Diagnostic accuracy of combined cardiac troponin and copeptin assessment for early rule-out of myocardial infarction: a systematic review and meta-analysis

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Abstract

Aims: This systematic review aimed to investigate the diagnostic accuracy of combined cardiac troponin (cTn) and copeptin assessment in comparison to cTn alone for early rule-out of acute myocardial infarction (AMI).

Methods: Primary studies were eligible if they evaluated diagnostic accuracy for cTn with and without copeptin in patients with symptoms suggestive of AMI. AMI was defined according to the universal definition, using detection of cTn as a marker for myocardial necrosis. Eligible studies were identified by searching electronic databases (Medline, EMBASE, Science Citation Index Expanded, CINAHL, Pascal, and Cochrane) from inception to March 2013, reviewing conference proceedings and contacting field experts and the copeptin manufacturer.

Results: In 15 studies totalling 8740 patients (prevalence of AMI 16%), adding copeptin improved the sensitivity of cTn assays (from 0.87 to 0.96, $p=0.003$) at the expense of lower specificity (from 0.84 to 0.56, $p<0.001$). In 12 studies providing data for 6988 patients without ST-segment elevation, the summary sensitivity and specificity estimates were 0.95 (95% CI 0.89 to 0.98) and 0.57 (95% CI 0.49 to 0.65) for the combined assessment of cTn and copeptin. When a high-sensitivity cTnT assay was used in combination with copeptin, the summary sensitivity and specificity estimates were 0.98 (95% CI 0.96 to 1.00) and 0.50 (95% CI 0.42 to 0.58).

Conclusion: Despite substantial between-study heterogeneity, this meta-analysis demonstrates that copeptin significantly improves baseline cTn sensitivity. Management studies are needed to establish the effectiveness and safety of measuring copeptin in combination with high-sensitivity cTnT for early rule-out of AMI without serial testing.

Keywords

copeptin, diagnostic accuracy, myocardial infarction, troponin

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CK-MB = creatine kinase-myocardial band
 HFABP = heart-type fatty acid-binding protein
 NSTEMI = non-ST-segment elevation myocardial infarction
 QUADAS-2 = Quality Assessment of Diagnostic Accuracy Studies-2
 STEMI = ST-segment elevation myocardial infarction

Introduction

Initial evaluation for acute myocardial infarction (AMI) relies on 12-lead electrocardiography recording and biomarker analysis, in complement to clinical assessment.¹ Cardiac troponin (cTn) T and I are considered standard markers for myocardial necrosis and their elevation is part of the universal definition of myocardial infarction.² Due to a delayed release of cTn into the bloodstream, cTn assays lack sensitivity within the first hours of myocardial injury, a phenomenon referred as the ‘troponin-blind period’. Serial blood sampling is therefore required, with cTn measured on admission and 3–9 h later, in order to confirm or rule out AMI.

There is growing interest in alternative biomarkers that might be more sensitive to early myocardial injury. In 2009, a single-centre study reported that the combined assessment of cTn and copeptin at the time of presentation accurately ruled out AMI, potentially allowing prompt discharge from the emergency department and obviating the need for serial blood sampling.³ Copeptin forms the C-terminal part of pro-vasopressin and is secreted stoichiometrically with arginine vasopressin, a neurohypophysis hormone.⁴ Copeptin is stable at room temperature and can be easily measured using automated assays,⁵ with results available within 20–60 min. Elevated circulating levels of copeptin are observed in heart failure, stroke, traumatic brain injury, and haemorrhagic or septic shock.⁵ In AMI patients, copeptin levels are elevated 0–4 h after symptoms appear,⁵ whereas cTn levels peak 12 h after symptom onset. In this systematic review with meta-analysis, we aimed to determine the diagnostic accuracy of combined cTn and copeptin assessment on admission in comparison to cTn alone for early rule-out of AMI.

Methods

This review complied with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement. Inclusion criteria and meta-analysis methods were prespecified (protocol registration number: PROSPERO 2012:CRD42012003399) and are reported in detail in Supplementary Data 1 (available online).

Eligibility criteria

Types of studies. Primary diagnostic accuracy studies evaluating cTn with and without copeptin were eligible. We focused primarily on cross-sectional studies enrolling

consecutive patients. Prognostic studies were not within the scope of this review.

Participants. Eligible studies enrolled adult patients presenting to the emergency department or admitted to the ward with symptoms suggestive of AMI with or without evidence of ST-segment elevation.

Index tests. Only studies examining diagnostic accuracy for baseline cTn and copeptin values measured in blood samples obtained on admission were included in the present review. Troponin index tests included conventional and high-sensitivity assays. Copeptin index tests included manual immunoluminometric assays and automated immunofluorescent assays based on Time-Resolved Amplified Cryptate Emission (TRACE) technology.

Reference tests. The appropriate reference standard consisted of a review of all available medical records coupled with serial cTn measurement results. AMI was defined according to the contemporary definition, using detection of cTn rise or fall with at least one value above the upper reference limit as a marker for myocardial necrosis.

Study identification

Studies were identified by searching electronic databases (Medline, EMBASE, Science Citation Index Expanded, CINAHL, Pascal, and Cochrane) from inception, reviewing conference proceedings, and contacting field experts and the copeptin manufacturer. The last electronic search was undertaken on 2 March 2013. No language or type of document restrictions and no methodology filters were used.

Data collection

Two review authors extracted information for each primary study using a data abstraction form. Primary data were requested from corresponding authors when outcome data yielded inconsistencies or could not be extracted from the main record or additional relevant citations. Studies with insufficient details on outcome data despite contacting the authors were excluded from the meta-analysis.

Assessment of methodological quality

The two review authors assessed the methodological quality of the primary studies, using a checklist adapted from the Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 tool.⁶ We anticipated that a key methodological issue would be the potential for incorporation bias arising from the fact that admission cTn measurement results formed part of the reference standard.⁷ No primary study was excluded based on methodological quality assessment results.

Statistical analysis

For each primary study, sensitivity and specificity point estimates and corresponding 95% confidence intervals (CI) were computed from extracted data for cTn with and without copeptin. Two-tailed p -values <0.05 were considered statistically significant.

Meta-analytical model. Data were synthesized and compared using an 'exact' binomial extension of the bivariate mixed-effect regression model for meta-analysis of diagnostic test accuracy studies.⁸ This model hierarchically accounts for within- and between-study variability of index test sensitivity and specificity.

Summary diagnostic accuracy estimates. Summary estimates of sensitivity, specificity, positive and negative likelihood ratios, and diagnostic odds ratio were derived from bivariate mixed-effect regression model parameter estimates. A hierarchical summary receiver operating characteristic (ROC) curve was plotted using logit estimates of sensitivity and specificity and the respective variance and covariance.

Investigation of heterogeneity. Between-study heterogeneity was evaluated graphically by examining coupled forest plots of sensitivity and specificity and statistically by using the I^2 inconsistency index.⁹

Sensitivity analyses. A secondary analysis was planned a priori, restricted to studies evaluating the diagnostic accuracy of combined cTn and copeptin assessment for non-ST-segment elevation myocardial infarction (NSTEMI). We also performed subgroup analyses using bivariate mixed-effect regression to examine the following sources of heterogeneity in diagnostic accuracy estimates: fulfillment of QUADAS-2 criteria, prevalence of AMI, median time from chest pain onset, and copeptin assays. We also performed a subgroup analysis restricted to studies that reported paired comparisons of conventional or sensitive versus high-sensitivity cTn assays in combination with copeptin.

Reporting bias. Evidence of publication bias was assessed statistically and graphically by examining a scatterplot of the log of the diagnostic odds ratio versus the inverse of the square root of the effective sample size.¹⁰

Clinical implications. We calculated post-test probability values through Bayes' rule using summary estimates of positive and negative likelihood ratios. To examine the influence of pretest probability, we performed these analyses for the median, lowest, and highest prevalence of AMI observed across the studies reviewed.

Quality of evidence. We rated the quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.¹¹

Results

Literature search

A total of 168 records were identified through database searching (Figure 1) and 17 additional records were identified through other sources. After removing 21 duplicates, the titles and abstracts for 164 records were screened for eligibility. Of these, 41 records were identified as being potentially relevant and full-text articles were retrieved for more thorough review. After excluding 26 records based on full-text articles (Supplementary Data 2), 15 studies enrolling 9074 patients were included in the meta-analysis (Supplementary Data 3).

Characteristics of included studies

Eight studies enrolled patients with suspected AMI, while seven studies excluded patients with ST-segment elevation myocardial infarction (STEMI). One study was conducted in 16 emergency departments in the USA, whereas all the other studies enrolled patients in Western Europe. All studies were cross-sectional in design and recruited consecutive patients. The median prevalence of AMI was 15%, ranging from 8 to 46% across studies.

Eleven studies evaluated automated immunofluorescent copeptin assays based on TRACE technology (Supplementary Data 4). In 10 studies, the diagnostic threshold for copeptin was 14 pmol/l. cTn index tests consisted of conventional or sensitive assays in six studies and high-sensitivity assays in 14 studies, with five studies evaluating two or more assays. For cTn T methods, 10 studies evaluated high-sensitivity assays with a diagnostic threshold equivalent to the 10% coefficient of variation (CV) (14 ng/l), whereas three studies evaluated conventional assays with a diagnostic threshold equivalent to the 10% CV (30 ng/l, two studies) or the limit of detection (10 ng/l, one study). For cTn I methods, three studies evaluated conventional assays using a diagnostic threshold equivalent to the 99th percentile value (two studies) or the 10% CV (one study) and five studies evaluated the Siemens TnI-Ultra assay with a diagnostic threshold equivalent to the 99th percentile value (40 ng/l, four studies) or the local laboratory 10% CV (50 ng/l, one study).

Troponin reference tests consisted of either local or core laboratory assays with varying thresholds (Supplementary Data 4). Timing of repeated cTn measurements after admission varied across studies, ranging from 1.5 to 24 h.

Assessment of study quality

Six studies fulfilled five or more of the QUADAS-2 tool criteria (Supplementary Data 5). Seven studies wherein cTn measurement on admission formed part of the reference standard were considered at high risk for incorporation bias. Seven studies also yielded a high risk for flow or timing bias because of missing values for serial

Figure 1. Study selection.

cTn measurements for more than 20% of patients (three studies), an inappropriate interval between copeptin and/or cTn measurement and the reference standard (four studies), or inappropriate exclusion of patients with unstable angina pectoris from analysis (one study). Applicability concerns existed for three studies that enrolled patients in cardiology departments or coronary care units and three studies with timing from chest pain onset greater than 12 h for more than 20% of patients.

Diagnostic accuracy of combined cTn and copeptin assessment for AMI

Point estimates for the combined assessment of cTn and copeptin ranged from 0.79 to 1.00 for sensitivity (I^2 78%) and from 0.23 to 0.76 for specificity (I^2 96%) across 15 studies totalling 8740 patients with a 16% prevalence of AMI (Figure 2). The summary estimates were 0.96 (95% CI 0.93 to 0.99) for sensitivity and 0.56 (95% CI 0.49 to 0.63) for specificity (Supplementary Data 6), with an area under the summary ROC curve equal to 0.80 (95% CI 0.76 to 0.83; Figure 3). No evidence of selective reporting was found graphically (Supplementary Data 7, Figure 1) or statistically ($p=0.52$).

Diagnostic accuracy of combined cTn and copeptin assessment for NSTEMI

When restricting the analysis to 12 studies providing data for 6988 patients without persistent ST-segment elevation at the time of presentation (NSTEMI prevalence 13%), sensitivity point estimates ranged from 0.68 to 1.00 (I^2 76%) for combined cTn and copeptin assessment, with specificity point estimates ranging from 0.23 to 0.76 (I^2 96%; Supplementary Data 7, Figure 2). The summary estimates were 0.95 (95% CI 0.89 to 0.98) for sensitivity and 0.57 (95% CI 0.49 to 0.65) for specificity (Supplementary Data 6), with an area under the summary ROC curve equal to 0.80 (95% CI 0.76 to 0.83). There was no evidence of selective reporting ($p=0.64$).

Diagnostic accuracy of combined cTn and copeptin assessment across subgroups

No significant association was found between diagnostic accuracy estimates and fulfilment of the QUADAS-2 criteria, prevalence of AMI, median time from chest pain onset, or copeptin or cTn assays (Supplementary Data 8). When restricting the analysis to 10 studies that used a 14-pmol/l

Figure 2. Coupled Forest plot of sensitivity and specificity for the combined assessment of cardiac troponin and copeptin for early rule-out of acute myocardial infarction (15 studies).

*Data were reported in Freund et al., 2012 (see supplementary data 2, available online).

Figure 3. Summary ROC curve for the assessment of cardiac troponin with and without copeptin for early rule-out of acute myocardial infarction (15 studies).

The areas under the curve for the assessment of cardiac troponin without and with copeptin are 0.91 (95% CI 0.89 to 0.94) and 0.80 (95% CI 0.76 to 0.83), respectively.

diagnostic threshold for copeptin in 5115 patients, the summary estimates for combined cTn and copeptin assessment were 0.95 (95% CI 0.88 to 0.98) for sensitivity and 0.56 (95% CI 0.45 to 0.66) for specificity (Supplementary Data 7, Figure 8).

Four studies used high-sensitivity (hs)-cTn T as the reference standard (Supplementary Data 7, Figure 9), totalling 1429 patients (AMI prevalence 18%): the summary point estimates were 0.99 for sensitivity (95% CI 0.92 to 1.00) and 0.40 for specificity (95% CI 0.28 to 0.54), with an area under the summary ROC curve equal to 0.90 (95% CI 0.88 to 0.93).

Comparison of diagnostic accuracy for cTn with versus without copeptin

Overall, adding copeptin significantly improved the sensitivity of cTn assays at the expense of decreased specificity (Table 1). More specifically, the addition of copeptin increased sensitivity from 0.91 to 0.98 for hs-cTn T (difference 0.07, 95% CI 0.03 to 0.11, $p=0.002$) and from 0.79 to 0.93 for the Siemens TnI-Ultra assay (difference 0.14, 95% CI 0.06 to 0.21, $p=0.001$; Supplementary Data 7, Figures 10 and 11). The incremental diagnostic accuracy value of copeptin could not be computed for other cTn assays due to the limited number of studies (Supplementary Data 7, Figures 12 and 13).

Diagnostic accuracy for copeptin alone

Copeptin alone yielded sensitivity ranging from 0.45 to 0.84 (I^2 75%) with specificity ranging from 0.41 to 0.77 (I^2 93%) across 12 studies totalling 6083 patients (Supplementary Data 7, Figure 14). The summary estimates were 0.67 (95% CI 0.60 to 0.73) for sensitivity and 0.63 (95% CI 0.57 to 0.69) for specificity, with an area under the summary ROC curve of 0.70 (95% CI 0.66 to 0.74).

Clinical implications

Overall, the negative and positive likelihood ratio estimates for combined cTn and copeptin assessment were 0.07 (95% CI 0.02 to 0.11) and 2.19 (95% CI 1.89 to 2.49), respectively. At a 0.15 pretest probability, the probability of having non-elevated cTn and copeptin values on admission would be 0.48 with a post-test probability of AMI of 0.012 (95% CI 0.003 to 0.020). The post-test probability of AMI after non-elevated cTn and copeptin values ranged from 0.006 to 0.055 for a pretest probability varying between 0.08 and 0.46 (Table 2).

The probability of having non-elevated hs-cTn T and copeptin values would be 0.42 with a post-test probability of AMI as low as 0.006 (95% CI 0.0007 to 0.014), at a pre-test probability of 0.15. Comparable, although less precise,

estimates were found for patients without evidence of ST-segment elevation on admission.

Quality of evidence

The quality of evidence supporting the diagnostic accuracy for the combined cTn and copeptin assessment on admission was low. We downgraded one point for the risk of incorporation bias and one point for inconsistency in study results. The quality of evidence for the diagnostic accuracy for copeptin testing alone was moderate (Supplementary Data 9).

Discussion

This systematic review included 15 studies that evaluated the diagnostic accuracy for the combined assessment of cTn and copeptin on admission as a dual-marker strategy for AMI in 8740 patients. As demonstrated by this meta-analysis, adding copeptin significantly improved the baseline sensitivity of cTn (from 0.87 to 0.96) but at the expense of decreased specificity (from 0.84 to 0.56). However, the summary sensitivity estimate (0.95, 95% CI 0.89 to 0.98) for the combined cTn and copeptin assessment appears to be insufficiently high to rule out NSTEMI in routine practice. This meta-analysis also confirms that copeptin has only modest sensitivity and specificity and therefore cannot be used as a single diagnostic test for AMI.

The early diagnosis of AMI has considerably improved with the recent development of high-sensitivity assays, which reliably measure cTn concentrations that were not detected by previous generations of tests.^{7,12,13} However, an hs-cTn T value below the 99th percentile on admission cannot be used as a single parameter to rule out AMI and serial cTn measurements remain necessary, especially in early presenters.¹⁴

Interestingly, our meta-analysis showed that copeptin significantly improved the sensitivity of the hs-cTn T assay at the time of presentation, with a summary sensitivity estimate of 0.98 (95% CI 0.96 to 1.00). At a 0.15 pretest probability, testing hs-cTn T in combination with copeptin on admission could rule out AMI in 42% of consecutive patients with a post-test probability lower than 0.01.

Only non-elevated values for both hs-cTn T and copeptin on admission are relevant for diagnostic work-up of suspected AMI. Yet, the 7% increase in sensitivity may be offset by the 25% decrease in specificity for this dual marker strategy. Indeed, the estimated post-test probability of AMI after receiving an elevated hs-cTnT and/or copeptin value on admission was 0.26, indicating that false-positive cases would be much more likely than true-positive cases. This finding highlights the need for careful assessment of the consequences of false-positive results on admission, including anxiety for patients and physicians, resource implications, and potential harm resulting from additional

Table 1. Paired comparison of diagnostic accuracy for cardiac troponin with and without copeptin.

	No. of studies	No. of patients ^a	Sensitivity (95% CI)		Specificity (95% CI)			
			Troponin	Troponin with copeptin	Difference	p-value	Troponin	Troponin with copeptin
Overall	15	8740	0.87 (0.80 to 0.95)	0.96 (0.93 to 0.99)	0.09 (0.03 to 0.15)	0.003	0.84 (0.76 to 0.92)	0.56 (0.49 to 0.63)
Suspicion of NSTEMI ^b	11	6534	0.80 (0.73 to 0.88)	0.95 (0.91 to 0.98)	0.14 (0.08 to 0.20)	<0.001	0.89 (0.82 to 0.96)	0.57 (0.37 to 0.77)
High-sensitivity cardiac troponin T	10	4330	0.91 (0.86 to 0.97)	0.98 (0.96 to 1.00)	0.07 (0.03 to 0.11)	0.002	0.75 (0.64 to 0.86)	0.50 (0.42 to 0.58)
Siemens TnI-Ultra™	5	3996	0.79 (0.74 to 0.85)	0.93 (0.88 to 0.98)	0.14 (0.06 to 0.21)	0.001	0.94 (0.90 to 0.98)	0.63 (0.61 to 0.65)

p-values were adjusted for multiple comparisons using Holm's method (see methods in Supplementary Data 1).

^aThe prevalence of target condition was 16% for the overall cohort, 12% for the cohort of patients with suspicion of NSTEMI, 17% for the cohort evaluating high-sensitivity cardiac troponin T, and 12% for the cohort evaluating the Siemens TnI-Ultra assay.

^bBecause one study did not report diagnostic accuracy data for cardiac troponin alone for NSTEMI,²³ paired comparisons of cardiac troponin with and without copeptin included only 11 studies. NSTEMI, non-ST-segment elevation myocardial infarction.

testing.^{12,15} Interestingly, hs-cTn T and copeptin levels at the time of admission independently correlate with short- and long-term mortality.¹⁶ Although considered false-positive cases, patients with elevated hs-cTn T and/or copeptin levels on admission but no final diagnosis of AMI are at higher risk for major adverse cardiac events and might benefit from prolonged monitoring and additional investigations.

Although early recognition and appropriate management of AMI is critical, the diagnosis is missed in 2–6% of patients.¹⁷ This missed diagnosis rate includes not only prevalent AMI at the time of presentation but also AMI that develops in the short-term after admission (i.e. within a few days of emergency department presentation). Even if repeated hs-cTn T measurement within 3 h of admission accurately rules out prevalent AMI with sensitivity approaching 100%, it does not indicate that the short-term risk for developing AMI is null.

It remains unknown how the combined assessment of cTn and copeptin on admission compares with currently recommended strategies, which advocate measuring hs-cTn T at the time of presentation and 3 h later.¹⁸ The diagnostic incremental value of copeptin should also be examined in the context of recently developed and internally validated accelerated diagnostic protocols,¹⁹ which may allow rapid exclusion of AMI and help to address specificity concerns related to the use of hs-cTn assays.¹²

Because the results of cTn and copeptin testing are claimed to be available within 20–60 min, it is assumed that the combined assessment of the two markers on admission may speed up discharge of patients without AMI or hasten their access to investigations for alternate diagnoses.³ This hypothesis remains speculative given that the amount of time saved before ruling out AMI may be influenced by delays in patient triaging at the emergency department, blood sampling, transporting samples, running more than one analyser in the laboratory, or receiving and interpreting the results. Neither primary nor meta-analysis of diagnostic accuracy studies can provide direct evidence on the clinical benefits of the combined cTn and copeptin assessment on admission. Prospective management studies or randomized controlled trials are needed to evaluate processes of care, patient outcomes, and resource use associated with the implementation of this dual marker strategy into routine practice. The findings from the recently completed Effect of the Biomarker Copeptin in Managing Patients With Suspected Acute Coronary Syndrome (BiC-8) multicentre randomized controlled trial should provide evidence on the effectiveness and safety of early discharge into the ambulatory setting for patients who test negative for cTn and copeptin at the time of presentation. Yet, physicians should be aware that early discharge may prevent low-income patients from receiving appropriate work up in the ambulatory setting.

Table 2. Post-test probability of acute myocardial infarction.

Pretest probability	Non-elevated troponin and copeptin	Elevated troponin and/or copeptin
Patients with or without ST-segment elevation on admission		
All cardiac troponin assays (15 studies)		
0.08	0.006 (0.002 to 0.010)	0.16 (0.14 to 0.18)
0.15	0.012 (0.003 to 0.020)	0.28 (0.25 to 0.31)
0.46	0.055 (0.016 to 0.090)	0.65 (0.62 to 0.68)
High-sensitivity cardiac troponin T assays (10 studies)		
0.08	0.003 (0.0004 to 0.007)	0.14 (0.13 to 0.16)
0.15	0.006 (0.0007 to 0.014)	0.26 (0.23 to 0.28)
0.46	0.027 (0.003 to 0.063)	0.62 (0.59 to 0.65)
Patients without ST-segment elevation on admission		
All cardiac troponin assays (12 studies)		
0.08	0.007 (0.003 to 0.016)	0.16 (0.14 to 0.18)
0.15	0.015 (0.007 to 0.031)	0.28 (0.25 to 0.31)
0.46	0.067 (0.032 to 0.135)	0.65 (0.62 to 0.69)
High-sensitivity cardiac troponin T assays (7 studies)		
0.08	0.006 (0.001 to 0.022)	0.15 (0.13 to 0.17)
0.15	0.012 (0.003 to 0.044)	0.26 (0.23 to 0.29)
0.46	0.054 (0.014 to 0.183)	0.63 (0.59 to 0.67)

Values in parentheses are 95% confidence intervals. Post-test probability values were calculated through Bayes' rule using summary estimates of negative and positive likelihood ratios, respectively.

Although considered a marker of endogenous stress,⁵ some studies failed to report an association between copeptin levels and myocardial ischaemia. In animal AMI models, an increase of copeptin levels was found to be associated with a decrease of mean arterial blood pressure but not with myocardial ischaemia or infarction size.²⁰ A study of 253 consecutive patients who underwent rest and/or exercise myocardial perfusion single-photon-emission computed tomography reported only limited accuracy of copeptin for the detection of inducible myocardial ischaemia.²¹ In the Rule Out Myocardial Infarction by Computed Tomography study, the copeptin level did not relate to coronary angiographic morphology or left ventricular ejection fraction, although a moderate association with regional left ventricular dysfunction was observed.²²

Some studies have compared the combined assessment of cTn and copeptin with other dual biomarker strategies, with contradictory findings. The reasons for the discrepancies likely relate to the populations studied and the troponin assays used.¹⁵ In a mixed population of patients with and without ST-segment elevation on presentation, Keller et al.²³ reported a higher area under the ROC curve for the combination of cTn with copeptin as compared with the combined assessment of cTn with myoglobin or creatine kinase-myocardial band (CK-MB). In contrast, the multi-centre Randomised Assessment of Treatment using Panel

Assay of Cardiac markers study¹⁵ did not find a significant incremental diagnostic value for copeptin, conventional biomarkers (myoglobin, CK-MB), and novel cytoplasmic biomarkers (heart-type fatty acid-binding protein, HFABP) as compared with hs-cTn alone, for detecting AMI in a low-risk group of patients. The Advantageous Predictors of Acute Coronary Syndrome Evaluation study²⁴ also failed to evidence any incremental diagnostic value for the addition of either copeptin or HFABP to the measurement of hs-cTn T alone, in patients without ST-segment elevation on presentation.

This meta-analysis included 15 studies that have been completed since 2009, summarizing the most recent evidence on the diagnostic accuracy for combined cTn and copeptin assessment on admission. All included studies evaluated cTn with and without copeptin in the same patients, providing unconfounded data on the incremental diagnostic accuracy of copeptin compared with cTn alone. However, this meta-analysis has a few caveats that must be considered.

First, substantial statistical and clinical between-study heterogeneity inevitably limited the interpretation of summary diagnostic accuracy estimates, although we used bivariate mixed-effect regression and performed subgroup analyses. The reasons for heterogeneity in estimates related to variations across original studies in terms of exclusion

criteria, prevalence of AMI, timing of enrolment, copeptin assays and thresholds, and index and reference cTn assays and thresholds. Despite the manufacturer's instructions advocating copeptin levels below 14 pmol/l for ruling out AMI, varying thresholds with potentially inadequate sensitivity were used across primary studies. The lack of standardization among cTn assays also contributed to heterogeneity in sensitivity. We therefore derived summary ROC curves that depicted sensitivity and specificity observed across primary studies with varying thresholds for both cTn and copeptin assays.

Second, primary studies were identified by carrying out an extensive literature search and contacting field experts and the copeptin manufacturer. We did not find evidence of selective reporting, although statistical tests and graphical methods for detecting publication bias may be misleading when applied to meta-analyses of diagnostic accuracy studies.¹⁰

Third, this systematic review was limited to primary studies using a reference standard of AMI. Unless separate data for AMI were available, studies that used a broader reference standard of acute coronary syndrome were not eligible. The reasons were that the definition of acute coronary syndrome involves clinical judgment, may vary between studies, and may not be independent of the tests under investigation.²⁵ However, early recognition and appropriate management of unstable angina pectoris is critical because a missed diagnosis may lead to more severe ischaemia and potentially preventable death.

Fourth, a major methodological concern with the primary studies relates to the potential for incorporation bias with the baseline cTn value serving as the index test and being part of the reference standard of AMI. This may result in overestimating diagnostic accuracy for cTn and therefore decreasing the apparent incremental diagnostic value of copeptin. Although incorporation bias cannot be eliminated, it may be limited by using different cTn assays for index and reference tests.^{7,26} Yet, using an analytically less sensitive cTn assay as part of the reference standard may lead to underestimating the specificity of cTn index tests.

Fifth, four primary studies reported retrospective analyses with an inappropriate interval between copeptin and/or cTn measurement and the reference standard. Because limited evidence exists on the stability of analytes after several years of storage, the possibility that copeptin or cTn levels have been influenced by sample instability cannot be formally excluded.

Sixth, most assays examined in this review were commercially available, although hs-cTn assays are not approved for use in all countries. The studies reviewed were conducted in the USA or in Western Europe and these findings may not apply to patients from other regions.

Despite substantial between-study heterogeneity, this meta-analysis suggests that the addition of copeptin significantly improves baseline cTn sensitivity for the diagnosis

of AMI. The combined assessment of hs-cTn T and copeptin on admission may make it possible to rule out AMI without performing serial testing. Yet, further evaluation is warranted to determine the effectiveness and safety of clinical decision rules incorporating hs-cTn T and copeptin assessment for triaging patients with symptoms suggestive of AMI.

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Conflict of interest

RT has received speaker honoraria from Brahms and Roche. TK has received speaker honoraria from Siemens Diagnostics and his institution has received grant support from Brahms and Abbott Diagnostics. DG has received research support from Thermo Fisher Scientific. KME has received honoraria from Roche Diagnostics and Siemens Healthcare Diagnostics and has served as a consultant for Abbott Laboratories. CC-G has received lecture fees from Roche Diagnostics. C Meune has received honoraria from Roche Diagnostics. AM has received consulting honoraria from Alere, BG Medicine, and Critical Diagnostics and has received research or speaking honoraria from BG Medicine, Abbott Laboratories, Alere, and Siemens Healthcare. C Mueller has received research support from Abbott Laboratories, Alere, Beckman Coulter, Brahms, Critical Diagnostics, Nanosphere, Roche Laboratories, Siemens Healthcare, and 8sense and has received speaker honoraria from Abbott Laboratories, Alere, Brahms, Novartis, Roche Laboratories, and Siemens Healthcare. The other authors declare no conflict of interest.

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