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Copeptin Does Not Add Diagnostic Information to High-Sensitivity Troponin T in Low- to Intermediate-Risk Patients with Acute Chest Pain: Results from the Rule Out Myocardial Infarction by Computed Tomography (ROMICAT) Study

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PURPOSE: Copeptin, a stable peptide derived from the AVP precursor, has been linked to presence and severity of myocardial ischemia. We sought to evaluate the predictive value of copeptin and its incremental value beyond that of high-sensitivity cardiac troponin T (hs-cTnT) in patients with acute chest pain and low to intermediate risk for acute coronary syndrome (ACS).

METHODS: We recruited patients who presented with acute chest pain to the emergency department and had a negative initial conventional troponin T test (<0.03 μg/L). In all patients, hs-cTnT and copeptin measurements were taken. Each patient also underwent cardiac computed tomography (CT) and coronary angiography.

RESULTS: Baseline copeptin concentrations, in contrast to hs-cTnT, were not significantly higher in patients with ACS than in those without ($P = 0.24$). hs-cTnT showed an earlier rise in patients with ACS than copeptin, when analyses were stratified by time. A copeptin concentration $\geq$7.38 pmol/L had a negative predictive value (NPV) of 94% and a sensitivity of 51%, whereas hs-cTnT ($\geq$13.0 pg/mL) had a NPV of 96% and a sensitivity of 63%. The combination of copeptin and hs-cTnT resulted in a lower diagnostic accuracy than hs-cTnT alone. Finally, on cardiac CT, copeptin concentrations were not associated with coronary artery morphology, although they were related to the presence of left ventricular dysfunction ($P = 0.02$).

CONCLUSIONS: Among patients with acute chest pain and low to intermediate risk for ACS, copeptin concentrations are not independently predictive of ACS and do not add diagnostic value beyond that of hs-cTnT measurements.

A substantial proportion of patients presenting to the emergency department (ED)[6] with acute chest discomfort have normal electrocardiograms (ECGs) and initially reassuring conventional cardiac troponin concentrations, but still subsequently develop myocardial infarction (MI) *(1)*. Because early-invasive strategies for acute coronary syndrome (ACS) management have been shown to be associated with significantly better patient outcome in higher-risk patients, additional biochemical measures for diagnosis and initial risk stratification of patients presenting with chest pain are needed *(2)*.

The role of the antidiuretic and vasoconstricting hormone arginine-vasopressin (AVP) in myocardial ischemia is still unclear. Copeptin, the C-terminal part of the AVP prohormone, is a stable peptide derived from the AVP precursor, thereby monitoring AVP levels *(3)*. Secretion of copeptin is prompted by individual stress and seems to mirror moderate levels of stress even more subtly than cortisol *(4)*. Copeptin concentrations are associated with measures of insulin resistance and metabolic syndrome in hypertensive adults

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[6] Nonstandard abbreviations: ED, emergency department; ECG, electrocardiogram; MI, myocardial infarction; ACS, acute coronary syndrome; AVP, arginine-vasopressin; cTnT, cardiac troponin T; hs, high-sensitivity; CT, computed tomography; CTA, CT angiography; UAP, unstable angina pectoris; AHA, American Heart Association; ACC, American College of Cardiology; CRP, C-reactive protein; AUC, area under the curve; NRI, net reclassification index; TIMI, Thrombolysis in Myocardial Infarction; CAD, coronary artery disease; BMI, body mass index; NPV, negative predictive value; PPV, positive predictive value; NSTEMI, non–ST-elevation myocardial infarction; APACE, Advantageous Predictors of Acute Coronary Syndromes Evaluation; IQR, interquartile range.

and have been linked to survival in critically ill patients suffering from hemorrhagic and septic shock *(5, 6)*. Furthermore, copeptin has prognostic implications in patients with decompensated heart failure, patients with heart failure after acute MI, and post-MI patients *(7–9)*. These findings suggest the potential of copeptin for diagnostic evaluation of suspected ACS. Whereas conventional cardiac-specific troponin T (cTnT) takes at least 3–6 h to rise to measureable circulating concentrations after myocardial injury, and does not always adequately predict ACS in patients with low to intermediate risk, copeptin concentrations were reported to be increased at baseline in patients who were initially negative for cTnT and detectable within 1–3 h after onset of ischemia *(10, 11)*. Accordingly, we sought to evaluate the predictive value of copeptin in patients with acute chest pain and low to intermediate risk of ACS. We also aimed to analyze the correlation of copeptin concentrations with cardiac structure and function using cardiac computed tomography (CT). In addition, we sought to evaluate the incremental predictive value of copeptin beyond that of the high-sensitivity (hs)-cTnT assay, the Roche fourth-generation cTnT assay, which was recently shown to allow an earlier diagnosis of ACS *(12)*.

Materials and Methods

METHODS

The ROMICAT study was designed to determine the clinical utility of coronary CT angiography (CTA) in patients with acute chest pain. The study was approved by the local ethics committee. Written informed consent was obtained from all participating patients. The study methods have been described in detail *(13)*. Briefly, patients were recruited who presented with acute chest pain to the ED of the Massachusetts General Hospital and had a negative initial conventional cTnT test based on a cutoff of 0.03 μg/L (Roche Diagnostics) and a normal or nondiagnostic ECG on admission. The blood sample for biomarker testing was taken at a median of 4.3 h after the initial presentation. CTA was performed at the same time. In all patients, hs-cTnT measurements were performed by an assay equivalent to an actually available commercial assay (Roche Diagnostics). Copeptin concentrations were determined by a commercial assay (Brahms AG) in the chemiluminescence/coated-tube format *(11)*.

STUDY DESIGN AND POPULATION

Patients presenting to the ED within 24 h after the onset of chest pain of suspected cardiac origin lasting at least 5 min were eligible. Detailed exclusion criteria have been described *(13)*. The institutional review board approved the study protocol, and all patients provided written informed consent. ACS was a combined endpoint including acute MI and unstable angina pectoris (UAP), and was diagnosed according to AHA (American Heart Association), ACC (American College of Cardiology), and European Society of Cardiology guidelines *(14–16)*. The final diagnosis of ACS was made retrospectively based on the judgment of 2 physicians, blinded to the results of copeptin, hs-cTnT, and CT imaging, with access to the history and nature of the presenting symptoms, medical history, results of physical examination, and all of the medical records available from index hospitalization (including the results of standard troponin testing) through 180 days from presentation. Events subsequent to 180 days from enrollment did not influence the final diagnosis. Disagreement in final diagnosis occurred in 4% of cases and was resolved by consensus involving a third reviewer. A total of 377 individuals were enrolled. After excluding those with missing blood samples and missing information, data from 366 individuals formed the basis for the present analyses.

DIAGNOSTIC PROCEDURES

All study participants underwent an initial clinical assessment, including patient history, physical examination, ECG, and standard blood tests. Trained medical staff collected information on sociodemographic variables, smoking habits, and history of CHD through standardized interviews. In addition, all study participants underwent an initial conventional cTnT test (Roche Diagnostics, Elecsys, fourth generation, detection limit 0.01 μg/L, 10% imprecision cutpoint 0.03 μg/L). The interassay CVs were 6.6% and 3.8% at concentrations of 0.07 and 2.2 μg/L, respectively.

CORONARY CTA

At a median of 4.3 h from initial presentation, CT imaging was performed using a 64-slice CT scanner (Sensation 64, Siemens Medical Solutions) *(17)*. Assessment of coronary CTA datasets for the presence of significant coronary stenoses and the presence of coronary atherosclerotic plaque was performed as a consensus reading by 2 experienced investigators blinded to the study participant's clinical presentation and biomarker testing using a modified 17-segment model of the coronary artery tree *(18)*. Furthermore, several structural and functional parameters, such as chamber volume in end-systole and end-diastole, left-ventricular ejection fraction, left ventricular mass, and regional left-ventricular dysfunction, were assessed.

BIOCHEMICAL ANALYSES

Blood for additional biomarker testing was taken at the time of CT angiography. Blood samples were immediately processed and stored at −80 °C. All biomarkers

were analyzed on the first freeze–thaw cycle. C-reactive protein (CRP) concentrations were measured with a high-sensitivity latex-enhanced nephelometric assay on a BN II analyzer (Dade Behring) *(19)*. hs-cTnT measurements were performed with an experimental assay that has since become available commercially (Roche Diagnostics) on an Elecsys 2010 platform. A value of 13 pg/mL has recently been reported to represent the 99th percentile in a healthy reference population *(20)*. The interassay CVs were 3.6% and 2.9% at concentrations of 42 and 2.82 pg/mL, respectively. Copeptin concentrations were determined in a single batch using a novel commercial sandwich immunoluminometric assay (LIA assay, CT-proAVP, Brahms AG), as described in detail *(4)*. The lower detection limit for the test is 0.4 pmol/L, and the functional assay sensitivity is <1 pmol/L. Unlike hs-cTnT, the copeptin assay was evaluated for diagnostic performance by using the ROC-optimized cutpoint in all study participants, and the results in this patient population were clearly better than the 99th percentile obtained in a healthy reference population. Laboratory analyses were done without knowledge of clinical presentation.

STATISTICAL METHODS

We computed means and SDs or proportions for baseline demographic and clinical characteristics. In case of nonnormality, we calculated medians and interquartile ranges. For categorical variables, tests were carried out using asymptotic Pearson χ^2 tests. Associations between continuous variables were performed using Wilcoxon tests or Kruskal–Wallis tests for comparing 2 or more groups. We calculated Spearman correlation coefficients in the cohort sample to assess univariate associations between copeptin, hs-cTnT, and continuous risk factors for CHD. For dichotomous risk factors, we performed logistic regression and obtained the β-coefficient. The diagnostic performance of the copeptin and hs-cTnT assay and their combination were assessed by use of ROC curves, with area under the curve (AUC) as a quality criterion for the diagnostic test exhibiting a range of 0.5–1, where 0.5 mirrors poor performance, i.e., a completely random choice of diagnosis. Furthermore, we evaluated sensitivity and specificity, as well as the positive and negative predictive value, for a copeptin concentration of 7.38 pmol/L (the ROC-optimized cutpoint in all study participants). The extent to which copeptin reassigned individuals to risk categories that better reflected their final outcome was assessed by use of the net reclassification index (NRI) measure *(21)*. For individuals with ACS, risk classification is considered improved if the individual moves to a higher risk category with the addition of copeptin, and worsened if the individual moves to a lower one. For individuals without ACS, the converse is true. In ACS patients, the difference in the proportion of individuals moving up and down a category was calculated, and in patients without ACS, the proportion of individuals moving down minus the proportion moving up a category was calculated. The NRI was obtained as the sum of these 2 values. In all analyses, values exhibiting a P value <0.05 were considered to be statistically significant. All statistical evaluations were performed using the SAS software package (version 9.1 and 9.2, SAS Institute).

Results

In the overall study population, ACS occurred in 35 of 366 patients, of whom 27 had UAP using standard criteria. Baseline demographic, clinical, and laboratory characteristics of the study population are shown in Table 1. According to Thrombolysis in Myocardial Infarction (TIMI) risk score, 89% of the patients were at low risk, whereas 10% were at medium risk. According to Framingham risk score, 63% were at low risk (<10%) and 22% at medium risk (10%–20%). Known coronary artery disease (CAD) was uncommon (n = 44; 12.0%); 37% of the UAP patients (10 of 27), 12.5% of the MI patients (1 of 8), and 10% of the non-ACS patients (33 of 331) had a history of CAD. Individuals with ACS were older and more often male, whereas body mass index (BMI), systolic blood pressure, and smoking status did not differ, comparing cases with noncases. Furthermore, cases more frequently reported hypertension, hyperlipidemia, diabetes, and prior MI. hs-cTnT concentrations were higher in patients with ACS, whereas concentrations of CRP did not differ. Copeptin concentrations were somewhat higher in cases, although the difference did not reach statistical significance. The geometric mean (median) of log copeptin was 7.5 (6.9) pmol/L in cases with UAP, 6.2 (7.4) pmol/L in cases with MI, and 5.0 (4.6) pmol/L in noncases. CT angiography revealed a substantially higher plaque burden and an increased number of vessels with clinically significant stenoses in ACS patients.

Spearman correlation coefficients (r) were calculated between copeptin, hs-cTnT, conventional risk factors, and CRP (see Supplemental Table 1, which accompanies the online version of this article at http://www.clinchem.org/content/vol57/issue8). The β-coefficients for copeptin and hs-cTnT were calculated for dichotomous variables from logistic regression. A weak but statistically significantly increased probability for a history of CAD as well as hypertension with rising copeptin concentrations was seen. Furthermore, a modest positive correlation between copeptin and hs-cTnT was observed ($r = 0.137$, $P = 0.009$), whereas no correlation was found with CRP ($P = 0.760$). hs-cTnT correlated weakly with systolic blood pressure ($r = 0.144$, $P = 0.006$) and strongly with age

Table 1. Baseline characteristics of participants with and without ACS at evaluation.[a]

	UAP	MI	No ACS	*P*
n	27	8	331	
Mean age, years (SD)	64.0 (11.2)	55.3 (10.4)	52.9 (11.7)	<0.001[a]
Male sex, n (%)	21 (77.8)	8 (100.0)	206 (62.2)	0.0276[b]
Diabetes, n (%)	8 (29.63)	0 (0.0)	37 (11.2)	0.0110[b]
Hypertension, n (%)	19 (70.4)	4 (50.0)	131 (39.6)	0.0070[b]
Hyperlipidemia, n (%)	19 (70.4)	3 (37.5)	129 (39.0)	0.0061[b]
Mean BMI, kg/m^2 (SD)	29.42 (4.3)	28.09 (6.0)	28.93 (6.0)	0.52[a]
Mean systolic blood pressure, mmHg (SD)	135.7 (23.4)	138.4 (17.8)	138.6 (22.5)	0.94[a]
Mean diastolic blood pressure, mmHg (SD)	71.5 (13.8)	83.1 (6.2)	80.5 (13.5)	0.0069[a]
Current smoker, n (%)	8 (29.6)	1 (12.5)	82 (24.8)	0.61[b]
History of CAD, n (%)	10 (37.0)	1 (12.5)	33 (10.0)	<0.001[b]
Prior MI, n (%)	7 (25.9)	1 (12.5)	24 (7.3)	0.0040[b]
Computed tomography				
Mean segments with calcified plaques, n (SD)	6.80 (3.46)	5.75 (3.96)	1.74 (3.04)	<0.001[a]
Mean segments with non-calcified plaques, n (SD)	3.76 (3.38)	4.00 (2.73)	0.90 (1.83)	<0.001[a]
Mean segments with any plaque, n (SD)	7.72 (3.42)	6.38 (4.03)	2.01 (3.22)	<0.001[a]
Mean segments with significant stenosis, n (SD)	1.40 (1.50)	1.25 (1.67)	0.10 (0.43)	<0.001[a]
Mean vessels with plaque, n (SD)	3.08 (1.00)	2.75 (1.16)	1.06 (1.37)	<0.001[a]
Mean vessels with significant stenosis, n (SD)	0.88 (0.97)	1.00 (0.93)	0.07 (0.31)	<0.001[a]
Mean left ventricular mass, g/m^2 (SD)	161.3 (44.1)	160.7 (25.5)	150.3 (42.6)	0.39[a]
Mean left ventricular ejection fraction, % (SD)	64.7 (13.9)	63.1 (8.7)	67.3 (9.8)	0.42[a]
Regional left ventricular dysfunction, n (%)	18 (66.7)	8 (100.0)	33 (10.4)	<0.001[b]
Median hs-cTnT, pg/mL (IQR)	16.2 (44.7)	118.0 (117.2)	5.1 (5.6)	<0.001[a]
Median CRP, mg/L (IQR)	2.2 (3.0)	0.91 (2.3)	1.3 (2.2)	0.38[a]
Median copeptin, pmol/L (IQR)	7.5 (6.9)	6.2 (7.4)	5.0 (4.6)	0.24[a]

[a] Kruskal–Wallis test for continuous variables.
[b] Symptotic Pearson χ^2 test for categorical variables.

($r = 0.362$, $P < 0.001$), while again no association was found with CRP ($P = 0.228$).

As Table 2 shows, concentrations of copeptin were not associated with characteristics of coronary CT angiography and global left-ventricular ejection fraction, when stratified for the ROC-optimized cutpoint 7.38 pmol/L (calculated for all patients, n = 366), although in patients with increased copeptin concentrations, a significantly increased rate of regional left-ventricular dysfunction was found. In total, 68 patients had stenosis >50%, of whom 44 (65%) were called not ACS. The ROC-optimized cutpoint performed clearly better than the 99th percentile in a healthy reference population (data not shown).

Table 3 summarizes the diagnostic performance of copeptin. A copeptin concentration below the ROC-optimized cutpoint 7.38 pmol/L would have correctly ruled out ACS 4 h after presentation in the ED, with a negative predictive value (NPV) of 94%, but a low sensitivity of 51%, an acceptable specificity of 74%, and a low positive predictive value (PPV) of 18%. Using the 99th, 97.5th, or 95th percentile values of our cohort, the NPVs were 91.1%, 91.0%, and 90.8% (corresponding PPVs: 60%, 30%, and 15%), respectively, and therefore lower than calculated with the ROC-optimized cutpoint (data not shown). By comparison, hs-cTnT, using the 99th percentile in a healthy population (13 pg/mL), would have correctly ruled out ACS in 96%, with a sensitivity of 63% and a specificity of 88%, and a PPV of 36%.

Owing to the clinical standard of 0.09, several (n = 4) patients classified as having unstable angina had troponin values between 0.03 and 0.09. Exclusion of these patients (data not shown) resulted in a specificity performance for copeptin of 74.0% (instead of 74.3%, as shown in Table 3) that was clearly lower than the specificity performance of hs-cTnT (88.5%).

Table 2. Comparison of CT angiography characteristics as a function of copeptin concentrations (ROC-optimized cutpoint).

	Copeptin <7.38 pmol/L[a]	Copeptin ≥7.38 pmol/L	*P*
n	263	103	
Computed tomography			
Segments with calcified plaques ≥1, n (%)	118 (44.87)	46 (44.66)	0.9715[c]
Segments with non-calcified plaques ≥1, n (%)	102 (38.78)	37 (35.92)	0.6121[c]
Segments with any plaque ≥1, n (%)	133 (50.57)	48 (46.60)	0.4947[c]
Segments with significant stenosis ≥ 1, n (%)	27 (10.27)	15 (14.56)	0.2461[c]
Vessels with plaque ≥ 1, n (%)	133 (50.57)	48 (46.60)	0.4947[c]
Vessels with significant stenosis ≥ 1, n (%)	21 (7.98)	14 (13.59)	0.1009[c]
Median left-ventricular mass, g/m^2 (IQR)	144.0 (55.0)	157.0 (51.0)	0.0568[b]
Median left-ventricular ejection fraction, % (IQR)	68.6 (10.3)	67.7 (13.4)	0.3182[b]
Regional left-ventricular dysfunction, n (%)	35 (13.89)	24 (24.24)	0.0196[c]

[a] ROC-optimized cutpoint in all study participants.
[b] Wilcoxon test for continuous variables.
[c] Pearson χ^2 test for categorical variables.

Table 4 shows the NRI analysis for copeptin. Overall, 6 patients without ACS were reclassified false positive, whereas none of the patients with ACS was reclassified correctly. Thus, the NRI was below 0 (−0.018; $P = 0.56$), suggesting no benefit in adding copeptin to existing risk prediction tools in ACS.

If patients with ACS were divided into groups according to the time since onset of symptoms, copeptin concentrations on admission were highest in the group of patients presenting between 0–4 h (n = 12, median 7.97 pmol/L) and >10 h after onset of symptoms (n = 12, median 7.74 pmol/L), with lower concentrations in between (5–10 h, n = 11, median 4.05 pmol/L) (Fig. 1). By contrast, hs-cTnT concentrations were highest in those presenting between 0–4 h (median 74.1 pg/mL) with a clearly decreasing pattern thereafter (5–10 h, median 28.0 pg/mL; >10 h, median 22.95 pg/mL). Of note, 8 of 35 ACS patients had non–ST-elevation myocardial infarction (NSTEMI), in 6 of whom copeptin and hs-cTnT concentrations were determined 0–4 h after onset of symptoms, while in the remaining 2 MI patients they were determined 5–10 h after onset of chest pain.

Fig. 2 shows that the diagnostic accuracy of hs-cTnT in the diagnosis of ACS, as quantified by the area under the ROC curve, was 0.795, which was significantly higher ($P = 0.0015$) than the diagnostic accuracy of copeptin (AUC 0.588). The combination of both markers showed a lower diagnostic power for ACS than hs-cTnT alone (AUC 0.771), although the difference was not statistically significant ($P = 0.447$). Calculating the diagnostic value for copeptin as a function of time did not yield a significant difference between the 3 time periods (data not shown). The AUC for copeptin concentrations determined 0–4 h after onset of symptoms was 0.616, for copeptin concentrations between 5 and 10 h it was 0.545, and it was 0.682 for copeptin concentrations quantified ≥10 h after onset of symptoms.

Discussion

Comparing copeptin and hs-cTnT, we report 4 major findings. First, in contrast to hs-cTnT, copeptin concentrations were not significantly higher in patients

Table 3. Copeptin and hs-cTnT to rule out acute coronary syndrome.

Analyte, cutoff concentration	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	AUC
Copeptin, 7.38 pmol/L	51.4 (46.3–56.6)	74.3 (69.8–78.8)	17.5 (13.6–21.4)	93.5 (91.0–96.1)	0.588
hs-cTnT, 13.0 pg/mL	62.9 (58.0–67.8)	88.2 (84.9–91.5)	36.1 (31.2–41.0)	95.7 (93.6–97.8)	0.795

Table 4. NRI analysis for copeptin.[a]

Model without copeptin	Model with copeptin				Reclassified		
	<8%	8%–12%	>12%	Total	Increased risk	Decreased risk	Net correctly reclassified
Patients with ACS							
<8%	6 (85.71)	0 (0.00)	1 (14.29)	7	2	2	0
8–12%	1 (8.33)	10 (83.33)	1 (8.33)	12			
>12%	0 (0.00)	1 (6.25)	15 (93.75)	16			
Total	7	11	17	35			
Patients without ACS							
<8%	151 (75.50)	47 (23.50)	2 (1.00)	200	56	50	−6
8–12%	50 (40.32)	67 (54.03)	7 (5.65)	124			
>12%	0 (0.00)	0 (0.00)	7 (100.00)	7			
Total	201	114	16	331			

[a] Data are frequency (row percentage). NRI = −0.018 (P = 0.56).

with ACS than in patients without ACS. Second, copeptin provided no additional diagnostic information to that of hs-cTnT in patients with ACS presenting early (0–4 h) to the ED. Thus, copeptin was not an earlier marker of ACS. Third, we were able to show that copeptin did not directly reflect coronary artery status, but was associated with the presence of left ventricular dysfunction, suggesting that its increases occurred in

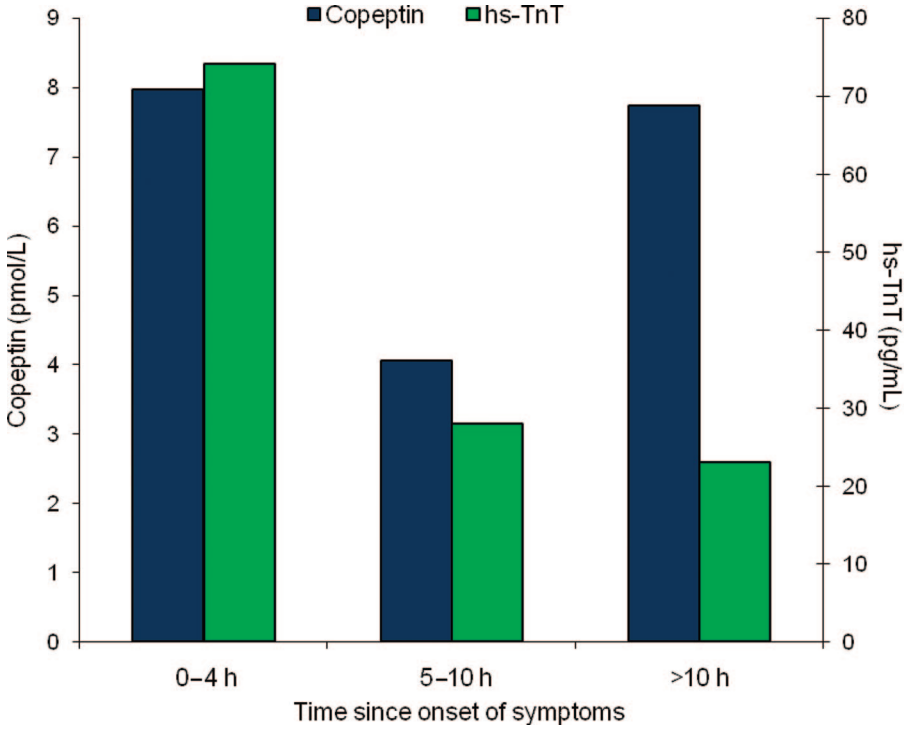

Fig. 1. Copeptin and hs-TnT concentrations in ACS patients in relation to time since onset of symptoms.

Median concentrations of copeptin (blue bars) and hs-TnT (green bars) at presentation to the ED according to the time since onset of symptoms, in patients with the adjudicated diagnosis of ACS.

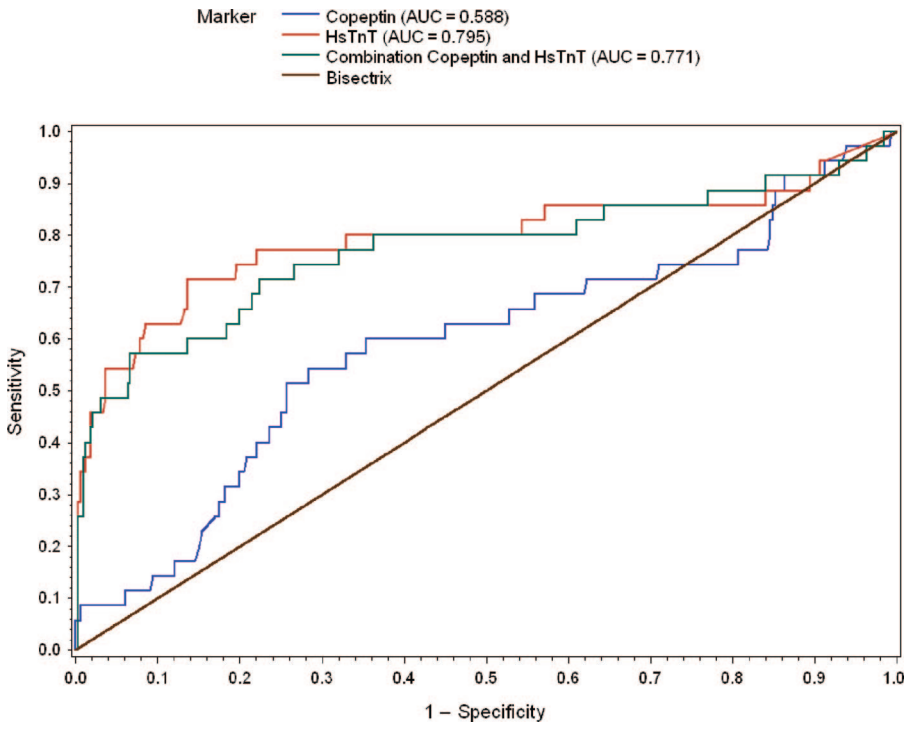

Fig. 2. ROC curves for the diagnosis of ACS.
ROC curves for hs-TnT (red line), copeptin (blue line), and the combination of both markers (green line) in the diagnosis of ACS.

response to systemic stress, such as seen in myocardial ischemia. Fourth, in this population of low to intermediate risk patients with chest discomfort, a copeptin concentration interpreted according to a ROC-optimized cutpoint (7.38 pmol/L) would have correctly ruled out ACS 4 h after presentation in the ED with a NPV of 94% and a sensitivity of 51%, whereas hs-cTnT (cutoff 13.0 pg/mL) had a NPV of 96% and a sensitivity of 63%. Thus, given the endorsement by consensus groups *(10)* and increasing clinical use of hs-cTnT assays, the role of copeptin in the diagnostic evaluation of patients with suspected ACS may be limited.

Despite several reports linking copeptin to insulin resistance, metabolic syndrome *(6)*, heart failure *(8)*, acute destabilized heart failure *(9)*, and outcome after acute MI *(11)*, further prospective data on the association of copeptin and subsequent coronary events is sparse. There are only 2 studies reporting on copeptin in the diagnosis of acute MI. In the APACE (Advantageous Predictors of Acute Coronary Syndromes Evaluation) study, Reichlin et al. *(11)* determined copeptin concentrations in 487 consecutive patients with moderate to high risk presenting to the ED within 12 h after onset of symptoms. Baseline copeptin concentrations were significantly higher in 81 study participants who subsequently experienced a coronary event compared with controls (median 20.8 vs 6.0 pmol/L; $P < 0.001$). Comparing the outcomes of APACE with ROMICAT, several differences are of particular interest. First, the accuracy of copeptin in the diagnosis of acute MI as quantified by the area under the ROC curve seems to be better in high-risk populations (AUC 0.75 in APACE vs 0.59 in ROMICAT), and one would also expect the accuracy of hs-cTnT for MI to be higher in those with higher pretest probability. Second, there seems to be an inverse correlation between copeptin and time since onset of symptoms in high-risk populations. Whereas in APACE, copeptin concentrations were highest in the group of patients presenting at 0–4 h with a falling pattern thereafter, there was no significant difference in time pattern in ROMICAT. Third, baseline copeptin measurements in ROMICAT, at a median of 4.3 h from initial presentation, showed much lower concentrations in ACS patients, namely 7.4 pmol/L [interquartile range (IQR) 2.7–10.1], than in the AMI patients of APACE. However, it has to be considered that 27 of 35 ACS patients in our study were diagnosed as UAP. In contrast to APACE, in our cohort no significant differences in copeptin concentrations were seen between

UAP and NSTEMI patients. If only UAP was analyzed, there was no significant difference between both studies. This suggests that copeptin may be of less value in those with UAP, a group of patients traditionally defined by negative troponin values. Another difference might arise from inclusion criteria: in APACE copeptin was predominantly evaluated in AMI patients with significant ECG abnormalities and/or positive initial cTn test (76 of 81 AMIs), and only 5 patients had neither a positive initial troponin T nor diagnostic ECG changes, whereas in our study, patients with positive findings were excluded.

In a more recent study by Keller et al. *(22)*, in a high-risk population of 1386 patients, 299 (21.6%) had a discharge diagnosis of AMI, and in 184 (13.3%) the discharge diagnosis was UAP. The authors found that combined measurement of copeptin and cTnT improved the *c*-statistic from 0.84 for conventional troponin alone to 0.93 in the overall population, and from 0.77 to 0.90 in patients presenting within 3 h after chest pain onset. However, when high-sensitivity cardiac troponin I (hs-cTnI) was defined as the reference marker instead of conventional TnT in the same population, the benefit of adding copeptin to hs-cTnI was seen only in AMI patients (STEMI + NSTEMI) but not in UAP patients presenting within 3 h after chest pain onset. Here the combination of copeptin with hs-cTnI only marginally improved the AUC from 0.96 (0.95–0.98, hs-cTnI alone) to 0.97 (0.96–0.98, hs-cTnI + copeptin combined).

We recently reported that hs-cTnT concentrations are associated with coronary angiographic morphology in ACS patients *(23)*. This was not the case for copeptin in the present analysis. In CTA only the presence of regional left ventricular dysfunction was found to be associated with increased copeptin concentrations, but even in these results we caution that an association between copeptin and left ventricular ejection fraction was not apparent. Interestingly, a prior study by Kelly et al. *(24)* also showed a positive association between copeptin concentrations and left ventricular dysfunction in 274 survivors of an acute MI. One could hypothesize that because acute left ventricular dysfunction causes a reduction in cardiac output, resulting in arterial underfilling and increased osmolality, this might activate baroreceptors in the aortic arch and the carotid sinus, with subsequent acute release of copeptin *(25)*.

Our study has several limitations that need to be addressed. First, measurements of copeptin and hs-cTnT concentrations were performed an average of 4 h after presentation in the ED, and this might be responsible for the lack of an association between copeptin and ACS, although stratification by time did not change the predictive value significantly. Second, in the study by Reichlin et al. *(11)*, increased copeptin was associated with NSTEMI but not with UAP. In our study, the majority of patients, however, had UAP as an ACS endpoint; this is not unimportant, as UAP is a common diagnosis, and an area of weakness for other biomarkers such as troponin. Third, because the diagnosis of ACS relies on troponins, there is a circular logic in favor of troponin vs copeptin. Fourth, the cohort studied was of moderate size only. Fifth, there is some selection bias in our study based on the fact that patients with serum creatinine >1.3 mg/dL, concomitant treatment with metformin, and hyperthyroidism were excluded, thus most likely resulting in a lower pretest probability. Sixth, owing to the prior clinical cTnT standard of 0.09 μg/L used for the enrollment criteria of the ROMICAT study (chosen according to the prior standard at the study site), several (n = 4) patients classified as having unstable angina had troponin concentrations >0.03 μg/L; however, exclusion of these patients (n = 4) did not result in a better specificity performance for copeptin (74.0% instead of 74.3%, as shown in Table 3), which was clearly lower than the specificity performance of hs-cTnT (88.5% instead of 88.2%). Seventh and last, although the diagnosis of ACS was based on 2 physicians using clinical data as well as conventional cTnT results, there is potential inherent bias against biomarkers such as copeptin in that a biochemical diagnosis may be more biologically sound than a clinical one. However, the same bias affects hs-cTnT, and with CTA results to back up the diagnosis, our finding that copeptin adds little to the clinical picture will likely stand.

Exclusion of patients with a history of CAD had no effect on our results. Indeed, the strength of our study consists in the availability of data on coronary anatomy by CTA, allowing pathophysiological insights into copeptin secretion.

In conclusion, for the clinical situation where hs-cTnT was not diagnostic for low-risk patients with ACS, copeptin did not contribute additional information. Thus, our study does not suggest a clinically important diagnostic role for copeptin in low- to intermediate-risk ACS patients.

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