Acute myocardial infarction (AMI) is the major cause of death and disability worldwide, with an ongoing increase in incidence. Approximately 15 million patients per year present to the emergency department (ED) with chest pain or other symptoms suggestive of AMI in the U.S. and Europe (1). Rapid assessment of these patients is critical to direct further diagnostic and therapeutic strategies. Electrocardiography (ECG) and cardiac troponin form the current diagnostic cornerstones and complement clinical assessment in current AMI guidelines (2,3). They allow for a rule in of AMI within the first 3 h after presentation in the majority of patients (4) and offer the opportunity to initiate appropriate, evidence-based treatment (5,6).

The vast majority of patients presenting to the ED with suspected AMI, however, finally prove not to have AMI (7). Current rule out of AMI is time-consuming and expensive (8). One-quarter to one-third of patients with AMI present without significant ECG changes indicative of acute ischemia; therefore, ECG is of little help to rule out AMI (7,9). The major limitation of current troponin assays is a sensitivity deficit at presentation due to a delayed increase of...
circulating levels (10). Exclusion of AMI consequently requires prolonged monitoring over 6 to 9 h and serial blood sampling. This procedure contributes to overcrowding in the ED, and the associated costs probably exceed several billion U.S. dollars each year (11,12). The rapid and reliable rule out of AMI, therefore, represents one of the large unmet needs in clinical medicine.

The arginine-vasopressin system plays a crucial role in the regulation of the individual endogenous stress response (13). Levels of arginine-vasopressin have been shown to be elevated in heart failure (14) and in different states of shock (15), but investigation of the arginine-vasopressin system has been limited so far because arginine-vasopressin is unstable (half-life: 5 to 15 min) and largely attached to platelets (16,17). Copeptin, the c-terminal part of the vasopressin prohormone, is secreted stoichiometrically with arginine-vasopressin from the neurohypophysis and is much more stable, thus overcoming the limitations and difficulties of assessing the arginine-vasopressin system (18). In a recent study, copeptin was markedly elevated in patients after AMI and predicted adverse outcome (19); however, nothing is known about the diagnostic value of copeptin in AMI.

We hypothesized that the combination of a marker of cardiac necrosis, such as troponin, with a pathophysiologically different biomarker reflecting acute endogenous stress, such as copeptin, might allow for a rapid and accurate rule out of AMI already at initial presentation without serial blood sampling.

**Methods**

**Study design and population.** From April 2006 to September 2007, a total of 492 consecutive patients presenting to the ED of the University Hospital Basel, Switzerland, with symptoms suggestive of AMI such as chest pain and angina pectoris with onset or peak within the last 12 h were recruited in this prospective cohort study. Patients with terminal kidney failure requiring dialysis were excluded. The study was performed according to the principles of the Declaration of Helsinki and approved by the local ethics committee. Written informed consent was obtained from all participating patients.

**Routine clinical assessment.** All patients underwent an initial clinical assessment that included clinical history, physical examination, 12-lead ECG, continuous ECG monitoring, pulse oximetry, standard blood tests, and chest radiography. Troponin T, the myocardial band (MB) fraction of creatine kinase and myoglobin, were measured at presentation and after 3 and 6 to 9 h, as long as clinically indicated. The timing and treatment of patients were left to the discretion of the attending physicians.

**Adjudicated final diagnosis.** To determine the causal diagnosis at presentation for each patient, 2 independent cardiologists blinded to the results of copeptin reviewed all available medical records (including patient history, physical examination, results of laboratory and radiologic testing, ECG, echocardiography, cardiac exercise test, coronary angiography) pertaining to the patient from the time of ED presentation to 60-day follow-up. In diagnostic disagreement, cases were reviewed and adjudicated in conjunction with a third cardiologist. AMI was defined as recommended in current guidelines (2,3). In brief, AMI was diagnosed when there was evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Necrosis was diagnosed by a rising and/or falling pattern of troponin T with at least 1 value above the 99th percentile, with an imprecision of <10% (20). For the troponin T assay, the lower limit of detection is 0.01 μg/l. Thus, to manifest a rising pattern, patients with normal initial values had to increase troponin T levels to the cutoff level of ≥0.04 μg/l to fulfill AMI criteria (21). Unstable angina was diagnosed in patients with normal troponin T levels and typical angina at rest, a sudden increase in episodes of a previously stable angina, in cases of positive cardiac exercise testing or cardiac catheterization with coronary arteries found to have stenosis of ≥70%, and in ambiguous cases in which follow-up information revealed AMI or a sudden unexpected cardiac death within 60 days. Pre-defined further diagnostic categories included cardiac but not coronary symptoms (e.g., perimyocarditis, tachyarrhythmias) and noncardiac symptoms. If AMI was excluded in the ED, but no sufficient further diagnostic procedures were performed for conclusive diagnosis, symptoms were classified as of unknown origin.

**Biochemical analysis.** Troponin T was determined immediately using a 1-step enzyme immunoassay based on electrochemiluminescence technology. The MB fraction of creatine kinase (by mass assay) and myoglobin were measured by immunoassays (all Elecsys 2010, Roche Diagnostics, Mannheim, Germany).

Blood samples for determination of copeptin were collected at presentation to the ED in all patients, and as long as there was diagnostic uncertainty, after 1, 2, 3, and 6 h into tubes containing potassium ethylenediaminetetraacetic acid. After centrifugation, samples were frozen at −80°C until assayed in a blinded fashion in a single batch using a novel commercial sandwich immunoluminometric assay (B.R.A.H.M.S. LUMItest CT-proAVP, B.R.A.H.M.S AG, Hennigsdorf/Berlin, Germany), as described in detail elsewhere (18). Since this initial publication, the assay was modified as follows: the capture antibody was replaced by a murine monoclonal antibody directed to amino acids 137-144 (GPAGAL) of proAVP. This modification improved the sensitivity of the assay. The lower detection limit was 0.4 pmol/l, and the functional assay sensitivity (<20% interassay CV) was <1 pmol/l.
median copeptin level in 200 healthy persons was 3.7 pmol/l and the 97.5 percentile was 16.4 pmol/l.

Glomerular filtration rate was calculated using the abbreviated Modification of Diet in Renal Disease formula (22).

ECG analysis. All 12-lead admission ECGs were assessed in a core laboratory by internal medicine specialists blinded to the clinical and biochemical patients’ details. The ECG manifestations indicative of AMI were defined as recommended in current guidelines (2,3).

Statistical analysis. Continuous variables are presented as mean ± SD or median (with interquartile range [IQR]), categorical variables as numbers and percentages. Continuous variables were compared with the Mann-Whitney U test and categorical variables using the Pearson chi-square test. Correlations among continuous variables were assessed with the use of the Spearman rank-correlation coefficient. Logistic regression was used to combine troponin T and copeptin in the diagnosis of AMI and to adjust for other baseline variables. Receiver-operator characteristic (ROC) curves were constructed to assess the sensitivity and specificity throughout the concentrations of troponin T and copeptin and to compare the ability of troponin T, copeptin, and its combination to diagnose AMI. Comparison of areas under the ROC curves was performed as recommended by DeLong (23). All hypothesis testing was 2-tailed, and a p value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS for Windows 15.0 (SPSS Inc., Chicago, Illinois) and MedCalc 9.6.4.0 (MedCalc Software, Mariakerke, Belgium).

Results

Characteristics of patients. Of the 492 consecutive patients enrolled in the study, 5 were excluded from the analysis because of missing copeptin or troponin T values. Baseline characteristics of the remaining 487 patients are shown in Table 1. The adjudicated final diagnosis was AMI in 17% of patients, unstable angina in 17%, cardiac symptoms of origin other than coronary artery disease in 13%, noncardiac symptoms in 43%, and symptoms of unknown origin in 11%. Of the 81 patients with AMI, 30 (37%) were diagnosed having ST-segment elevation MI and 51 (63%) as having non–ST-segment elevation MI.

Troponin T levels. Among patients with AMI, troponin T at presentation was ≤0.01 μg/l in 25% and below the decision limit of 0.04 μg/l in 35% of patients. Of the 406 patients without AMI, 5.9% had a troponin T at presenta-
tion >0.01 μg/l and 2.2% above the decision limit for AMI of 0.04 μg/l.

**Copeptin levels.** As shown in Figure 1A, copeptin levels were significantly higher in patients with AMI as compared with patients having other diagnoses (AMI, median 20.8 pmol/l, IQR 7.9 to 60.6 pmol/l; unstable angina, median 7.4 pmol/l, IQR 4.0 to 12.3 pmol/l; cardiac symptoms of origin other than coronary artery disease, median 7.9 pmol/l, IQR 3.5 to 20.5 pmol/l; noncardiac symptoms, median 5.4 pmol/l, IQR 3.3 to 10.4 pmol/l; symptoms of unknown origin, median 7.8 pmol/l, IQR 4.2 to 20.5 pmol/l, noncardiac symptoms, median 5.4 pmol/l, IQR 3.5 to 10.4 pmol/l; p < 0.001 for all comparisons with AMI patients). None of the other groups differed significantly from each other. Copeptin levels differed significantly between patients with ST-segment elevation MI (median 45.5 pmol/l, IQR 21.0 to 123 pmol/l), non–ST-segment elevation MI (median 11.7 pmol/l, IQR 6.2 to 50.8 pmol/l), and unstable angina (Fig. 1B).

Among the 81 patients with AMI, copeptin was significantly higher in patients with an initial troponin T level >0.01 μg/l (median 75.9 pmol/l, IQR 26.0 to 158.3 pmol/l) than in patients with a troponin T level >0.01 μg/l (median 11.7 pmol/l, IQR 6.2 to 45.5 pmol/l; p < 0.001). Furthermore, in patients with AMI, there was a significant inverse correlation between copeptin and the time since onset of symptoms (r = −0.44, p < 0.001), whereas troponin T was positively correlated with the time since onset of symptoms (r = 0.51, p < 0.001). If patients with AMI were divided into groups according to the time since onset of symptoms, copeptin levels at admission were highest in the group of patients presenting 0 to 4 h after onset of symptoms (median 52.5 pmol/l, IQR 13.6 to 110.8 pmol/l) with a falling pattern thereafter (5 to 10 h, median 30.8 pmol/l, IQR 12.2 to 69.4 pmol/l; >10 h, median 9.9 pmol/l, IQR 5.4 to 25.5 pmol/l; p < 0.001). Troponin T levels were lowest in patients presenting earliest and rising with increasing time since onset of symptoms (0 to 4 h, median 0.01 μg/l, IQR 0.01 to 0.08 μg/l; 5 to 10 h, median 0.11 μg/l, IQR 0.02 to 0.38 μg/l; >10 h, median 0.18 μg/l, IQR 0.06 to 0.61 μg/l; p < 0.001) (Fig. 2).

The distribution of several baseline characteristics across copeptin quartiles are shown in Table 2. Patients in the different quartiles of copeptin were comparable regarding most baseline characteristics, including history of coronary artery disease and history of MI. Patients in the highest quartile were older, more often male, and more often had hypertension, a higher body mass index, and a worse renal function. In a subgroup of 25 AMI patients with diagnostic uncertainty until 6 h after presentation, serial sampling was performed. Copeptin kinetics in the subgroup of 25 AMI patients were analyzed and compared to a group of 83 patients with noncardiac symptoms, in whom samples were available at presentation, after 3 h, and after 6 h as well (AMI median copeptin values were 14.1 pmol/l at presentation, 7.7 pmol/l at 3 h, and 11.0 pmol/l at 6 h; vs. those of noncardiac patients: 5.6 pmol/l at presentation, 5.1 pmol/l at 3 h, and 5.4 pmol/l at 6 h).

Figure 3 describes levels of copeptin according to ECG findings and troponin T status at presentation. If troponin T was ≤0.01 μg/l at presentation, copeptin was significantly higher in patients with AMI than in patients with other diagnoses, regardless of presence or absence and type

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**Figure 1 Copeptin Levels at Presentation**

Copeptin levels at presentation to the emergency department (A) in all patients according to adjudicated final diagnosis and (B) in patients with acute coronary syndrome only. Boxes represent interquartile ranges and whiskers display ranges (without outliers further than 1.5 interquartile ranges from the end of the box). AMI = acute myocardial infarction; CAD = coronary artery disease; NSTEMI = non–ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction.
of ECG abnormalities (p < 0.001 for groups with no significant ECG abnormalities and ST-segment elevation/left bundle branch block not known to be old; p = 0.016 for group with ST-segment depression/T-wave inversion). However, if patients presented late after onset of symptoms and troponin T was >0.01 μg/l already at presentation, no significant differences in copeptin levels were observed between patients with and without AMI.

Incremental diagnostic value of copeptin. The diagnostic accuracy of troponin T at presentation in the diagnosis of AMI as quantified by the area under the ROC curve (AUC) was 0.86 (95% confidence interval [CI]: 0.80 to 0.92), which was significantly higher than the diagnostic accuracy of copeptin at presentation (AUC 0.75; 95% CI: 0.69 to 0.81; p = 0.009) (Fig. 4). However, the combination of the 2 markers significantly increased the diagnostic accuracy provided by troponin T alone, with an AUC of 0.97 (95% CI: 0.95 to 0.98; p < 0.001) for the combination of troponin T and copeptin. In contrast, the combination of troponin T with either the MB fraction of creatine kinase or myoglobin did not result in a significantly higher diagnostic accuracy as compared with troponin T alone. After adjusting for the variables with significant imbalances across copeptin quartiles, troponin T and copeptin invariably remained highly significant predictors of AMI (for both biomarkers, p < 0.001), whereas no other variable reached significance.

If patients with ST-segment elevation MI—who are in general triaged on the basis of symptoms and ECG rather than on initial biomarkers—were excluded from the analysis, the combination of troponin T and copeptin yielded very similar diagnostic accuracy, as observed in the whole study population (AUC 0.96, 95% CI: 0.94 to 0.98).

Rapid rule out of AMI using troponin T and copeptin. Table 3 summarizes the diagnostic performance of various copeptin levels used in conjunction with a troponin T level ≤0.01 μg/l at presentation. A copeptin level <14 pmol/l in combination with a troponin T level ≤0.01 μg/l would have correctly ruled out AMI at presentation with a sensitivity of 98.8%, a negative predictive value of 99.7%, a specificity of 77.1%, and a positive predictive value of 46.2%. In other

| Table 2 Baseline Characteristics of the Patients in Relation to Copeptin Quartiles |
|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|
| Characteristic                   | Quartile 1 <3.8 pmol/l (n = 122) | Quartile 2 3.82–7.3 pmol/l (n = 122) | Quartile 3 7.4–14.9 pmol/l (n = 122) | Quartile 4 >14.9 pmol/l (n = 121) |
| Age, yrs                         | 58 ± 17                          | 59 ± 16                          | 61 ± 16                          | 69 ± 16                          | <0.001                          |
| Male                             | 61 (50)                          | 83 (68)                          | 96 (79)                          | 81 (67)                          | <0.001                          |
| Risk factors                     |                                  |                                  |                                  |                                  |                                 |
| Hypertension                     | 65 (53)                          | 61 (50)                          | 70 (57)                          | 86 (71)                          | 0.005                           |
| Hyperlipidemia                   | 44 (36)                          | 53 (43)                          | 44 (36)                          | 51 (42)                          | 0.502                           |
| Diabetes mellitus                | 15 (12)                          | 18 (15)                          | 18 (15)                          | 26 (22)                          | 0.234                           |
| Current smoking                  | 33 (27)                          | 37 (30)                          | 25 (21)                          | 32 (26)                          | 0.364                           |
| History of smoking               | 29 (24)                          | 39 (32)                          | 48 (39)                          | 38 (31)                          | 0.077                           |
| Coronary artery disease          | 36 (30)                          | 40 (33)                          | 40 (33)                          | 50 (41)                          | 0.247                           |
| Previous myocardial infarction   | 24 (20)                          | 27 (22)                          | 29 (24)                          | 37 (31)                          | 0.225                           |
| Previous revascularization       | 29 (24)                          | 33 (27)                          | 33 (27)                          | 36 (30)                          | 0.774                           |
| Peripheral artery disease        | 6 (5)                            | 5 (4)                            | 6 (5)                            | 16 (13)                          | 0.014                           |
| Previous stroke                  | 9 (7)                            | 6 (5)                            | 5 (4)                            | 16 (13)                          | 0.029                           |
| Time from onset of symptoms      | 10 (3–30)                        | 11 (3–72)                        | 12 (3–39)                        | 7 (3–18)                         | 0.250                           |
| Body mass index, kg/m² (range)   | 24.7 (23.0–28.6)                 | 26.1 (23.1–28.5)                 | 26.5 (24.2–29.7)                 | 27.4 (23.9–30.0)                 | 0.007                           |
| Estimated glomerular filtration rate, ml/min/1.73 m² (range) | 104 (87–119) | 100 (82–114) | 96 (80–114) | 73 (52–100) | <0.001 |

Values are presented as n (%) or mean ± SD unless otherwise indicated.
words, AMI would have correctly been excluded at admission with only 1 laboratory assessment in 316 of 487 patients (65% of the entire study cohort). Of the remaining one-third of patients with positive results for either copeptin or troponin T or both, roughly one-half of patients finally received the diagnosis of AMI.

**Discussion**

This prospective study involving unselected patients presenting to the ED with symptoms suggestive of AMI examined the value of a dual marker strategy using troponin T, a marker of cardiac necrosis, and copeptin, a marker of endogenous stress, for rapid rule out of AMI.

We report 4 major findings: First, copeptin levels were significantly higher in patients with AMI than in patients with other adjudicated diagnoses. Second, copeptin was significantly higher in patients with AMI presenting early to the ED and still negative for troponin T. Conversely, copeptin provided no additional information in late presenters who were already positive for troponin T at admission. Third, the combination of troponin T and copeptin resulted in a very high diagnostic accuracy in the diagnosis of AMI already at presentation (AUC 0.97). Fourth, an algorithm based on the combination of troponin T and copeptin ruled out AMI at presentation with a sensitivity of 98.8% and a negative predictive value of 99.7%. Accordingly, continuous ECG monitoring and serial blood sampling, today needed in all patients to rule out AMI, could be limited to the one-third of patients positive for either troponin T (>0.01 μg/l) or copeptin (≥14 pmol/l), whereas these resources would no longer be required for patients negative for both markers (nearly two-thirds of patients in our cohort).

These findings have important clinical implications. The rapid and reliable exclusion of AMI in patients presenting with chest pain is one of the large unmet needs in clinical medicine. Because of the delayed increase in troponins and normal or unspecific ECG findings, >10 million patients worldwide require prolonged monitoring and serial blood sampling each year before AMI can safely be excluded. The additional costs associated with the remaining diagnostic uncertainty after the first troponin measurement are estimated to exceed several billion U.S. dollars each year (11,12). Thus, the improvement in the early rule out of AMI offered by copeptin testing may have the potential to improve allocation of resources in the ED and to markedly reduce total treatment cost (24). Acute MI could be rapidly and reliably ruled out at admission in two-thirds of patients, and only the remaining one-third of patients (instead of all patients) would need monitoring and serial blood sampling, with roughly one-half of them (positive predictive value 46%) finally suffering from AMI.
Cardiac troponins currently are the biomarker of choice for the serologic diagnosis of AMI (3,25). Our results confirm the delay of several hours between onset of symptoms and rise of troponin in AMI observed in previous studies (4,10). In this study, 25% of patients with AMI initially presented with a troponin T level \( \leq 0.01 \) g/l. This rate was identical to that observed with a contemporary troponin I assay in a recent study (4). In addition, the AUC for AMI at presentation was 0.86 in a prospective study using a novel sensitive troponin I assay, which is equal to the AUC of troponin T in our study (26). It is unknown whether the development of even more sensitive troponin assays will improve the utility of troponin to rapidly rule out AMI, without resulting in a significant increase in false positive test results (27).

Our data suggest that a dual marker strategy combining troponin T and copeptin benefits from the integration of complementary information provided by pathophysiologically different processes: troponin T for the detection and quantification of myocardial necrosis, and copeptin for the quantification of endogenous stress. It is important to note that despite extensive research with markers representing various pathophysiological pathways including inflammation, platelet activation, and ischemia, none of the markers previously assessed was able to consistently show incremental value in the early rule out of AMI when used in combination with troponins (28–32).

Clinical research of the arginine-vasopressin system was impaired until very recently by the instability of the active peptide. The introduction of a novel immunoassay measuring copeptin, the c-terminal part of the vasopressin prohormone, provided a unique window into the role of this system in common medical disorders (18). Research by our group and others has suggested that copeptin and therefore the vasopressin system is a major determinant of outcome in patients with community-acquired pneumonia, exacerbated chronic obstructive pulmonary disease, sepsis, and AMI (19,33–35). A recent study furthermore showed a correlation between copeptin and the individual stress level (36). Our findings suggest that endogenous stress occurring with the onset of AMI results in a rapid release of vasopressin and copeptin. It is unknown whether vasopressin/copeptin secretion merely reflects the acute endogenous stress reaction associated with AMI (13) or has additional pathophysiological beneficial effects, for example, on coronary artery blood flow (37). With increasing time after onset of symptoms, we observed decreasing levels of copeptin, in contrast to increasing levels of troponin T. The fall in copeptin levels may reflect a mechanism of adaptation by the endogenous stress system facing a continuous stress such as AMI or may be the consequence of the resolution or at least reduction of chest pain after the onset of AMI, or both. This extends and corroborates recent findings in 132 patients with AMI and blood sampling for 5 days after diagnosis of AMI, showing a copeptin peak with similar levels on day 1 and falling levels thereafter, until reaching a plateau by day 3 to 5 (19).

In contrast to patients with AMI, patients with unstable angina had similar copeptin levels as did patients with other causes of chest pain. These data suggest that AMI induces a higher level of endogenous stress than unstable angina does, potentially related at least in part to the more prolonged course of chest pain in patients with AMI. Ischemia, as long as not accompanied by necrosis (i.e., unstable angina), does not seem to be a stronger trigger of copeptin release than are other causes of chest pain. This finding is well in agreement with a recent study showing comparable increases in copeptin levels during exercise in patients with or without exercise-induced ischemia (38).

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<tr>
<th>Copeptin Cutoff Level (pmol/l)</th>
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Copeptin therefore cannot discriminate patients with unstable angina from patients with nonischemic chest pain. **Study limitations.** First, this is a single-center study. However, as patient demographics were comparable to several recent studies including consecutive patients with symptoms suggestive of AMI (28–30,39), we consider our results representative for unselected patient cohorts presenting to the ED with suspected AMI. Second, 81 patients with AMI is a small number for an AMI rule out claim, and confirmation by larger studies is warranted before copeptin can be adopted into clinical practice. Furthermore, long-term follow-up data would be valuable in future studies. Third, as a prospective observational study, we cannot quantify exactly the benefit regarding the allocation of resources in the ED and treatment cost associated with the more rapid exclusion of AMI provided by the additional use of copeptin. Our hypothesis regarding the economic impact needs to be confirmed (or rejected) in a randomized controlled trial with time to discharge and treatment cost as pre-defined end points (24). Fourth, further studies, specifically addressing the ability of copeptin to assist with guiding therapy (e.g., invasive therapy) will be important.

**Conclusions**

Copeptin seems to be an ideal partner for cardiac troponins for the rapid rule out of AMI. The combination of copeptin and troponin significantly improved the diagnostic accuracy for AMI at presentation as compared to troponin alone. Consequently, the additional use of copeptin may allow for a rapid and accurate rule out of AMI and might obviate the need for prolonged monitoring and serial blood sampling in the ED for the majority of patients. This fundamental change in clinical practice may provide the opportunity to significantly improve patient management in the ED and to reduce treatment cost.

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Key Words: copeptin ● rule out ● acute myocardial infarction ● troponin.