C-Terminal Provasopressin (Copeptin) as a Novel and Prognostic Marker in Acute Myocardial Infarction

Leicester Acute Myocardial Infarction Peptide (LAMP) Study

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Background—The role of the vasopressin system after acute myocardial infarction is unclear. Copeptin, the C-terminal part of the vasopressin prohormone, is secreted stoichiometrically with vasopressin. We compared the prognostic value of copeptin and an established marker, N-terminal pro-B-type natriuretic peptide (NTproBNP), after acute myocardial infarction.

Methods and Results—In this prospective single-hospital study, we recruited 980 consecutive post–acute myocardial infarction patients (718 men, median [range] age 66 [24 to 95] years), with follow-up over 342 (range 0 to 764) days. Plasma copeptin was highest on admission (n=132, $P<0.001$, day 1 versus days 2 to 5) and reached a plateau at days 3 to 5. In the 980 patients, copeptin (measured at days 3 to 5) was elevated in patients who died (n=101) or were readmitted with heart failure (n=49) compared with survivors (median [range] 18.5 [0.6 to 441.0] versus 6.5 [0.3 to 267.0] pmol/L, $P<0.0005$). With logistic regression analysis, copeptin (odds ratio, 4.14, $P<0.0005$) and NTproBNP (odds ratio, 2.26, $P<0.003$) were significant independent predictors of death or heart failure at 60 days. The area under the receiver operating characteristic curves for copeptin (0.75) and NTproBNP (0.76) were similar. The logistic model with both markers yielded a larger area under the curve (0.84) than for NTproBNP ($P<0.013$) or copeptin ($P<0.003$) alone, respectively. Cox modeling predicted death or heart failure with both biomarkers (log copeptin [hazard ratio, 2.33], log NTproBNP [hazard ratio, 2.70]). In patients stratified by NTproBNP (above the median of ≈900 pmol/L), copeptin above the median (≈7 pmol/L) was associated with poorer outcome ($P<0.0005$). Findings were similar for death and heart failure as individual end points.

Conclusions—The vasopressin system is activated after acute myocardial infarction. Copeptin may predict adverse outcome, especially in those with an elevated NTproBNP (more than ≈900 pmol/L). **(*Circulation*. 2007;115:2103-2110.)**

Key Words: heart failure ■ myocardial infarction ■ natriuretic peptides ■ peptides ■ plasma

The outcome of patients after acute myocardial infarction (AMI) has improved with advances in medical therapy, but heart failure (HF) remains a leading cause of morbidity and mortality after AMI. Clinical features may be useful for predicting patients who are at risk of developing such complications after AMI, but they lack sensitivity and specificity. Biomarkers are emerging as a useful tool for predicting prognosis in such patients. B-type natriuretic peptide and its more stable counterpart, N-terminal pro-B-type natriuretic peptide (NTproBNP), have shown great promise in this area,[1] covering a range of acute coronary syndromes.[2] Newer peptides are emerging that may also be of use. Arginine vasopressin (AVP), also termed antidiuretic hormone, is a nonapeptide produced in the hypothalamus. AVP is released from the neurohypophysis to promote renal water conservation, which contributes to osmoregulation and cardiovascular homeostasis,[3] and it may have a role in cardiopulmonary resuscitation.[4] AVP is derived from a larger precursor peptide (preprovasopressin) along with 2 other peptides, neurophysin II and copeptin.[5] Copeptin, the C-terminal portion of provasopressin, is a 39-amino acid glycopeptide of unknown function in the circulation.[6] The structure of copeptin has recently been characterized with size-exclusion chromatography and found to have a molecular mass around 5 kDa. Lectin chromatography also revealed that serum copeptin is glycosylated.[7] The diagnostic use of AVP has been described in HF and septic shock.[8] There are concerns about the validity of measurement of AVP in plasma, because it is known to be

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unstable and rapidly cleared.[9] Thus, measurement of AVP has not been widely adopted. Investigation of the role of the vasopressin system after AMI was hampered by the instability of this peptide. Copeptin, however, is stable for days after blood withdrawal and can be quickly and easily measured, being secreted in equimolar amounts to vasopressin.[10]

The role of the AVP system as measured by its surrogate, copeptin, in the prognostication of AMI is unknown. In the present study, we investigated whether copeptin would be of benefit in determining the prognosis after AMI, particularly for death and HF. We compared this with NTproBNP, a peptide of established prognostic value benefit in this group of patients.[1,11,12]

Methods

Study Population

We studied 980 consecutive AMI patients admitted to the coronary care unit of the Leicester Royal Infirmary. The study complied with the Declaration of Helsinki and was approved by the local ethics committee; written informed consent was obtained from patients. AMI was diagnosed if a patient had chest pain lasting >20 minutes, diagnostic serial ECG changes consisting of new pathological Q waves or ST-segment and T-wave changes, and a plasma creatine kinase-MB elevation greater than twice normal or cardiac troponin I level >0.1 ng/mL.[13] AMI was subcategorized into ST-segment elevation myocardial infarction (STEMI) or non-STEMI. Exclusion criteria were known malignancy or surgery in the previous month.

Healthy volunteers (n=700, 409 males, median age 60.7 [range 45.5 to 80.6] years) were derived from an HF screening study that was being performed concurrently in the community[14] and were taking no medical therapy and had no history of hypertension, diabetes mellitus, or ischemic heart disease and no ECG or echocardiographic abnormalities (including segmental wall-motion abnormalities, valvular disease, and left ventricular [LV] hypertrophy). The estimated glomerular filtration rate (eGFR) of these subjects was calculated from the simplified formula derived from the Modification of Diet in Renal Disease (MDRD) study, recently validated in patients with HF.[15]

Plasma Samples

Blood samples were drawn at 3 to 5 days after the onset of chest pain for determination of plasma copeptin and NTproBNP levels. After 15 minutes' bed rest, 20 mL of blood was collected into tubes containing EDTA and aprotinin. All plasma was stored at −70°C until assayed in a blinded fashion in a single batch. In a subgroup of 132 patients from the original 980-patient cohort, blood sampling was performed daily for 5 days from admission to discharge.

Echocardiography

Transthoracic echocardiography was performed in patients with a Sonos 5500 instrument (Philips Medical Systems, Reigate, UK). A 16-segment LV wall-motion index based on the American Society of Echocardiography mode was derived by scoring each LV segment (1=normal, 2=hypokinesis, 3=akinesis, and 4=dyskinesis; Paradoxical Motion) and dividing the total by the number of segments scored. LV ejection fraction was calculated with the biplane method of discs formula.[16] Impaired LV systolic function was defined as an LV ejection fraction <40% or an LV wall-motion index >1.8.

NTproBNP Assay

The NTproBNP assay used in the present study was based on a noncompetitive assay as published previously.[2] Sheep antibodies were raised to the N-terminal of human NTproBNP, and monoclonal mouse antibodies were raised to the C-terminal. Samples or NTproBNP standards were incubated in C-terminal IgG-coated wells with the biotinylated N-terminal antibody for 24 hours at 4°C. Detection was with methyl-acridinium ester–labeled streptavidin on an MLX plate luminometer (Dynex Technologies Ltd, Worthing, UK). The lower limit of detection was 0.3 pmol/L. There was no cross-reactivity with atrial natriuretic peptide, B-type natriuretic peptide, or C-type natriuretic peptide.

Copeptin Assay

Copeptin was detected with a novel commercial assay in the chemiluminescence/coated-tube format (BRAHMS AG, Hennigsdorf, Germany), as described previously.[10] Briefly, tubes were coated with a purified sheep polyclonal antibody raised against a peptide that represented amino acids 132 to 147 of preproAVP. A purified sheep polyclonal antibody raised against a peptide representing amino acids 149 to 164 of preproAVP was labeled with methyl acridinium N-hydroxysuccinimide ester (InVent GmbH, Bielefeld, Germany) and used as tracer. Dilutions of a peptide representing amino acids 132 to 164 of preproAVP in normal horse serum served as standards. The immunoassay was performed by incubating 50 μL of samples/standards and 200 μL of tracer in coated tubes for 2 hours at room temperature. Tubes were washed 4 times with 1 mL of wash solution (BRAHMS AG), and bound chemiluminescence was measured with an LB952T luminometer (Berthold, Bad Wildbad, Germany).

End Points

We assessed the value of both copeptin and NTproBNP for the prediction of the primary end point (death or HF). We also investigated death, HF, and recurrent AMI as individual secondary end points. Hospitalization for HF was defined as a hospital readmission for which HF was the primary reason. Myocardial infarction was diagnosed on the basis of established criteria as described above.[13] End points were obtained by reviewing the Office of National Statistics Registry and by contacting each patient. There was a minimum 60-day follow-up of all surviving patients.

Statistical Analysis

Statistical analyses were performed on SPSS version 14 (SPSS Inc, Chicago, Ill). The continuous variables in the 2 independent groups were compared with the Mann-Whitney *U* test. Comparisons in the daily sampling study were performed with the general linear model with repeated measures, with correction for multiple comparisons by the Bonferroni method. Spearman correlations were performed. To test the independent predictive power for death or HF of peptide levels, binary logistic regression analyses and survival analyses with Cox proportional hazards modeling and Kaplan-Meier models were conducted. Levels of NTproBNP and copeptin were normalized by log transformation. Thus, odds ratios and hazard ratios refer to a 10-fold rise in the levels of these markers. Logistic regression and Cox models were always constructed with the same variables entered simultaneously (which included variables statistically significant in univariate analyses and those variables that may have an effect on the end point on the basis of previous studies). These included age; gender; past medical history of AMI, HF, diabetes mellitus, hypertension, or hypercholesterolemia; smoking history; anterior site of AMI; STEMI; Killip class; eGFR; use of thrombolysis; therapy with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and β-blockers; NTproBNP; and copeptin (with addition of echocardiographic data in a substudy; see below). To compare the accuracy of NTproBNP and copeptin, receiver operating characteristic curves were generated, and the area under the curves was calculated. Comparisons between receiver operating characteristic curves were by the method of Hanley and McNeil.[17] A 2-tailed probability value of less than 0.05 was deemed to be statistically significant.

All authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Healthy Control Subjects

In the healthy volunteers with no cardiovascular disease or treatment (demographic features are listed in Table 1), fe-

TABLE 1. Characteristics of Patients and Healthy Control Subjects

	Control Subjects (n=700)	AMI Patients (n=980)	P
Age, y	60.7 (45.5 to 80.6)	66 (24 to 95)	NS
Male gender	409	718	NS
eGFR, mL · min^{-1} · 1.73 m^{-2} surface area	74.6 (40 to 114)	68.4 (14.9 to 166)	<0.0005
NTproBNP, pmol/L	29.3 (5.7 to 991.9)	914 (0.3 to 28886.8)	<0.0005
Copeptin, pmol/L	3.8 (0.44 to 44.3)	7.0 (0.3 to 441)	<0.0005
Previous medical history			
Angina pectoris	None	250 (25.5)	...
Myocardial infarction	None	164 (16.7)	...
Hypertension	None	429 (43.8)	...
Diabetes mellitus	None	214 (21.8)	...
Heart failure	None	57 (5.4)	...
Hypercholesterolemia	None	223 (22.7)	...
STEMI	None	780 (79.6)	...

Values are median (range) or n (%).

males had higher NTproBNP levels, whereas for copeptin, males had higher levels (Table 2). Plasma NTproBNP was significantly correlated with eGFR and age, but plasma copeptin was not correlated with either eGFR or age (Table 2).

Patient Characteristics

The demographic features of the patient population are shown in Table 1. Median length of follow-up was 342 days, with a range of 0 to 764 days. No patient was lost to follow-up, and the minimum length of follow-up for survivors was 60 days, which enabled a censored primary end point of death or HF to be determined at this time point for logistic regression analysis. During follow-up, 101 patients (10.3%) died, and 49 (5.0%) were readmitted with HF. There were 780 STEMI patients, 67.8% of whom received thrombolytic therapy.

Plasma Profile of Copeptin and NTproBNP

Daily blood samples were obtained for 5 days after admission in a subgroup of 132 patients (102 males, median age [range] 64 [32 to 90] years), 16 of whom subsequently experienced the primary end point of death or HF. Figure 1 illustrates the time course of plasma NTproBNP, showing significant changes with day of sampling ($P<0.001$), with peak levels on day 2 ($P<0.001$ and 0.02 compared with day 1 and day 3, respectively, using the Bonferroni correction). In contrast, the plasma copeptin peak was most evident on day 1 (significantly elevated compared with days 2, 3, 4, and 5, $P<0.001$ with the Bonferroni correction), falling to a plateau by days 3 to 5.

Copeptin Levels (Univariate Analysis)

Plasma levels of copeptin obtained in the plateau phase (days 3 to 5) in 980 patients with AMI were elevated compared with the normal range (Table 1). Copeptin was raised in patients with death or HF compared with event-free survivors (Table 3). There were no significant differences in copeptin levels between males and females, anterior or other site of AMI, patients with a past history of AMI or hypertension, and whether thrombolysis was administered or not; however, there was a significantly higher level in patients who had a past history of HF or diabetes mellitus (Table 3). Copeptin levels were higher in STEMI versus non-STEMI patients and in those with Killip class above 1 (Table 3). Plasma copeptin levels were correlated with age, eGFR, Killip class (Table 3), and NTproBNP ($r=0.36$, $P<0.0005$).

NTproBNP Levels (Univariate Analysis)

Plasma NTproBNP obtained in the plateau phase (days 3 to 5) was significantly higher in patients who died or were readmitted with HF than in event-free survivors (Table 3). Significant differences in NTproBNP levels were noted between males and females, in those with a Killip class above 1, and in patients with a past medical history of HF,

TABLE 2. Univariate Analysis of Copeptin and NTproBNP in the Normal Control Population

	Copeptin	P	NTproBNP	P
Males, median (range), pmol/L	4.3 (0.4 to 44.3)*		13.5 (5.7 to 932.8)*	...
Females, median (range), pmol/L	3.2 (1.0 to 14.8)		54.1 (5.7 to 991.9)	...
Spearman correlation				
Age	0.05	NS	0.37	<0.001
eGFR	−0.01	NS	−0.22	<0.001

*$P<0.0005$, males vs females.

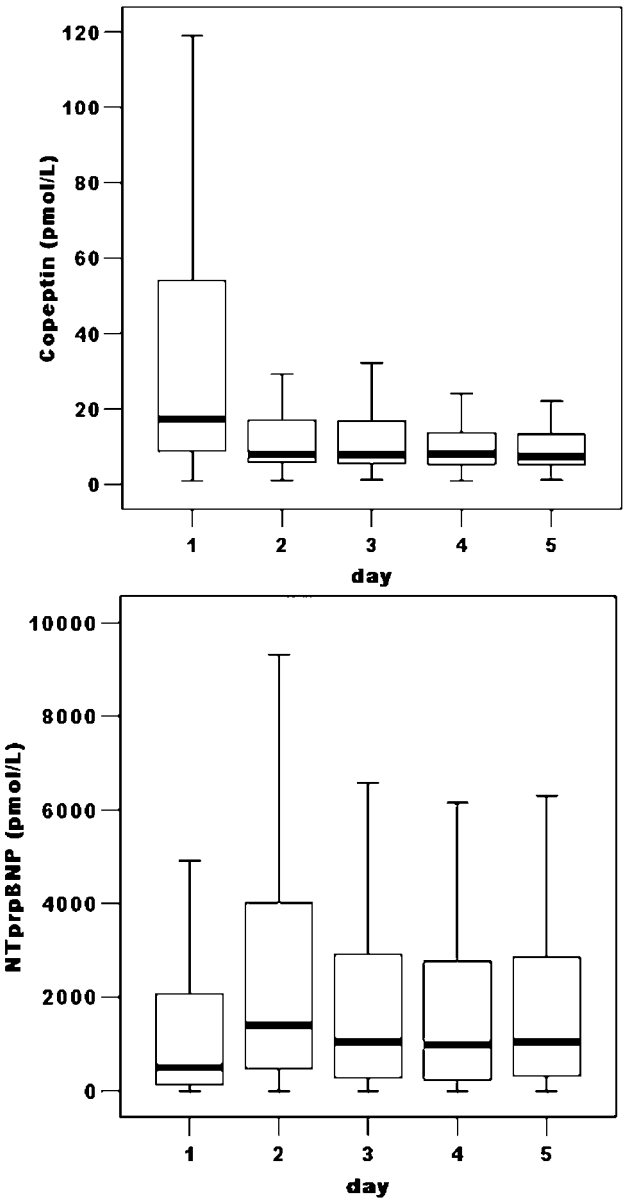


Figure 1. Box plots (median, interquartile ranges) of plasma NTproBNP and copeptin in the first 5 days after AMI (n=132).

hypertension, AMI, or diabetes mellitus (Table 3). Plasma NTproBNP levels were also higher in STEMI than in non-STEMI patients and in those with anterior site of AMI. Plasma NTproBNP was correlated with age, eGFR, and Killip class (Table 3).

Primary End Points: Copeptin and NTproBNP as Predictors of Death and HF

Univariate predictors of death or HF are reported in Table 4. When clinical characteristics (as listed under Statistical Analysis above) were entered into a multivariate binary logistic model (Table 2), copeptin (odds ratio, 4.14) and NTproBNP (odds ratio, 2.26), together with gender, use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and presence of STEMI, independently predicted the primary end point at a censored time of 60 days after AMI, when 86 events had accrued. Past history of AMI, hypertension, HF, or diabetes mellitus, Killip class, and eGFR were not predictors.

The areas under the receiver operating characteristic curve for copeptin (0.75; 95% CI, 0.69 to 0.81) and NTproBNP (0.76; 95% CI, 0.71 to 0.82) were similar. The logistic model combining these 2 markers yielded an area under the curve of 0.84 (95% CI, 0.79 to 0.89; $P<0.001$), which exceeded that of copeptin ($P<0.003$) or NTproBNP alone ($P<0.013$; comparison of areas under the receiver operating characteristic curves by the method of Hanley and McNeil[17]).

For prediction of 60-day mortality and HF, stratification by NTproBNP (less than or greater than the median) correctly identified 68 end points, with an additional 10 identified by stratification by copeptin (less than or greater than the median). When copeptin levels were used for risk stratification, 69 end points were identified correctly, with an additional 9 identified with stratification by NTproBNP. Thus, only 8 end points were identified incorrectly when both markers were used.

Cox proportional hazards modeling using the same predictors revealed NTproBNP, copeptin, age, gender, use of β-blockers, and past history of AMI as independent predictors of death or HF (Table 5). Neither Killip class nor eGFR was an independent predictor.

Kaplan-Meier survival curves that plot quartiles of copeptin or NTproBNP (Figure 2) provide visual confirmation of the findings from the Cox models, that both copeptin and NT-proBNP are useful predictors of death or HF after AMI. In patients stratified by NTproBNP (median 914 pmol/L), copeptin gave additional information on death or HF in those patients who had an NTproBNP level above the median ($P<0.0005$; Figure 3). Thus, patients can be classified into low (both markers less than the median), intermediate (either marker greater than the median), or high risk (both markers greater than the median) groups (log rank for trend, $P<0.0005$).

Relationship of Primary End Points With Copeptin, NTproBNP, and Echocardiographic Parameters

Echocardiographic parameters were available for 628 subjects (64%) for the index admission. Plasma copeptin and NTproBNP levels were elevated in patients with impaired LV systolic function (Table 3). In this echocardiography subgroup, there were 96 deaths or HF readmissions. Multivariate logistic regression analysis of clinical and biomarker variables listed under Statistical Analysis with echocardiographic presence of impaired LV systolic function revealed copeptin, gender, and presence of STEMI as significant independent predictors of death or HF at 60 days (Table 4). Cox modeling of predictors of death or HF revealed copeptin, NTproBNP, echocardiographic evidence of HF, age, gender, and Killip class >1 as predictors (Table 5). eGFR was not an independent predictor in either logistic or Cox models.

Secondary End Points: Copeptin and NTproBNP as Predictors of Death

Copeptin and NTproBNP were significantly higher in patients who died than in event-free survivors (Table 3). Cox proportional hazards modeling suggested that the same variables (copeptin,

TABLE 3. Univariate Analysis of Copeptin and NTproBNP in AMI Patients

	Copeptin	*P*	NTproBNP	*P*
Males vs females, median (range), pmol/L	6.7 (0.3 to 226) vs 7.6 (0.6 to 441)	NS	795 (0.3 to 28886) vs 1590 (5.7 to 24016)	<0.0005
Previous medical history				
AMI vs none	8.5 (0.3 to 203) vs 6.8 (0.3 to 441)	NS	1269 (0.3 to 11259) vs 847 (0.3 to 28886)	<0.001
Hypertension vs none	7.7 (0.4 to 373) vs 6.5 (0.3 to 441)	NS	1106 (5.7 to 28886) vs 802 (0.3 to 24016)	<0.0005
HF vs none	11.6 (0.9 to 224) vs 6.8 (0.3 to 441)	<0.012	2720 (9.5 to 12933) vs 882 (0.3 to 28886)	<0.0005
Diabetes vs none	8.9 (0.4 to 441) vs 6.5 (0.3 to 373)	<0.0005	1259 (0.3 to 28886) vs 835 (0.3 to 24016)	<0.0005
STEMI vs NSTEMI	7.2 (0.3 to 441) vs 5.6 (0.4 to 203)	<0.006	1019 (0.3 to 28886) vs 662 (1.8 to 24016)	<0.004
Anterior AMI vs other	6.2 (0.3 to 373) vs 7.2 (0.3 to 441)	NS	1011 (1.8 to 24016) vs 858 (0.3 to 28886)	<0.048
Thrombolysed vs not thrombolysed	6.9 (0.3 to 441) vs 7.3 (0.3 to 226)	NS	888 (0.3 to 15733) vs 972 (0.3 to 28886)	NS
Killip class >1 vs Killip class 1	9.1 (0.3 to 441) vs 5.7 (0.3 to 373)	<0.0005	1595 (0.3 to 28886) vs 632 (0.3 to 24016)	<0.0005
Echocardiographic evidence of HF vs no HF	10.1 (0.4 to 373) vs 5.9 (0.3 to 226	<0.0005	2287 (0.3 to 16994) vs 810 (0.3 to 28886)	<0.0005
End points				
Death or HF vs event-free survival	18.5 (0.6 to 441) vs 6.5 (0.3 to 267)	<0.0005	5343 (2.4 to 16994) vs 740 (0.3 to 28886)	<0.0005
Death vs event-free survival	21.3 (0.6 to 441) vs 6.5 (0.3 to 267)	<0.0005	5929 (104 to 16994) vs 740 (0.3 to 28886)	<0.0005
HF vs event-free survival	16.0 (0.9 to 145) vs 6.5 (0.3 to 267)	<0.0005	3867 (2.4 to 12933) vs 740 (0.3 to 28886)	<0.0005
Recurrent AMI vs event-free survival	5.7 (0.9 to 41.6) vs 6.5 (0.3 to 267)	NS	1036 (2.6 to 10646) vs 740 (0.3 to 28886)	NS
Spearman correlation				
Age	0.328	<0.0005	0.428	<0.0005
eGFR	−0.347	<0.0005	−0.422	<0.0005
Killip class	0.248	<0.0005	0.322	<0.0005

Echocardiographic evidence for presence/absence of HF was available for 628 patients.

NTproBNP, age, gender, use of β-blockers, and past history of AMI) were independent predictors of death. Kaplan-Meier analysis confirmed lower mortality in patients with copeptin levels below the median and the highest mortality in those with both biomarkers elevated above the median ($P<0.0005$).

Secondary End Points: Copeptin and NTproBNP as Predictors of HF

Copeptin and NTproBNP levels were significantly higher in patients who were readmitted with HF than in event-free survivors. Cox modeling revealed the following independent

TABLE 4. Logistic Regression Analysis for Death or HF at 60 Days

	Univariate Analysis		Multivariate Analysis (Whole Group)		Multivariate Analysis (Echocardiography Subgroup)	
	Odds Ratio (95% CI)	*P*	Odds Ratio (95% CI)	*P*	Odds Ratio (95% CI)	*P*
Age	1.07 (1.05 to 1.10)	<0.0005	1.03 (1.0 to 1.06)	<0.076	1.02 (0.98 to 1.06)	NS
Gender	0.39 (0.25 to 0.60)	<0.0005	0.52 (0.29 to 0.90)	<0.02	0.35 (0.17 to 0.71)	<0.004
Previous history						
AMI	1.74 (1.06 to 2.87)	<0.03	1.30 (0.71 to 2.42)	NS	1.41 (0.62 to 3.18)	NS
HF	0.99 (0.39 to 2.54)	NS	0.43 (0.15 to 1.27)	NS	0.66 (0.18 to 2.46)	NS
Hypertension	1.57 (1.03 to 2.39)	<0.038	1.25 (0.73 to 2.12)	NS	1.18 (0.59 to 2.36)	NS
Diabetes mellitus	1.62 (1.01 to 2.60)	<0.045	1.33 (0.74 to 2.36)	NS	1.12 (0.52 to 2.45)	NS
Hypercholesterolemia	1.14 (0.69 to 1.85)	NS	1.30 (0.70 to 2.38)	NS	1.61 (0.76 to 3.41)	NS
Smoking	0.73 (0.47 to 1.12)	NS	1.22 (0.69 to 2.15)	NS	1.19 (0.57 to 2.48)	NS
Anterior AMI	1.03 (0.67 to 1.57)	NS	1.06 (0.63 to 1.79)	NS	0.87 (0.43 to 1.76)	NS
STEMI	1.68 (0.95 to 2.99)	<0.077	2.43 (1.11 to 5.35)	<0.027	3.60 (1.20 to 10.86)	<0.023
Thrombolytic use	0.68 (0.45 to 1.04)	<0.078	0.65 (0.37 to 1.14)	NS	0.58 (0.28 to 1.18)	NS
Killip class >1	2.74 (1.72 to 4.36)	<0.0005	1.02 (0.57 to 1.84)	NS	1.50 (0.68 to 3.34)	NS
Use of β-blockers	0.43 (0.28 to 0.68)	<0.0005	0.74 (0.43 to 1.29)	NS	1.05 (0.48 to 2.30)	NS
Use of ACE/angiotensin receptor blockers	0.62 (0.40 to 0.95)	<0.029	0.56 (0.32 to 0.98)	<0.044	0.66 (0.31 to 1.41)	NS
Log NTproBNP	4.93 (3.21 to 7.59)	<0.0005	2.26 (1.32 to 3.87)	<0.003	1.77 (0.87 to 3.57)	NS
Log copeptin	7.58 (4.71 to 12.19)	<0.0005	4.14 (2.24 to 7.67)	<0.0005	6.09 (2.71 to 13.66)	<0.0005
eGFR	0.95 (0.94 to 0.96)	<0.0005	1.00 (0.98 to 1.01)	NS	1.00 (0.97 to 1.02)	NS
Echocardiographic evidence of HF	1.86 (1.09 to 3.16)	<0.022	...	...	1.12 (0.54 to 2.33)	NS

ACE indicates angiotensin-converting enzyme.
Multivariate analysis results are reported for the whole group and for the subgroup with echocardiography data (n=628).

TABLE 5. Cox Regression Analysis for Death or HF After AMI

	Univariate Analysis		Multivariate Analysis (Whole Group)		Multivariate Analysis (Echocardiography Subgroup)	
	Hazard Ratio (95% CI)	*P*	Hazard Ratio (95% CI)	*P*	Hazard Ratio (95% CI)	*P*
Age	1.08 (1.06 to 1.09)	<0.0005	1.04 (1.01 to 1.06)	<0.001	1.03 (1.00 to 1.06)	<0.022
Gender	0.53 (0.38 to 0.72)	<0.0005	0.67 (0.46 to 0.97)	<0.036	0.57 (0.35 to 0.92)	<0.021
Previous history						
AMI	2.54 (1.83 to 3.52)	<0.0005	1.67 (1.15 to 2.43)	<0.008	1.56 (0.95 to 2.56)	<0.077
HF	1.60 (0.94 to 2.72)	<0.084	0.70 (0.39 to 1.24)	NS	0.69 (0.33 to 1.42)	NS
Hypertension	1.48 (1.09 to 2.01)	<0.012	1.17 (0.83 to 1.65)	NS	1.48 (0.96 to 2.29)	<0.079
Diabetes mellitus	1.75 (1.25 to 2.43)	<0.001	1.43 (0.99 to 2.08)	<0.06	1.35 (0.84 to 2.18)	NS
Hypercholesterolemia	1.18 (0.83 to 1.67)	NS	0.99 (0.66 to 1.50)	NS	1.00 (0.62 to 1.63)	NS
Smoking	0.73 (0.54 to 0.99)	<0.048	1.17 (0.81 to 1.70)	NS	1.08 (0.67 to 1.74)	NS
Anterior AMI	1.05 (0.77 to 1.43)	NS	0.96 (0.69 to 1.35)	NS	0.72 (0.47 to 1.11)	NS
STEMI	1.04 (0.72 to 1.50)	NS	1.18 (0.74 to 1.88)	NS	1.14 (0.63 to 2.08)	NS
Thrombolytic use	0.68 (0.50 to 0.93)	<0.015	0.88 (0.60 to 1.29)	NS	0.89 (0.55 to 1.43)	NS
Killip class >1	2.88 (2.05 to 4.05)	<0.0005	1.23 (0.82 to 1.82)	NS	1.76 (1.02 to 3.05)	<0.043
Use of β-blockers	0.42 (0.31 to 0.58)	<0.0005	0.69 (0.49 to 0.97)	<0.033	0.72 (0.46 to 1.12)	NS
Use of ACE/angiotensin receptor blockers	0.89 (0.64 to 1.23)	NS	0.80 (0.55 to 1.17)	NS	0.98 (0.60 to 1.63)	NS
Log NTproBNP	5.24 (3.83 to 7.18)	<0.0005	2.70 (1.84 to 3.95)	<0.0005	1.93 (1.19 to 3.12)	<0.007
Log copeptin	4.79 (3.52 to 6.53)	<0.0005	2.33 (1.55 to 3.49)	<0.0005	2.74 (1.66 to 4.52)	<0.0005
eGFR	0.96 (0.95 to 0.96)	<0.0005	0.99 (0.98 to 1.01)	NS	0.99 (0.98 to 1.01)	NS
Echocardiographic evidence of HF	2.49 (1.71 to 3.63)	<0.0005	...	...	1.64 (1.04 to 2.59)	<0.034

ACE indicates angiotensin-converting enzyme.
Multivariate analysis results are reported for the whole group and for the subgroup with echocardiography data (n=628).

significant predictors; copeptin, NTproBNP, past history of diabetes mellitus, and Killip class >1. Kaplan-Meier analysis revealed a lower readmission rate for HF in those with submedian copeptin levels ($P<0.0005$) and the highest HF readmission rates in those with both biomarkers elevated above the median ($P<0.0005$).

Secondary End Points: Copeptin and NTproBNP as Predictors of Recurrent Myocardial Infarction

Compared with survivors with no end points, patients who had recurrent AMI had similar NTproBNP and copeptin levels (Table 3).

Discussion

The present study is the first report to investigate the prognostic potential of copeptin in a substantial cohort of AMI patients from a single center and to compare this with NTproBNP, a well-established marker of death and HF. The present data indicated that taken individually, NTproBNP and copeptin were powerful predictors of death or HF. Analysis of individual end points revealed that both NTproBNP and copeptin contributed to prediction of HF and death. Consideration of both markers gave added prognostic information above existing clinical characteristics, which enabled patients to be stratified into low-, intermediate-, or high-risk groups. Neither marker, however, was predictive of recurrent myocardial infarction.

Risk stratification at an early stage after AMI remains important and may be useful in helping to select treatment regimens in the future. A multimarker strategy for outcome after AMI using independent biomarkers has benefits in that it integrates the different pathways involved, in the hope that complementary information can be gained.[18] Receiver operating characteristic curve analysis indicated that NTproBNP and copeptin were of similar accuracy in prediction of death or HF, but the combination of copeptin and NTproBNP in a multimarker risk stratification approach provided greater predictive accuracy. Kaplan-Meier analysis revealed that copeptin was particularly useful in the group of patients who had a raised NTproBNP (above ≈900 pmol/L). In this group, levels of copeptin above ≈7 pmol/L were predictive of poor outcome, thus defining a high-risk group. These levels are within 1 SD of the normal range and are in contrast to the grossly elevated levels seen in septic patients.[10] Thus, even minor perturbation of the AVP system may be relevant to adverse prognosis after AMI. Even though water intake may affect copeptin levels,[10] blood samples in the present study were obtained with no restriction on water or food intake.

The complementary information provided by copeptin to NTproBNP may suggest that the stimuli to the secretion of both markers are different, and plasma levels are likely to reflect different aspects of cardiovascular homeostasis. In support of this is the clear difference in secretion profile of both markers after AMI, with the copeptin peak on day 1 compared with the NTproBNP peak by day 2. There is also no gender difference in copeptin levels after AMI, in contrast to NTproBNP. In the subset with echocardiography data, both biomarkers remained independent predictors of poor out-

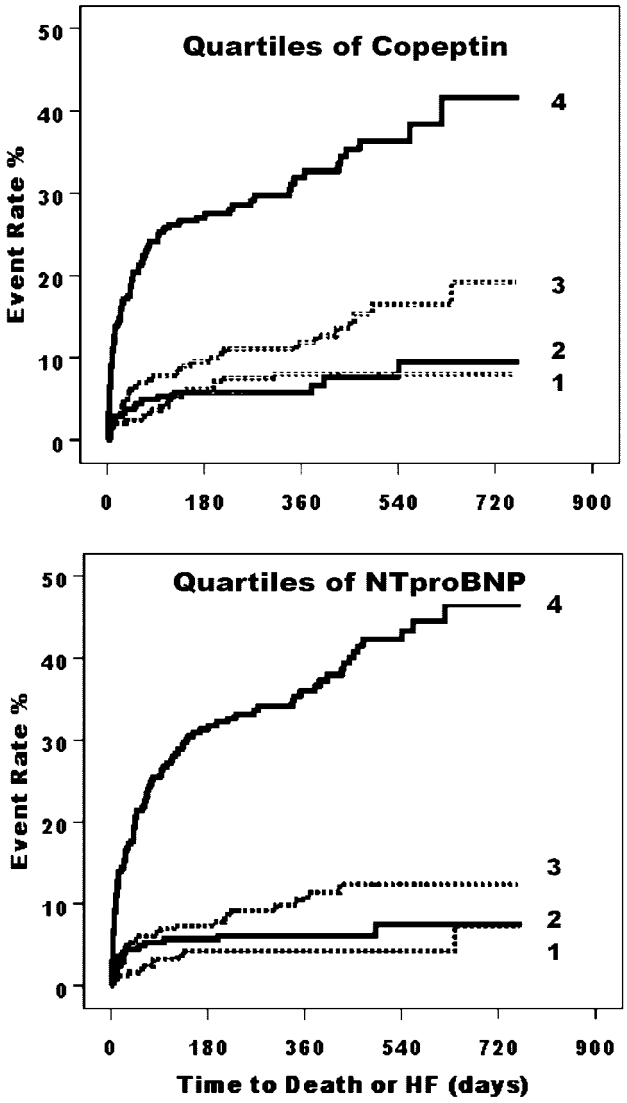
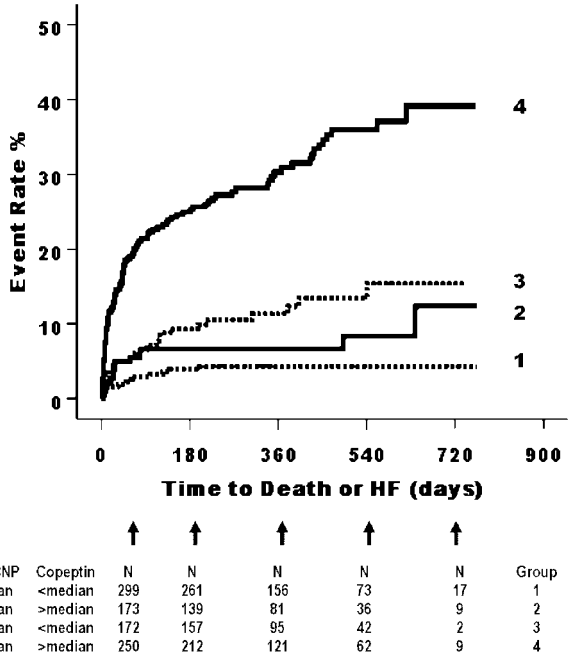


Figure 2. Kaplan-Meier curves: event rate (death or HF) in patients grouped according to quartiles of plasma copeptin or NTproBNP.



NTproBNP	Copeptin	N	N	N	N	N	Group
<median	<median	299	261	156	73	17	1
<median	>median	173	139	81	36	9	2
>median	<median	172	157	95	42	2	3
>median	>median	250	212	121	62	9	4

Figure 3. Kaplan-Meier analysis for copeptin levels (< or > the median) predicting the primary end point of death or HF, in patients stratified by NTproBNP < or > the median. N represents the numbers of subjects at risk at 60, 180, 360, 540, and 720 days.

come, but assessment of ventricular function by scanning was retained in the Cox model, which provides further evidence that these biomarkers may be providing information beyond an assessment of LV function.

The benefit of measuring both prohormones over their bioactive peptides include the lack of receptor binding or protein interactions and the longer half-lives, which result in higher plasma levels. The prohormones are also more stable in blood ex vivo, and this makes them generally more applicable in clinical practice.[10]

Vasopressin may have a number of deleterious effects in the post-AMI period. Acting through the V1a receptor, it has the following actions: (1) peripheral vasoconstrictor activity[19] that increases afterload and ventricular stress; (2) increasing protein synthesis in myocytes,[20] which leads to hypertrophy; and (3) vasoconstriction of coronary arteries. Through the V2 receptor, it retains water in the kidney tubules and contributes to an increased preload. The present findings suggest that the AVP system is another candidate neurohormonal pathway, in addition to the renin-angiotensin and sympathetic nervous systems, that may be associated with poor outcome after AMI. With the introduction of nonspecific (V1 and V2) and specific AVP V2 receptor antagonists, or "vaptans,"[21,22] it may be possible to tailor therapy to those at highest risk after AMI, depending on their neurohumoral profile.

Study Limitations

The present study was a single-center study, and the results need to be replicated in larger multicenter studies. There was a preponderance of STEMI, and cut points for non-STEMI may need to be established independently. The present study used blood samples in the recovery phase of AMI, and the utility of initial triage blood samples should be investigated. Finally, although both markers predicted 78 of the 86 events at 60 days, 8 remaining events eluded prediction.

Conclusions

The present study is the first report showing copeptin to be a new prognostic marker of death or HF in patients with AMI, independent of established conventional risk factors. A multimarker approach with copeptin and NTproBNP is more informative than either marker alone and may be useful for risk stratification in AMI patients.

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Disclosures

Dr Ng has submitted patents on behalf of the University of Leicester on biomarkers of cardiac disease. Dr Bergmann holds ownership in

BRAHMS AG, owns patent rights to the markers of the study, and is a member of the board of directors of BRAHMS AG. Dr Struck holds patent rights to the markers and is an employee of BRAHMS AG. Dr Morgenthaler is an employee of BRAHMS AG, a mid-sized company, based in Hennigsdorf, Germany, that commercializes immunoassays and has developed the copeptin assay, for which it owns patent rights. The present study was not financed by BRAHMS AG. The remaining authors report no conflicts.

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CLINICAL PERSPECTIVE

The role of the vasopressin system after acute myocardial infarction is unclear due to lack of accurate, reproducible, and easily available robust assays. Copeptin, the C-terminal part of the vasopressin prohormone, is secreted stoichiometrically with vasopressin and may be used as a surrogate marker of this system. It is also more stable in storage and is not bound by plasma proteins or receptors. In the present study, we compared the prognostic value of copeptin and an established marker, N-terminal pro-B-type natriuretic peptide (NTproBNP), after acute myocardial infarction. Patients (n=980) were recruited from a single university teaching hospital and followed up for the primary end point of death or heart failure readmission. Both markers performed equally well in stratifying risk for the primary end point and for death and heart failure as separate end points. In survival analyses, both markers had independent predictive value. Copeptin was especially useful in those with high NTproBNP levels, further predicting adverse events in this high-risk group. The profile of secretion of copeptin differed from that of NTproBNP, which suggests differences in stimuli to secretion. Neither marker was accurate in predicting reinfarction. In conclusion, copeptin and NTproBNP have independent predictive value for risk stratification after acute myocardial infarction for death or heart failure readmission, and this may permit future tailoring of the most appropriate therapy to high-risk patients.

C-Terminal Provasopressin (Copeptin) as a Novel and Prognostic Marker in Acute Myocardial Infarction: Leicester Acute Myocardial Infarction Peptide (LAMP) Study

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