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# Copeptin for Discriminating Two-Year Mortality in Heart Failure Patients with Moderate to Severe Systolic Dysfunction

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## Abstract

**Background:** Patients with heart failure and impaired systolic function may have a highly variable clinical course that renders it difficult to assess the individual prognosis. We hypothesized that ejection fraction would incompletely characterize prognosis in systolic heart failure and that biomarkers would add significant information. This study addresses the specific question whether co-peptin may add value in the evaluation of two-year prognosis in heart failure patients with known systolic dysfunction.

**Methods:** Prospective observational cohort study in 37 patients with symptomatic chronic heart failure (classes II to IV of the NYHA classification) and moderate to severe left ventricular systolic dysfunction. We evaluated clinical, echo-cardiographic and laboratory predictors of 24-month mortality specifically assessing the role of co-peptin.

**Results:** Six patients (16%) died during the follow-up. Patients who died had significant higher prevalence of NYHA class IV heart failure, higher blood osmolality and higher levels of NT-proBNP and co-peptin. In unvariable analysis NYHA functional class (p=0.013), serum creatinine (p=0.034), osmolality (p=0.009), NT-proBNP (p=0.013) and copeptin (p=0.003) were predictors of mortality at 24 months. Only copeptin (p=0.004) remained an independent predictor of death in Cox regression analysis.

**Conclusions:** Our results suggest that, in patients with heart failure and impaired left ventricular systolic function, copeptin level determination may be useful for predicting mortality at two years.

**Keywords:** Systolic heart failure; Biological markers; Copeptin; Prognosis

## Introduction

Chronic Heart Failure (HF) has high incidence, prevalence and prognostic impact. Current therapeutic options to improve morbidity and mortality include pharmacological interventions, implantable devices and heart transplant [1]. The identification of prognostic markers for the appropriate classification of disease severity and to guide therapy is a rational approach. Multiple clinical, hemodynamic, biochemical, structural and electrophysiological factors have been related to prognosis in patients with chronic HF [2]. In clinical practice, the conventionally used prognostic variable has been the Left Ventricular Ejection Fraction (LVEF) and is currently used to guide the implantation of cardiac defibrillators in primary prevention [1]. However, patients with systolic HF may have a highly variable clinical course [3] that renders it difficult to assess the prognosis of an individual patient. Biomarkers, including natriuretic peptides and co-peptin may provide additive prognostic information [4,5]. However, the additional value of co-peptin over known prognostic variables in heart failure with systolic function has not been elucidated so far.

We sought to identify predictive markers of two-year mortality in chronic HF patients with moderate to severe systolic dysfunction. We hypothesized that ejection fraction would incompletely characterize prognosis in systolic heart failure and that biomarkers would add significant information. This study addresses the specific question whether copeptin provides incremental prognostic information in the evaluation of heart failure patients with known systolic dysfunction in a two-year follow-up.

## Patients and Methods

### Study design

We conducted a prospective observational cohort study in 37 patients with stable symptomatic chronic HF (classes II to IV of the New York Heart Association (NYHA) classification) and Left Ventricular (LV) systolic dysfunction. Patients were consecutively included at the Echocardiography Laboratory of our University Hospital. The study was approved by the local Ethics Committee and all participants gave informed consent.

Inclusion criteria were age older than 18 years, stable chronic HF NYHA classes II to IV, LV end-diastolic diameter >55 mm and LVEF ≤ 40%. Patients were excluded if they had moderate or severe primary valvular disease and history of cancer with expected survival under 2 years. Patients were also excluded if they had history of chronic renal failure or baseline serum creatinine above 3 mg/dL.

All patients underwent baseline clinical examination, hematologic and biochemistry tests, and transthoracic echocardiography. We

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evaluated the baseline predictors of all-cause mortality at 24 months of follow-up. Vital status was obtained by telephone interview and by consulting the hospital records. Clinical follow-up and treatment was the responsibility of the patient's attending physician that was blinded for the study baseline parameters.

### Assays

All blood samples were drawn from an anticubital vein after 5 minutes of rest in the supine position. Blood count, serum levels of creatinine, sodium, and NT-proBNP were processed and analyzed in the Hospital clinical laboratory. The levels of NT-proBNP were determined with solid-phase immunometric assay on Immulite 2000 (Siemens Healthcare Diagnostics, Breda, Netherlands) commercially available and validated in clinical practice. Osmolality was calculated using the formula [6]: osmolality = 1.86 x [sodium (mmol/L)] + [glucose (mg/dL)]/18 + [urea (mg/dL)]/5.992 + 9.

Part of the blood was collected in EDTA tube, to which aprotinin was added (500 KIU/mL). It was centrifuged at 1600 xg for 15 min at 4°C and plasma was removed, divided into aliquots and stored at -80°C. Copeptin concentration was determined by radioimmunoassay according to the protocol established by the laboratory (Phoenix Pharmaceutical Inc., CA, USA). Briefly, the test is based on the competition of $^{125}$I-copeptin and copeptin (either standard or unknown) binding to limited quantity of specific copeptin antibodies in each reaction. As the quantity of copeptin in the standard or unknown sample increases, the amount of $^{125}$I-copeptin able to bind to the antibody is decreased. By measuring the amount of $^{125}$I-peptide bound as a function of the concentration of the peptide in standard reaction mixtures, it was possible to construct a "standard curve" from which the concentration of copeptin in the samples could be determined.

### Echocardiography

We used ATL HDI 5500 (ATL Philips Medical Systems, Bothell, Washington, USA) or AlokaProsound alpha 10 (Aloka, Tokyo, Japan) equipment in the echo-cardiographic assessment. The protocol included conventional 2D echocardiography, M-mode, Doppler and pulsed-wave tissue Doppler of the mitral annulus.

The LV systolic function was evaluated using several parameters: the E-septum distance, LV shortening fraction, Simpson biplane LVEF and LV dP/dT when there was significant mitral regurgitation (> II / IV).

The assessment of LV diastolic function was performed by Doppler flow analysis of the LV filling and also by the E/E' ratio. Ventricular remodeling was assessed using the relative wall thickness and ventricular mass index.

### Statistical analysis

Continuous variables are presented as median and interquartile range. We used the Mann-Whitney U test to assess different characteristics between survivors and non-survivors.

Categorical variables are presented as number and percentage. The differences between these variables were calculated using the Chi-square test.

Receiver-operator characteristic (ROC) analysis was calculated to assess the utility of copeptin and NT-proBNP to distinguish between survivors and non-survivors. The 24-month survival was calculated using the Kaplan-Meier method, in which patients were divided according to the best discriminatory value of copeptin according to sensitivity-specificity analysis of the ROC curve. Differences among Kaplan-Meier curves were tested using the log-rank test.

We applied uni-variable and multivariable Cox regression models to identify predictors of 24-month mortality. The multivariable model was based on a forward stepwise algorithm using the variables significantly related to mortality in the univariable analysis. All results of the regression model are presented using hazard ratios EXP (B) for increase per unit.

Correlations between copeptin and the other variables were explored using two-tailed Pearson test.

A p value <0.05 was considered significant in all tests. We used the statistical software SPSS version 17.0 (SPSS Inc., Chicago, Illinois).

## Results

### Patient characteristics

The baseline patient clinical, analytical and echocardiographic characteristics are listed in Table 1. The median age of the study group was 72 (62.5-75.0) years old. There were 29 (78%) men and 8 (22%) women. All patients were symptomatic with 51% in NYHA class II, 33% in class III and 16% in class IV. Most patients (95%) were taking angiotensin-converting enzyme inhibitors, 57% were taking aldosterone antagonists and 43% were treated with beta-blockers. Only three patients (8%) had an Implantable Cardiac Defibrillator (ICD) at baseline and one other patient was implanted a device during follow-up. Ischemic etiology was present in 41%. Median serum creatinine was 1.1 (1.0-1.4) mg/dL, NT-proBNP was 2951.0 (1226.8-7801.0) pg/mL and copeptin was 36.9 (26.5-72.1) pg/mL. Median LV end-diastolic diameter was 64.0 (58.5-71.5) mm and LV EF was 31.5 (25.3-33.6)%. The predominant ventricular remodeling pattern was eccentric hypertrophy.

Six patients (16%) died during the follow-up. In the survivor group 27 subjects (87%) completed the two-year follow-up. Four patients were lost to follow-up with median follow-up time of 110.5 (6.8-480.5) days.

Patients who died had significantly higher prevalence of NYHA class IV HF, higher blood osmolality and higher levels of NT-proBNP and copeptin (Table 1). Although median LV end-diastolic volume was higher and LV EF was lower in patients who subsequently died, no echo-cardiographic baseline characteristic was significantly different between the patient outcome groups. When we exclude patients that did not complete the follow-up from the analysis blood osmolality (p=0.024), NT-proBNP (p=0.12) and copeptin (p=0.002) remain significantly different between groups.

### Cox regression analysis to predict death within 24 months (Table 2)

In univariable analysis NYHA functional class (p=0.013), serum creatinine (p=0.034), osmolality (p=0.009), NT-proBNP (p=0.013) and copeptin (p=0.003) were predictors of mortality at 24 months. Of all variables analyzed only copeptin (p=0.004) remained an independent predictor of death.

To exclude that ICD carriers might be affecting the predictive power of the model we ran a forward stepwise Cox regression analysis excluding the four patients with ICD. Copeptin remained the only independent predictors of death with a hazardous ratio of 1.021 (p=0.004).

| Variables | Global (n=37) | Group I (Survivors) (n=31) | Group II (Non-Survivors) (n=6) | p |
|---|---|---|---|---|
| **Clinic and Demographic** | | | | |
| Age (years), median (IQR) | 72.0 (62.5-75.0) | 71.0 (62.0-75.0) | 73.0 (71.0-76.0) | 0.302 |
| Male gender, No. (%) | 29 (78) | 23 (74) | 6 (100) | 0.160 |
| BMI (Kg/m2), median (IQR) | 26.0 (23.7-29.3) | 26.0 (23.7-29.1) | 25.2 (22.4-30.7) | 0.837 |
| Mean BP (mmHg), median (IQR) | 90.0 (80.3-102.0) | 91.0 (82.5-102.8) | 86.0 (78.0-97.0) | 0.198 |
| HR (/min), median (IQR) | 76.5 (70-84.3) | 73.0 (69.3-84.8) | 79.0 (76.5-88.5) | 0.213 |
| HTN, No. (%) | 29 (78) | 23 (74) | 6 (100) | 0.160 |
| Diabetes, No. (%) | 11 (30) | 8 (26) | 3 (50) | 0.235 |
| Ischemic etiology, No. (%) | 15 (41) | 11 (35) | 4 (67) | 0.154 |
| ACEi/ BB/ spironolactone, No. (%) | 35 (95)/ 16 (43)/ 21 (57) | 28 (90)/ 14 (45)/ 18 (58) | 6 (100)/ 2 (33)/ 3 (50) | 0.427/ 0.592/ 0.715 |
| CRT-D or ICD, No. (%) | 4 (11) | 4 (13) | 0 (0) | 0.351 |
| NYHA class (II /III /IV), No. (%) | 19 (51)/ 12 (33)/ 6 (16) | 18 (58)/ 10 (32)/ 3 (10) | 1 (17)/ 2 (33)/ 3 (50) | 0.035* |
| **Blood tests** | | | | |
| Hemoglobin (g/dL), median (IQR) | 12.8 (12.1-14.0) | 13.1 (12.3-14.0) | 12.5 (11.1-13.2) | 0.187 |
| Creatinine (mg/dL), median (IQR) | 1.1 (1.0-1.4) | 1.1 (0.9-1.3) | 1.4 (1.0-2.2) | 0.129 |
| Sodium (mmol/L), median (IQR) | 140.0 (137.5-142.0) | 140.0 (138.0-142.0) | 137.5 (134.3-143.8) | 0.442 |
| Osmolality (mOsmol/Kg), median (IQR) | 288.0 (282.0-296.0) | 287.0 (279.0-293.0) | 297.0 (291.3-309.3) | 0.027* |
| NT-proBNP (pg/mL), median (IQR) | 2951.0 (1226.8-7801.0) | 1959.5 (1143.3-6445.3) | 9341.5 (6464.3-15210.8) | 0.012* |
| Copeptin (pg/mL), median (IQR) | 36.9 (26.5-72.1) | 33.4 (24.1-48.4) | 74.6 (55.0-162.4) | 0.002* |
| **Echocardiography** | | | | |
| LV end-diastolic diameter (mm), median (IQR) | 64.0 (58.5-71.5) | 64.0 (58.0-72.0) | 65.0 (61.8-69.8) | 0.533 |
| LV end-diastolic volume (mL), median (IQR) | 159.0 (128.5-198.0) | 155.0 (124.5-193.0) | 174.5 (112.5-210.5) | 0.680 |
| Simpson EF (%),median (IQR) | 31.5 (25.3-33.6) | 31.8 (27.3-33.8) | 26.8 (18.0-32.8) | 0.187 |
| septal E/E' , median (IQR) | 16.7 (12.3-23.6) | 14.8 (11.6-24.1) | 20.1 (17.9-22.4) | 0.149 |
| E-septum (mm), median (IQR) | 18.0 (16.0-24.0) | 18.0 (15.5-23.5) | 21.0 (17.5-26.3) | 0.211 |
| Shortening fraction (%),median (IQR) | 17.5 (12.7-21.1) | 18.5 (13.6-21.1) | 16.2 (8.9-25.6) | 0.967 |
| dP/dT (mmHg/s), median (IQR) | 591.5 (514.0-715.0) | 604.0 (495.0-719.0) | 581.5 (444.5-693.5) | 0.596 |
| RWT, median (IQR) | 0.32 (0.27-0.35) | 0.32 (0.28-0.35) | 0.27 (0.25-0.33) | 0.209 |
| Ventricular Mass Index (g/m2), median (IQR) | 149.1 (123.9-176.3) | 149.1 (123.1-188.1) | 151.9 (123.4-166.8) | 0.742 |

*significant; ACEi- angiotensin converter enzyme inhibitors; BB- beta-blockers; BMI- body mass index; BP- blood pressure; CRT-D- cardiac resynchronization therapy defibrillator; EF- ejection fraction; HR- heart rate; HTN- hypertension; ICD- implantable cardiac defibrillator; LV- left ventricular; RWT- relative wall thickness

**Table 1:** Baseline clinical, laboratorial and echocardiographic characteristics and comparison of Survivors vs Non-Survivors

| Variables | Univariable Model for Survival | | | Multivariable Model for Survival | | |
|---|---|---|---|---|---|---|
| | Hazard ratio | 95% confidence interval | p | Hazard ratio | 95% confidence interval | p |
| Functional class | 4.125 | 1.344-12.66 | 0.013 | | | |
| Creatinine | 4.923 | 1.124-21.566 | 0.034 | | | |
| Osmolality | 1.118 | 1.029-1.216 | 0.009 | | | |
| NT-proBNP | 1.012 | 1.003-1.022 | 0.013 | | | |
| Copeptin | 1.022 | 1.007-1.037 | 0.003 | 1.022 | 1.007-1.037 | 0.003 |

**Table 2:** Univariable and Multivariable Stepwise Cox Regression Analysis for 24-Month Mortality for Various Clinical Variables

## ROC curves for biomarkers

The area under the ROC curve with respect to 2-year all-cause mortality was 0.828 for NT-proBNP and 0.900 for copeptin (Figure 1). A copeptin cutoff of 54 ng/mL predicted death at 2 years with 83% sensitivity and 83% specificity.

The other biomarkers selected from univariable Cox regression analysis were not useful tests for predicting mortality at 24 months. Creatinine had a non-significant (p=0.113) area under the ROC curve of 0.696.

## Kaplan-Meier analysis for copeptin

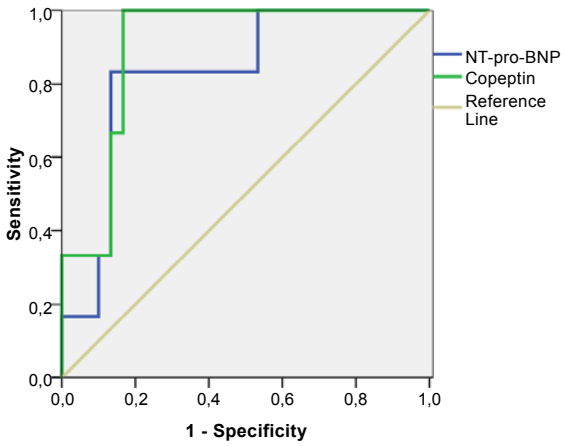
Using a Kaplan-Meier model for two-year survival, patients had a decreasing survival rate dependent on copeptin distribution using the 54 ng/mL cutoff obtained from the ROC curve analysis (p=0.001) (Figure 2- Panel A). Also, mortality only afflicted those patients in the higher tertile of copeptin at baseline (Figure 2- Panel B).

## Correlation of copeptin to other variables

To explore what variables accounted for the outcome predictive power of copeptin we searched for significant correlation with clinical, serological and echo-cardiographic parameters. Copeptin significantly correlated with creatinine (r=0.512, p=0.001), osmolality (r=0.473, p=0.004), NT-proBNP (r=0.707, p<0.001) and estimated peak pulmonary systolic pressure (r=0.395, p=0.028).

## Discussion

In the present study we have shown an independent correlation between plasma copeptin levels and all-cause mortality in a cohort of patients with chronic HF and impaired systolic function. Patients with increased levels of copeptin had worse prognosis and a cutoff of 54 ng/mL could predict mortality at 24 months with good diagnostic accuracy in our cohort. Furthermore, the information provided by this biomarker was superior to widely used and validated NT-proBNP. Therefore, we suggest that assessment of copeptin should be included in large studies of survival in systolic HF in order to validate these preliminary findings.




Area Under the Curve

| Variables | Area | p | 95% Confidence Interval |
|---|---|---|---|
| NT-pro-BNP (pg/mL) | 0.83 | 0.012 | 0.66-0.99 |
| Copeptin (pg/mL) | 0.90 | 0.002 | 0.79-1.00 |

**Figure 1:** Receiver-operator characteristic curve analysis with respect to two-year all-cause mortality for NT-proBNP and copeptin. A copeptin cutoff of 54ng/mL predicted death at two years with 83% sensitivity and 83% specificity.

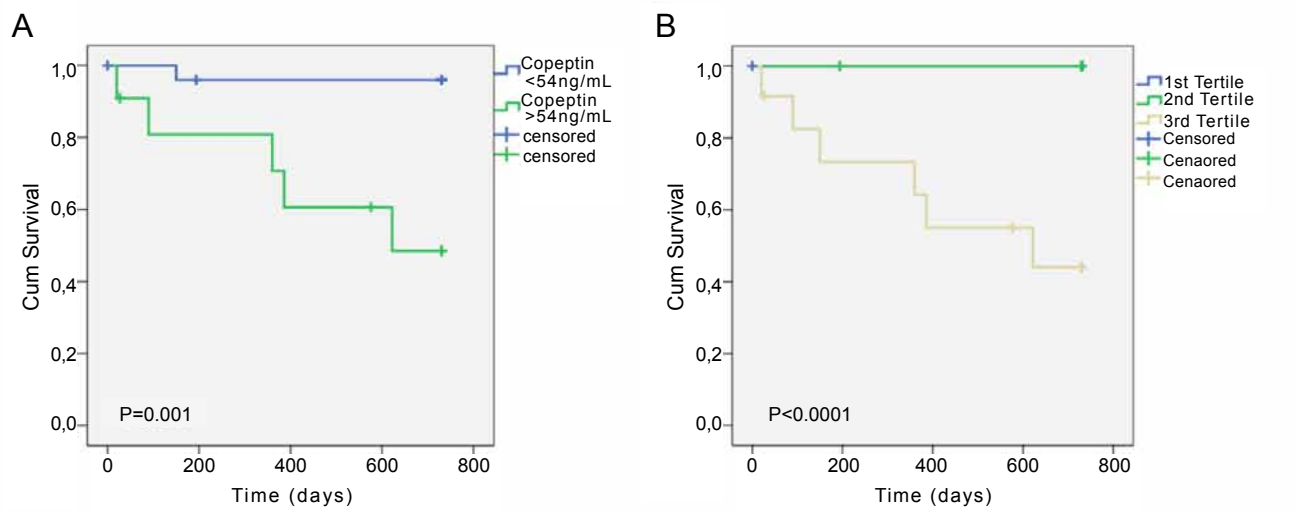



**Figure 2:** Kaplan-Meier survival curves for copeptin using the cutoff selected form ROC curve analysis (A) and according to copeptintertiles (B).

Copeptin is a glycopeptide of unknown function in the circulation [7]. It is derived from a larger precursor peptide, pre-provasopressin, along with Arginine-Vasopressin (AVP) and Neurophysin II [8]. AVP is the active hormone and elevated blood levels have been documented in patients with CHF and LV dysfunction [9-11]. Its concentration also relates to HF clinical severity [12]. AVP causes peripheral vasoconstriction [13] and ventricular hypertrophy [14] by acting through the V1A receptor. In the kidney, V2 receptor activation leads to insertion of aquaporin channels that mediate fluid retention and hyponatremia [15]. Although AVP would be an attractive target to become a biomarker in HF its measurement is affected by instability in plasma and rapid clearance [16]. However, copeptin is a stable glycopeptide that can be easily measured [17]. Furthermore, it is secreted in equimolar amounts to AVP, reflecting the activation of this Neurohormone [17].

Previous studies have documented the power of copeptin to predict mortality in several clinical scenarios. They include cardiovascular diseases like acute myocardial infarction [18], acute [19] and chronic HF [5] and also other broad medical conditions comprising ventilator associated pneumonia [20], traumatic brain injury [21], stroke [22] and patients with nonspecific complaints presenting to the emergency department [23]. Although these findings suggest nonspecific elevation in patients at risk for increased mortality, there is a rational pathophysiologic basis for the outcome predicting capabilities of copeptin in HF. In fact, the AVP pathway is up-regulated in HF to increase intravascular volume and maintain cardiac output [24].

Similarly to other neurohormones, it has been hypothesized that chronically elevated levels of circulating AVP may be maladaptive on the long run. In fact, high AVP levels were associated with one year cardiovascular mortality in ischemic cardiomyopathy [25]. Moreover, copeptin levels were found to predict mortality in patients with severe HF (NYHA class III and IV) [5]. This prognostic predictive power remained true in a broader group of HF patients in NYHA class I to IV recruited from several clinical trials [26]. However, the question whether copeptin could identify vulnerable patients for increased mortality among symptomatic patients with moderate to severe LV systolic dysfunction, a particularly high risk group, remained unanswered. In the present study we addressed this question and copeptin was a powerful independent predictor of mortality. In fact, it was the only independent predictor of two-year mortality. Although this is a significant finding that may impact future prognostic stratification strategies in HF it has to be validated in larger populations. If replicated these results may have future therapeutic implications as vasopressin antagonists have reached clinical trials [27]. Although they have failed to decrease mortality in the whole HF population, hypothetically, patients with increased copeptin levels may derive more benefit from this treatment.

Mortality in HF is affected by several variables [2]. In fact, our small sample was underpowered to assess further independent variables. This fact justifies why other well-known clinical and laboratory variables failed to add significant prognostic information to copeptin in the multiple regression model. Echo-cardiographic indexes including sensitive parameters such as tissue Doppler velocities were also unable to predict survival status at two years. Contributing factors may have been patient pre selection according to a narrow range of LVEF and also known variability in echo-cardiographic measurements [28]. However, our results are robust in finding copeptin as the most powerful predictor of mortality in this patient group.

Although patients with significantly impaired renal function were excluded in this study, we found that copeptin directly correlates to creatinine levels. This correlation has been previously described in a different setting [29] and may be relevant because kidney function is a well-known prognostic marker in HF [30]. The observation that osmolality directly correlates to copeptin suggests that the AVP system is appropriately up-regulated by osmolality triggers in this population. Pulmonary hypertension is also a known predictor of poor prognosis in HF [31] and we found a correlation between peak pulmonary artery systolic pressure and copeptin. NT-proBNP was the variable with the strongest relation to copeptin. Natriuretic peptide BNP and the precursor NT-proBNP are recognized in current guidelines as powerful markers of increased cardiovascular risk [1] and are considered the benchmark in HF biomarkers. NT-proBNP was a univariable predictor of mortality in this study but it didn't add relevant information to mortality prediction when copeptin was used. Similar observations were previously made in larger unselected HF populations [26]. These findings suggest that fluid regulatory functions and baroreceptor response of both hormonal systems may underlie mortality prediction of NT-proBNP and copeptin. However, in this study, we found that osmolality is an unvariable predictor of mortality and that it relates to copeptin levels suggesting that osmo-regulatory functions of the AVP pathway may be implicated in the better performance of copeptin over NT-proBNP. This should be further explored in future studies.

We recognize some limitations. Selection bias cannot be ruled out in our study. Sample size was relatively small and patients were not randomly selected. However, results are consistent with previous findings [5,26]. Also, variables were determined at a single time and temporal evolution and modification by therapy were not considered. Likewise, device therapy was under used in this non interventional study but, nonetheless, is above contemporary clinical trials figures [32]. However this study has the merit of suggesting, for the first time, that copeptin may be useful in further stratifying patients with known HF and moderate to severe LV systolic dysfunction.

## Conclusion

Our results suggest that in stable patients with HF and impaired LV systolic function copeptin level determination may be useful for predicting mortality at two years.

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