Comparison of Copeptin, B-Type Natriuretic Peptide, and Amino-Terminal Pro-B-Type Natriuretic Peptide in Patients With Chronic Heart Failure

Prediction of Death at Different Stages of the Disease

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Objectives	This study sought to evaluate the predictive value of copeptin over the entire spectrum of heart failure (HF) and compare it to the current benchmark markers, B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP).
Background	Vasopressin has been shown to increase with the severity of chronic HF. Copeptin is a fragment of pre–pro-vasopressin that is synthesized and secreted in equimolar amounts to vasopressin. Both hormones have a short lifetime in vivo, similar to BNPs, but in contrast to vasopressin, copeptin is very stable in vitro. The predictive value of copeptin has been shown in advanced HF, where it was superior to BNP for predicting 24-month mortality.
Methods	This was a long-term observational study in 786 HF patients from the whole spectrum of heart failure (New York Heart Association [NYHA] functional class I to IV, BNP 688 ± 948 pg/ml [range 3 to 8,536 pg/ml], left ventricular ejection fraction 25 ± 10% [range 5% to 65%]).
Results	The NYHA functional class was the most potent single predictor of 24-month outcome in a stepwise Cox regression model. The BNP, copeptin, and glomerular filtration rate were related to NYHA functional class (p < 0.0001 for trend). Copeptin was the most potent single predictor of mortality in patients with NYHA functional class II (p < 0.0001) and class III (p < 0.0001). In NYHA functional class IV, the outcome of patients was best predicted by serum sodium, but again, copeptin added additional independent information.
Conclusions	Increased levels of copeptin are linked to excess mortality, and this link is maintained irrespective of the clinical signs of severity of the disease. Copeptin was superior to BNP or NT-proBNP in this study, but the markers seem to be closely related. (J Am Coll Cardiol 2008;52:266–72) © 2008 by the American College of Cardiology Foundation

The use of natriuretic peptides such as atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) and their precursors N-terminal pro-B-type natriuretic peptide (NT-proBNP) and N-terminal pro-atrial natriuretic peptide (NT-proANP) for the assessment of cardiovascular risk is firmly established in cardiovascular guidelines (1). Higher levels of natriuretic peptides have been shown to be associated with advanced patient age, renal impairment, cardiac arrhythmias, and systolic and diastolic dysfunction (2). These peptides therefore reflect an integral of risk factors resulting in the current functional cardiovascular status of individual patients, making them an invaluable tool for risk stratification (3–5).

Vasopressin, unlike the natriuretic peptides, is an antidiuretic and vasoconstricting hormone (6,7). Regulation of free water reabsorption, body fluid osmolarity, blood volume, vascular tone, and probably cell proliferation are mediated via interactions with specific receptors termed V_2 (renal) and V_{1a} (vascular). There are robust data showing that vasopressin is related to the severity of heart failure and probably to outcome as well (8–10). However, vasopressin is

difficult to measure because it is a hormone that is unstable, considerably bound to platelets, and rapidly cleared (11).

Copeptin is a fragment of pre–pro-vasopressin that is synthesized and secreted in equimolar amounts to vasopressin. Its advantages are its long stability and that it can be quickly and reliably measured in unprocessed plasma or serum. The predictive value of this marker has been shown in critically ill patients (12–15), in coronary artery disease (16), and in the context of advanced heart failure (17).

Little is known about the role of the vasopressin system as measured by its surrogate copeptin over the entire clinical spectrum of heart failure because research in this area so far has focused on advanced heart failure. In this study we investigated the predictive value of copeptin over the entire spectrum of heart failure.

Methods

We included 786 patients from several clinical trials in this long-term observational study. The study population represents the entire spectrum of severity of heart failure. At index time, clinical variables were obtained. Blood was drawn in every patient. Left ventricular ejection fraction (LVEF) was determined by echocardiography or technetium scintigraphy. In a subset of 177 patients, right heart catheterization was performed.

At follow-up, patients were treated as clinically appropriate. Most patients were cared for in our tertiary care heart failure outpatient clinic. The follow-up period was 2 years. The end point was defined as all-cause mortality within 24 months. If patients failed to attend their scheduled visits, survival status was obtained either by telephone calls or by the Austrian Central Office of Civil Registration (Zentrales Melderegister Österreich). The study was conducted in accordance with the Helsinki II declaration and approved by the ethics committee of our institution. All participants gave written informed consent.

Neurohumoral measurements. At index evaluation, blood samples were taken from an antecubital vein. The samples were centrifuged, transferred into chilled tubes, and placed on ice. Plasma was frozen at −20°C until it was assayed. The BNP level was determined using a commercially available rapid test purchased from Biosite Diagnostics (San Diego, California). The NT-proBNP level was determined using a commercially available test purchased from Roche Diagnostics (Basel, Switzerland).

Determination of copeptin (C-terminal pro-vasopressin) in the chemiluminescence/coated-tube format was performed as described (18). Briefly, the tubes were coated with a purified sheep polyclonal antibody raised against a peptide representing positions 132 to 147 of pre–pro-vasopressin. A purified sheep polyclonal antibody raised against a peptide representing positions 149 to 164 of pre–pro-vasopressin was labeled with MACN-akridinium-N.hydroxysuccinimide-ester and used as tracer. Dilutions of

a peptide representing positions 132 to 164 of pre–pro-arginine vasopressin 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 h at room temperature. The tubes were washed 4 times with 1 ml of LUMItest wash solution (B.R.A.H.M.S. AG, Hennigsdorf, Germany), and bound chemiluminescence was measured with an LB952T luminometer (Berthold, Bad Wildbach, Germany).

Statistical analysis. Continuous variables are expressed as mean ± standard deviation. To test differences in characteristics between survivors and nonsurvivors, Student t tests are used. The t test statistics require normal distributed differences of sample means, which is expectable for large samples (sum of both samples exceeding 100) due to the central limit theorem. This is the case for our data. To avoid problems arising from inhomogeneous variances, we use the t test based on the Welch formula. Differences among New York Heart Association (NYHA) functional classes were tested using 1-factorial analysis of variance and the t test based contrast statistics. Correlations of BNP, copeptin, and glomerular filtration rate (GFR) with NYHA functional class were calculated based on the Spearman rank correlation.

Categorical variables are given as number and percent. Differences between dichotomous variables (e.g., gender) were calculated using the Fisher exact test. Differences in the distribution of NYHA functional classes between survivors and nonsurvivors were tested using a chi-square test.

A stepwise logistic regression model was performed to identify independent predictors of copeptin. A stepwise Cox regression model was performed to identify independent predictors of outcome. Both models are based on a stepwise algorithm, with the p value set at 0.05 for entering and 0.1 for exclusion. All results of the regression model were presented using odds ratios EXP (B). Odds ratios were given for increase per unit. Receiver-operator characteristic (ROC) analysis was calculated to assess the utility of copeptin to distinguish between survivors and nonsurvivors. The 24-month survival was calculated using the Kaplan-Meier method, in which patients were divided into quartiles of copeptin plasma levels. Differences among Kaplan-Meier curves were tested using a log-rank test. A value of p < 0.05 was considered significant in all analyses; SPSS version 15.0 (SPSS Inc., Chicago, Illinois) was used for all statistical analyses.

Abbreviations and Acronyms

ANP = atrial natriuretic peptide

BNP = brain natriuretic peptide

GFR = glomerular filtration rate

LVEF = left ventricular ejection fraction

NT-proANP = N-terminal pro-atrial natriuretic peptide

NT-proBNP = N-terminal pro-B-type natriuretic peptide

NYHA = New York Heart Association

ROC = receiver-operator characteristic

Results

The total study population comprised 786 patients. Characteristics of this population represent the whole spectrum of heart failure based on systolic dysfunction (NYHA functional classes I through IV, BNP 688 ± 948 pg/ml [range 3 to 8,536 pg/ml], NT-proBNP 494 ± 724 pg/ml [range 2 to 8,877 pg/ml], copeptin 18.9 ± 24.2 pmol/l [range 0.7 to 224 pmol/l], LVEF 25 ± 10% [range 5% to 65%]). The mean age of our population was 57 ± 11 years; the gender ratio (male/female) was 81%:19%. The BNP and copeptin levels escalated with increasing NYHA functional class and decreasing glomerular filtration rate (Fig. 1). This was significant for trend for all 4 variables ($p < 0.0001$). Fifty percent of patients had a history of hypertension, 27% had signs of kidney dysfunction (GFR <60 ml/min), 22% had diabetes mellitus, and 40% had ischemic heart disease. The majority of patients (79%) were in sinus rhythm; the patients' mean weight was 80 ± 15 kg. Mean blood pressure values were 117 ± 23 mm Hg systolic and 74 ± 14 mm Hg diastolic. Heart rate was 75 ± 16 beats/min on average. Seventy percent of the patients were treated with a beta-blocker, 94% with a renin-angiotensin-aldosterone system antagonist, and 31% with an aldosterone antagonist; 66% of patients received furosemide requiring a mean dose of 75 ± 84 mg. The mean duration of the observation period was 15.8 ± 6.6 months (range 0.1 to 24 months). At the follow-up investigation, 233 (30%) patients had died. The patients' clinical characteristics dependent on outcome are presented in Table 1.

Correlations between copeptin and several dependent variables. Copeptin significantly correlated with GFR ($r = -0.343$; $p < 0.0001$), sodium ($r = -0.165$; $p < 0.0001$), systolic blood pressure ($r = -0.076$; $p < 0.034$), and the presence of leg edema ($r = -0.187$; $p < 0.0001$) in the entire population. Whereas this held true for GFR throughout all NYHA functional classes (I: $r = -0.347$; $p < 0.0001$, II: $r = -0.377$; $p < 0.0001$, III: $r = -0.290$; $p < 0.0001$, IV: $r = -0.290$; $p < 0.0001$), systolic blood pressure did not reach statistical significance in distinct NYHA functional classes. Sodium only reached statistically significant correlations in advanced stages (III: $r = -0.147$; $p < 0.007$, IV: $r = -0.201$; $p < 0.012$). Interestingly the occurrence of leg edema only correlated in NYHA functional class I with copeptin, but this correlation was very strong ($r = -0.568$; $p < 0.0001$).

In a subset of 77 patients in NYHA functional class III and 100 patients in NYHA functional class IV, right heart catheterization was performed. Regarding patients in NYHA functional class III, there was a bivariate correlation with copeptin and cardiac index ($r^2 = 0.228$; $p < 0.046$), pulmonary capillary wedge pressure ($r = -0.221$; $p < 0.053$), pulmonary vascular resistance index ($r = -0.271$; $p < 0.017$), and systemic vascular resistance index ($r = -0.277$; $p < 0.015$). Copeptin in patients in NYHA functional class IV only correlated with pulmonary vascular resistance index ($r = -0.253$; $p < 0.011$).

Stepwise Cox regression analysis to predict death within 24 months. ENTIRE POPULATION. Of all variables analyzed, NYHA functional class ($p < 0.0001$), GFR ($p < 0.0001$), systolic blood pressure ($p < 0.006$), and gender ($p < 0.014$) predicted death in the entire population. The NYHA functional class gave the most potent single information (Table 2). The models were similar if BNP or NT-proBNP was entered (data only shown for BNP).

DICHOTOMIZED BY NYHA FUNCTIONAL CLASS. Because NYHA functional class was the strongest predictor, we used this variable to dichotomize the severity of the disease to analyze the predictive power of copeptin at different stages
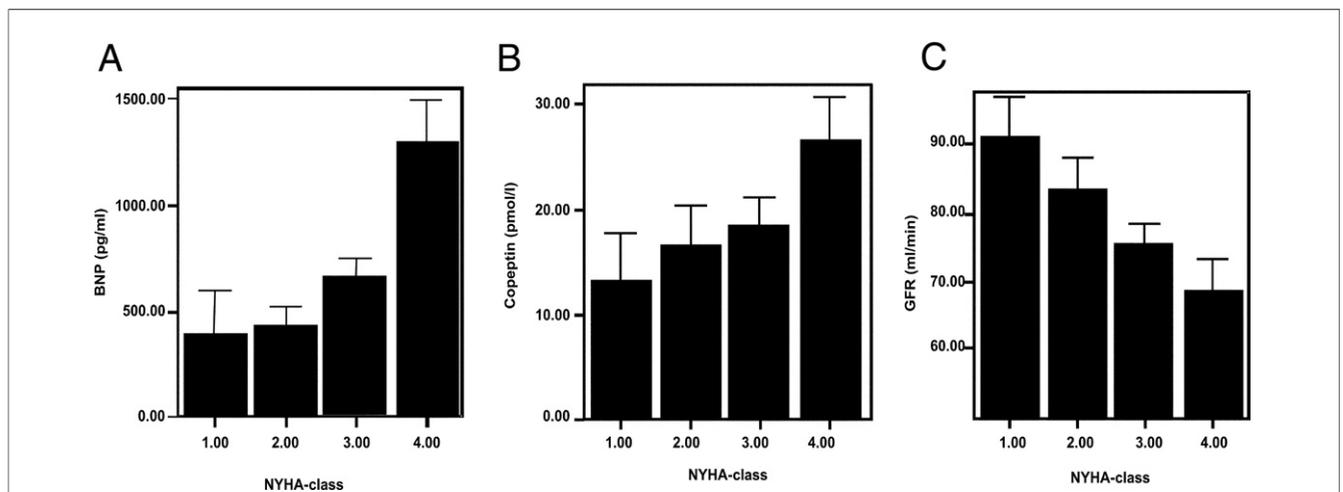

Figure 1   Box Plots of Plasma BNP, Copeptin, and GFR

Median levels of BNP, copeptin, and GFR depending on NYHA functional class.
BNP = brain natriuretic peptide; GFR = glomerular filtration rate; NYHA = New York Heart Association.

Table 1	Patients' Clinical Characteristics		
	Survivors (n = 553)	Nonsurvivors (n = 233)	p Value (2-Tailed)
Age (yrs)	56 ± 12	59 ± 10	0.0003
Female gender (%)	107 (19%)	34 (15%)	NS*
LVEF (%)	26 ± 11	23 ± 9	0.0001
NYHA functional class I/II/III/IV (%)	15.6/27.3/43.0/14.1	6.4/16.4/43.8/33.0	0.0001†
SBP (mm Hg)	120 ± 24	110 ± 18	0.0001
Sodium (mmol/l)	139 ± 5	137 ± 5	0.0001
GFR (ml/min)	82 ± 30	69 ± 29	0.0001
BMI (kg/m^2)	26.8 ± 4.3	26.3 ± 4	NS
BNP (pg/ml)	551 ± 890	1,018 ± 1,013	0.0001
Copeptin (pmol/l)	15.5 ± 9.4	27.2 ± 26.9	0.0001

All differences tested using *t* test, except those noted by footnote symbols. *Fisher exact test; †chi-square test.
BMI = body mass index; BNP = brain natriuretic peptide; GFR = glomerular filtration rate; LVEF = left ventricular ejection fraction; NS = not significant; NYHA = New York Heart Association; SBP = systolic blood pressure.

of heart failure. For patients in NYHA functional class I, the low mortality precluded statistical analysis. Copeptin was the most potent single predictor of mortality in patients with NYHA functional classes II (p < 0.0001) and III (p < 0.0001). For patients with NYHA functional class IV, sodium levels gave the most potent single information (p < 0.005), with stepwise additional information provided by gender (p < 0.0001), GFR (p < 0.0001), and copeptin (p < 0.022) (Table 3). The models were similar if BNP or NT-proBNP was entered (data only shown for BNP).

Stepwise logistic regression with copeptin as a dependent variable. To better understand the information provided by the respective individual values of copeptin, we performed a regression analysis with copeptin as a dependent variable. We found that BNP (p < 0.0001) was the best predictor of copeptin values, followed by GFR (p < 0.0001). Age and gender were additional influencing factors (both p < 0.0001). This strong relationship between copeptin, BNP, and GFR held true over every distinct NYHA functional class.

Kaplan-Meier analysis. Using a Kaplan-Meier model for 2-year survival, patients had a decreasing survival rate dependent on quartiles of copeptin distribution (p < 0.0001) (Fig. 2). This held true for subanalysis of NYHA

functional classes I (p < 0.02), II (p < 0.02), and III (p < 0.0001), but not for class IV.

ROC curves. The area under the ROC curve with respect to 2-year all-cause mortality was 0.711 for BNP and 0.711 for copeptin. The predictive power increased to an area under the ROC curve of 0.744 if both variables were added in one model (Fig. 3).

Discussion

In the present study we have shown a strong and independent correlation between plasma copeptin levels and all-cause mortality in a cohort of patients with chronic heart failure. Patients with increased levels of copeptin had a worse prognosis. This held true over the entire cohort of symptomatic patients (NYHA functional class II, III, and IV). Increased levels of copeptin were best predicted by natriuretic peptides and kidney function.

Prognostic implications. The prognostic role of neurohumoral markers in heart failure is of great interest and clinical importance. Natriuretic peptides such as ANP and BNP or their inactive N-terminal precursors NT-proBNP or NT-proANP are currently certainly the benchmark against which all novel biomarkers must be measured.

Table 2	Single-Predictor and Multivariable Stepwise Cox Regression Analysis for 24-Month Mortality for Various Clinical Variables					
	Single-Predictor Model for Survival			Multivariable Model for Survival		
	Odds Ratio	95% Confidence Interval	p Value	Odds Ratio	95% Confidence Interval	p Value
BNP (pg/ml)	1.0003	1.0002–1.0003	0.0005			
Copeptin (pmol/l)	1.0101	1.0069–1.0133	0.0005			
Age (yrs)	1.0205	1.0085–1.0326	0.0008			
NYHA functional class	1.6963	1.4527–1.9808	0.0005	1.5038	1.2683–1.7830	0.0005
GFR (ml/min)	0.9871	0.9824–0.9918	0.0005	0.9881	0.9827–0.9936	0.0005
LVEF (%)	0.9706	0.9562–0.9852	0.0001			
SBP (mm Hg)	0.9820	0.9755–0.9885	0.0005	0.9899	0.9828–0.9970	0.0055
Sodium (mmol/l)	0.9673	0.9553–0.9795	0.0005			
BMI (kg/m^2)	0.9742	0.9443–1.0051	0.1009			
Female gender (%)	1.3312	0.9253–1.9253	0.1232	1.6671	1.1092–2.5057	0.0140

Abbreviations as in Table 1.

Table 3	Stepwise Cox Regression Analysis for Predicting Survival Depending on NYHA Functional Class		
	Odds Ratio	95% Confidence Interval	p Value
NYHA functional class II			
Copeptin (pmol/l)	1.0138	1.0066–1.0209	0.0001
LVEF (%)	0.9584	0.9218–0.9965	0.0327
NYHA functional class III			
Copeptin (pmol/l)	1.0098	1.0031–1.0165	0.0039
Age (yrs)	1.0378	1.0147–1.0614	0.0012
SBP (mm Hg)	0.9850	0.9739–0.9962	0.0086
NYHA functional class IV			
Sodium (mmol/l)	0.9272	0.8802–0.9767	0.0044
Female gender (%)	3.720	1.6995–8.1951	0.0010
GFR (ml/min)	0.9805	0.9694–0.9917	0.0007
Copeptin (pmol/l)	0.9864	0.9752–0.9977	0.0181

Abbreviations as in Table 1.

In an earlier article we showed that copeptin is a reliable outcome predictor in advanced heart failure, at least comparable to BNP (17). In this study we evaluated the predictive aptitude of copeptin for the entire spectrum of heart failure, including patients with NYHA functional class I to IV, BNP levels from 3 to 8,536 pg/ml, and the entire spectrum of progressive kidney dysfunction.

The most potent independent, single prediction was provided by the clinical marker NYHA functional class, which was even superior to BNP. An explanation for this surprising finding may be that this investigation was done at a tertiary care center with great experience in heart failure. The expertise of a clinical assessment undertaken in a heart failure unit is most likely not applicable to the general setting, where laboratory markers are more objective.
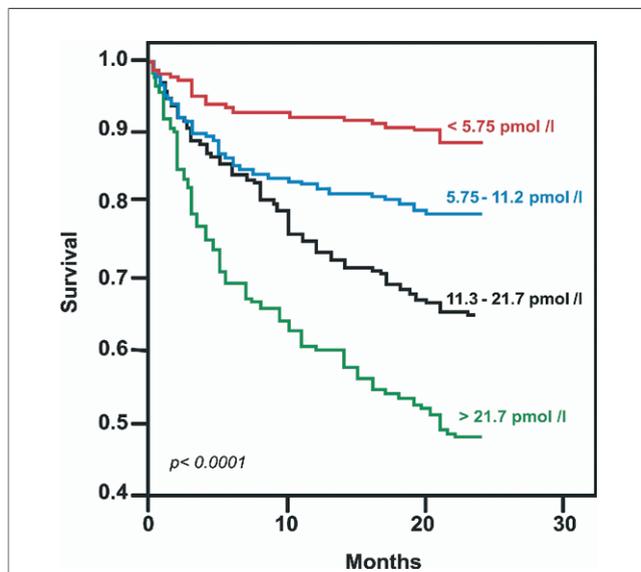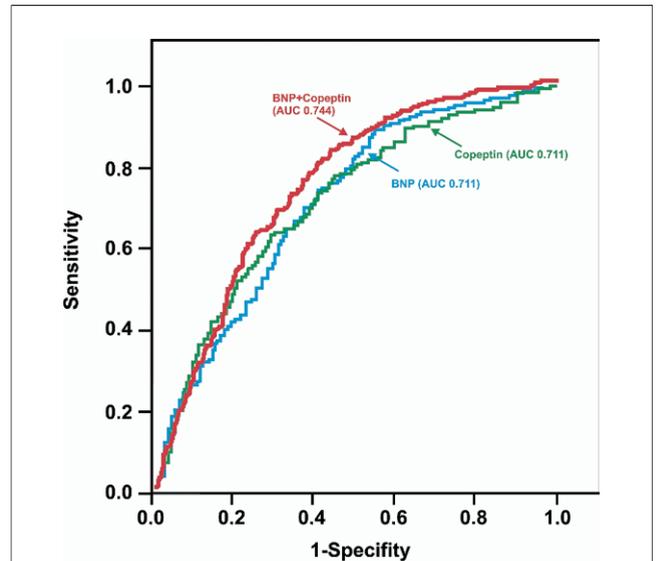

Figure 3   **ROC for 24-Month Survival**

Area under receiver-operator characteristic (ROC) curves for 24-month survival for copeptin, BNP, and copeptin plus BNP. AUC = area under the receiver-operator characteristic curve; other abbreviations as in Figure 1.

Because NYHA functional class was the strongest predictor, we used this variable to dichotomize the severity of the disease to analyze the predictive power of copeptin at different stages of heart failure. Copeptin was independently related to mortality in each symptomatic stage of heart failure; it was most compelling in NYHA functional classes II and III. This is an important finding because NYHA functional classes II and III, the intermediate classes, are more difficult to judge in the ambulatory setting than the more obvious NYHA functional classes I and IV.

For asymptomatic patients (NYHA functional class I), the event rate was too low to provide any information from our cohort. Recent data presented by Khan et al. (16) show that copeptin is a powerful predictor of outcome after acute myocardial infarction. Because myocardial infarction can be seen as stage A to B heart failure, it can be presumed that copeptin might also provide some predictive information in this early stage.

For patients in the most severe stage of heart failure, NYHA functional class IV, copeptin provided independent additional information, but was inferior to sodium levels and especially GFR. Again, BNP provided no additional information. It can be presumed that in the case of end-stage heart failure, fluid-regulating hormones might be of limited value for prognosis because kidney function as the morphologic substrate of fluid regulation becomes paramount. The importance of kidney function as a prognostic marker is well described and might concern especially severe heart failure patients (19). Considering the whole system of diuretic and antidiuretic hormones as well as kidney function in one model could probably provide some additional information.

Figure 2   **Quartiles of Copeptin**

Kaplan-Meier plots: survival in patients grouped according to quartiles of plasma copeptin.

Regression analysis revealed a strong interdependence between this triad of fluid homoeostasis. It could be hypothesized that an uncoupling of the whole system corresponds to an advanced dysregulation with an increasing risk for future events, as already described in other patterns (20). This would imply that in the future, one marker could not be sufficient to provide the full prognostic information of the fluid-regulating system in heart failure. More sophisticated models are warranted to test this hypothesis.

Clinical implications. What makes vasopressin and its precursor copeptin exciting for heart failure research today is not only the prognostic information provided by these markers, but also the role of vasopressin blockade as a potential new therapeutic target. Newly developed agents targeting vasopressin receptors are under investigation and might result in a novel adjunct treatment of both acute and chronic heart failure (21–24).

V_2 antagonists are viewed as a new class of diuretics, termed "aquaretics" because of their ability for free water diuresis without an accompanying significant depletion of electrolytes or worsening of renal function (24,25). Although excellent results were found based on their diuretic properties, no survival benefit could be shown (26,27).

Only a post hoc analysis of an earlier trial suggested a survival benefit for patients with severe heart failure (22). This is in accordance with our previous data, in which copeptin was markedly increased especially in this population (17).

Our current data confirm that increased levels of copeptin are linked to excess mortality, and this link is maintained irrespective of the clinical signs of severity of the disease. Copeptin could therefore emerge as an independent marker to identify heart failure patients from the whole spectrum of the disease, who could benefit from adjunct therapy with a V_2 antagonist. This could in the future permit a more tailored therapy for heart failure patients. This hypothesis should be proven in further studies.

In advanced stages of heart failure (NYHA functional classes III and IV), we performed right heart catheterization in a subpopulation of patients and found a significant correlation between copeptin and indexes of vascular resistance. This offers some evidence for the importance of V_{1a} receptor signaling in heart failure, which directly affects the myocyte and vasoconstriction. This could provide a rationale to pursue V_{1a} antagonists in chronic heart failure.

Study limitations. During follow-up, therapy was adapted as clinically appropriate and according to guidelines. Thus, a treatment effect during follow-up cannot be excluded. Patients investigated in our study were younger and have more hypertension and less coronary artery disease than in other large clinical studies. This might be the result of this investigation being performed at a tertiary care unit known to care for younger patients. The large number of patients with hypertensive cardiomyopathy (compared with other studies) might be based on the growing awareness about this disease entity in recent years.

Conclusions

Copeptin is a novel predictive marker in chronic systolic heart failure, not only in advanced but also in less severe stages. Copeptin was superior to BNP in this study, but both markers seem to be closely related.

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REFERENCES

1. The Task Force for the Diagnosis and Treatment of CHF of the European Society of Cardiology. Guidelines for the diagnosis and treatment of chronic heart failure: full text (update 2005). Eur Heart J 2005;26:1115–40.
2. Omland T, Persson A, Leong NG, et al. N-terminal pro-b-type peptide and long-term mortality in acute coronary syndromes. Circulation 2002;106:2913–18.
3. Maisel A, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 2002;347:161–6.
4. Hobbs FDR, Davis RC, Roalfe AK, Hare R, Davies MK, Kenkre JE. Reliability of N-terminal pro-brain natriuretic peptide assay in diagnosis of heart failure: cohort study in representative and high risk community populations. BMJ 2002;324:1498–500.
5. Wang TJ, Larson MG, Levy D, et al. Plasma natriuretic peptide levels and risk of cardiovascular events and death. N Engl J Med 2004;350:655–63.
6. Kalra PR, Anker STD, Coats JS. Water and sodium regulation in chronic heart failure: the role of natriuretic peptides and vasopressin. Cardiovasc Res 2001;51:495–509.
7. Chatterjee K. Neurohormonal activation in congestive heart failure and the role of vasopressin. Am J Cardiol 2005;95 Suppl:8B–13B.
8. Francis GS, Benedict C, Johnstone DE, et al. Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure: a substudy of the Studies of Left Ventricular Dysfunction (SOLVD). Circulation 1990;82:1724–9.
9. Rouleau JL, Packer M, Moye L, et al. Prognostic value of neurohumoral activation in patients with an acute myocardial infarction: effect of captopril. J Am Coll Cardiol 1994;24:583–91.
10. Nakamura T, Funayama H, Yoshimura A, et al. Possible vascular role of increased plasma arginine vasopressin in congestive heart failure. Int J Cardiol 2006;106:191–5.
11. Struck J, Morgenthaler NG, Bergmann A. Copeptin, a stable peptide derived from the vasopressin precursor, is elevated in serum of sepsis patients. Peptides 2005;26:2500–4.
12. Jochberger St, Morgenthaler NG, Mayr VD, et al. Copeptin and arginine vasopressin concentrations in critically ill patients. J Clin Endocrinol Metab 2006;91:4381–6.
13. Westermann I, Dünser MW, Hass T, et al. Endogenous vasopressin and copeptin response in multiple trauma patients. Shock 2007;28:644–9.
14. Morgenthaler NG, Müller B, Struck J, Bergmann A, Redl H, Christ-Grain M. Copeptin a stable peptide of the arginine vasopressin precursor is elevated in septic and hemorrhagic shock. Shock 2007;2:219–26.
15. Müller B, Morgenthaler N, Stolz D, et al. Circulating levels of copeptin, a novel biomarker, in lower respiratory tract infections. Eur J Clin Invest 2007;37:145–52.
16. Khan SQ, Dhillon OS, O'Brien RJ, et al. C-terminal provasopressin (copeptin) as a novel and prognostic marker in acute myocardial infarction: Leicester Acute Myocardial Infarction Peptide (LAMP) study. Circulation 2007;115:2103–10.
17. Stoiser B, Mörtl D, Hülsmann M, et al. Copeptin, a fragment of the vasopressin precursor, as a novel predictor of outcome in heart failure. Eur J Clin Invest 2006;36:771–8.

18. Morgenthaler NG, Struck J, Alonso C, Bergmann A. Assay for the measurement of copeptin, a stable peptide derived from the precursor of vasopressin. Clin Chem 2006;52:112–9.

19. Hillege HL, Nitsch D, Pfeffer MA, et al. Candesartan in heart failure. Assessment of Reduction in Mortality and Morbidity (CHARM) Investigators. Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. Circulation 2006;113:671–8.

20. Hülsmann M, Stefenelli T, Berger R, et al. Response of right ventricular function to prostaglandin E1 infusion predicts outcome for severe chronic heart failure patients awaiting urgent transplantation. J Heart Lung Transplant 2000;19:939–45.

21. Gheorghiade M, Niazi I, Ouyang J, et al. Vasopressin V2-receptor blockade with tolvaptan in patients with chronic heart failure: results from a double-blind randomized trial. Circulation 2003;107:2690–6.

22. Gheorghiade M, Gattis W, O'Connor C, et al. Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: a randomized controlled trial (ACTIV). JAMA 2004;291:1963–71.

23. Thibonnier M. Vasopressin receptor antagonists in heart failure. Curr Opin Pharmacol 2003;3:683–9.

24. Goldsmith SR, Gheorghiade M. Vasopressin antagonism in heart failure. J Am Coll Cardiol 2005;46:1785–91.

25. Verbalis JG. AVP receptor antagonists as auqaretics: review and assessment of clinical data. Cleve Clin J Med 2006;73 Suppl 3:24–33.

26. Konstam MA, Gheorghiade M, Burnett JC, et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST outcome trial. JAMA 2007;297:1319–31.

27. Gheorghiade M, Konstam MA, Burnett JC, et al. Short-term clinical effects of Tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure. The EVEREST clinical status trial. JAMA 2007;297:1332–43.