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Copeptin as a prognostic biomarker in acute myocardial infarction

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ABSTRACT

Background: Copeptin - the C-terminal section of vasopressin precursor - is a novel biomarker, that has been shown to be a useful prognostic factor in heart failure, ischemic stroke and in acute myocardial infarction (MI) but with restricted population and follow-up in ST-segment elevation MI (STEMI) setting. We evaluated in this study the hypothesis that copeptin measured on admission is an independent predictor of one-year all-cause mortality after a STEMI.

Methods: Copeptin was measured immediately on arrival in the catheterization laboratory in a cohort of unselected STEMI patients and was compared to the peak of cardiac troponin I as a prognosis marker. One-year follow-up was performed.

Results: We included 401 STEMI patients (77% of men, mean age 64 ± 14 years) treated by primary percutaneous coronary intervention. Copeptin on admission was significantly higher in patients who died during the one-year follow-up than in survivors (154.8 pmol/L; IQR [63.9–304.8] vs 30.3 pmol/L; IQR [10.8–93.5]); $p < 0.0001$). There was an increase in mortality at one year from the lowest to the highest quartile of copeptin. After Cox regression analysis, copeptin was an independent predictor of death at one year (adjHR 3.1, 95% CI [1.5–6.2], $p = 0.001$). When compared to the peak value of cardiac troponin I, copeptin measured on admission had a better prognostic value to predict one-year mortality (AUC of 0.74 vs 0.60, $p = 0.022$).

Conclusion: Copeptin measured on admission is a reliable and independent prognostic biomarker of one-year mortality in acute myocardial infarction patients.

1. Introduction

During acute myocardial infarction (MI), damaged myocytes release various proteins such as myoglobin, the MB fraction of creatine kinase and cardiac troponin. Those markers are established biomarkers of diagnosis in MI. Higher peak of creatine kinase or troponin are associated with a larger MI size or myocardial injury and both of these biomarkers have been validated as prognostic biomarker of heart failure and mortality in acute ST-segment elevation myocardial infarction (STEMI) but also in non-ST segment elevation myocardial infarction [1,2].

It has been demonstrated that copeptin rise early after the onset of acute MI [3–5] and has been evaluated in emergency department as an additional diagnostic biomarker to troponin to rule out the diagnosis of MI [6–11]. As the C-terminal section of vasopressin precursor, copeptin has also been shown to be a biomarker of poor clinical outcomes and mortality in heart failure patients [12–16]. Similar results were found in non-cardiovascular diseases such as pneumonia, diabetes, sepsis and acute pancreatitis as copeptin was linked to the severity of the clinical situation [17–20] but also in vascular disease such as ischemic stroke [21]. Recent studies showed that copeptin could predict infarct size and myocardial function alteration in patients presenting with a STEMI [22,23] but data are very sparse concerning the prognostic value of copeptin on long-term mortality in this high cardiovascular risk population.

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The hypothesis of this study was to evaluate if copeptin, measured on admission, is an independent factor of one-year all-cause mortality after a STEMI.

2. Methods

2.1. Study population

All consecutive patients suffering from a STEMI admitted at the Pitié-Salpêtrière University Hospital (Paris, France) for an emergency primary percutaneous coronary intervention (PCI) are included prospectively since 2005 in the ePARIS database with an average of 400 STEMI patients treated each year. However, only a fraction of these patients have biomarkers available, as patients presenting off-hours (night and week-ends) are excluded. In this study, blood samples were randomly selected within the sample available from 2005 and 2010 and patients were compared to the overall clinical registry and had similar demographics [24,25].

ST-segment elevation myocardial infarction was defined by the presence of symptoms of myocardial ischemia associated with new electrocardiographic abnormalities and later elevation of cardiac biomarkers (troponin I) above the 99th percentile of a normal reference population. [26] ST-segment elevation, measured at the J point, should be found in two contiguous leads and be ≥0.25 mV in men below the age of 40 years, ≥0.2 mV in men over the age of 40 years, or ≥0.15 mV in women in leads V2–V3 and/or ≥0.1 mV in other leads, or with new or presumed new Left bundle branch block. Likewise, ST-segment depression in leads V1–V3 suggests myocardial ischemia, especially when the terminal T-wave is positive (ST-elevation equivalent) and may be confirmed by concomitant ST elevation ≥0.1 mV recorded in leads V7–V9). Late MI patients with ischemic time superior to 24 h or patients without a final discharge diagnosis of STEMI were excluded from the analysis.

All patients were treated with aspirin, $P2Y_{12}$ inhibitors and anticoagulants according to international guidelines at the time of the study [27]. Subsequent medical treatment included anti-ischemic, lipid-lowering and antithrombotic drugs according to current evidence-based medicine.

2.2. Baseline data

The baseline data were prospectively collected for all patients and were entered into the web-based registry e-PARIS. Data regarding key time points such as symptom onset and sheath insertion were recorded as well as in-hospital events until discharge. A particular attention was given to co-morbidities and a risk profile was defined for each patient according to the TIMI risk score for STEMI [28]. Our registry was approved by the local ethical committee of the University Hospital Pitié-Salpêtrière of Paris in accordance to guidelines of Declaration of Helsinki.

2.3. Biomarkers

All patients had copeptin and cardiac troponin I measured concomitantly at the beginning of the PCI procedure from blood sampling drawn from the arterial sheath in the radial of femoral artery. Cardiac Troponin I (cTnI; Dade Behring) measurements were performed on samples taken at baseline, and every 6 h until peak was obtained, with serum concentrations measured by immunoassay using an AXSYM analyzer (Abbott, Rungis, France). Copeptin was measured using the commercial sandwich immunoluminometric assay (Thermo Scientific BRAHMS Copeptin Kryptor®, BRAHMS GmbH Neuendorfstr, Hennigsdorf, Germany). The assay principle lies in Time-Resolved Amplified Cryptate Emission (TRACE) technology. In our laboratory, the interassay CV was found to be <5% (4.4% at 28.9 pmol/L and 4.6% at 95.8 pmol/L). The median copeptin level was measured in 200 healthy people in our center to confirm the cut-off value of 14.0 pmol/L, representing the 99th percentile, to classify patients with a negative or positive copeptin value.

2.4. Follow-up and clinical endpoints

After hospital discharge, patients were followed up at 1 month, 3 months, 6 months and 12 months by consultation or phone interview. Information about death was obtained from hospital records, interviews with relatives and/or the national registry on mortality. The clinical endpoint was all-cause-mortality at one year.

2.5. Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD) or median ± inter-quartile range (IQR) and were compared with Student's *t*-test or by Mann-Whitney *U* test (if not normally distributed). Categorical variables were expressed as rate or proportion and compared by the Chi square test or the Fisher's exact test. Time intervals were expressed as median with inter-quartile range (IQR) [25th–75th percentile] and the non-parametric Wilcoxon rank-sum test was adopted for group comparisons. Univariate and multivariate Cox regression analyses were conducted to identify and account for significant predictors of the clinical outcome. Troponin was log-transformed in order to adjust for skewness effect. All baseline variables that were significantly related to one-year-mortality in univariate analysis were included in a multivariate Cox regression model using a forward likelihood ratio method (with a 0.05 p-value to be retained in the model). The following variables were included in the multivariate model: age (per 1 year), cardiogenic shock, copeptin >128.2 pmol/L (Q4), troponin (per 1 log), chronic renal insufficiency, TIMI risk score > 4, radial access. Ejection fraction and procedural data (number of stents, number of lesions, angioplasty results) could not be included due to missing values. The accuracy for predicting the clinical end point was determined by the area under the receiver operating characteristic curve (AUC). Prognostic performance difference between copeptin and troponin was assessed using Delong's AUC comparison. Predictive performance and ability of copeptin to classify patients into categories of predicted mortality risk were evaluated. Using the risk difference definition without categories, the Net Reclassification Improvement (NRI) was calculated. In this definition, any movement in probabilities counts as an up or down movement. In addition, we calculated the Integrated Discrimination Improvement (IDI) to evaluate the improvement of the models' ability to discriminate mortality and no mortality without using categories. The IDI reflects difference between the mean estimated risk for mortality and no mortality up to one year. Kaplan–Meier plots were used to illustrate survival probability over time. All tests were 2-sided with a significance level fixed at 5%. We undertook all analyses with Prism for Mac OS X, Graphpad Software, Inc., SPSS Statistics 2.0.

3. Results

3.1. Patient population and baseline characteristics

After the screening of 484 patients, 401 patients with a final diagnosis of STEMI and admitted within 24 h of symptom onset were included in this study (Supplemental data – Fig. A). Follow-up at 365 days was possible for all but 4 patients who were lost in follow-up. Baseline characteristics of the patients included in this study according to a positive or negative copeptin value on admission are shown in Table 1. Our population was representative of a typical all-comer STEMI cohort with high prevalence of cardiovascular risk factors with almost half of the patients with hypertension and 25% with at least moderate chronic renal insufficiency (>stage 3). Over one third of patients had features associated with high TIMI risk (TIMI score > 4). The median ischemic time, as defined by the time from symptoms onset to sheath insertion was 220 min, IQR [140–476]. During the follow-up period, a total of 46 patients died (11.5%) and the majority of death occurring in-hospital (34 of 46 patients).

3.2. Copeptin measurement on admission

The distribution of copeptin value measured on admission is represented in Fig. B (Supplemental data). The range of copeptin value

Table 1
Baseline characteristics of the patients according to copeptin value.

Characteristic (% or mean ± SD)	Copeptin (>14 pmol/L) (n = 294)	Copeptin (<14 pmol/L) (n = 107)	p value
Age (years)	64.3 ± 14.2	63.1 ± 14.2	0.44
Male	223 (75.8)	87 (81.3)	0.25
Body Mass Index (kg/m^2) ≥ 30	49 (17.2)	10 (9.6)	0.06
Dyslipidemia or lipid lowering therapy	119 (40.5)	47 (43.9)	0.54
Active smoking	116 (39.5)	51 (47.7)	0.14
Hypertension	147 (50.0)	42 (39.6)	0.07
Family history of cardiovascular disease	62 (21.2)	26 (24.3)	0.51
Diabetes	53 (18.0)	18 (16.8)	0.79
TIMI risk score > 4	111 (37.8)	33 (30.8)	0.20
Creatinine clearance <60 mL/min	83 (28.2)	19 (17.8)	0.03
Prior PCI	58 (19.7)	12 (11.2)	0.05
Prior coronary artery bypass graft surgery	24 (8.2)	8 (7.5)	0.82
Median time delay from symptoms onset to blood sampling (mn)	197 (130.0–341.3)	255 (165–575)	<0.01
Killip ≥ 2	47 (16.0)	8 (7.5)	0.03
Cardiogenic shock	19 (6.5)	0 (0)	0.01
Intra-aortic balloon pump	16 (5.5)	1 (0.9)	0.05
Anterior myocardial infarction	122 (43.3)	48 (46.6)	0.56
Out of hospital cardiac arrest	20 (6.8)	1 (0.9)	0.02
Radial access	260 (88.4)	102 (95.3)	0.04
Left ventricular ejection fraction <40%	36 (12.2)	12 (11.2)	0.64
TIMI 3 flow before PCI	58 (20.6)	33 (33.3)	0.01
TIMI 3 flow after PCI	247 (90.1)	83 (88.3)	0.69

PCI indicates percutaneous coronary intervention and TIMI, thrombolysis in myocardial infarction.

varied from a minimal value of 5.1 pmol/L to a maximum of 1890 pmol/L with a median value of 36.2 pmol/L (quartile 1 [5.1–12.1], quartile 2 [12.1–36.2], quartile 3 [36.2–128.2] pmol/L, quartile 4 [128.2–1890.0] pmol/L). As a comparison, the median copeptin in 200 healthy people was found to be 3.7 pmol/L and the 97.5 percentile was 16.4 pmol/L. When using a threshold value of 14 pmol/L, the initial value of copeptin was considered to be positive for 73.3% of patients. The mean copeptin value measured on admission according to symptoms duration is shown in the additional Fig. C (Supplemental data). The Fig. D (Supplemental data) shows the proportion of patients with copeptin and troponin values on admission according to symptom duration. Among the 107 patients with a negative copeptin value on admission, all but 8 patients had positive troponin value on admission. Moreover, copeptin allowed refining diagnosis and prognosis with 23.7% of patients with positive value while troponin was negative.

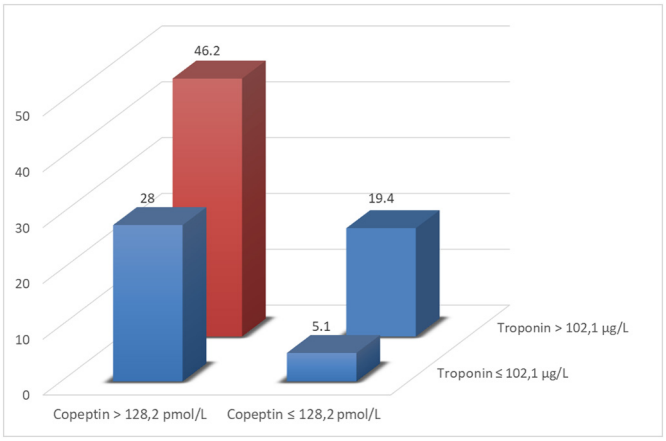

Fig. 2. Mortality of STEMI patients with one or two elevated biomarkers (above 75th percentile).

3.3. Copeptin and mortality

Copeptin measured on admission was significantly higher in patients who died during the first 30 days than in survivors (median 211.1 pmol/L; IQR [102.1–400.1] vs 30.7 pmol/L; IQR [10.7–93.1]; $p < 0.01$) but also after one-year of follow-up (median 154.8 pmol/L; IQR [63.9–304.8] vs 30.3 pmol/L; IQR [10.8–93.5]; $p < 0.01$). When the population was divided in quartiles of copeptin, Kaplan-Meier survival analysis showed a two-way distribution of patients with a highest mortality at one year for the upper quartile (Q4 copeptin > 128.2 pmol/L) (Fig. 1). Patients with biomarkers within the higher quartile of both copeptin and cardiac troponin I had a markedly higher mortality compared to those who had only one biomarker in the highest quartile (46.2% for both biomarkers versus 28% and 19.4% for copeptin and cardiac troponin I alone respectively; $p < 0.001$ for trend) (Fig. 2). On the opposite, the 107 patients with a negative copeptin value on admission had a very low rate of morbidity (heart failure symptoms in 7.4%) or mortality (0.1% at 30 days and 0.4% at one year).

3.4. Predictive factors of mortality

Analysis of ROC curves showed that copeptin on admission had a better area under the curve (AUC) than troponin to predict one-year mortality (0.74 vs. 0.60, $p = 0.022$) with a similar result of combination of troponin and copeptin (0.73 for combination) (Supplemental data – Fig. E). The predictive performance of additional dosage of copeptin at admission was not significantly better than troponin peak with a slight increase of mortality risk probability (0.389 for troponin and 0.398 for association of troponin and copeptin) and a slight decrease of free-mortality risk probability (0.070 for troponin and 0.069 for association of troponin and copeptin). The Integrated Discrimination Improvement indicated no significant improvement in risk discrimination (+0.0098; $p = 0.4315$). However, additional dosage of copeptin allowed a significant better reclassification of profile risk of patients with a global Net Reclassification Improvement of 0.64 ([0.30–0.97]; $p = 0.0002$). More precisely, copeptin dosage allowed 61% of reclassification from occurrence of mortality to no mortality at one year ($p < 0.0001$).

Predictors of one-year mortality before and after adjustment are displayed in Table 2. Traditional clinical risk factors such as older age and cardiogenic shock were found to be associated with a higher mortality, while the radial approach was associated with a lower mortality. The fourth quartile of copeptin values was significantly associated to higher rate of mortality at one year [HR = 4.6; CI [2.8–7.6]]; $p < 0,001$] and remained an independent predictive factor after adjustment for potential confounders (adjusted HR 3.1; CI [1.5–6.2]; $p = 0.001$) while the peak of cardiac troponin I was no longer associated with one-year mortality after adjustment. Considering copeptin as a continuous variable, results of the multivariate analysis were similar (adjusted HR 2.89 (1.57–5.34); $p = 0.001$).

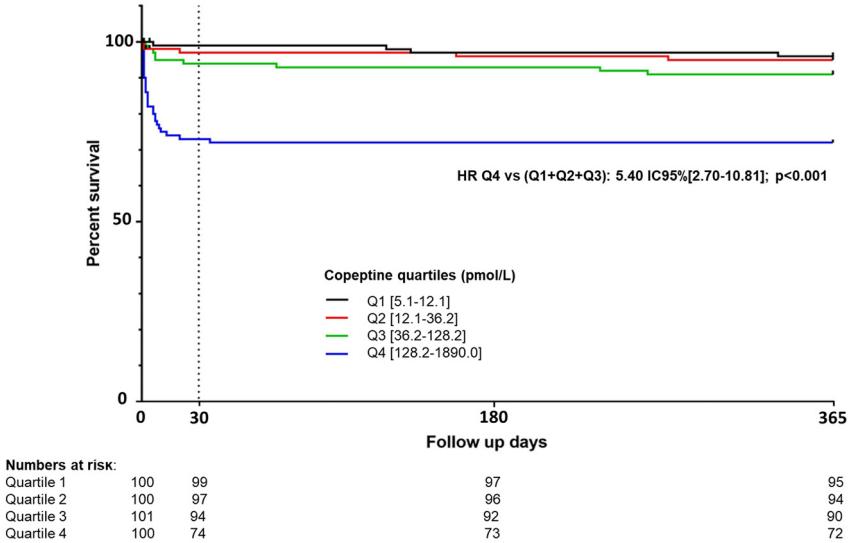

Fig. 1. Kaplan-Meier analysis of survival to 30 and 365 days according to the strata of quartile of copeptin.

Table 2
Unadjusted and adjusted Cox regression model for analysis of Death.

Variables	Unadjusted HR	p value	Adjusted HR	p value
Cardiogenic shock	16.5 [8.5–32.0]	<0.001	9.9 [3.9–25]	<0.001
Age (per 1 year)	1.1 [1.0–1.1]	<0.001	1.09 [1.06–1.12]	<0.001
Copeptin > 128.2 pmol/L (Q4)	4.6 [2.8–7.6]	<0.001	3.1 [1.5–6.2]	0.001
Radial access	0.11 [0.06–0.20]	<0.001	0.31 [0.14–0.66]	0.003
Troponin (per 1 log)	1.8 [1.0–3.0]	0.041	–	NS
Creatinine clearance < 60 mL/min	5.3 [2.9–9.7]	<0.001	–	NS
TIMI risk score > 4	5.0 [2.6–9.5]	<0.001	–	NS

Cardiogenic shock, age, copeptin, troponin, chronic renal insufficiency, radial access and TIMI risk score were included in the multivariate model. TIMI indicates thrombolysis in myocardial infarction.

4. Discussion

Several biomarkers have been suggested in the last years in the field of cardiology but only cardiac troponin and BNP/Nt-Pro BNP (Brain Natriuretic Peptide/N-terminal pro-brain natriuretic peptide) have integrated routine clinical practice as diagnostic and prognostic biomarkers for MI and heart failure. Nevertheless, the search for new biomarkers is still ongoing with the objectives of being more performant, easier to use or cheaper than the existing ones. We hypothesized that an early value of copeptin, a promising diagnostic biomarker, measured on admission in the catheterization laboratory, could reflect the degree of initial myocardial injury in STEMI patients and help predict patients' prognosis.

The results of our study can be summarized as follow: 1/ Early measurement of copeptin on admission in STEMI patients, showed that 73.3% of patients had a positive value of copeptin as compared to healthy volunteers. 2/ Patients who died during the first 30 days of follow-up, a period that reflects the initial severity of the acute MI, had a ten-fold higher copeptin than survivors. 3/ Long-term survival was independently predicted by copeptin either used in quartile or as a continuous variable. 4/ When compared to the peak of cardiac troponin I, copeptin measured on admission had a better predictive value of long-term survival. 5/There was no additive value of both biomarkers combined on mortality prediction.

Copeptin is a relatively new biomarker which is now mostly being used in emergency departments as a diagnostic biomarker in combination with troponin [6]. Studies in patients with MI [4,29] showed a rapid release of copeptin with a return to normal values up to 12 h after the myocardial injury. The underlying mechanism of this rapid release is still not precisely known but might be directly linked to myocyte injury allowing the use of this marker as a diagnostic tool. As such, copeptin could be considered a marker of both myocardial injury and hemodynamical stress. On the basis of the distribution of copeptin, different potential cutoff values were considered [10,30–32] and a recent systematic review [11] suggested that the use of different cut-points did not significantly impact diagnostic accuracy. In our study, the median copeptin was 36.2 pmol/L, which is higher than previous studies performed in the same clinical setting [5,15,22,33] which could be explained by the early measurement in our study as compared with the others. However, we found that one quarter of the patients had a negative copeptin value despite a confirmed acute MI. Copeptin negative patients on arrival presented a longer time delay from symptoms onset to blood sampling as well as less renal insufficiency than copeptin positive patients.

On the prognostic value of copeptin, we found that copeptin was an independent marker of mortality at one-year, results that are driven by the prognostic value on the first 30 days and coherent with a stress biomarker reflecting acute myocardial injury. This is supported by our findings demonstrating that patients within the highest quartile of copeptin had a mortality rate reaching 27% at 30 days when patients in the lowest quartile had an excellent prognosis. Moreover, we found that one third of the patients who had values of copeptin above the 90th percentile (>267.4 pmol/L) died during hospitalization. The highest mortality was found in patients with both elevated troponin and copeptin although, in multivariate analysis, troponin lost statistical significance. Although copeptin and troponin are both markers of myocardial injury with a statistical correlation, copeptin appeared as a better prognostic factor after adjustment. Moreover, additional dosage of copeptin at admission allowed a significant better reclassification of profile risk of patients, particularly for patients whose death was initially predicted with only use of troponin.

Very few studies were published concerning the prognostic value of copeptin in coronary artery disease [34] and focused on heart failure or systolic function alteration [5,15]. Meanwhile, our study shows an independent correlation between one-year mortality and copeptin taken either as a continuous variable or when characterized in quartiles, which confirms the good prognostic value of copeptin. Of interest, patients with values within the highest quartile of both copeptin and cardiac troponin I had the highest mortality rate reaching almost half of the patients, results that supports a multimarker approach to optimize prognostic evaluation. Finally, we believe that our results suggest that copeptin could be particularly useful in identifying short term high risk acute MI patients. Because most of the prognostic impact of copeptin concerns short-term mortality, we believe that patients with high concentrations of copeptin on admission should be monitored in an intensive care unit for a longer time. Particular attention to medical therapy optimization during hospital stay should also be paid for those patients.

The present work has to be considered in the light of the following limitations. Firstly, it was a single-center study with a relatively small population although our cohort is the largest published in this clinical setting. Secondly, copeptin assay was not systematically proposed for all admitted patients in our center during the study period, particularly for patients presenting off-hours, although the characteristics of the presented population are consistent with our usual STEMI population. Thirdly, only one value of copeptin was measured on admission, when other studies evaluated the dosage after the first or the second day. However, we believe this is the best timing in acute MI. Fourthly, we did not perform a simultaneous dosage of BNP. Lastly, the present work is hypothesis generating, and should require external validation in larger cohorts to confirm the prognostic value of copeptin as compared to other biomarkers and precise its role in clinical practice.

In conclusion, the results of the present work suggest that copeptin could be a rapid and reliable prognostic biomarker in acute MI patients. Initial elevated value targeting high-risk patient could allow individualizing therapeutic management more aggressive treatment and follow-up.

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