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Biomarkers

Copeptin Helps in the Early Detection of Patients With Acute Myocardial Infarction

Primary Results of the CHOPIN Trial (Copeptin Helps in the early detection Of Patients with acute myocardial INfarction)

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Objectives The goal of this study was to demonstrate that copeptin levels <14 pmol/L allow ruling out acute myocardial infarction (AMI) when used in combination with cardiac troponin I (cTnI) <99th percentile and a nondiagnostic electrocardiogram at the time of presentation to the emergency department (ED).

Background Copeptin is secreted from the pituitary early in the course of AMI.

Methods This was a 16-site study in 1,967 patients with chest pain presenting to an ED within 6 hours of pain onset. Baseline demographic characteristics and clinical data were collected prospectively. Copeptin levels and a contemporary sensitive cTnI (99th percentile 40 ng/l; 10% coefficient of variation 0.03 μg/l) were measured in a core laboratory. Patients were followed up for 180 days. The primary outcome was diagnosis of AMI. Final diagnoses were adjudicated by 2 independent cardiologists blinded to copeptin results.

Results AMI was the final diagnosis in 156 patients (7.9%). A negative copeptin and cTnI at baseline ruled out AMI for 58% of patients, with a negative predictive value of 99.2% (95% confidence interval: 98.5 to 99.6). AMIs not detected by the initial cTnI alone were picked up with copeptin >14 pmol/l in 23 (72%) of 32 patients. Non–ST-segment elevation myocardial infarctions undetected by cTnI at 0 h were detected with copeptin >14 pmol/l in 10 (53%) of 19 patients. Projected average time-to-decision could be reduced by 43% (from 3.0 h to 1.8 h) by the early rule out of 58% of patients. Both abnormal copeptin and cTnI were predictors of death at 180 days ($p < 0.0001$ for both; c index 0.784 and 0.800, respectively). Both were independent of age and each other and provided additional predictive value (all $p < 0.0001$).

Conclusions Adding copeptin to cTnI allowed safe rule out of AMI with a negative predictive value >99% in patients presenting with suspected acute coronary syndromes. This combination has the potential to rule out AMI in 58% of patients without serial blood draws. (Investigation of the Biomarker Copeptin in Patients With Acute Myocardial Infarction [NCT00952744]) (J Am Coll Cardiol 2013;62:150–60) © 2013 by the American College of Cardiology Foundation

An estimated 6 to 8 million patients present to US emergency departments (EDs) each year with suspected acute coronary syndromes (ACS) (1). In this population, biomarkers are a critical component of their evaluation. Although an elevation of cardiac troponin (cTn) with a rising and/or falling pattern in the setting of suspected ACS represents the gold standard for a non–ST elevation myocardial infarction (NSTEMI) diagnosis, the absence of an elevated value at the time of presentation does not rule out an acute ischemic event. Because symptoms are nonspecific, a method to rapidly rule out AMI would be helpful for early ED disposition. A biomarker that provides additional value to cTn would improve resource allocation and clinical decision making, particularly if it could be assessed at the time of presentation.

Arginine vasopressin (AVP) is responsible for a variety of hemodynamic functions that contribute to vascular tone and the maintenance of blood volume. Despite a theoretical diagnostic role in cardiovascular disease, its clinical application as a useful laboratory test has been limited by its short half-life in the circulation. Copeptin (the C-terminal portion of the AVP precursor peptide) is more stable and provides an easily measured surrogate biomarker for AVP release (2,3). After acute myocardial infarction (AMI), circulating copeptin levels rise to peak values rapidly and then decline over the next 2 to 5 days (4).

Measurement of copeptin has been reported to rapidly exclude AMI in patients presenting with suspected ACS (5,6). In 1 study of 487 consecutive ED patients (5), copeptin was elevated (>14 pmol/l) within 4 h of symptom onset, despite undetectable levels of cardiac troponin T (<99th percentile of the upper reference range). These studies suggest that the addition of copeptin may be useful to rule out AMI in patients presenting to the ED with suspected ACS.

The multicenter CHOPIN (Copeptin Helps in the Early Detection of Patients With Acute Myocardial Infarction) trial was designed to determine if copeptin could improve the ability to rule out AMI in patients presenting within 6 h of the onset of chest pain.

Abbreviations and Acronyms

ACS = acute coronary syndromes
AMI = acute myocardial infarction
AUC = area under the curve
AVP = arginine vasopressin
CI = confidence interval
cTn = cardiac troponin
cTnI = cardiac troponin I
ECG = electrocardiogram
ED = emergency department
IQR = interquartile range
NPV = negative predictive power
NSTEMI = non–ST elevation myocardial infarction
PPV = positive predictive power
STEMI = ST-segment elevation myocardial infarction
VAS = visual analog scale

Methods

Study design and population. The CHOPIN study was a 16-center prospective trial enrolling patients who presented with chest pain or ischemic-equivalent symptoms within 6 h of onset of symptoms. Patients >18 years of age were included if the treating physician had suspicion for the diagnosis of ACS. Patients were excluded if the symptoms were clearly not related to an ACS (i.e., penetrating chest wounds, crush injury). A detailed description of the study population and protocol is provided in the Online Appendix. The study was conducted in compliance with International Conference on Harmonisation/

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Good Clinical Practice regulations, and all 16 study sites received local institutional review board or ethics committee approval. All patients provided written informed consent for participation.

Patients were seen and evaluated in the ED of the participating trial sites by emergency physicians who performed their usual standard of care assessment and treatment. For each patient enrolled in the study, the emergency physicians, blinded to the investigational marker results, documented their impression of: 1) the likelihood that the patient was experiencing an ACS; and 2) the likelihood that the patient was experiencing an AMI. These assessments were made on 2 separate visual analog scales (VAS), assigning a value of 0% to 100% clinical diagnostic certainty. This VAS scoring was performed at 2 different time points for each patient: the first scoring was done within 15 min of the physician seeing and evaluating the patient and before seeing the first troponin results; the second scoring was completed after the initial troponin result was reported. Samples were obtained at the time of presentation (0 h) and then 2, 6, and 24 h later if the patient was still hospitalized. Local site biomarker values were used to guide patient management as per usual care. In addition, the blood was centrifuged, and plasma was stored at −60°C and later analyzed at the study core laboratory. Patients were followed up via telephone or medical records for the occurrence of death, AMI, and/or revascularization within the follow-up time frames of 30, 90, and 180 days.

Gold standard/adjudicated final diagnosis. After the 30-day follow-up was completed, each case report form was reviewed by at least 2 board-certified cardiologists, who each made a determination of the final diagnosis. In the event that the cardiologist reviewers did not agree, the case was adjudicated by the Endpoints Committee. All evaluations were reviewed for consistency by the Endpoints Committee. The final clinical diagnosis was based on predetermined guidelines (see Online Appendix for details). All final diagnoses were assigned to 1 of the following 6 categories: 1) ST-segment elevation myocardial infarction (STEMI); 2) NSTEMI; 3) unstable angina pectoris; 4) cardiovascular disease but non-ACS etiology; 5) noncardiac diagnosis; and 6) unclassified cause of chest pain. The local cardiac troponin values and the local cutoff values in use at that center were used for this determination.

Investigational assays of cardiac biomarkers. Subsequent to local measurement, cardiac troponin I (cTnI) was also measured in the core laboratory at the University of Maryland (R.C., Principal Investigator) with the cTnI Ultra assay on an ADVIA Centaur XP system (Siemens Healthcare Diagnostics, Norwood, Massachusetts). The assay detection limit as described by the manufacturer was 6 ng/l, measuring range was 6 to 50,000 ng/l, 99th percentile was 40 ng/l, and 10% coefficient of variation was 30 ng/l.

Ethylenediaminetetraacetic acid plasma concentrations of copeptin were measured in the core laboratory on a Kryptor Compact platform (BRAHMS GmbH, Hennigsdorf, Germany). The assay detection limit as described by the manufacturer was 4.8 pmol/l. The direct measuring range was 4.8 to 500 pmol/l (up to 1,200 pmol/l with automatic dilution) with a functional assay sensitivity (lowest value with an interassay coefficient of variation <20%) of <12.0 pmol/l.

Study end points. The CHOPIN primary hypothesis was whether a copeptin level <14 pmol/l on the initial blood draw in combination with cTnI and an electrocardiogram (ECG) would rule out the diagnosis of AMI in patients with symptoms of ACS. For the centralized cTnI values, the 99th percentile (40 ng/l) was used as a cutoff. For copeptin, based on review of the previous literature (5,6), a rule-out cutoff value of 14 pmol/l was pre-specified in the protocol. Additional secondary hypotheses examined the utility of copeptin in the evaluation of ACS. A complete listing of the secondary hypotheses can be found in the Methods section of the Online Appendix.

Statistical analysis. Values are expressed as mean ± SD, non-normally distributed continuous variables are expressed as medians and interquartile range (IQR), or counts and percentages, as appropriate. Group comparisons of continuous variables were performed by using the Student *t* test, analysis of variance models, or the Kruskal-Wallis test, as appropriate. Biomarker data were log-transformed if necessary. Categorical data were compared by using the Pearson chi-square test. All statistical tests were 2-tailed, and a 2-sided p value of 0.05 was considered significant.

For a simple model of time to diagnostic decision of AMI versus no AMI, we assumed that patients with an STEMI (immediate rule-in based on ECG) or negative copeptin and cTnI (immediate rule-out) could be identified within 1 h after presentation, whereas all others would need at least a 3-h interval until the second cTnI could be determined. Average time to decision was calculated by taking the mean time to decision for all patients.

Cox proportional hazards regression was used to analyze the effect of risk factors on survival in univariable and multivariable analyses (7). The assumptions of proportional hazard were tested via scaled Schoenfeld residuals for all variables. None of the variables showed a significant deviation from the proportional hazards assumption. Log-transformed values of copeptin and cTnI were evaluated in a Cox regression model to determine the contribution of copeptin over and above that of cTnI by using the likelihood ratio chi-square test for nested models. The predictive value of each model was assessed by using the model likelihood ratio chi-square statistic. The concordance index (c index) is given as an effect measure. It is equivalent to the concept of area under the curve (AUC) adopted for binary outcomes. For multivariable models, a bootstrap-corrected version of the c index is given. Survival curves plotted according to the Kaplan-Meier method were used for illustrative purposes. Time-dependent receiver-operating characteristic curves and time-dependent AUC values were determined from censored survival data by using the Kaplan-Meier method (8).

According to consensus recommendations, a diagnostically relevant rise or fall in cTnI was defined as a change

>2.77 times the SD from the precision curve of the cTnI assay as reported by the manufacturer (9); that is, a rise or fall was considered positive if there was a change >60% for patients with a maximum cTnI value <20 ng/l, >30% for change of maximum cTnI between 20 and 40 ng/l, and >20% for cTnI >40 ng/l.

The statistical analyses were performed by using R version 2.5.1 (Hmisc and Design Libraries, ROCR, R Foundation for Statistical Computing, Vienna, Austria) and SPSS version 16.0 (IBM SPSS Statistics, IBM Corporation, Armonk, New York).

The data management center (VA San Diego) was responsible for data quality control and statistical analysis. The academic principal investigators of the trial hold an independent copy of the trial database and were able to perform independent statistical analysis.

Results

A total of 2,071 patients were recruited. Of these, 63 presented >6 h after symptom onset, and 8 did not have a gold standard diagnosis documented. Of the remaining, 33 had either a missing copeptin or cTnI value at time of presentation (18 missing each, including 3 missing both). Therefore, our final dataset contained 1,967 eligible patients. Of these, 75% (n = 1,474) presented within 3 h of symptom onset. The final adjudicated diagnosis was STEMI in 40 (2.0%), NSTEMI in 116 (5.9%), unstable angina in 127 (6.5%), cardiovascular non-ACS in 413 (21.0%), a noncardiac diagnosis in 599 (30.5%), and an unclassified cause of chest pain in 672 (34.2%). Concordance between final adjudicated and final ED diagnosis was seen in 96.7% of patients. Follow-up blood samples were available in 1,802 patients at 2 h; 1,464 patients at 6 h; and 567 patients at 24 h. Baseline characteristics are summarized in Table 1.

Copeptin and cTnI by diagnostic categories and time since symptom onset. Median cTnI and copeptin concentrations at time of presentation were higher in patients with AMI (0.181 vs. 0.003 μg/l for cTnI and 19.9 vs. 9.2 pmol/l for copeptin; both $p < 0.001$, Kruskal-Wallis). Copeptin levels were elevated in STEMI and NSTEMI patients who had normal cTnI values at the time of presentation (cTnI <40 ng/l, 99th percentile): median copeptin concentration in initial cTnI-negative STEMI patients was 129.2 pmol/l (IQR: 33.4 to 184.4; n = 13); in NSTEMI, it was 17.8 pmol/l (IQR: 8.1 to 28.8; n = 19). In patients with other diagnoses, it was 8.7 pmol/l (IQR: <5 to 16.2; n = 1,627). For patients with elevated cTnI at presentation, median values were 23.0 pmol/l (IQR: 9.5 to 136.5; n = 27), 17.4 pmol/l (IQR: 8.4 to 60.9; n = 97), and 14.9 pmol/l (IQR: 8.2 to 42.7; n = 184) for STEMI, NSTEMI, and other diagnosis, respectively (Fig. 1).

Figure 2 displays the median values of copeptin and cTnI for time since symptom onset according to main diagnosis (AMI vs. other), combining all data available from the blood draws at time of presentation, and at 2, 6, and 24 h later. Although copeptin levels slowly decreased with increasing time from symptom onset, cTnI levels rose, with a peak at 8 to 10 h. Median values for patients without AMI stayed flat for both copeptin and cTnI.

Primary hypothesis: rule out AMI by using copeptin and cTnI. Figure 3 illustrates the combined performance of first ECG plus cTnI and copeptin measured at time of presentation. For patients with a nondiagnostic ECG (i.e., those without STEMI), initially normal cTnI (<99th percentile/<40 ng/l), and negative copeptin (<14 pmol/l) (n = 1,143 [58%]), the negative predictive power (NPV) was 99.2% (95% confidence interval [CI]: 98.5 to 99.6). The positive predictive power (PPV) for patients with either elevated cTnI or copeptin (n = 784) was 13.6% (95% CI: 11.4 to 16.2). Sensitivity for the dual marker combination was 92.2% (95% CI: 85.9 to 95.9), and specificity was 62.6% (95% CI: 60.4 to 64.8). Ten of the 19 NSTEMI patients (53%) who did not have an elevated cTnI at the time of presentation were copeptin positive.

Negative copeptin at presentation in combination with a negative cTnI ruled out 58% of all patients without need for a second blood draw. Assuming a 3-h interval until the second cTnI could be determined, the addition of copeptin to the initial cTnI and ECG would reduce the time to decision for AMI diagnosis from an average of 2.96 to 1.80 h (43%).

Figure 4 illustrates the incremental value of copeptin in groups stratified based on the physician estimate of AMI probability after the first cTnI result was available. Low risk was defined as a value of 0% to 5%, intermediate risk from 5% to 25%, and high risk as >25%. Bars in the graphic represent the observed risk of AMI in the study. Of 466 patients deemed intermediate risk by emergency physicians according to VAS assessment, 294 (63%) had a copeptin level <14 pmol/l. For this group, the AMI risk was significantly lower compared with that of patients with copeptin levels >14 pmol/l (2.0% vs. 9.3%; $p < 0.01$), and the AMI risk was comparable to that of VAS low-risk patients (observed AMI risk 2% for both: 16 of 816 for the low-risk group and 6 of 294 for the intermediate-risk group with AMI). The NPV for patients with a negative copeptin and negative cTnI value in patients with VAS <25% was 99.6%, and for patients with VAS <5%, it was 99.8%. These data suggest that a low copeptin level is associated with low risk even if physicians think that AMI is possible with a pretest likelihood of up to 25%.

Diagnosis after second cTnI sample. To better understand the added value of copeptin, we examined the overall performance of cTnI at time of presentation, of cTnI 6 h later, and of first ECG when used per guideline recommendations. This performance was compared with that of the same algorithm but also including copeptin measured at time of presentation for early rule out. A patient was defined as "serial cTnI positive" if a rise or fall in cTnI between the time of presentation and 6 h later was observed (see Methods for details), and the cTnI value was >99th percentile on at least 1 occasion. All other patients were counted as "serial

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Table 1 Patient Characteristics According to AMI Diagnosis

Variables	N valid	All Patients	No AMI (n = 1,811*)	AMI (n = 156*)	p Value
Demographics					
Male	1,967	1,118 (56.8)	1,001 (55.3)	117 (75)	<0.0001
Hispanic ethnicity	1,959	106 (5.4)	98 (5.4)	8 (5.1)	1.0000
Race	1,967				0.2664
Asian		47 (2.4)	44 (2.4)	3 (1.9)	
Black		766 (38.9)	716 (39.5)	50 (32.1)	
White		1,024 (52.1)	931 (51.4)	93 (59.6)	
Other/unknown		130 (6.6)	120 (6.6)	10 (6.4)	
Age (yrs)	1,967	56.4±12.8	56 ± 12.8	61.6 ± 11.4	<0.0001
Vital signs at presentation					
Heart rate (beats/min)	1,962	81.3 ± 19.1	81.1 ± 19.1	83.8 ± 19.7	0.0941
Temperature (°C)	1,841	36.6 ± 0.4	36.6 ± 0.4	36.6 ± 0.5	0.7666
Systolic BP (mm Hg)	1,960	142.3 ± 26.9	142 ± 26.6	145.5 ± 30.3	0.0886
Diastolic BP (mm Hg)	1,960	80.6 ± 16.1	80.3 ± 15.8	84 ± 19.1	0.0094
Respiratory rate (per min)	1,955	18.5 ± 3.5	18.4 ± 3.3	19.5 ± 5.1	0.0032
Pulse (beats/min)	1,942	97.9 ± 2.9	97.9 ± 2.8	97.7 ± 3.8	0.9790
BMI (kg/m^2)	1,824	30.7 ± 7.7	30.8 ± 7.9	29.8 ± 6.2	0.2214
Ischemic equivalents					
Symptoms at presentation	1,960	1,579 (80.6)	1,449 (80.2)	130 (84.4)	0.2431
Time since symptom onset (h)	1,950	2.1 ± 1.4	2.1 ± 1.4	2.1 ± 1.4	0.8007
Time since symptom onset 3–6 h	1,950	476 (24.4)	438 (24.4)	38 (24.8)	0.9219
Symptom onset, sudden	1,904	1,409 (74)	1,306 (74.4)	103 (69.6)	0.2055
Symptoms occurrence, intermittent	1,885	866 (45.9)	806 (46.4)	60 (40.5)	0.1974
Symptom duration	1,848				0.2004
<2 min		101 (5.5)	98 (5.8)	3 (2)	
2–10 min		248 (13.4)	229 (13.5)	19 (12.8)	
10–30 min		288 (15.6)	267 (15.7)	21 (14.2)	
>30 min		1,211 (65.5)	1,106 (65.1)	105 (70.9)	
Physical examination					
Bilateral rales	1,929	83 (4.3)	73 (4.1)	10 (6.5)	0.2091
Wheezing	1,937	101 (5.2)	93 (5.2)	8 (5.2)	1.0000
S3	1,881	43 (2.3)	36 (2.1)	7 (4.6)	0.0779
Cardiac risk factors					
Hypertension	1,956	1,366 (69.8)	1,248 (69.3)	118 (76.1)	0.0830
CAD family history	1,512	685 (45.3)	625 (44.8)	60 (51.7)	0.1740
Diabetes mellitus	1,959	565 (28.8)	502 (27.8)	63 (40.4)	0.0012
Tobacco	1,966				0.0020
Current		651 (33.1)	600 (33.1)	51 (32.7)	
Ever		484 (24.6)	428 (23.6)	56 (35.9)	
Never		831 (42.3)	782 (43.2)	49 (31.4)	
Hypercholesterolemia	1,894	1,059 (55.9)	960 (54.9)	99 (68.3)	0.0017
Cocaine	1,959				0.6007
Current		125 (6.4)	118 (6.5)	7 (4.5)	
Ever		187 (9.5)	171 (9.5)	16 (10.3)	
Never		1,647 (84.1)	1,514 (84)	133 (85.3)	
Renal insufficiency	1,699	140 (8.2)	124 (7.9)	16 (12.3)	0.0947
AMI	1,929	538 (27.9)	478 (26.9)	60 (38.7)	0.0027
CAD	1,927	741 (38.5)	655 (36.9)	86 (56.2)	<0.0001
Revascularization	1,936	575 (29.7)	513 (28.8)	62 (40.8)	0.0029
Heart failure	1,941	332 (17.1)	305 (17.1)	27 (17.6)	0.8235
COPD	1,948	212 (10.9)	191 (10.6)	21 (13.6)	0.2793
Ventricular tachycardia	1,931	60 (3.1)	54 (3)	6 (4)	0.4623
Cardiac arrest	1,954	56 (2.9)	50 (2.8)	6 (3.9)	0.4461
Atrial fibrillation	1,933	192 (9.9)	179 (10.1)	13 (8.5)	0.6721
Peripheral vascular disease	1,930	109 (5.6)	92 (5.2)	17 (11.1)	0.0053
Stroke	1,958	195 (10)	177 (9.8)	18 (11.7)	0.4822
AICD pacemaker	1,963	143 (7.3)	133 (7.4)	10 (6.4)	0.7502

Continued on the next page

Table 1 Continued

Variables	N valid	All Patients	No AMI (n = 1,811*)	AMI (n = 156*)	p Value
Medications being taken at home					
Aspirin	1,884	892 (47.3)	811 (46.8)	81 (54)	0.1051
Clopidogrel	1,883	303 (16.1)	272 (15.7)	31 (20.7)	0.1311
Warfarin	1,884	151 (8)	147 (8.5)	4 (2.7)	0.0075
Beta-blocker	1,883	791 (42)	722 (41.7)	69 (46)	0.3024
ACE inhibitor	1,882	800 (42.5)	733 (42.3)	67 (44.7)	0.6058
Calcium channel blocker	1,882	384 (20.4)	354 (20.4)	30 (20)	1.0000
Statins	1,883	814 (43.2)	737 (42.5)	77 (51.3)	0.0393
Diuretics	1,884	556 (29.5)	517 (29.8)	39 (26)	0.3517
Digoxin	1,884	50 (2.7)	47 (2.7)	3 (2)	0.7936
Aldosterone inhibitor	1,883	24 (1.3)	24 (1.4)	0 (0)	0.2527
Antiarrhythmic agents	1,883	49 (2.6)	47 (2.7)	2 (1.3)	0.4271
Analgesics	1,884	551 (29.2)	516 (29.8)	35 (23.3)	0.1115
Nitroglycerine	1,884	428 (22.7)	395 (22.8)	33 (22)	0.9191
Antibiotics	1,884	80 (4.2)	76 (4.4)	4 (2.7)	0.4020
Biomarker (median [IQR])					
Copeptin (pmol/l)	1,967	9.7 [2.5–19.0]	9.2 [2.5–17.2]	19.9 [9.2–63.5]	<0.0001
cTnI (ng/l)	1,967	3 [3–18]	3 [3–13]	181 [55–825]	<0.0001

Values are mean ± SD, median [25%–75% percentile], or n (%) and compared with Student *t* test, Kruskal-Wallis rank sum test, or the Pearson chi-square test (categorical variables). *Actual total number by diagnostic subgroup may be lower for variables with missing data.

AICD = automated implantable cardioverter-defibrillator; ACE = angiotensin-converting enzyme; AMI = acute myocardial infarction; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; cTnI = cardiac troponin I; IQR = interquartile range.

cTnI negative." Patients diagnosed with STEMI were considered correctly diagnosed. Using this cTnI plus ECG approach resulted in an NPV of 97.5% (95% CI: 96.5 to 98.3; 32 false-negative findings for NSTEMI), and a PPV of 62.1% (95% CI: 54.4 to 69.2). Adding copeptin to this algorithm provided a similar NPV of 97.3% (95% CI: 96.2 to 98.1; 35 false-negative finding for NSTEMI [p = 0.75]) and a PPV of 64.8% (95% CI: 56.9 to 72.0; p = 0.68) (Table 2). Outcome of both diagnostic procedures differed for only 12 patients (9 additionally correct and 3 additionally wrong using the algorithm including copeptin; p = 0.14, McNemar's chi-square test).

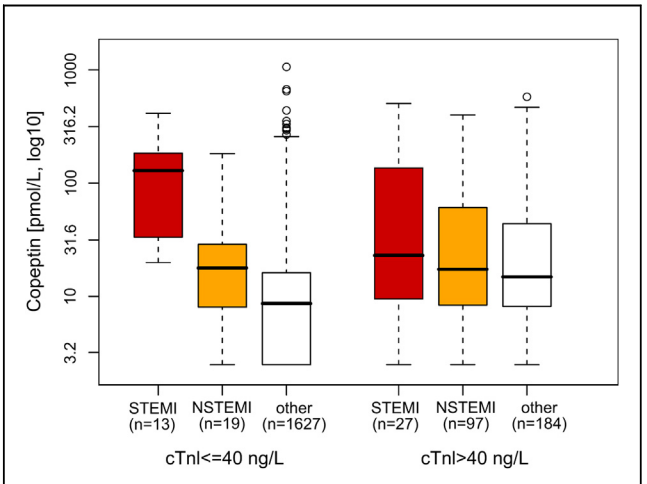

Figure 1 Box Plot of Copeptin by cTnI>/<99th Percentile and GSD

cTnI = cardiac troponin I; GSD = gold standard diagnosis; NSTEMI = non–ST elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction.

The main reason for the relatively high rate of false-negative findings for the serial cTnI algorithm was that the rise or fall of cTnI was not observable while looking at 0- and 6-h data only; that is, the cTnI change was apparent only if all available blood draws were included (n = 21). For the 11 remaining false-negative results, differences between local laboratory results and cTnI were responsible: for the majority (n = 7), small absolute differences around the 99th percentiles between the local laboratory results (used for gold standard diagnosis) and central laboratory results (used for evaluation) were responsible. For 4 patients, no obvious reason could be identified.

In total, 503 patients were without a cTnI value at 6 h. Of those, 10 were diagnosed with STEMI (2%) and 6 with NSTEMI (1%). The proportion of STEMI was therefore comparable to that in the overall population (2%), whereas the proportion of NSTEMI was substantially lower (6% of all patients). Of the 1,464 patients with a cTnI value at 6 h, 30 were diagnosed with STEMI (2%) and 110 with NSTEMI (7.5%). The proportion with STEMI was therefore comparable to that in the overall population (2%), whereas the proportion with NSTEMI was slightly higher (6% of all patients). Therefore, missing values of cTnI at 6 h seem to be due to both early rule-out (low NSTEMI rate) and rule-in (equal STEMI rate), as well as missing at random (NSTEMIs did occur, and data at other time points were available: 376 of 503 had a nonmissing cTnI at 2 h; 58 of 503 had a nonmissing cTnI at 24 h).

All-cause mortality within 180 days. At the 180-day follow-up, 36 patients had died (1.8%; estimated 180-day

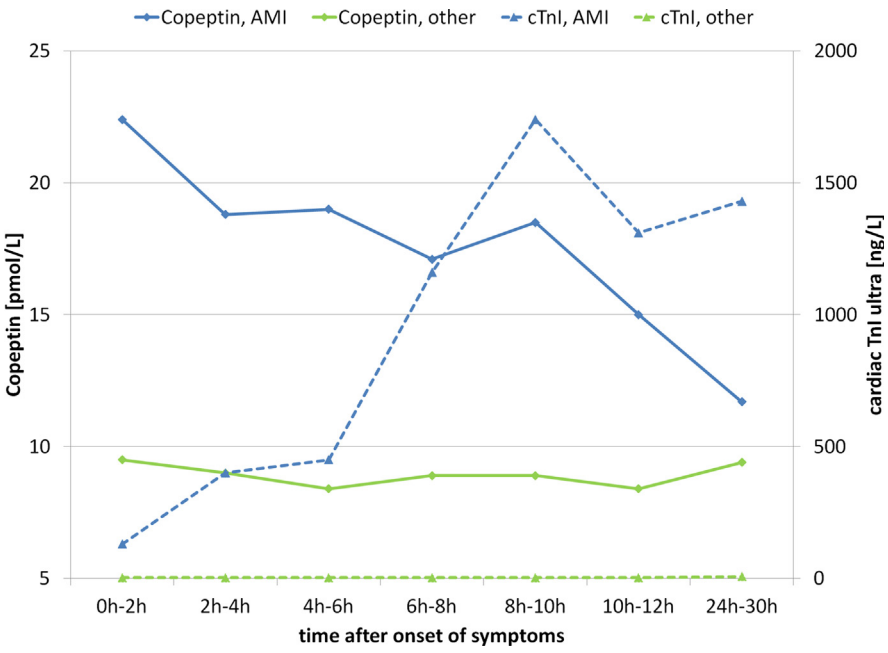

Figure 2 **Biomarker Kinetics by AMI Diagnosis**

Median copeptin **(solid lines)** and cTnI **(dashed lines)** concentrations by time since symptom onset and GSD (acute myocardial infarction [AMI] in **blue**, patients diagnosed with other disease in **green**). Analysis based on data from blood draws at 0, 2, 6, and 24 h. Other abbreviation as in Figure 1.

survival rate 98.1% [95% CI: 97.4 to 98.7]). Median copeptin and cTnI concentrations were lower in patients who survived compared with those who died (9.5 pmol/l [IQR: <5 to 18.4] vs. 45.8 pmol/l [IQR: 15.8 to 102.5] for copeptin and <3 ng/l [IQR: <3 to 17] vs. 50 ng/l [IQR: 20 to 140] for cTnI; both $p < 0.0001$).

Both abnormal copeptin and cTnI levels were predictors of death (chi-square test 39.4 and 33.7, respectively

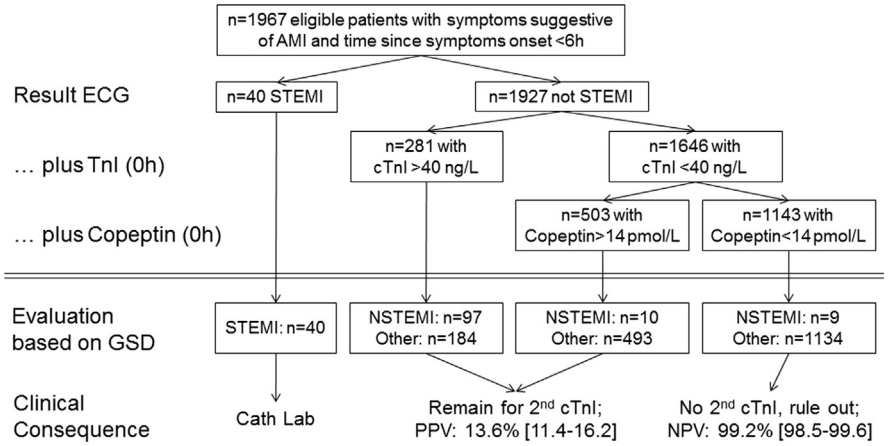

Figure 3 **Primary Endpoint**

Patient distribution according to initial electrocardiogram (ECG), cTnI (cutoff 99th percentile; 40 ng/L), and copeptin (cutoff 14 pmol/L) status at presentation (0 h). Assuming that STEMI patients will be identified by using ECG, sensitivity was 92.2% (95% confidence interval [CI]: 85.9 to 95.9) and specificity was 62.6% (95% CI: 60.4 to 64.8) to identify NSTEMI patients. Therefore, negative predictive value (NPV) for copeptin levels <14 pmol/L and cTnI levels <40 ng/L is 99.2% (95% CI: 98.5 to 99.6). The positive predictive value (PPV) for patients with a positive cTnI or positive copeptin for NSTEMI is 13.6% (95% CI: 11.4 to 16.2). In absolute numbers, 10 (53%) of 19 NSTEMI patients with a negative cTnI value have an elevated copeptin value. For a final diagnosis of AMI, patients either cTnI or copeptin positive are assumed to undergo a second cTnI measurement. Conversely, patients negative for both copeptin and cTnI are assumed to be ruled out of having an AMI. Other abbreviations as in Figures 1 and 2.

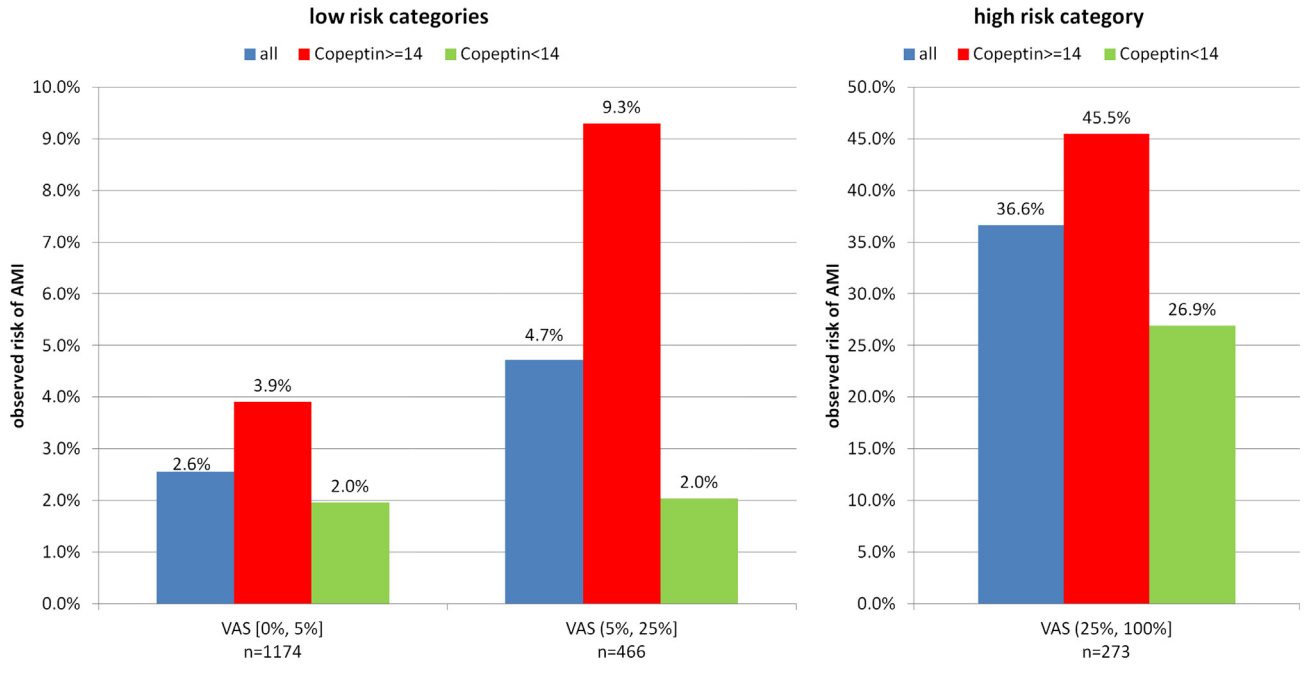

Figure 4 Addition of Copeptin to VAS

Visual analog scale (VAS) scores reflect the estimated risk for AMI determined in the emergency department after the first cTnI measurement. VAS scores were categorized as low risk (0% to 5%), intermediate risk (5% to 25%), and high risk (>25%). **Bars** represent observed risk of AMI in the study. Of 466 patients with VAS 5% to 25%, 294 (63%) had a copeptin level <14 pmol/l and an AMI risk comparable to that of patients with VAS 0% to 5% (observed AMI risk 2% for both). Other abbreviations as in Figures 1 and 2.

[$p < 0.0001$ for both]; c index 0.784 and 0.800, respectively). Both were independent of age and each other, and provided additional predictive value (all $p < 0.0001$). Copeptin and cTnI combined (as continuous variables) resulted in a chi-square test of 59.2 and a c index of 0.842 ($p < 0.0001$). Figure 5 illustrates the added value of copeptin with cTnI. Copeptin was particularly strong for short-term prediction of death. For outcome prediction at 30 days (n = 13 deaths; survival rate 99.3%), copeptin was associated with outcome, with a chi-square test of 29.2 and a c index of 0.872, and cTnI had a chi-square test of 13.7 and a c index of 0.828. Both markers were independent of each other and combining them provided significant added value ($p = 0.01$ for added value of cTnI, $p < 0.0001$ for added value of copeptin) (Fig. 6).

Discussion

The early differential diagnosis of acute chest pain is 1 of the major clinical challenges in the ED. Although it is mandatory to correctly identify those patients with AMI, the vast majority of patients presenting with the symptoms suggestive of ACS do not have AMI. In CHOPIN, 1 of the largest multicenter studies on consecutive patients with chest pain, only approximately 8% had a final gold standard

Table 2 Summary of the Primary Hypothesis: the Diagnostic Performance of the Current Guideline (no rule out at 0 h) Versus a Negative Troponin in Conjunction With a Negative Copeptin for Early Rule Out

	Performance Based on First Blood Draw (plus ECG)			Performance of Full Diagnostic Procedure (after second blood draw)		
NSTEMI Prediction	Guideline (no rule out)	Troponin Negative	Negative Troponin and Copeptin	Guideline	Troponin Negative	Negative Troponin and Copeptin
NPV	–	98.8	99.2	97.5	96.8	97.3
Sensitivity	–	79.5	92.2	77.1	70.0	75.0
PPV	–	34.5	13.6	62.1	68.1	64.8
Specificity	–	89.8	62.6	95.0	96.5	95.7
False- negative NSTEMI (n)	–	19	9	32	42	35
Total rule out, t = 0 h (%)	0 (0%)	1,658 (84%)	1,143 (58%)	0 (0%)	1,658 (84%)	1,143 (58%)

For comparison, we also included results for early rule out based on a negative cTnI at 0 h. First, we focused on the safety of the early rule out (results based on first draw); second, we compared the performance of the full diagnostic procedures (after second blood draw). Negative predictive value (NPV), sensitivity, positive predictive value (PPV), and specificity are shown for this combination on both the first draw and with serial troponin draws. Patients diagnosed as having ST-segment elevation myocardial infarction were considered correctly diagnosed (i.e., diagnostic decision was based on electrocardiogram [ECG] only, and biomarker data were not taken into account for those). Therefore, NPV reflects non–ST elevation myocardial infarction (NSTEMI) results, because ST-segment elevation myocardial infarction can never be incorrect. None of the false-negative rates or the NPVs differed significantly (all $p > 0.1$).

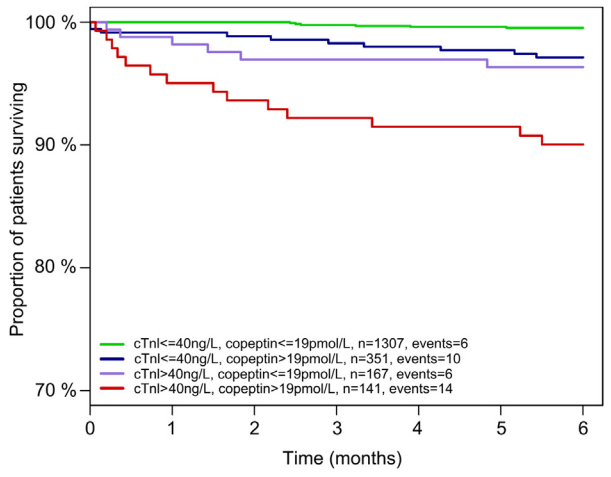

Figure 5 **Kaplan-Meier Plot Illustrating Added Value of Copeptin in Addition to cTnI**

Outcome is all-cause mortality within 180 days after presentation. Cutoff for cTnI was the 99th percentile (40 ng/l); the cutoff for copeptin was third quartile (19 pmol/l). Estimated survival rates were 99.5% (95% CI: 99.0 to 99.8) if both biomarkers were below the cutoff and 90.0% (95% CI: 83.7 to 94.0) if both were above the cutoff. With both copeptin and cTnI negative as reference group, the hazard ratio (HR) for elevated copeptin levels but normal cTnI values was 6.3 (95% CI: 2.3 to 17.2); HR for elevated cTnI but low copeptin was 8.1 (95% CI: 2.6 to 25.1); HR for both biomarkers above the defined cutoff points was 22.7 (95% CI: 8.7 to 59.1) (all $p < 0.01$). Other abbreviations as in Figures 1 and 3.

diagnosis of AMI (STEMI and NSTEMI), whereas >60% had a noncardiac origin of their symptoms. According to current guidelines, the management of suspected ACS involves serial troponin measurements and monitoring over many hours, which is a logistic challenge and a financial burden for already overcrowded EDs and hospitals.

If the ED physicians follow the current guideline recommendations, all patients with a nondiagnostic ECG require an ED stay of at least 3 to 6 h or admission to the hospital to rule out an AMI. The present study shows that adding copeptin allowed 58% of all patients with nondiagnostic ECG to be ruled out for an AMI, whereas the number of undetected AMI cases only increased by 0.2% (from 32 to 35 of 1,967 patients). Assuming a 3-h delay before the second cTnI is determined, the availability of copeptin at baseline would reduce the time to decision for AMI diagnosis from an average of 3 to 1.8 h (43% reduction). The clinical benefit seems to be most prominent in those patients with an intermediate risk of AMI (5% to 25%), as assessed by ED physicians. A low copeptin level in these patients (<14 pmol/l) identifies a subset with a risk comparable to those who present with a low pretest probability (<5%) for AMI. There is particular synergism between a low pretest probability of AMI and nonelevated copeptin values. Most (72%) of the AMIs detected who had normal copeptin values were in those who were not low risk. Copeptin is the glycosylated, 39-amino-acid-long C-terminal part of pro-AVP and is released together with AVP during precursor processing. In contrast to AVP, copeptin is very stable in the serum or plasma at room temperature, and is easy and robust to measure (2). An increase in copeptin concentrations after AMI was first reported by Khan et al. (4), with the highest values reported on day 1 and a subsequent decline over the next 2 to 5 days. Copeptin concentrations were higher in patients who died or were readmitted with heart failure compared with event-free survivors. This finding led to 2 independent studies examining the potential role of copeptin in the diagnosis of AMI. The first, by Reichlin et al. (5), evaluated the contribution of copeptin to the management of 487 consecutive patients with chest pain presenting to the ED. In those patients with the final gold standard diagnosis of AMI (17%), copeptin concentrations were already elevated 4 h after the onset of symptoms, at a time when troponin T was still undetectable in many patients. As copeptin concentrations declined, and troponin concentrations increased, these distinct kinetics resulted in an additive value of both markers for the diagnosis of AMI. The AUC of troponin alone in the first blood sample taken in the ED was 0.86, and increased to 0.97 by adding copeptin. Using this double marker approach, a negative troponin and copeptin <14 pmol/l at presentation allowed AMI to be ruled out, with an NPV >99%. A second study confirmed these findings and demonstrated that the combined measurement of copeptin and troponin T in the first blood sample improved the c index from 0.85 for troponin

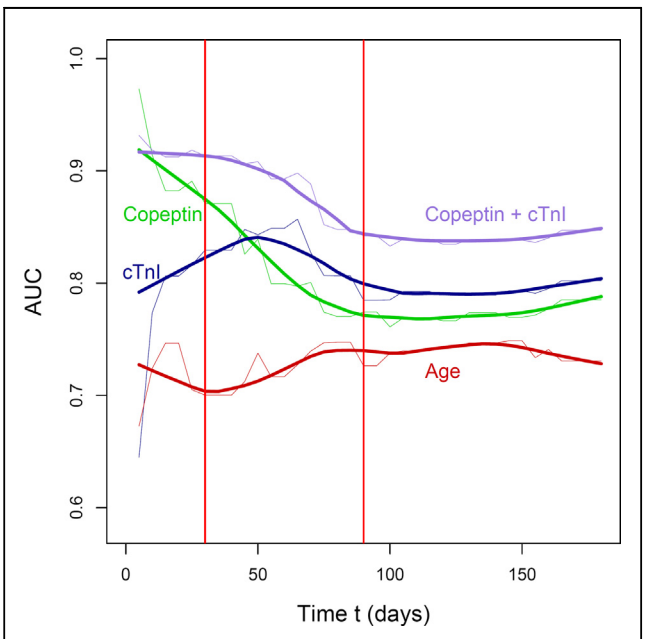

Figure 6 **Time-Dependent AUC for Survival to 180 Days**

Area under the receiver-operating characteristic curve (AUC) for survival to 90 days for copeptin **(green)**, cTnI **(blue)**, age **(red)**, and the combination of copeptin and cTnI **(purple)**. Curves smoothed by a locally weighted polynomial regression; **horizontal lines** at 30 and 90 days after presentation. Time-dependent receiver-operating characteristic curves and time-dependent AUC values were determined from censored survival data by using the Kaplan-Meier method. Copeptin was particularly strong for short-term mortality prediction (<30 days), whereas cTnI was stronger for long-term outcome prediction (>60 days).

T alone to 0.94 for a combination of copeptin and troponin T (6). The effect was particularly prominent in patients presenting within 3 h after symptom onset. In this group, the combination increased the c index from 0.77 to 0.91. Gu et al. (10) have demonstrated that copeptin peaks within the first hour after symptom onset, falling to normal ranges within the first day.

CHOPIN is the first evaluation of copeptin in a US cohort of a trial prospectively designed with predefined cutoff points to specifically evaluate NPV for rule out of NSTEMI. In addition, CHOPIN is the largest trial of this type to date. This large, multicenter trial confirms that the combination of a negative troponin and negative copeptin value on presentation allows the rule out of AMI with an NPV >99%. It is important to remember that a large part of the NPV is contributed by troponin. Thus, using an analytically sensitive troponin assay, in combination with copeptin, will likely lead to an even higher NPV than the less sensitive troponin assay used here. Other reports on a direct comparison of high-sensitive troponin assays and copeptin confirm the additive effect reported in this study (11). This is true for patients presenting early after symptom onset, and it is likely that this added benefit of copeptin may be lost for patients who present late. Although copeptin is a relatively new biomarker, it is an excellent surrogate for AVP, which has been shown to also be elevated in AMI (12,13). However, based on the complexity of AVP measurements, this observation has never been clinically relevant for diagnosis. In a sheep model of AMI, the peak response of AVP occurred at 40 min after embolization, and AVP was elevated for >12 h (14). But despite the very early rise of AVP (and other hormones related to stress response), none of these markers was followed up as a potential candidate for the diagnosis of AMI due to severe limitations in the measurement of these hormones. Neither AVP nor adrenocorticotropic hormone is available as a rapid and sensitive assay that would allow a fast enough "vein-to-brain time" to influence the early ED diagnosis. Although cortisol measurements are readily available, diurnal variation makes them of less value.

There are several hypotheses to explain the rapid release of AVP/copeptin after AMI. A likely explanation is that AVP responds rapidly as part of the endocrine stress axis, resulting in release of adrenocorticotropic hormone and cortisol. Copeptin is believed to be a rapid and immediate biomarker of the individual stress response (15). An alternative trigger of AVP/copeptin secretion from the posterior pituitary could be baroreceptor stimulation by the threat of hypotension as a result of the AMI or direct damage to the cardiac baroreceptors. The latter possibility is supported by the fact that the highest copeptin elevation after AMI is seen in patients with STEMI (5). Because copeptin is elevated in many clinical states in which endocrinologic stress signals are present, it will have low specificity for an individual disease such as myocardial infarction, however; because myocardial infarctions present with activation of the hypothalamic stress axis, copeptin biomarkers demonstrate good sensitivity for the disease state.

A second important result of the present study is the prognostic role of copeptin. Voors et al. (16) demonstrated that copeptin is a strong marker for mortality and morbidity in patients with heart failure after AMI. Kelly et al. (17) reported an association of copeptin with the degree of left ventricular remodeling after AMI. These observations were strengthened by the increased risk of elevated copeptin concentrations and clinical heart failure in those patients. This risk stratification at an early stage after AMI remains important and may be useful for selecting treatment regimens in the future, such as the use of AVP receptor antagonists (the "vaptan" class of drugs). Reports on these drugs have been conducted for congestive heart failure (18,19), but no study has yet examined the use of vaptans in humans after AMI. Only animal data are available on the improved cardiac hemodynamics after administration of conivaptan (20). In addition, these data suggest that even if AMI is excluded, some scrutiny to determine the etiology of the elevated copeptin level is likely warranted.

The independent prognostic information provided by applying copeptin and troponin values was also seen in a recent study of patients with heart failure treated in an outpatient clinic (21). This study found that copeptin and cardiac troponin T elevations, alone and in combination, are powerful predictors of death and hospitalization. The investigators suggest that simultaneous assessment of myocardial damage and the activated vasopressin system might be of prognostic relevance. The prognostic role of copeptin in congestive heart failure has been reported by others as well (22–25).

Study limitations. Our data confirmed that copeptin may have clinical value if the early rule out of AMI is operationally of benefit to the clinicians or hospital. However, if the resources in a given institution are not limiting, then the value of the time saved by more rapid diagnosis provided by copeptin may be marginal. Whether the more expedient rule out of AMI can improve the diagnostic performance for other diseases in the differential diagnosis is beyond the scope of the present report and would likely need to be demonstrated in an interventional study. Due to the broad heterogeneity of non-AMI diagnoses in patients presenting with chest pain, this might be very difficult to demonstrate in a trial. Copeptin seems to provide added predictive value on top of cTn, particularly for short-term prognosis. However, the clinical relevance of this prognostic information remains to be demonstrated. A significant proportion of patients had no second blood draw to determine troponin levels as required by the guideline. Therefore, there is the potential risk that this may bias the results evaluating serial blood draws. Finally, the present analysis does not evaluate copeptin in relation to a highly sensitive cTn with greater precision around the rule-out cutoff. This may change the added benefit of copeptin.

Conclusions

This large multicenter trial suggests that the combination of copeptin and troponin at the time of presentation provides an NPV strong enough to avoid serial testing past 3 h and hence improves medical decision making in patients with chest pain presenting to the ED. Future research should investigate the cost savings to EDs through use of such a strategy.

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The authors dedicate this paper to the memory of our CHOPIN investigative colleague, Dr. Jana Papassotiriou, who died unexpectedly and prematurely before the trial results could be published.

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Key Words: copeptin ■ emergency department ■ myocardial infarction ■ quality improvement ■ troponin.

APPENDIX

For a detailed description of the study population and protocol, please see the online version of this article.