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Elevated copeptin is a prognostic factor for mortality even in patients with renal dysfunction☆

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ABSTRACT

Background: Copeptin has turned out to give valuable prognostic information for future cardiovascular events. However, since its plasma concentration directly depends on renal function, the value of copeptin as a predictor for outcome also in patients with chronic kidney disease (CKD) is unknown.
Methods: In this single-center substudy of the German Coronary Artery Disease–REnal Failure (CAD-REF) registry, 301 patients with an angiographically diagnosed stenosis ≥50% in at least one major coronary vessel were included. Estimated glomerular filtration rate (eGFR) was determined using the MDRD formula and patients were classified according to their CKD stage. Copeptin concentrations were measured before initial angiography. Follow-up was performed at 180 days, study endpoint was all-cause mortality.
Results: Of the 301 included patients, 35 (11.6%) patients had no CKD, 113 (37.5%) had CKD stage 1 or 2, 117 (38.9%) had CKD stage 3, and 36 (12.0%) had CKD stage 4 or 5. Copeptin was elevated (≥14 pmol/L) in 81 (26.9%) patients and normal (<14 pmol/L) in 220 (73.1%) patients. Copeptin values significantly increased with decreasing eGFR ($p < 0.001$) and were strongly correlated with creatinine values ($r = 0.567$, $p < 0.001$). During 180 days of follow-up, 15 patients (5.0%) died, 10 of them with elevated copeptin values. Multivariate Cox regression analysis showed that copeptin was the sole predictor for mortality (HRR 5.317 (95% CI 1.653–17.098), $p = 0.005$), independent of serum creatinine.
Conclusion: Elevated copeptin can be used as a valuable prognostic factor for intermediate-term mortality in patients with both coronary artery and renal disease.

1. Introduction

Copeptin has been discussed as a novel, easy-to-measure biomarker [1,2]. Copeptin is the C-terminal part of the arginine vasopressin (AVP) precursor protein which is synthesized in the hypothalamus and processed during axonal transport. Copeptin is released in equimolar amounts with AVP, also named antidiuretic hormone (ADH), from the precursor protein. Although the physiological function of copeptin is still not understood, it can be used as a surrogate marker for AVP because of its stability and its easy and fast measurability [1–3].

Copeptin is associated with several disease entities and is described as a stress hormone in acute illness [4]. Elevated levels of copeptin serve as a prognostic marker for unfavorable outcome in sepsis, shock, pneumonia, stroke, and acute coronary syndrome [4–7]. In healthy patients serum values of copeptin are <5 pmol/L [8]. Elevated copeptin levels are found early in myocardial infarction and the optimal cutoff for ruling out acute myocardial infarction has been proposed at 14 pmol/L [9].

Besides association of copeptin with cardiovascular disease, increased copeptin concentrations are linked to renal insufficiency: copeptin is negatively associated with estimated glomerular filtration rate (eGFR) [10] and positively associated with microalbuminuria [11]. Whether copeptin can be used as a predictor for negative outcome in patients with renal insufficiency and cardiovascular disease is still unclear.

In the Coronary Artery Disease–REnal Failure (CAD-REF) registry, patients with angiographically diagnosed coronary artery disease were included and their renal status prior to angiography was recorded [12,13]. Copeptin values of 301 patients were determined and thus, in this

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substudy, we could investigate the influence of normal and elevated plasma copeptin levels in patients with normal and decreased renal function on their intermediate-term survival.

2. Methods

The present study is a substudy of the multicenter Coronary Artery Disease – REnal Failure (CAD-REF) registry. The detailed trial design has been published previously [12]. Briefly, for this analysis, only patients ≥18 years from the University Hospital Muenster who underwent coronary angiography from January 2008 to September 2010 were consecutively enrolled. Inclusion criteria were an angiographical diagnosed stenosis ≥50% in at least one major coronary vessel, blood and urine samples prior to intervention, and written informed consent. Exclusion criteria were age < 18 years, pregnancy, known malignancy, polycystic kidney disease, immunosuppressive therapy, or condition after organ transplantation except kidney transplantation. Blood samples were directly transported in the core lab of the University Hospital Muenster and immediately processed. Patients from other CAD-REF centers were not included because copeptin concentration might have altered during transport of the blood samples by mail.

2.1. Ethical standards

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethic Committee of the Landesärztekammer Westfalen–Lippe and the Medical Faculty of the Westfälische Wilhelms–University Muenster (date August 16, 2007; No 2007–315-f-S). The CAD-REF registry was registered at ClinicalTrials.gov (identifier number NCT00679419, http://clinicaltrials.gov/). All patients gave written informed consent prior to their inclusion.

The CAD-REF Registry is conducted under the auspices of the German Cardiac Society (DGK) (http://dgk.org) and the German Society of Nephrology (DGFN) (http://www.dgfn.eu). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

2.2. Definition of risk factors

Cardiovascular risk factors were assessed at enrollment and were defined as follows: hypertension was self-reported, hyperlipidemia if total cholesterol levels were >200 mg/dl, LDL-cholesterol levels >150 mg/dl, or levels of lipoprotein (a) >25 mg/dl; history of smoking was defined if patients are current smokers or have previously smoked; family history of cardiovascular disease if stroke, myocardial infarction, or coronary intervention occurred in a first degree relative; diabetes mellitus was assumed if a patient was on diabetic diet or was treated with oral antidiabetics or insulin.

Peripheral artery occlusive disease (PAOD) was defined according to the Fontaine classification (stages I, IIa, IIb, III, and IV).

2.3. Renal function and copeptin concentration

Serum creatinine was measured in blood samples collected prior to angiography and was used to calculate the eGFR by the MDRD equation. Proteinuria was determined by dipstick test of the urine samples collected prior to angiography. Patients were subdivided into four groups according to their eGFR and proteinuria: group 1: patients with normal eGFR (eGFR ≥ 90 ml/min/1.73 m^2) and no proteinuria; group 2: patients with chronic kidney disease (CKD) stage 1 (eGFR ≥ 90 ml/min/1.73 m^2 and with proteinuria) and CKD stage 2 (eGFR 60–89 ml/min/1.73 m^2); group 3: patients with CKD stage 3 (eGFR 30–59 ml/min/1.73 m^2); group 4: patients with CKD stage 4 and 5 (eGFR <30 ml/min/1.73 m^2).

Copeptin plasma values were measured from EDTA blood samples collected prior to angiography. A commercial automated immunofluorescent assay (Copeptin, B.R.A.H.M.S. GmbH, Hennigsdorf, Germany) was performed on a Kryptor® analyzer. Patients were divided into two copeptin groups according to normal (<14 pmol/L) and elevated (≥14 pmol/L) copeptin levels in accordance with other studies [2,7,14].

2.4. Statistics

Differences in basic clinical characteristics between the CKD groups and copeptin groups were tested by ANOVA F-test for continuous variables, and overall chi-square test for dichotomous variables. The p-values for all of these tests are given in the tables. Correlation analysis was performed by two-sided Spearman test. Univariate and multivariate analysis of 180 days mortality was performed by Cox regression analyses for copeptin groups alone (crude HRR) and with potential covariates (adjusted HRR), taking normal copeptin level as reference.

For all tests, p-values < 0.05 were taken as significant. All statistical analyses were performed with SPSS version 23.0.0.0 (SPSS, Chicago, IL, USA) for Windows.

3. Results

The present study comprises a subgroup of the CAD-REF registry. Detailed baseline characteristics of the whole CAD-REF cohort have been published elsewhere [13]. For this analysis, a total of 301 patients (75.4% men) from the study center Muenster with copeptin blood values were included.

Baseline clinical data and cardiovascular risk factors (Table 1) as well as angiographic characteristics and percutaneous coronary intervention (PCI) data (Table 2) were analyzed according to CKD stages. Of all patients, 11.6% had no CKD (eGFR ≥90 ml/min/1.73 m^2, no proteinuria), 37.5% of the patients were grouped in CKD stage 1 (eGFR ≥90 ml/min/1.73 m^2, with proteinuria) and 2 (eGFR 60–89 ml/min/1.73 m^2), 38.9% in CKD stage 3 (eGFR 30–59 ml/min/1.73 m^2), and 12.0% in CKD stage 4 and 5 (eGFR <30 ml/min/1.73 m^2).

3.1. Baseline clinical data and cardiovascular risk factors

The average age was 69 years; with decreasing renal function patients' average age significantly increased from 60 years with no renal impairment to 74 years in CKD stage 3 ($p < 0.0001$). The percentage of male patients significantly decreased with decreasing renal function from 91.4% in patients without CKD to 66.7% with CKD stage 4 and 5 ($p = 0.011$). Patients with CKD stage 4 and 5 suffered significantly more often from hypertension than patients without CKD (94.4% vs. 85.7%, $p = 0.042$). PAOD was documented in 20.4% of all patients with significant differences between CKD stages ($p = 0.033$). The average serum creatinine value was 1.41 mg/dL. The scatter plot in Fig. 1a shows a strong and positive correlation between copeptin and serum creatinine concentration ($r = 0.567$, $p < 0.001$). Vice versa, the mean copeptin values rose from 6.0 pmol/L in the controls to 36.7 pmol/L in patients with CKD stage 4 and 5 ($p < 0.0001$, Fig. 1b).

No significant differences according to CKD stages were observed in body mass index (BMI), waist hip ratio (WHR), hyperlipidemia, family history of cardiovascular disease, diabetes mellitus, previous stroke, previous myocardial infarction, previous PCI, and previous coronary artery bypass grafting (CABG).

3.2. Baseline characteristics according to copeptin

Normal copeptin values (<14 pmol/L) were measured in 220 (73.1%) and elevated copeptin values (≥14 pmol/L) in 81 (26.9%) patients. The distribution of patients according to copeptin concentration is shown in Fig. 1c. Patients with elevated copeptin values were significantly older than patients with normal copeptin values (72.8 vs. 68.2 years, $p < 0.001$, Supplementary Table 1) and suffered almost twice as often from PAOD than patients with normal levels (31.3% and 16.4%, resp., $p = 0.004$). Creatinine levels were significantly higher in patients with elevated copeptin concentrations than in patients with normal copeptin concentrations (2.05 mg/dL vs. 1.17 mg/dL, $p < 0.0001$). eGFR values were significantly lower in patients with elevated copeptin values compared to patients with normal copeptin concentrations (41.4 ml/min/1.73 m^2 vs. 70.1 ml/min/1.73 m^2, $p > 0.001$). Proteinuria was present in 35.8% of all patients with elevated copeptin, but only in 15.5% of all patients with normal copeptin values ($p < 0.001$, Supplementary Table 1).

3.3. Angiographic characteristics and PCI data

Patients were characterized according to the number of vessel diseases. Half of the patients ($n = 153$; 50.8%) suffered from a three-vessel disease, 67 (22.3%) patients from a one and 81 (26.9%) patients from a two vessel disease ($p = 0.32$).

Data for left ventricular ejection fraction (LVEF) were available in 267 patients and showed significant differences according to CKD stages ($p = 0.001$). Regarding the different CKD stages, 75.9% (CKD stages 4 and 5) to 93.9% (no CKD) of the patients had normal (>50%) or slightly reduced (41–50%) LVEF; patients with severely reduced (<30%) LVEF were predominantly in CKD stage 3, as well as in CKD stages 4 and 5 (19.8% resp. 17.2% vs. 6.1% in patients without CKD).