operating characteristic (SROC) plots using the Moses-Shapiro-Littenberg method.⁸ Area under the ROC curves of individual studies were pooled using a random effect generic-inverse variance method. Sources of clinical and statistical heterogeneity were explored by means of subgroup analyses and meta-regression with unrestricted maximum-likelihood meta-regression (inverse variance-weighted regression) on diagnostic ORs.

Binary outcomes from individual studies were combined with random-effect models, leading to computations of ORs with 95% CIs. Between-study statistical heterogeneity was assessed using the Cochran Q χ^2 test. I^2 was calculated as a measure of statistical heterogeneity; I^2 values of 25%, 50%, and 75% represented mild, moderate, and severe inconsistency, respectively. Small study or publication bias was explored with funnel plots and Peters test.⁹ Statistical analysis was performed using Review Manager (RevMan) 5 version 5.1.7 freeware package (The Nordic Cochrane Centre, The Cochrane Collaboration, 2008, Copenhagen, Denmark), Meta-DiSc software,¹⁰ and NCSS 2007 (Kaysville, UT), with statistical significance for hypothesis testing set at the .05 two-tailed level and for heterogeneity testing at the .10 two-tailed level.

Results

Of the 824 citations we identified, we assessed 177 abstracts from which we performed detailed review of 91

Figure 1

Flow diagram of study selection.

full-text manuscripts. Articles were excluded if the study was limited to only patients with stable coronary artery disease or only patients with ACS, patient duplication, exclusion of patients with baseline positive troponins, use of a case-control design, lack of or inadequate cTn data, and lack of adjudication data for AMI (excluded studies are listed in the supplement). Authors of the APACE study (Drs Twerenbold and Mueller) provided comprehensive data not only for the patients published in Haaf et al.¹¹ but also on an additional 416 patients to provide the most updated data from their registry. Thus, our systematic review and collaborative meta-analysis comprises data from 18 published studies¹²⁻²⁹ (data from 3 studies were used to compile the findings of Aldous et al.¹²⁻¹⁴) and updated data from the APACE study to provide comprehensive data on 17 studies. The details of our flow diagram can be found in Figure 1. Study characteristics are presented in Table I, and appraisal of diagnostic study quality can be found in

Supplementary Table I.

The 17 studies included a total of 8,644 patients (median of 332 patients [range 58-1,818]). Patient characteristics are shown in Table II. The population had a weighted mean age of 62 ± 15 years, 63% of patients were male, and there was a typical distribution of cardiovascular risk factors. Of the included patients, 20.7% were diagnosed as having AMI, with 5.2% admitted with STEMI. In studies that reported

unstable angina, 13.4% of patients were diagnosed as having unstable angina. Most studies used cTn levels for the adjudication of AMI, whereas several studies used a combination of cTn and hs-cTn levels (Supplementary Table D).

Diagnostic performance of individual studies is summarized for baseline cTn and baseline hs-cTn

Supplementary Table II), along with the second cTn and the second hs-cTn

Supplementary Table III). In addition to adjudicating AMI with conventional cTn, 6 studies also performed separate adjudication for AMI using the hs-cTn levels as the criterion standard to define AMI, and diagnostic performance for baseline cTn and hs-cTn is provided (online

Supplementary Table IV). Finally, the area under the ROC curves for baseline cTn, baseline hs-cTn, second cTn, and second hs-cTn for diagnosis of AMI can be found in

Supplementary Table V.

Diagnostic accuracy of cTn and hs-cTn

The assays used in each study are shown in Table I. As seen in Table III, baseline hs-cTn had significantly greater sensitivity ($P < .001$) and NPV ($P < .001$), and significantly lower negative LR ($P < .01$), whereas baseline cTn had significantly greater specificity ($P < .001$), PPV ($P < .001$), and positive LR ($P < .01$). The SROC curves suggest a trend toward better diagnostic accuracy with baseline hs-cTn (Table III, Figure 2). Comparison of pooled area under the ROC curves also suggested a trend toward better performance for baseline hs-cTn compared with baseline cTn (0.91 [95% CI 0.89-0.93] vs 0.89 [95% CI 0.86-0.91], respectively; $P = .22$, $I^2 = 33\%$).

The second cTn was checked 2.6 ± 1.5 hours after the baseline cTn, and the second hs-cTn was checked 2.5 ± 1.4 hours after the baseline hs-cTn in 10 studies with 5,174 patients (

Supplementary Table III).

These data demonstrated that the sensitivity remained significantly greater for the second hs-cTn compared with the second cTn ($P < .05$), whereas the second cTn had significantly greater specificity ($P < .001$), PPV ($P < .001$), and positive LR ($P < .01$) compared with the second hs-cTn (Table III). Summary receiver operating characteristic curves demonstrated no difference in diagnostic accuracy (Table III). Pooled area under the ROC curve was not significantly different between the second cTn and the second hs-cTn (0.95 [95% CI 0.93-0.97] vs 0.96 [95% CI 0.94-0.97], respectively; $P = .42$, $I^2 = 0\%$)

Supplementary Table V). Sensitivity analyses of conventional cTn or hs-cTn with exclusion of one study at a time did not appear to significantly change the sensitivity or specificity.

Meta-regression analysis

Meta-regression demonstrated that time from onset of chest pain to presentation was significantly associated with improved test performance for baseline cTn (regression coefficient $0.61 \pm \text{SE } 0.20$, $P = .02$) but not

Table I. Study characteristics

Study	Year published	Patients	Centers	Inclusion criteria for chest pain	Conventional Tn assay (cut-point)	HS-Tn assay (cut-point)	Follow-Up (mo)
Aldous et al ¹⁵	2012	939	Multi	No exclusion	Abbott Architect cTnI, 30 ng/L (10% CV, 32 ng/L)	Roche HS TnT, 14 ng/L (99th percentile)	12
Aldous et al ¹²⁻¹⁴	2011	332	Single	No exclusion	Abbott Architect cTnI, 30 ng/L (10% CV, 32 ng/L)	Roche HS TnT, 14 ng/L (99th percentile)	24
APACE	N/A	1533	Multi	<12 h	Roche cTnT 4th gen, 35 ng/L (10% CV) but Siemens RxL TnI, 140 ng/L (10% CV) to define AMI	Roche HS TnT, 14 ng/L (99th percentile)	24
Christ et al ¹⁶	2010	137	Single	No exclusion	Roche cTnT 4th gen, 35 ng/L (10% CV)	Roche HS TnT, 14 ng/L (99th percentile)	8
Collinson et al ¹⁷	2013	850	Multi	No exclusion	Siemens Stratus CS cTnI, 70 ng/L (99th percentile)	Beckman AccuTnI, 40 ng/L (99th percentile)	3
Eggers et al ¹⁸	2012	360	Multi	<8 h	Siemens Stratus CS cTnI, 70 ng/L (99th percentile)	Roche HS TnT, 14 ng/L (99th percentile)	6
Freund et al ¹⁹	2011	317	Multi	<6 h	Siemens Xpand HM cTnI, 140 ng/L or Beckman Coulter Access cTnI, 60 ng/L (both 10% CV)	Roche HS TnT, 14 ng/L (99th percentile)	1
Hammerer-Lercher et al ²⁰	2013	440	Single	No exclusion	Roche Elecsys cTnT 4th gen, 10 ng/L (99th percentile)	Roche HS TnT, 14 ng/L (99th percentile)	8
Inoue et al ²¹	2011	283	Multi	<24 h	Roche cTnT 4th gen, 35 ng/L (10% CV) but 100 ng/L (WHO criteria) to define AMI	Roche HS TnT, 14 ng/L (99th percentile)	No
Keller et al ²²	2009	1818	Multi	No exclusion	Roche Elecsys cTnT 4th gen, 30 ng/L (10% CV), but Siemens RxL TnI, 140 ng/L (10% CV) to define AMI	Siemens sensitive TnI Ultra, 40 ng/L (99th percentile)	1; unable to abstract
Lotze et al ²³	2011	142	Single	No exclusion	Roche cTnT 4th gen, 100 ng/L (WHO Criteria)	Roche HS TnT, 14 ng/L (99th percentile)	No
Melki et al ²⁴	2011	233	Single	<12 h	Roche cTnT 4th gen, 40 ng/L (10% CV, 35 ng/L)	Roche HS TnT, 14 ng/L (99th percentile)	No
Meune et al ²⁵	2011	58	Single	<6 h	Siemens Xpand HM cTnI, 70 ng/L (99th percentile)	Roche HS TnT, 14 ng/L (99th percentile)	No
Pracon et al ²⁶	2012	187	Single	<24 h	Siemens Dimension Flex TnI, 70 mg/L (99th percentile)	Abbott Architect Stat TnI, 28 ng/L (99th percentile)	No
Santalo et al ²⁷	2013	356	Multi	No exclusion	Roche Cobas e401 cTnT 4th gen, 10 ng/L (99th percentile)	Roche HS TnT, 14 ng/L (99th percentile)	12
Schreiber et al ²⁸	2012	465	Single	No exclusion	Siemens Dimension RxL TnI, 140 ng/L (10% CV)	Singulex Erenna HS-TnI, 8 ng/L (99th percentile, 10.1 ng/L)	1
Sebbane et al ²⁹	2013	194	Single	<12 h	Beckman Access2 cTnI, 40 ng/L (intended 99th percentile)	Roche HS TnT, 14 ng/L (99th percentile)	No

Abbott (Abbott Park, IL), Roche (Indianapolis, IN), Siemens (Tarrytown, NY), Singulex (St Louis, MO).

baseline hs-cTn (regression coefficient $0.38 \pm SE 0.20$, $P = .10$). Neither time from presentation to the second cTn nor the second hs-cTn was significantly associated with test performance. The percentage of patients with STEMI (regression coefficient -4.6 ± 1.1 , $P = .001$), male sex (regression coefficient $-8.3 \pm SE 3.0$, $P = .02$), diabetes (regression coefficient $-8.0 \pm SE 2.9$, $P = .02$), and prevalence of AMI (regression coefficient $-3.2 \pm SE 1.2$, $P = .02$) were significantly associated with test performance for baseline cTn but was not associated with test performance for baseline hs-cTn. Age, creatinine levels, and estimated glomerular filtration rate were not associated with test performance for baseline cTn or baseline hs-cTn. The definition of the delta, or the change by rise and/or fall of troponin, used to diagnosis AMI was also not significantly associated with test performance.

Subgroup analysis

When comparing studies that used the 10% coefficient variance (CV) cut-point^{12,15,16,19,22,24,28} (see also APACE) vs 99th percentile cut-point^{17,18,20,25-27,29} for cTn to define AMI, baseline cTn using 10% CV cut-point had significantly greater specificity (0.957 [0.950-0.962] vs 0.921[0.908-0.933]), PPV (0.813 [0.788-0.836] vs 0.699 [0.657-0.738]), and positive LR (15.804 [10.699-23.345] vs 8.905[5.771-13.740]) than baseline cTn using 99th percentile cut-point, with no significant differences between the groups in terms of sensitivity (0.754 [0.728-0.778] vs 0.788 [0.747-0.824]), NPV (0.940 [0.932-0.946] vs 0.949 [0.938-0.959]), negative LR (0.260 [0.218-0.311] vs 0.238 [0.192-0.294]), diagnostic OR (60.651 [36.377-101.12] vs 44.054 [26.685-72.727]), or SROC (0.889 [0.756-0.990] vs 0.919 [0.879-0.959]).

Table II. Patient characteristics of included studies

Study	Age (y)	Male	Prior CAD	Prior MI	HTN	HLD	DM	Smoking	TTP (h)	STEMI	NSTEMI	AMI	UA
Aldous et al 2012 ¹⁵	65	59.7%	51.8%	NR	60.8%	57.6%	16.5%	60.6%	6.3	0	21.8%	21.8%	NR
Aldous et al 2011 ^{12,14}	64	60.2%	53.9%	NR	45.8%	38.0%	16.3%	17.2%	4	0	33.1%	33.1%	17.2%
APACE	63 ± 16	67.0%	36.2%	24.2%	65.9%	50.8%	19.2%	24.1%	5	3.7%	11.5%	15.3%	14.3%
Christ et al ¹⁶	66 ± 16	63.5%	34.3%	32.8%	66.4%	35.0%	22.6%	21.9%	NR	2.9%	11.7%	14.6%	19.0%
Collinson et al ¹⁷	54	59.6%	NR	5.8%	35.4%	23.6%	8.1%	28.5%	5.9	0	8.0%	8.0%	NR
Eggers et al ¹⁸	66 ± 12	65.6%	42.8%	37.5%	42.8%	38.3%	18.3%	18.1%	4.5	0	35.6%	35.6%	18.9%
Freund et al ¹⁹	57 ± 17	64.7%	31.6%	26.2%	36.6%	35.8%	13.9%	40.6%	NR	4.1%	10.1%	14.2%	3.5%
Hammerer-Lercher et al ²⁰	56 ± 20	52.3%	19.1%	NR	46.4%	NR	7.5%	NR	3	5.9%	3.2%	9.1%	NR
Inoue et al ²¹	65 ± 12	74.0%	NR	NR	51.9%	44.2%	29.4%	35.5%	3	50.9%	6.7%	57.6%	10.2%
Keller et al ²²	61 ± 14	66.4%	35.8%	NR	73.7%	73.0%	15.7%	24.3%	NR	7.2%	15.6%	22.7%	13.2%
Lotze et al ²³	71 ± 14	76.0%	27.5%	15.5%	73.9%	16.9%	28.9%	7.7%	NR	6.3%	2.8%	9.2%	2.1%
Melki et al ²⁴	65	66.5%	NR	30.0%	50.2%	NR	22.7%	17.2%	5.3	0	48.9%	48.9%	12.0%
Meune et al ²⁵	58 ± 14	63.8%	NR	20.7%	46.7%	37.9%	22.4%	32.8%	7.5	0	22.4%	22.4%	29.3%
Pracon et al ²⁶	64 ± 14	63.6%	NR	17.6%	61.0%	36.4%	14.4%	13.9%	NR	23.0%	21.9%	44.9%	5.9%
Santalo et al ²⁷	69	67.9%	34.9%	NR	62.0%	NR	26.4%	NR	5	0	21.9%	21.9%	29.5%
Schreiber et al ²⁸	67	49.2%	NR	19.1%	62.2%	NR	17.4%	11.2%	NR	0	2.6%	2.6%	3.4%
Sebbane et al ²⁹	61 ± 17	63.4%	21.6%	14.8%	34.0%	35.1%	14.1%	36.6%	4.24	13.9%	12.4%	26.3%	16.0%
Weighted mean	62 ± 15	63.4%	37.5%	20.9%	58.1%	50.1%	16.8%	28.3%	5.1 ± 1.1	5.2%	15.5%	20.7%	13.4%

Abbreviations: CAD, Coronary artery disease; HTN, hypertension; HLD, hyperlipidemia; DM, diabetes mellitus; TTP, time from onset of chest pain to presentation; NSTEMI, non-ST elevation MI; UA, unstable angina.

Table III. Summary of sensitivity, specificity, PPV, NPV, positive LR, negative LR, diagnostic OR (DOR), and area under the SROC curves for the baseline and second serial conventional and hs-cTn (hs-cTn) for AMI

	Baseline cTn	Baseline hs-cTn	Second Serial cTn	Second Serial hs-cTn
Pooled sensitivity	0.749 (0.728-0.769)	0.884 (0.868-0.898)	0.895 (0.867-0.919)	0.928 (0.903-0.948)
Pooled specificity	0.938 (0.932-0.943)	0.816 (0.807-0.826)	0.952 (0.944-0.959)	0.807 (0.794-0.821)
Pooled PPV	0.759 (0.738-0.778)	0.558 (0.539-0.576)	0.758 (0.724-0.790)	0.443 (0.414-0.472)
Pooled NPV	0.935 (0.929-0.940)	0.964 (0.959-0.969)	0.982 (0.977-0.986)	0.985 (0.980-0.990)
Summary positive LR	9.913 (6.648-14.781)	4.393 (3.403-5.673)	13.163 (7.667-22.596)	4.663 (3.576-6.080)
Summary negative LR	0.262 (0.217-0.317)	0.156 (0.116-0.210)	0.137 (0.092-0.204)	0.112 (0.069-0.182)
Summary DOR	41.665 (24.732-70.191)	32.609 (20.477-51.931)	95.503 (45.727-199.46)	49.716 (25.238-97.938)
Area under the SROC curve	0.890 (0.839-0.941)	0.923 (0.899-0.947)	0.951 (0.919-0.983)	0.948 (0.912-0.984)

There was no significant difference in test performance for baseline cTn in studies that used a 10% CV cut-point compared with a 99th percentile cut-point to define AMI as assessed by pooled area under the ROC curves (0.90 [0.86-0.93] vs 0.91 [0.88-0.93], $P = .61$, $I^2 = 0\%$).

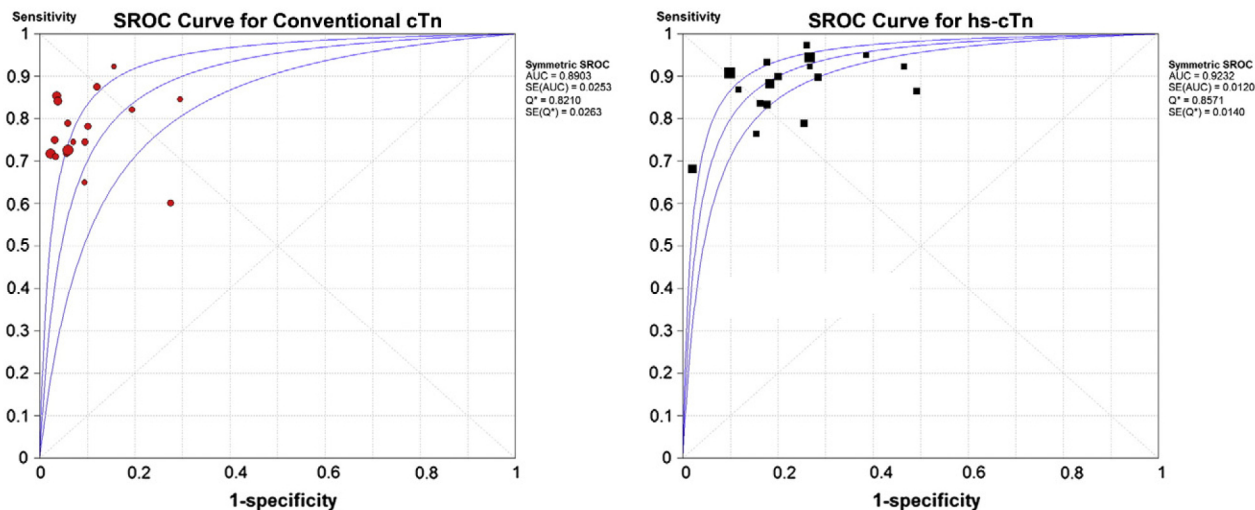
When comparing the diagnostic performance of baseline cTnT^{16,20,23,24,27} (see also APACE) and cTnI^{12,15,17-19,25,26,28,29} to define AMI, baseline cTnT had significantly lower specificity (0.931 [0.920-0.941] vs 0.950 [0.941-0.957]) and PPV (0.701 [0.661-0.740] vs 0.790 [0.759-0.820]) compared with baseline cTnI. There were no differences between baseline cTnT and baseline cTnI in sensitivity (0.758 [0.717-0.795] vs 0.790 [0.759-0.820]), NPV (0.947 [0.938-0.956] vs 0.950 [0.941-0.957]), positive LR (8.822 [3.996-19.478] vs 12.532 [7.848-20.010]), negative LR (0.263 [0.20-0.314] vs 0.235 [0.189-0.292]), diagnostic OR (42.289 [21.696-82.428] vs 57.519 [32.471-101.89]), or SROC (0.904 [0.860-0.948] vs 0.917 [0.863-0.971]). There was no significant difference

in test performance for baseline cTnT and baseline cTnI as assessed by pooled area under the ROC curves (0.89 [0.86-0.93] vs 0.91 [0.89-0.93], $P = .30$, $I^2 = 7.1\%$).

AMI definition based on hs-cTn

When limiting studies to those that provided a separate adjudication using hs-cTn to define AMI,^{12,14,16,17,24,27} (see also APACE), the mean prevalence of AMI increased from 23% ± 15% when AMI was defined by cTn to 29.6% ± 16.5% when AMI was defined by hs-cTn. When AMI was defined by hs-cTn, the baseline hs-cTn had significantly greater test performance based on pooled area under the ROC curves compared with baseline cTn (0.91 [95% CI 0.88-0.94] vs 0.80 [95% CI 0.74-0.87], respectively; $P = .004$). Baseline cTn had a significant reduction in sensitivity (0.666 vs 0.749, $P < .001$) and NPV (0.906 vs 0.935, $P < .001$) when AMI was defined by hs-cTn compared with when AMI was defined by cTn. Baseline hs-cTn also had a significant reduction in sensitivity (0.857 vs 0.884, $P < .05$) and NPV (0.953 vs 0.964,

Figure 2



Summary ROC curves for the baseline conventional cTn (left) and baseline hs-cTn (right), which plots sensitivity and 1 – specificity for each study, enabling comparison of the 2 assays. Studies were weighted by least-squares method using the inverse variance. Studies are plotted for conventional cTn with red circles and plotted for hs-cTn with black squares. Symmetric SROC curves are present with a 95% CI, and area under the SROC curve is provided along with SEs to the right in each figure.

Table IV. Summary of sensitivity, specificity, PPV, NPV, positive LR, negative LR, diagnostic OR (DOR), and area under the summary SROC curves for cTn and hs-cTn when AMI is based on using the cut-point for hs-cTn

	Baseline cTn	Baseline hs-cTn
Pooled sensitivity	0.666 (0.631-0.699)	0.857 (0.830-0.881)
Pooled specificity	0.941 (0.931-0.950)	0.854 (0.840-0.868)
Pooled PPV	0.768 (0.734-0.799)	0.632 (0.602-0.661)
Pooled NPV	0.906 (0.894-0.916)	0.953 (0.944-0.962)
Summary positive LR	8.797 (3.892-19.888)	7.482 (4.114-13.608)
Summary negative LR	0.314 (0.205-0.479)	0.145 (0.070-0.304)
Summary DOR	30.004 (14.080-63.937)	57.034 (24.958-130.33)
Area under the SROC curve	0.904 (0.817-0.991)	0.945 (0.907-0.983)

$P < .05$) with an increase in specificity (0.854 vs 0.816, $P < .001$) and PPV (0.632 vs 0.558, $P < .001$) when AMI was defined by hs-cTn compared with when AMI was defined by cTn (Table IV)

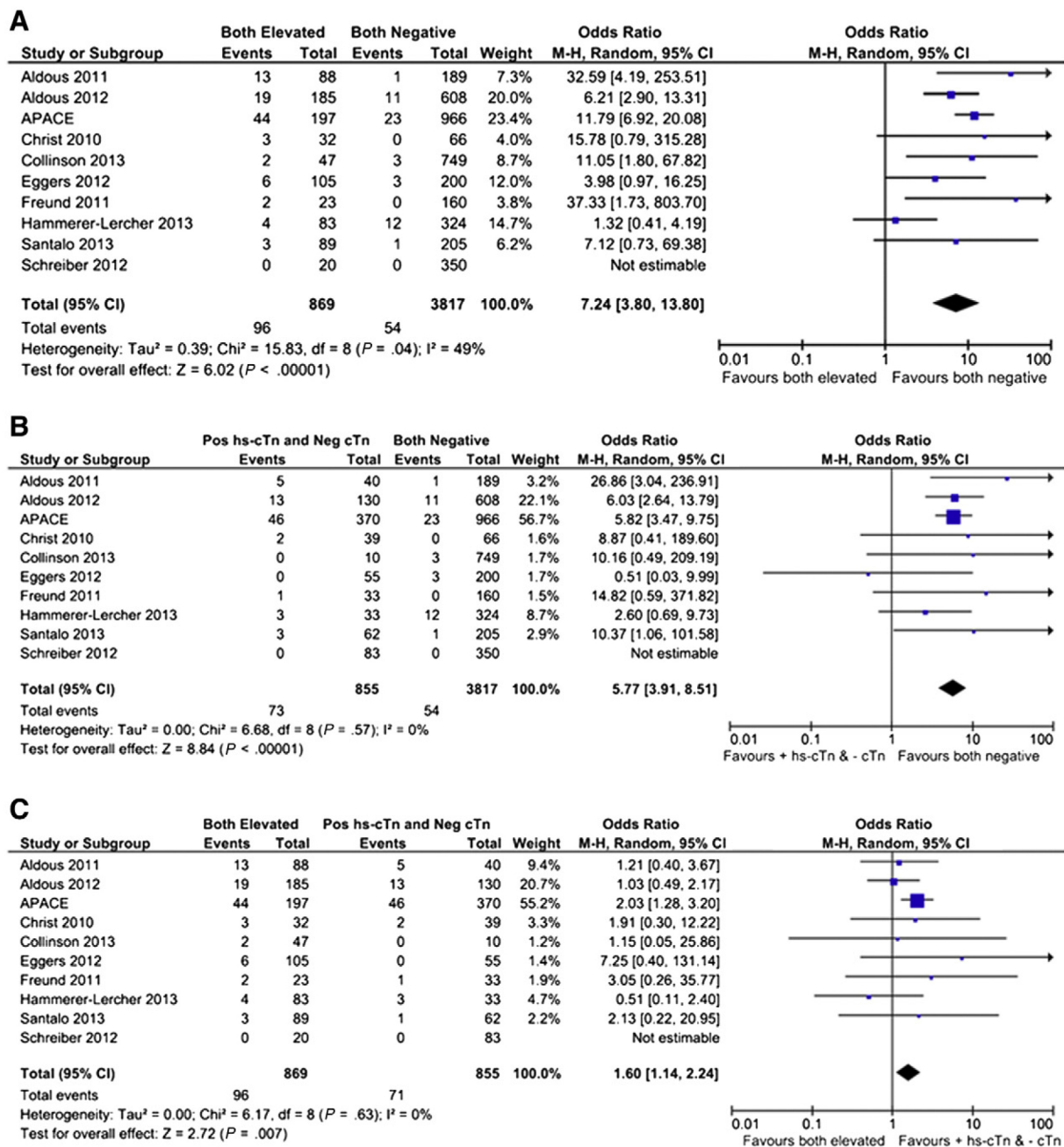
When strictly applying the definition of hs-cTn measuring the 99th percentile upper reference limit with an analytical imprecision of $<10\%$,^{30,31} Keller et al²² and Pracon et al²⁶ are no longer considered under the category of hs-cTn. Therefore, we repeated the previous analysis with 15 studies to determine whether this significantly affected our previous findings. When using studies that used strict hs-cTn assays, baseline cTn and hs-cTn had similar values to those before in regard to sensitivity (0.752 [0.727-0.775] vs 0.877 [0.857-

0.894]), specificity (0.939 [0.933-0.946] vs 0.793 [0.782-0.803]), PPV (0.750 [0.725-0.773] vs 0.505 [0.484-0.526]), NPV (0.940 [0.933-0.946] vs 0.964 [0.958-0.969]), positive LR (10.366 [6.475-16.595] vs 4.002[3.203-4.999]), negative LR (0.259 [0.204-0.329] vs 0.164 [0.119-0.225]), diagnostic OR (44.019 [23.073-83.983] vs 28.645 [18.135-45.247]), and SROC (0.893 [0.835-0.951] vs 0.916 [0.888-0.944]). Using a strict definition of hs-cTn compared with the study-defined hs-cTn (Table III) lowered specificity (0.793 vs 0.816, respectively; $P < .01$) and PPV (0.505 vs 0.558, respectively; $P < .01$) but was not significantly associated with sensitivity, NPV, positive LR, negative LR, diagnostic OR, or area under the SROC curve.

cTn and hs-cTn for prognosis

Outcome data were provided for 10 studies only because data could not be accurately extracted from Keller et al.²² During a mean follow-up of 12.3 months (Table D), our study demonstrated that patients with an elevated baseline cTn or elevated baseline hs-cTn have significantly higher incidence of death (Supplementary Figure 1A), nonfatal MI (Supplementary Figure 1B), or their combination (Supplementary Figure 1C) compared with patients who had a negative baseline cTn or negative baseline hs-cTn, respectively. The ORs for baseline cTn and baseline hs-cTn are not significantly different for the outcomes of death (Supplementary Figure 1A; $P = .46$, $I^2 = 0\%$), nonfatal MI (Supplementary Figure 1B; $P = .62$, $I^2 = 0\%$), or their combination (Supplementary Figure 1C; $P = .75$, $I^2 = 0\%$) during follow-up. However,

Figure 3

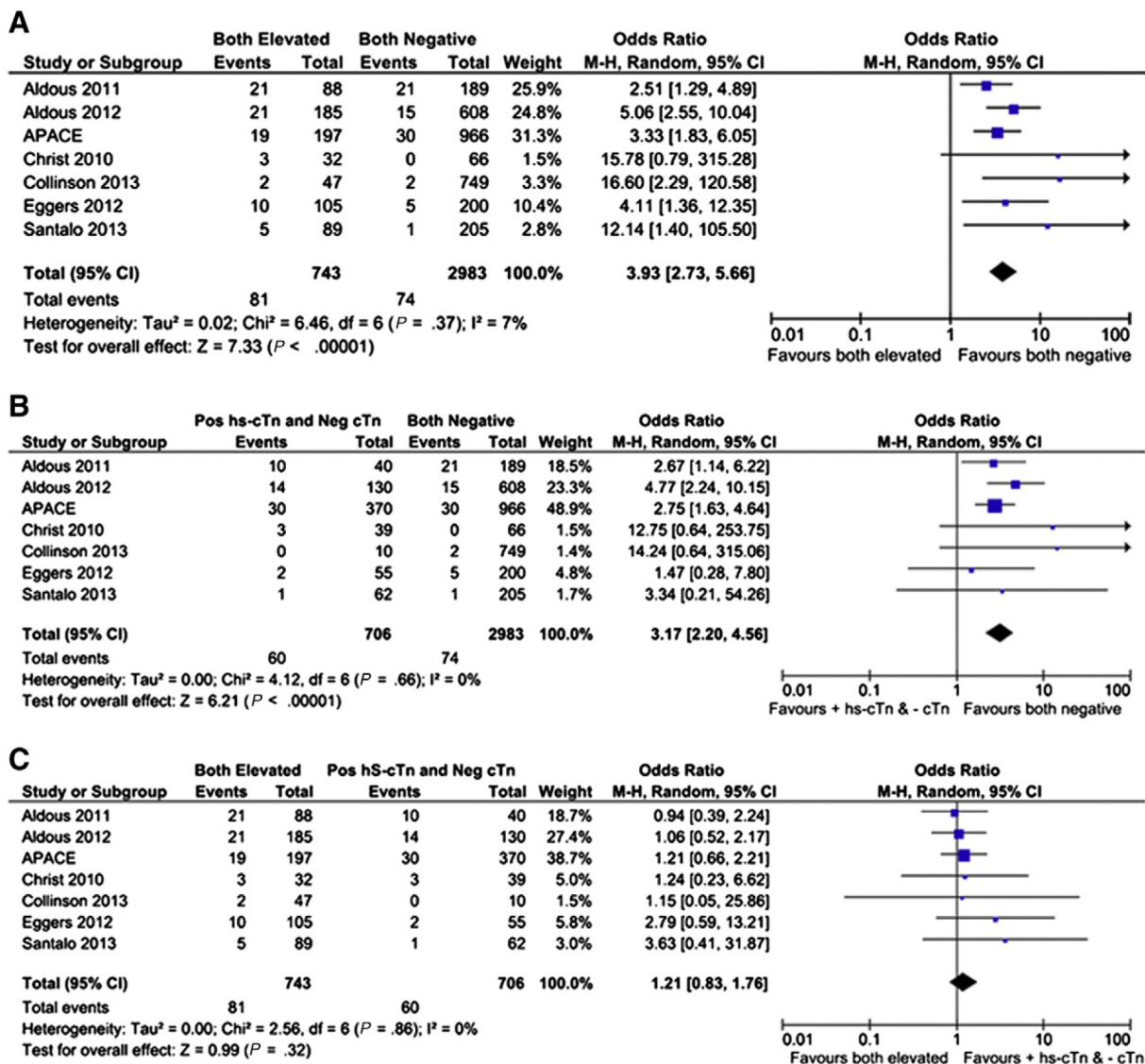


Forest plots comparing death during follow-up between patients with elevation of both baseline cTn and baseline hs-cTn and patients with both negative baseline cTn and baseline hs-cTn (A), death during follow-up between patients with elevation of baseline hs-cTn and negative baseline cTn and patients with both negative baseline cTn and baseline hs-cTn (B), and death during follow-up between patients with elevation of both baseline cTn and baseline hs-cTn and patients with elevation of baseline hs-cTn and negative baseline cTn (C) for patients that presented with chest pain.

significantly more individuals with an elevated baseline hs-cTn died (173 with elevated baseline hs-cTn died vs 105 with elevated baseline cTn died of the 231 total individuals who died during follow-up, $P < .001$) or developed AMI (143 with

elevated baseline hs-cTn developed MI vs 92 with elevated baseline cTn developed MI of 222 total individuals who had AMI, $P < .001$) during follow-up compared with individuals with an elevated baseline cTn.

Figure 4

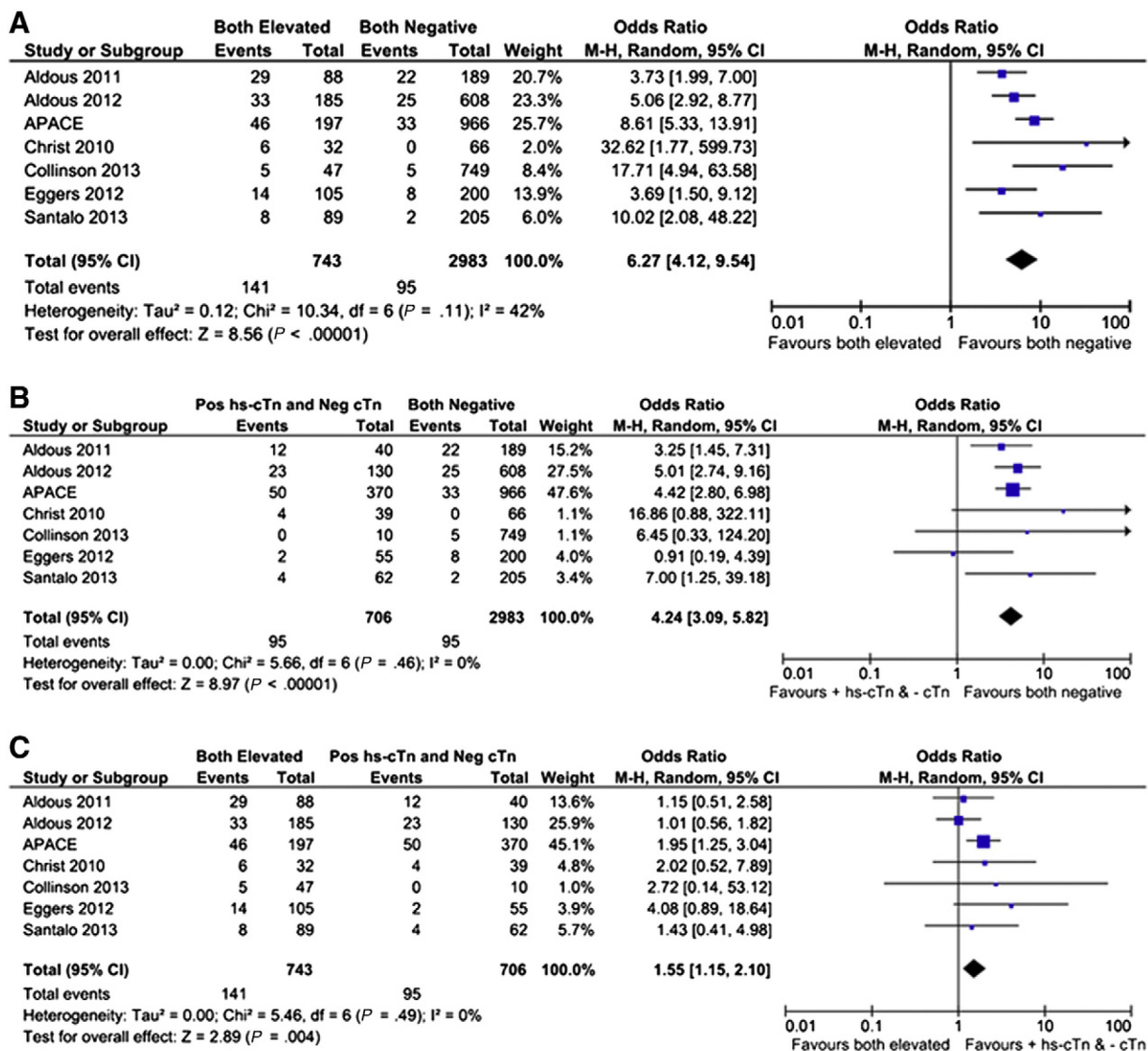


Forest plots comparing nonfatal MI during follow-up between patients with elevation of both baseline cTn and baseline hs-cTn and patients with both negative baseline cTn and baseline hs-cTn (A), nonfatal MI during follow-up between patients with elevation of baseline hs-cTn and negative baseline cTn and patients with both negative baseline cTn and baseline hs-cTn (B), and nonfatal MI during follow-up between patients with elevation of both baseline cTn and baseline hs-cTn and patients with elevation of baseline hs-cTn and negative baseline cTn (C) for patients that presented with chest pain.

Patients who had elevation of both baseline cTn and baseline hs-cTn had significantly greater death (Figure 3A), nonfatal MI (Figure 4A), and their combination (Figure 5A) during follow-up compared with patients with both negative baseline cTn and baseline hs-cTn. Patients who had elevation of baseline hs-cTn but a negative baseline cTn had significantly greater death (Figure 3B), nonfatal MI (Figure 4B), and their combination (Figure 5B) during follow-up compared with patients with both negative baseline cTn and

baseline hs-cTn. Patients with elevation of both baseline cTn and baseline hs-cTn had significantly greater death (Figure 3C) and the combination end point of death and nonfatal MI (Figure 5C) but no significant difference in nonfatal MI (Figure 4C) during follow-up compared with patients with an elevated baseline hs-cTn but a negative baseline cTn. Visual inspection of funnel plots along with Peters test did not show evidence of publication bias for baseline cTn (Peters test, $P = .75$) and for baseline hs-cTn (Peters test, $P = .53$).

Figure 5



Forest plots comparing the combination endpoint of death and nonfatal MI during follow-up between patients with elevation of both baseline cTn and baseline hs-cTn and patients with both negative baseline cTn and baseline hs-cTn (A), combination endpoint during follow-up between patients with elevation of baseline hs-cTn and negative baseline cTn and patients with both negative baseline cTn and baseline hs-cTn (B), and combination during follow-up between patients with elevation of both baseline cTn and baseline hs-cTn and patients with elevation of baseline hs-cTn and negative baseline cTn (C) for patients that presented with chest pain.

Discussion

This systematic review and collaborative meta-analysis on 8,644 patients demonstrated that hs-cTn and cTn have excellent overall diagnostic accuracy for AMI in patients with chest pain. The hs-cTn assay has the benefit of a significantly greater sensitivity and NPV with a lower negative LR compared with cTn. However, this is at the cost of specificity, PPV, and positive LR. Meta-regression analysis also suggested that time from onset of chest pain to presentation was significantly associated with test

performance for baseline cTn but was not associated with test performance accuracy for baseline hs-cTn. These data validate previous works suggesting that hs-cTn can more accurately diagnose or exclude AMI early after chest pain.³² Prevalence of AMI, STEMI, diabetes mellitus, and male sex also was associated with test performance for baseline cTn but not baseline hs-cTn. When AMI adjudication is performed with hs-cTn as the criterion standard to define AMI, baseline hs-cTn had better test performance as assessed by pooled area under

the ROC curve compared with baseline cTn. Elevation of baseline hs-cTn identified a greater number of patients who died or had nonfatal MI during follow-up compared with elevation of baseline cTn. Finally, these data demonstrate that baseline elevation of hs-cTn but a negative baseline cTn was associated with an incremental increase in risk for death or nonfatal MI during follow-up. Although troponin assays have previously been compared in meta-analysis,³³ our meta-analysis is the first to focus specifically on diagnostic and prognostic role of hs-cTn and conventional cTn and performed meta-regression to assess the affect of different variables on diagnostic accuracy. These data support a broader acceptance of hs-cTn.

The development of a universal definition for AMI³⁴ has greatly aided the field of cardiology by providing a means to reliably compare diagnostic tests and therapies. Likewise, establishment of standards for cardiac troponins and adoption of common cut-points^{30,31,35,36} may not only enable improved comparison between assays but also help provide uniform data that physicians can more readily and confidently apply to clinical practice. Adoption of hs-cTn into the ED evaluation of chest pain may significantly alter current practice. Although hs-cTn may enable rapid rule out of patients who present to the ED with chest pain,^{32,37} concern exists that the reduction in PPV and specificity may lead to more extensive cardiovascular testing. Although minimal elevations in hs-cTn may not necessarily identify AMI, it is important to recognize that these patients are at increased risk for adverse outcomes and should receive appropriate medical intervention.⁴ Finally, it is also critical to interpret these biomarkers in the clinical context of the patient. The importance of clinical history and appropriate electrocardiographic evaluation cannot be underestimated. For example, the diagnostic value of a negative troponin is less helpful if the patient's presentation is consistent with unstable angina because the clinical presentation will guide management rather than the biomarker result.

This meta-analysis has several important limitations. To enable appropriate comparison of cTn and hs-cTn in a "real-world" scenario, we excluded studies in which patients were limited to those with a baseline negative troponin because this inherently introduces bias. Similarly, we excluded studies that were limited to only patients with ACS or specific populations. We did not exclude studies with STEMI patients, although this is an electrocardiographic and clinical diagnosis, as we wished to assess the diagnostic accuracy of the assays in all patients with chest pain. The relatively high incidence of AMI in our population does lead to a bias in the PPV of the test, which is important to acknowledge. However, positive and negative LR should not be influenced by this bias. Other limitations are those inherent to meta-analyses, which include lack of raw or uniform data, and use of different troponin assays and cut-points. We were also unable to adjust the diagnosis of AMI based on the delta for the rise and/or fall of troponin and the

use of longer follow-up may admix events related to ACS with those related to the predictive value of cTn detected in the absence of ACS. Although a random-effect pooling method adjusts for it, another limitation of this meta-analysis is the heterogeneity observed among studies, although this appeared to be low. Finally, meta-regression techniques are limited given the lack of raw patient information and should therefore be viewed with caution and as hypothesis generating.

In conclusion, both cTn and hs-cTn have excellent diagnostic accuracy, but our data support broader use of hs-cTn given the improvements provided in sensitivity, NPV, and identification of patients at risk for adverse outcomes during follow-up.

Conflicts of Interest/Disclosures

M.J.L., N.C.B., R.O.E., R. Torguson, F.C., S.J.A., S.W.G., K.I., M.S., J.P.C., Y.F., R. Twerenbold, R.W.: none; M.C.: research support and speaker's honoraria from Roche Diagnostics; P.O.C.: consultant for Philips Health Care Incubator and Siemens Point of Care; J.M.: consultant for Philips Health Care Incubator; U.L.: study fees from St Jude Medical and Medtronic, lecture honoraria from St Jude Medical, Medtronic, Sanofi, Aventis, Boehringer Ingelheim, and Bristol:Myers Squibb; C.C.G.: honoraria from Brahms Thermofisher; C. Meune: grant support from Roche Diagnostics and Brahms Thermofisher, and lecture fees from Roche Diagnostics; K.M.E.: honoraria from Siemens Healthcare Diagnostics and consultant for Abbott Laboratories and Fiomi Diagnostics; R.P.: research grant from Abbott Diagnostics; DHS: research grant from Abbott Laboratories and Singulex, Inc; A.H.B.W.: research grant from Singulex, Inc, Roche Laboratories, Alere, and Beckman Coulter, and travel support from Abbott Laboratories; J.O.L.: research support and consultant honoraria from Abbott Diagnostics, Alere, and Roche Diagnostics; A.S.J.: consultant for Roche Laboratories, Radiometer, Abbott Laboratories, Alere Critical Diagnostics, Ortho Diagnostics, Beckman Coulter, and Amgen; C. Mueller: research support from the European Union, Swiss National Science Foundation, Swiss Heart Foundation, Basel University, University Hospital Basel, Cardiovascular Research Foundation Basel, Stanley Thomas Johnson Foundation, Abbott, ALERE, Beckman Coulter, Brahms, Bühlmann, Critical Diagnostics, Nanosphere, Pronota, Roche, Siemens, and 8sense, and speaker or consulting honoraria from Abbott, ALERE, BG Medicine, Bio Merieux, Brahms, Massachusetts General Hospital, Novartis, Roche, and Siemens.

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Appendix

Supplementary Table I. Appraisal of included studies

Study	Standard troponin assays	Prespecified cut-points	Study design	Consecutive patient inclusion	Withdrawals reported	AMI definition	Troponin used to define AMI
Aldous et al 2012	Yes	Yes	Prospective	No	Yes	Universal definition with physician adjudication. Biomarker elevation with a rise or fall or signs of CAD	Conventional
Aldous et al 2011	Yes	Yes	Prospective	No	Yes	Universal definition with physician adjudication. Biomarker elevation with a 20% rise or fall or signs of CAD	Conventional
APACE	Yes	Yes	Prospective	Yes	Yes	Universal definition with physician adjudication. Biomarker elevation with a 30% rise or fall or signs CAD	Conventional
Christ et al	Yes	Yes	Retrospective	Yes	Yes	Universal definition with physician adjudication. Biomarker elevation with a 20% rise or fall or signs of CAD	Conventional
Collinson et al	Yes	Yes	Prospective	No	Yes	Universal definition with physician adjudication. Biomarker elevation with a rise or fall or signs of CAD	Conventional
Eggers et al	Yes	Yes	Prospective	Yes	No	Universal definition with physician adjudication Biomarker elevation with a 20% rise or fall, an absolute change of ≥ 5 ng/L, or signs of CAD	Conventional
Freund et al	Yes	Yes	Prospective	Yes	Yes	Universal definition with physician adjudication. Biomarker elevation with symptoms or signs of CAD	Conventional
Hammerer-Lercher et al	Yes	Yes	Retrospective	Yes	Yes	Universal definition with physician adjudication. Biomarker elevation with a rise or fall or signs of CAD	Conventional
Inoue et al	Yes	Yes	Prospective	Yes	Yes	Universal definition with physician adjudication.	Conventional
Keller et al	Yes	Yes	Prospective	Yes	Yes	Universal definition with physician adjudication. Biomarker elevation with a 20% rise or fall or signs of CAD	Conventional
Lotze et al	Yes	Yes	Prospective	Yes	Yes	Universal definition with physician adjudication. Biomarker elevation with a rise or fall or signs of CAD	Combination
Melki et al	Yes	Yes	Prospective	No	Yes	Universal definition with physician adjudication. Biomarker elevation with a rise or fall or signs of CAD	Conventional
Meune et al	Yes	Yes	Prospective	Yes	Yes	Universal definition with physician adjudication. Biomarker elevation with a rise or fall	Conventional
Pracon et al	Yes	Yes	Prospective	Yes	Yes	Universal definition with physician adjudication. Biomarker elevation with a rise or fall or signs of CAD	Combination
Santalo et al	Yes	Yes	Prospective	Yes	Yes	Universal definition with physician adjudication. Biomarker elevation with a 20% rise or fall	Conventional
Schreiber et al	Yes	Yes	Prospective	No	Yes	Universal definition with physician adjudication. Biomarker elevation with a rise or fall	Combination
Sebbane et al	Yes	Yes	Prospective	Yes	Yes	Universal definition with physician adjudication. Biomarker elevation with a rise or fall or signs of CAD	Conventional

Supplementary Table II. Number of TPs, FPs, FNs, and TNs based on the baseline cTn at presentation or baseline hs-cTn at presentation cut-point and whether the patient experienced AMI

cTn									
Study	Conventional cTn cut-point	TP (n)	FP (n)	FN (n)	TN (n)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Aldous et al 2012	Abbott Architect cTnI, 30 ng/L	175	26	30	708	85.4	96.5	87.1	95.9
Aldous et al 2011	Abbott Architect cTnI, 30 ng/L	82	21	28	201	74.5	90.5	79.6	87.8
APACE	Roche cTnT 4th gen, 35 ng/L	168	29	66	1270	71.8	97.8	85.3	95.1
Christ et al	Roche cTnT 4th gen, 35 ng/L	13	11	7	106	65.0	90.6	54.2	93.8
Collinson et al	Siemens Stratus CS cTnI, 70 ng/L	53	29	10	739	84.1	96.2	64.6	98.7
Eggers et al	Siemens Stratus CS cTnI, 70 ng/L	92	13	36	219	71.9	94.4	87.6	85.9
Freund et al	Siemens Xpand HM cTnI, 140 ng/L or Beckman Coulter Access cTnI, 60 ng/L	32	9	13	263	71.1	96.7	78.0	95.3
Hammerer-Lercher et al	Roche Elecsys cTnT 4th gen, 10 ng/L	35	48	5	352	87.5	88.0	42.2	98.6
Inoue et al	Roche cTnT 4th gen, 35 ng/L	98	33	65	87	60.1	72.5	74.8	57.2
Keller et al	Roche Elecsys cTnT 4th gen, 10 ng/L	300	83	113	1322	72.6	94.1	78.3	92.1
Lotze et al	Roche cTnT 4th gen, 100 ng/L	11	38	2	91	84.6	70.5	22.4	97.8
Melki et al	Roche cTnT 4th gen, 40 ng/L	90	7	24	112	79.0	94.1	92.8	82.4
Meune et al	Siemens Xpand HM cTnI, 70 ng/L	12	7	1	38	92.3	84.4	63.2	97.4
Pracon et al	Siemens Dimension Flex TnI, 70 mg/L	69	20	15	83	82.1	80.6	77.5	84.7
Santalo et al	Roche Cobas e401 cTnT 4th gen, 10 ng/L	61	28	17	250	78.2	89.9	68.5	93.6
Schreiber et al	Siemens Dimension Rxl TnI, 140 ng/L	9	14	3	439	75.0	96.9	39.1	99.3
Sebbane et al	Beckman Access2 cTnI, 40 ng/L	38	10	13	133	74.5	93.0	79.2	91.1
hs-cTn									
Study	hs-cTn cut-point	TP (n)	FP (n)	FN (n)	TN (n)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Aldous et al 2012	Roche HS TnT, 14 ng/L	181	134	24	600	88.3	81.7	57.5	96.2
Aldous et al 2011	Roche HS TnT, 14 ng/L	92	36	18	186	83.6	83.8	71.9	91.2
APACE	Roche HS TnT, 14 ng/L	221	346	13	953	94.4	73.4	39.0	98.7
Christ et al	Roche HS TnT, 14 ng/L	19	45	1	72	95.0	61.5	29.7	98.6
Collinson et al	Beckman AccuTnI, 40 ng/L	43	15	20	757	68.2	98.1	74.1	97.4
Eggers et al	Roche HS TnT, 14 ng/L	101	59	27	173	78.9	74.6	63.1	86.5
Freund et al	Roche HS TnT, 14 ng/L	42	48	3	224	93.3	82.4	46.7	98.7
Hammerer-Lercher et al	Roche HS TnT, 14 ng/L	36	80	4	320	90.0	80.0	31.0	98.8
Inoue et al	Roche HS TnT, 14 ng/L	141	59	22	61	86.5	50.8	70.5	73.5
Keller et al	Siemens sensitive TnI Ultra, 40 ng/L	375	138	38	1267	90.8	90.2	73.1	97.1
Lotze et al	Roche HS TnT, 14 ng/L	12	60	1	69	92.3	53.5	16.7	98.6
Melki et al	Roche HS TnT, 14 ng/L	111	31	3	88	97.4	73.9	78.2	96.7
Meune et al	Roche HS TnT, 14 ng/L	12	12	1	33	92.3	73.3	50.0	97.1
Pracon et al	Abbott Architect Stat TnI, 28 ng/L	73	12	11	91	86.9	88.3	85.9	89.2
Santalo et al	Roche HS TnT, 14 ng/L	70	79	8	199	89.7	71.6	47.0	96.1
Schreiber et al	Singulex Erenna HS-TnI, 8 ng/L	10	80	2	373	83.3	82.3	11.1	99.5
Sebbane et al	Roche HS TnT, 14 ng/L	39	22	12	121	76.5	84.6	63.9	91.0

Abbreviations: TP, True positive; FP, false positive; FN, false negative; TN, true negative. Abbott (Abbott Park, IL), Roche (Indianapolis, IN), Siemens (Tarrytown, NY), Singulex (St Louis, MO).

Supplementary Table III. Number of TPs, FPs, FNs, and TNs based on the second cTn or second hs-cTn cut-point and whether the patient experienced AMI for studies providing this data

Study	Time since presentation (h)	TP (n)	FP (n)	FN (n)	TN (n)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
cTn at second serial blood sampling									
Aldous et al 2012	2	189	30	16	704	92.2	95.9	86.3	97.8
Aldous et al 2011	6	100	26	10	196	90.9	88.3	79.4	95.1
APACE	2	88	23	11	788	88.9	97.2	79.3	98.6
Christ et al	6	13	12	7	105	65.0	89.7	52.0	93.8
Collinson et al	1.5	13	12	1	643	92.9	98.2	52.0	99.8
Freund et al	6	9	2	1	107	90.0	98.2	81.8	99.1
Meune et al	3	11	9	2	36	84.6	80.0	55.0	94.7
Pracon et al	4	20	8	2	22	90.9	73.3	71.4	91.7
Santalo et al	2	63	28	8	239	88.7	89.5	69.2	96.8
Schreiber et al	1.5	7	14	2	384	77.8	96.5	33.3	99.5
hs-cTn at second serial blood sampling									
Aldous et al 2012	2	189	149	16	585	92.2	79.7	55.9	97.3
Aldous et al 2011	6	100	41	10	181	90.9	81.5	70.9	94.8
APACE	2	96	231	2	579	98.0	71.5	29.4	99.7
Christ et al	4	15	41	5	76	75.0	65.0	26.8	93.8
Collinson et al	1.5	9	7	2	647	81.8	98.9	56.3	99.7
Freund et al	6	5	12	0	44	100.0	78.6	29.4	100.0
Meune et al	3	13	14	0	31	100.0	68.9	48.1	100.0
Pracon et al	3	11	2	1	16	91.7	88.9	84.6	94.1
Santalo et al	2	65	75	4	213	94.2	74.0	46.4	98.2
Schreiber et al	1.5	9	72	0	326	100.0	81.9	11.1	100.0

Abbreviations: TP, True positive; FP, false positive; FN, false negative; TN, true negative.

Supplementary Table IV. Number of TPs, FPs, FNs, and TNs based on the baseline cTn or baseline hs-cTn cut-point and whether the patient experienced AMI when AMI was defined using the cut-point for the hs-cTn assay

Study	TP (n)	FP (n)	FN (n)	TN (n)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Baseline cTn								
Aldous et al 2011	105	26	24	177	81.4	87.2	80.2	88.1
APACE	163	20	149	1201	52.2	98.4	89.1	89.0
Christ et al	13	11	22	91	37.1	89.2	54.2	80.5
Collinson et al	54	28	12	737	81.8	96.3	65.9	98.4
Melki et al	92	9	39	93	70.2	91.2	91.1	70.5
Santalo et al	89	62	13	192	87.3	75.6	58.9	93.7
Baseline hs-cTn								
Aldous et al 2011	116	14	13	189	89.9	93.1	89.2	93.6
APACE	281	286	31	935	90.1	76.6	49.6	96.8
Christ et al	33	31	2	71	94.3	69.6	51.6	97.3
Collinson et al	45	13	21	756	68.2	98.3	77.6	97.3
Melki et al	128	18	3	84	97.7	82.4	87.7	96.6
Santalo et al	61	25	41	237	59.8	90.5	70.9	85.3

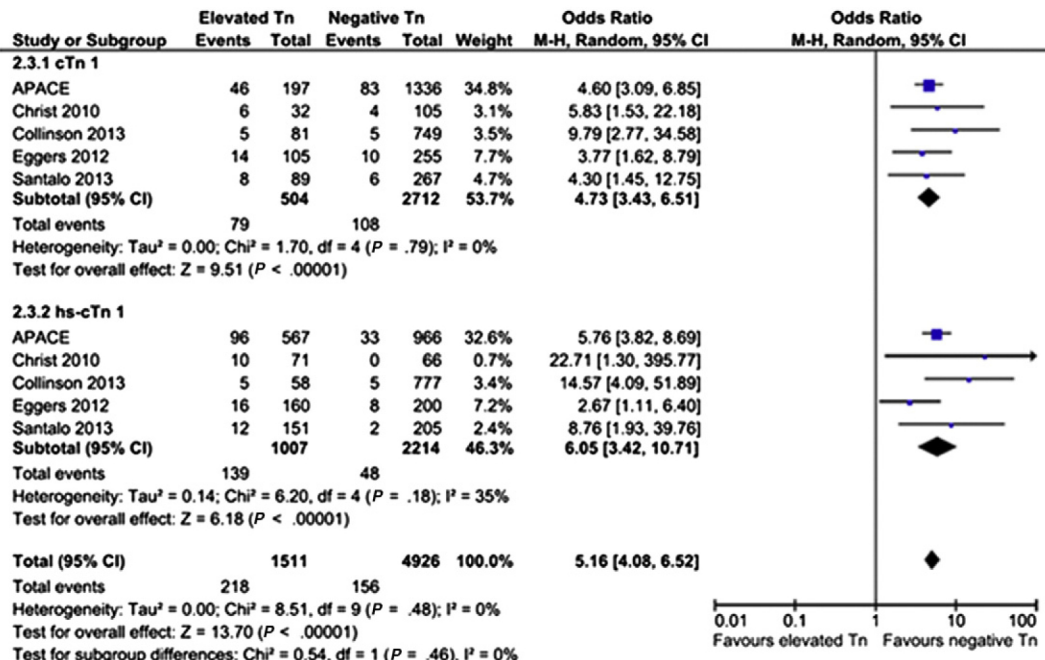
Abbreviations: TP, true positive; FP, false positive; FN, false negative; TN, true negative.

Supplementary Table V. Area under the ROC curves for the admission and second conventional and hs-cTn for the diagnosis of AMI

Study	Conventional cTn, AUC ± SE	Hs-cTn, AUC ± SE	Time to next troponin (h)	Next conventional cTn, AUC ± SE	Next Hs-cTn, AUC ± SE
Aldous et al 2012	0.96 ± 0.01	0.92 ± 0.01	2	0.98 ± 0.01	0.93 ± 0.01
Aldous et al 2011	0.88 ± 0.02	0.90 ± 0.02	6	0.93 ± 0.02	0.94 ± 0.02
APACE	0.79 ± 0.06	0.92 ± 0.02	2	0.97 ± 0.02	0.97 ± 0.01
Christ et al	0.89 ± 0.04	0.91 ± 0.03	6	0.97 ± 0.02	0.97 ± 0.01
Collinson et al	0.94 ± 0.02	0.92 ± 0.02	1.5	0.95 ± 0.05	0.94 ± 0.06
Eggers et al	0.91 ± 0.02	0.85 ± 0.02		NR	NR
Freund et al	0.93 ± 0.02	0.93 ± 0.02	6	0.85 ± 0.10	0.94 ± 0.05
Hammerer-Lercher et al	0.91 ± 0.02	0.94 ± 0.01		NR	NR
Inoue et al	0.68 ± 0.03	0.73 ± 0.03		NR	NR
Keller et al	0.85 ± 0.02	0.96 ± 0.02	3	0.98 ± 0.01	0.98 ± 0.01
Lotze et al	0.85 ± 0.03	0.87 ± 0.03		NR	NR
Melki et al	0.93 ± 0.02	0.95 ± 0.02	2	0.96 ± 0.01	0.96 ± 0.01
Meune et al	0.95 ± 0.05	0.92 ± 0.04	3	0.98 ± 0.02	0.97 ± 0.02
Pracon et al	0.86 ± 0.03	0.92 ± 0.02	4	0.86 ± 0.05	0.91 ± 0.06
Santalo et al	0.83 ± 0.12	0.81 ± 0.10	2	0.96 ± 0.04	0.84 ± 0.09
Schreiber et al	0.90 ± 0.01	0.94 ± 0.01	1.5	0.87 ± 0.02	0.98 ± 0.01
Sebbane et al	0.90 ± 0.03	0.89 ± 0.02		NR	NR

Abbreviations: AUC, Area under the ROC curve; NR, not reported.

Supplementary Figure 1



(Continued.)