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Copeptin predicts 10-year all-cause mortality in community patients: a 10-year prospective cohort study

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Abstract

Background: Copeptin, the C-terminal part of the arginine vasopressin (AVP) precursor peptide, is secreted in response to stress and correlates with adverse clinical outcomes in the acute-care hospital setting. There are no comprehensive data regarding its prognostic value in the community. We evaluated associations of copeptin levels with 10-year mortality in patients visiting their general practitioner (GP) for a respiratory infection included in a previous trial.
Methods: This is a post hoc analysis including data from 359 patients included in the PARTI trial. Copeptin was measured in batch-analysis on admission and after 7 days. We calculated Cox regression models and area under the receiver operating characteristic curve (AUC) to assess an association of copeptin with mortality and adverse outcome. Follow-up data were collected by GP, patient and relative tracing through phone interviews 10 years after trial inclusion.
Results: After a median follow-up of 10.0 years, mortality was 9.8%. Median admission copeptin levels (pmol/L) were significantly elevated in non-survivors compared to survivors (13.8, IQR 5.9–27.8; vs. 6.3 IQR 4.1–11.5; p<0.001). Admission copeptin levels were associated with 10-year all-cause mortality [age-adjusted hazard ratio 1.7 (95% CI, 1.2–2.5); p<0.001, AUC 0.68]. Results were similar for discharge copeptin levels. Copeptin also predicted adverse outcomes defined as death, pulmonary embolism and major adverse cardiac and cerebrovascular events.
Conclusions: In a sample of community-dwelling patients visiting their GP for a respiratory infection, copeptin levels were associated with 10-year all-cause mortality. In conjunction with traditional risk factors, this marker may help to better direct preventive measures in this population.

Keywords: biomarker; copeptin; primary care; respiratory tract infection; 10-year mortality.

Introduction

In primary care, detection of patients at increased risk of death and adverse clinical outcome is crucial to target intensified interventions for these high-risk individuals that may improve survival. Risk scores, such as the Framingham score, are well established and help to direct cardiovascular risk management, for instance, use of statin therapy. In addition to clinical parameters, novel inflammatory blood biomarkers have been proposed to improve prognostication [1–4]. However, as yet most biomarker research has looked at the acute care in a hospital setting, and the potential for primary care patients is incompletely understood [5, 4].

Among novel markers, copeptin, an osmo-dependent stress and inflammatory biomarker, has generated much interest [6, 7]. Copeptin, a 39-aminoacid glycopeptide, is the C-terminal part of the arginine vasopressin (AVP)

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precursor peptide and is produced in the hypothalamus [8]. Copeptin serves as a sensitive surrogate marker for AVP production and parallels AVP plasma osmolality changes [9]. A drop in blood pressure or a change in osmotic pressure induces AVP release. Further, AVP itself plays an important part in the endocrine stress response, acting as a potent synergistic factor of corticotropin-releasing hormone and is, therefore, a hypothalamic stimulator of the hypothalamo-pituitary-adrenal axis [10–14].

Several studies have reported a strong association of copeptin with long-term mortality mainly in hospital settings [15]. These studies include patients with sepsis [16, 17], pneumonia and lower respiratory tract infections [16, 18, 19], stroke [20, 21], acute myocardial infarction and congestive heart failure [22–25], as well as diabetes type 2 [26], metabolic syndrome [27] and diabetes insipidus [28]. Also in primary care, copeptin was found to predict risk in patients with heart failure [29, 30], but there is no comprehensive data assessing the usefulness of serum copeptin levels as a general "risk marker" in a patient sample from primary care contacting general practitioners (GPs) due to acute respiratory tract infections (ARTIs).

Herein, we evaluated the ability of copeptin to predict mortality and adverse clinical outcomes in community-dwelling patients visiting their GP for a respiratory infection followed over a 10-year-time period.

Materials and methods

Study design

This is a post hoc analysis of prognostic markers for death sampled 10 years ago in the context of a primary care intervention trial [31]. The initial cohort included 458 adult patients with an ARTI, of which 359 (78.5%) could be contacted to assess long-term outcomes between April and August 2015.

The initial PARTI trial ("Procalcitonin-Guided Antibiotic Use vs. a Standard Approach for Acute Respiratory Tract Infections in Primary Care") was a randomised, open, multicentre, non-inferiority trial [31]. A study protocol was published beforehand [32]. In brief, adult patients with an ARTI, and in their GP's opinion in need of antibiotics, were randomised to either a procalcitonin (PCT)-guided approach or a standard approach of antibiotic therapy from December 13, 2004 until April 30, 2006. For the PCT-guided therapy, the use of antibiotics was more or less strongly discouraged based on defined PCT cut-off ranges [33]. The standard approach followed evidence-based guidelines for the use of antibiotics. The aim of the trial was to prove the safety and efficacy of using PCT levels to guide antibiotic therapy.

The PARTI study protocol, as well as the present follow-up-trial, was approved by the local Ethics Committee of Basel (EKBB), and all procedures conformed to the Declaration of Helsinki. Written informed consent, including authorisation for secondary analyses, was obtained from all participating physicians and patients on the day of randomisation.

The initial PARTI trial is registered: isrctn.org; Identifier: ISRCTN73182671.

Data collection and endpoints

For the current analysis, we performed follow-up interviews with all GPs, patients and/or relatives based on their availability. We assessed outcomes using systematic questionnaires. There was no blinded assessment for outcomes.

Also, the register of death of the cantons Basel-Stadt and Basel-Land was consulted if no information about vital status was available. From a total of 458 patients with an ARTI included in the initial trial, 359 patients were included in the follow-up study (276 patients were assessed through 40 primary care physicians, 73 patients were contacted by phone calls, nine patients were detected via the registers of death and one patient died during the 28-day follow-up period of the initial trial).

The primary outcome was 10-year all-cause mortality. Secondary outcomes were adverse outcome events including death, pulmonary embolism and major adverse cardiac or cerebrovascular events (MACCE), which includes cardiac infarction, cardiac arrest, stroke and transient ischemic attack. We also looked separately at MACCE and stroke as secondary outcomes.

Analysis of blood biomarkers

Blood samples were collected in the primary care centre from each patient on the day of randomisation, as well as after 7 days, and sent by courier to the central Laboratory of the University Hospital Basel for measurement of PCT. Leftover blood samples were frozen and stored at −80 °C for the later measurement of prognostic markers. Copeptin serum values were determined using a novel sandwich immunoluminometric assay (B.R.A.H.M.S GmbH, Hennigsdorf, Germany) with intra- and inter-assay coefficients of variation of up to 20% using an automated immunofluorescent assay (Kryptor©, B.R.A.H.M.S GmbH, Hennigsdorf, Germany) [34, 35].

Statistical analyses

Categorical variables are expressed as percentages (numbers) and continuous variables as medians [interquartile ranges (IQRs)], unless stated otherwise. If applicable, 95% confidence intervals (CIs) are presented. The χ^2 (Wald) test is used for frequency comparisons, the non-parametric (Mann-Whitney-U) test for two-sample comparisons.

We analysed the associations of copeptin with primary and secondary outcomes using univariable and multivariable Cox regression analyses adjusting for age (bivariable model) as well as age, gender, randomisation arm, antibiotic use initially, smoking history, comorbidities and type of infection (fully adjusted model). We report hazard ratios (HRs) and 95% CIs as a measure of association and C-Statistics [area under the curve (AUC)] as a measure of discrimination. As the distribution of raw biomarker data was skewed, we used a natural logarithm (base *e*) transformation. Thereafter, the distribution of the

biomarker data approximated a normal distribution. The HR thereby corresponds to a nearly one-fourth-unit increase in the explanatory variable and to a 2.72-fold increase in log-transformed biomarker levels. Further, for illustration, we present Kaplan-Meier survival estimates of long-term survival by quartiles of copeptin levels.

Statistical analyses were performed using STATA 12.1 (STATA Corp, College Station, TX, USA). A p-value<0.05 indicated statistical significance.

Results

Patient characteristics

Baseline characteristics of the entire cohort (n=359) as well as stratified by the primary endpoint (10-year vital status) and the main secondary endpoint (adverse outcome) are shown in Table 1. The overall median age was 45.0 and 38.2% (137) of the patients were male. There were differences in age, comorbidities (arterial hypertension, chronic obstructive pulmonary disease), initial clinical classification for ARTI (lower vs. upper) at the day of randomisation and nicotine consumption according to the survival status.

However, there was no significant difference found between the traceable patients (n=359) and the population that was lost to follow-up (n=99) (see Supplemental Data, Table S1).

Primary outcome: 10-year all-cause mortality

A total of 35 of the 359 patients (9.8%) died during the 10.0 (IQR 9.5–10.3) years of follow-up. Median baseline copeptin blood levels (pmol/L) were significantly higher in non-survivors compared to survivors (13.8, IQR 5.9–27.8; vs. 6.3, IQR 4.1–11.5; p<0.001). Similarly, biomarker results at day 7 also showed significant differences between survivors and non-survivors (11.2, IQR 3.2–21.2; vs. 4.5, IQR 2.9–7.4; p<0.001).

A strong association of copeptin with an outcome was also found in Cox regression analysis as summarised for admission blood levels in Table 2 and for follow-up blood levels in Table 3. The age-adjusted HR of copeptin for prediction of mortality was 1.7 (95% CI 1.2–2.5, p=0.005) and 2.5 (95% CI 1.6–4.0, p<0.001) at day 7. We also found fair discrimination with AUCs of 0.68 (95% CI 0.6–0.8) at baseline and 0.71 (95% CI 0.6–0.8) at day 7 (Figure 1). The results also remained robust in a fully adjusted model including age, gender, randomisation arm, antibiotic use initially, smoking history, comorbidities and type of infection.

To further illustrate these associations, we generated Kaplan-Meier curves (Figure 2 and Supplemental Data, Figure S1), with patients stratified based on copeptin blood level quartiles. Mortality was significantly increased in patients in the highest copeptin quartile compared to quartiles 1–3.

We also performed several exploratory subgroup analyses as presented in Tables 2 and 3. Although discrimination was highest for patients <60 years of age (AUC 0.77) and for females (AUC 0.69), there was no evidence of significant effect modification (Figure 1). We also calculated sensitivity and specificity for different copeptin cut-off levels for all-cause mortality prediction. Sensitivity was 91.4% at a 3 pmol/L cut-off with however a low specificity of 13.6%. Conversely, specificity was 80.9% at the 15 pmol/L cut-off with a sensitivity of 42.9%. Detailed results including positive (PPV) and negative predictive values (NPV) are presented (see Supplemental Data, Table S2).

Secondary outcomes: 10-year incidence of adverse outcome events

A total of 52 patients (14.5%) reported to have experienced an adverse outcome event defined as death, pulmonary embolism or major adverse cardiac and cerebrovascular events. Copeptin blood levels were significantly elevated in these patients at baseline and at day 7 compared to the patients not having an event. Again, Cox regression models found significant associations between both initial and day 7 copeptin levels and adverse outcome, with fair discrimination (Tables 2 and 3).

Kaplan-Meier curves (Figure 2), with patients stratified based on copeptin quartiles, again found higher event rates in patients in the highest copeptin quartile.

We also explored associations of copeptin with different components of adverse outcome, namely MACCE (n=19) and stroke (n=8) (see Supplemental Data, Tables S3 and S4). Although copeptin was increased in patients reaching these endpoints, statistically significant associations were not found in regression models.

Discussion

The key finding of this first prospective, observational 10-year follow-up study including community-dwelling patients visiting their GP for a respiratory infection is that copeptin measured during the index visit and 7 days later was a predictor for 10-year all-cause mortality and incidence of adverse outcome. Thereby these data expand

Table 1: Baseline characteristics of the study population overall and by 10-year 1° and main 2° outcome.

Characteristics	Entire cohort	Survivors	Non-survivors	p-Value	No adverse outcome	Adverse outcome	p-Value
	n=359	n=324	n=35		n=307	n=52	
Demographic characteristics							
Age in years, mean (SD)	47.9 (18.3)	45.1 (16.8)	74.1 (9.1)	<0.001	44.2 (16.6)	69.7 (11.9)	<0.001
Age median (IQR)	45.0 (34.0, 63.0)	43.5 (31.0, 58.5)	77.0 (68.0, 81.0)	<0.001	42 (30.0, 57.0)	70 (63.5, 80.0)	<0.001
Male, no. (%)	137 (38.2)	116 (35.8)	21 (60.0)	0.005	105 (34.2)	32 (61.5)	<0.001
CV risk factors							
Smoker or former smoker (%)	119 (33.1)	103 (31.8)	16 (45.7)	0.096	98 (31.9)	21 (40.4)	0.23
Pack years median (IQR)	20.0 (2.5, 40.0)	20.0 (3.0, 35.0)	47.0 (2.0, 76.0)	0.024	20 (3.0, 35.0)	40 (2.0, 72.0)	0.064
Positive family history (%)	54 (15.3)	52 (16.1)	2 (6.7)	0.17	48 (15.7)	6 (12.8)	0.6
Comorbidities	80 (28.7)	64 (19.8)	16 (45.7)	<0.001	55 (17.9)	25 (48.1)	<0.001
Arterial hypertension (%)	58 (16.2)	48 (14.8)	10 (28.6)	0.036	44 (14.3)	14 (26.9)	0.023
Dyslipoproteinemia (%)	35 (9.7)	98 (19.6)	112 (22.1)	0.72	26 (8.5)	9 (17.3)	0.047
Diabetes mellitus (%)	10 (2.8)	8 (2.5)	2 (5.7)	0.27	5 (1.6)	5 (9.6)	0.001
COPD (%)	17 (4.7)	10 (3.1)	7 (20.0)	<0.001	9 (2.9)	8 (15.4)	<0.001
Initial clinical condition							
Lower ARTI (%)	196 (54.6)	165 (50.9)	31 (88.6)	<0.001	155 (50.5)	41 (78.8)	<0.001
Upper ARTI (%)	163 (45.4)	159 (49.1)	4 (11.4)	<0.001	152 (49.5)	11 (21.2)	<0.001
Laboratory findings							
Copeptin at baseline, pmol/L							
Median (IQR)	6.5 (4.1, 12.5)	6.3 (4.1, 11.5)	13.8 (5.9, 27.8)	<0.001	6.2 (4.0, 11.1)	12.3 (5.0, 24.9)	<0.001
Mean (SD)	10.2 (10.0)	9.4 (8.8)	18.1 (15.7)	<0.001	9.2 (8.7)	16.1 (14.2)	<0.001
Copeptin at day 7, pmol/L							
Median (IQR)	4.7 (2.9, 8.3)	4.5 (2.9, 7.4)	11.2 (3.2, 21.2)	<0.001	4.4 (2.9, 7.3)	7.9 (3.7, 17.4)	<0.001
Mean (SD)	6.6 (5.7)	6.0 (4.8)	13.0 (9.4)	<0.001	6.0 (4.8)	10.7 (8.6)	<0.001

Data are presented as median (IQR), mean (SD) or % (no.). p-Values are statistically significant at <0.05. IQR, interquartile range (25th–75th percentiles); SD, standard deviation; CV, cardiovascular; COPD, chronic obstructive pulmonary disease; ARTI, acute respiratory tract infection. Comorbidities were identified based on the medical record of GP, patient report, or both.

Table 2: Association between copeptin blood levels at baseline and outcomes: 10-year all-cause mortality and 10-year incidence of adverse outcome.

	10-Year all-cause mortality	10-Year incidence of adverse outcome
Overall	n=35	n=52
Unadjusted HR	2.2 (95% CI 1.5–3.4), **p<0.001**	2.0 (95% CI 1.4–2.8), **p<0.001**
Adjusted for age HR	1.7 (95% CI 1.2–2.5), **p=0.005**	1.6 (95% CI 1.2–2.2), **p=0.003**
Fully adjusted model HR	1.7 (95% CI 1.1–2.6), **p=0.027**	1.6 (95% CI 1.1–2.2), **p=0.021**
AUC	0.68 (95% CI 0.57–0.78)	0.66 (95% CI 0.58–0.75)
Specific subgroups		
Gender	p[a]=0.781	p[a]=0.554
Male	n=21	n=32
Unadjusted HR	1.8 (95% CI 1.1–3.2), **p=0.031**	1.6 (95% CI 1.0–2.5), **p=0.032**
Adjusted for age HR	1.3 (95% CI 0.8–2.4), **p=0.294**	1.2 (95% CI 0.8–2.0), **p=0.350**
AUC	0.63 (95% CI 0.49–0.78)	0.62 (95% CI 0.50–0.73)
Female	n=14	n=20
Unadjusted HR	2.5 (95% CI 1.4– 4.5), **p=0.003**	2.2 (95% CI 1.3–3.7), **p=0.003**
Adjusted for age HR	1.9 (95% CI 1.1–3.2), **p=0.030**	1.7 (95% CI 1.1–2.8), **p=0.028**
AUC	0.69 (95% CI 0.52–0.87)	0.66 (95% CI 0.52–0.80)
Nicotine abuse	p[a]=0.988	p[a]=0.925
Smoker	n=16	n=21
Unadjusted HR	2.1 (95% CI 1.1–3.9), **p=0.020**	2.0 (95% CI 1.1–3.5), **p=0.018**
Adjusted for age HR	1.8 (95% CI 1.0–3.1), **p=0.046**	2.0 (95% CI 1.1–3.4), **p=0.015**
AUC	0.67 (95% CI 0.50–0.83)	0.65 (95% CI 0.51–0.79)
Non-smoker	n=19	n=31
Unadjusted HR	2.4 (95% CI 1.4– 4.2), **p=0.001**	2.1 (95% CI 1.4–3.2), **p=0.001**
Adjusted for age HR	1.7 (95% CI 1.0–2.9), **p=0.038**	1.5 (95% CI 1.0–2.3), **p=0.059**
AUC	0.70 (95% CI 0.55–0.84)	0.68 (95% CI 0.56–0.79)
Age	p[a]=0.683	p[a]=0.596
>60	n=32	n=43
Unadjusted HR	1.6 (95% CI 1.1–2.4), **p=0.019**	1.6 (95% CI 1.1–2.2), **p=0.011**
Adjusted for gender HR	1.4 (95% CI 0.9–2.2), **p=0.089**	1.4 (95% CI 1.0–2.0), **p=0.070**
AUC	0.63 (95% CI 0.50–0.76)	0.64 (95% CI 0.52–0.75)
≤60	n=3	n=9
Unadjusted HR	3.2 (95% CI 0.8–13.2), **p=0.113**	1.6 (95% CI 0.7–3.9), **p=0.252**
Adjusted for gender HR	2.9 (95% CI 0.7–12.6), **p=0.155**	1.3 (95% CI 0.6–3.1), **p=0.539**
AUC	0.77 (95% CI 0.50–1.0)	0.63 (95% CI 0.44–0.81)

[a]p-Value for subgroup interaction. Data for univariable and multivariable analyses are given as HR (95% CI) and p-value. Data regarding prognostic analysis are given as AUC (95% CI). A higher AUC reflects greater accuracy: 0.5, the null value, indicates coin-toss accuracy, while 1.0, the maximum value indicates 100% accuracy. p-Values in bold type are statistically significant at <0.05. The univariable model includes: the natural logarithmic value of admission copeptin blood concentrations. The bivariable model includes: the natural logarithmic value of admission copeptin blood concentrations and patient age or gender, depending on the subgroup. The fully adjusted model includes: the natural logarithmic value of admission copeptin blood concentrations and patient age, gender, randomisation arm, antibiotic use initially, smoking history, comorbidities and type of infection.

data from the hospital setting to primary care and suggest that this marker may be useful in the risk assessment of this patient population.

Several studies have reported associations of copeptin levels with adverse outcomes, namely mortality [15–30].

It has been speculated that through its implication in the stress response, copeptin may help to detect higher severity of somatic disease. In patients with chest pain, for example, low copeptin levels can exclude myocardial infarction with high NPV [36]. Similarly, in patients with respiratory infection and low copeptin levels, adverse clinical outcomes are highly unlikely. In our study, a copeptin level of ≤3 pmol/L had an NPV of 93.6% for mortality and thus makes this endpoint highly unlikely. Conversely, in patients with copeptin ≥15 pmol/L mortality is much more likely as evidenced by a PPV of 19.5%.

Table 3: Association between copeptin blood levels at day 7 follow-up and outcomes: 10-year all-cause mortality and 10-year incidence of adverse outcome.

	10-Year all-cause mortality	10-Year incidence of adverse outcome
Overall	n=35	n=52
Unadjusted HR	3.3 (95% CI 2–5.4), **p<0.001**	2.4 (95% CI 1.6–3.5), **p<0.001**
Adjusted for age HR	2.5 (95% CI 1.6–4.0), **p<0.001**	1.9 (95% CI 1.3–2.7), **p=0.001**
Fully adjusted model HR	2.5 (95% CI 1.5–4.2), **p=0.001**	1.8 (95% CI 1.2–2.6), **p=0.006**
AUC	0.71 (95% CI 0.59–0.83)	0.66 (95% CI 0.56–0.76)
Specific subgroups		
Gender	p[a]=0.65	p[a]=0.951
Male	n=21	n=32
Unadjusted HR	3.5 (95% CI 1.9–6.8), **p<0.001**	2.3 (95% CI 1.4–3.8), **p=0.001**
Adjusted for age HR	2.6 (95% CI 1.4–4.9), **p=0.004**	1.7 (95% CI 1.0–2.8), **p=0.033**
AUC	0.72 (95% CI 0.55–0.89)	0.65 (95% CI 0.52–0.78)
Female	n=14	n=20
Unadjusted HR	2.6 (95% CI 1.3–5.6), **p=0.011**	2.1 (95% CI 1.1–4.0), **p=0.02**
Adjusted for age HR	2.1 (95% CI 1.0–4.2), **p=0.039**	1.7 (95% CI 1–3.2), **p=0.067**
AUC	0.67 (95% CI 0.49–0.85)	0.64 (95% CI 0.48–0.79)
Nicotine abuse	p[a]=0.552	p[a]=0.541
Smoker	n=16	n=21
Unadjusted HR	3.0 (95% CI 1.5–6.3), **p=0.003**	2.4 (95% CI 1.3–4.4), **p=0.007**
Adjusted for age HR	2.9 (95% CI 1.5–5.6), **p=0.002**	2.7 (95% CI 1.5–5.1), **p=0.001**
AUC	0.67 (95% CI 0.47–0.87)	0.62 (95% CI 0.45–0.78)
Non-smoker	n=19	n=31
Unadjusted HR	3.6 (95% CI 1.9–6.8), **p<0.001**	2.4 (95% CI 1.5–4.1), **p=0.001**
Adjusted for age HR	2.4 (95% CI 1.2–4.6), **p=0.011**	1.6 (95% CI 1.0–2.6), **p=0.073**
AUC	0.74 (95% CI 0.58–0.89)	0.69 (95% CI 0.57–0.80)
Age	p[a]=0.894	p[a]=0.744
>60	n=32	n=43
Unadjusted HR	2.4 (95% CI 1.4–3.9), **p=0.001**	1.8 (95% CI 1.2–2.8), **p=0.005**
Adjusted for gender HR	2.1 (95% CI 1.3–3.5), **p=0.003**	1.6 (95% CI 1.1–2.5), **p=0.023**
AUC	0.68 (95% CI 0.53–0.82)	0.63 (95% CI 0.51–0.76)
≤60	n=3	n=9
Unadjusted HR	5.2 (95% CI 1.0–26.2), **p=0.046**	2.3 (95% CI 0.9–6.0), **p=0.088**
Adjusted for gender HR	4.8 (95% CI 0.9–24.4), **p=0.058**	2.0 (95% CI 0.8–5.2), **p=0.168**
AUC	0.82 (95% CI 0.56–1.0)	0.66 (95% CI 0.43–0.88)

[a]p-Value for subgroup interaction. Data for univariable and multivariable analyses are given as HR (95% CI) and p-value. Data regarding prognostic analysis are given as AUC (95% CI). A higher AUC reflects greater accuracy: 0.5, the null value, indicates coin-tossaccuracy, while 1.0, the maximum value indicates 100% accuracy. p-Values in bold type are statistically significant at <0.05. The univariable model includes: the natural logarithmic value of day 7 follow-up copeptin blood concentrations. The bivariable model includes: the natural logarithmic value of day 7 follow-up copeptin blood concentrations and patient age or gender, depending on the subgroup. The fully adjusted model includes: the natural logarithmic value of day 7 follow-up copeptin blood concentrations and patient age, gender, randomisation arm, antibiotic use initially, smoking history, comorbidities and type of infection.

Copeptin also showed statistically significant associations with the incidence of adverse outcomes defined as death, pulmonary embolism or major adverse cardiac and cerebrovascular events. However, associations were not found for stroke and MACCE themselves, but there are possible explanations. First, our study had only a limited number of patients suffering events, owing to the generally healthy patient population under study with a low burden of comorbidities. Further, our results indicate that copeptin, as a marker of non-specific stress response, is better at tracking the risk of death than predicting the incidence of cardio- and/or cerebrovascular events. For example, Sun et al. found in a meta-analysis with 14,395 cardio-cerebrovascular patients that copeptin was associated with all-cause mortality [37]. Therefore, copeptin seems to be more accurate in identifying the patients at

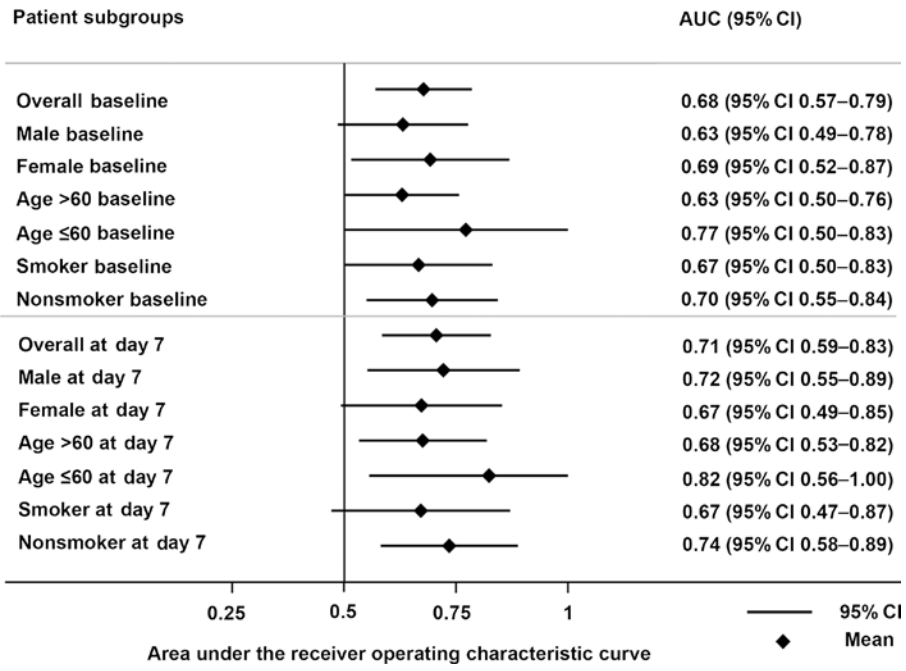

Figure 1: Forest plot of copeptins prognostic accuracy in predicting 10-year all-cause mortality in different patients subgroups.

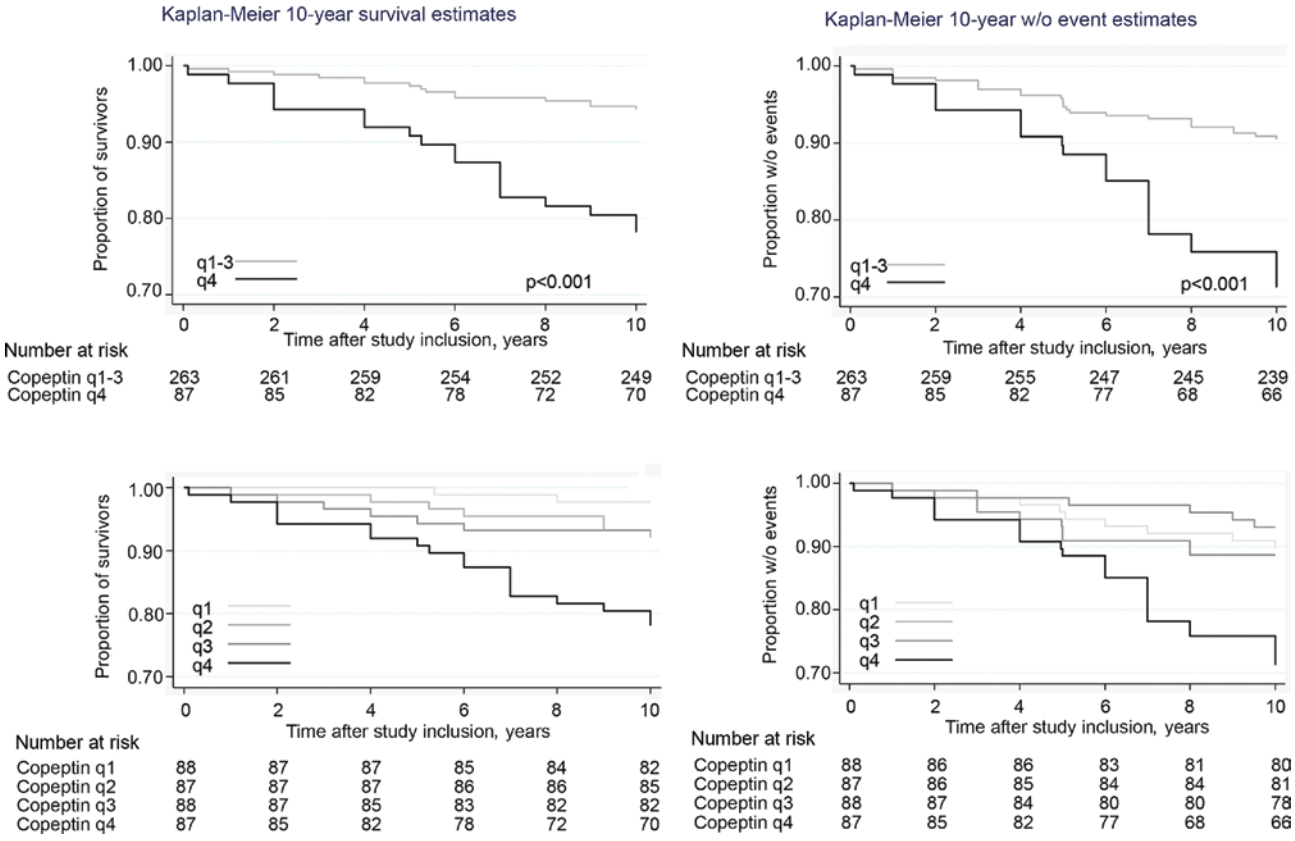

Figure 2: 10-year Kaplan-Meier survival and without adverse outcome curve according to baseline copeptin blood concentration. Plots showing the association between endpoint and copeptin quartiles, 4th quartile vs. 1st–3rd quartiles and between 1st, 2nd, 3rd and 4th quartile.

risk of death, rather than in predicting specific medical diagnosis in a long-term follow-up of generally healthy outpatients. Nonetheless, we are aware that there are studies showing an association of copeptin levels with MACCE and stroke in subpopulations such as patients with type 2 diabetes [27, 38] or undergoing haemodialysis [39], and that copeptin seems to be a valid biomarker to potentially rule out acute myocardial infarction, in the acute phase of the disease [36, 40–43].

In our study population, copeptin blood levels were not significantly influenced by age, gender or smoking status, confirmed statistically in the interaction analysis. Former studies demonstrated similar results with no significant correlation of copeptin with gender [44] or age [34]. Bosselmann et al. showed that copeptin and other cardiovascular biomarkers are closely associated with renal function in heart failure. Still, the marker was useful for risk stratification independently of renal function [45]. Also, Choi et al. found a standardised mean difference by study region with significant differences in copeptin blood levels, but a positive consistent association of copeptin with poor prognosis [46].

Interestingly, we had access to copeptin levels on admission to the GP's office, i.e. in patients suffering from ARTI and 7 days later when the infection may have been cured. Our results suggest that copeptin blood levels taken on a 7-day follow-up have a slightly stronger association with outcome compared to admission results for mortality and adverse clinical outcome prediction. In contrast, a meta-analysis of Choi et al. in a different setting showed that early measurement of plasma copeptin in the patients with acute stroke provides better prognostic information about the functional outcome and mortality [46]. Because differences in our study sample were small, further research is needed to define the optimal usage of this marker in the GP setting.

As mentioned before, measurements of copeptin levels have been demonstrated to be useful in a variety of clinical scenarios. The potential benefit of copeptin compared to other biomarkers is due to its central role as a marker for a key hormone in the body. It is not restricted to a single organ system and is triggered by many disease processes. This lack of specificity with regard to the underlying diagnosis may be an advantage as a more generalisable marker for severe disturbances in patient physiology [14].

Katan et al. have shown that copeptin levels mirror different levels of stress more accurately than cortisol [28]. Cortisol measurements are limited by, for example, cross-reactivity with other steroids [47]; its concentration varies with the amount of hormone-binding proteins, underlies a circadian rhythm [48] and changes with food intake [49].

The main strengths of this study include the participation of multiple GP practices, the long follow-up period of 10 years and the community sample of patients with ARTI of different severity representative for patients mainly treated in primary care.

However, we are aware of several limitations. Firstly, the incomplete baseline risk assessment in the original cohort, in particular, missing certain blood parameters such as lipid values or blood pressure, does not allow us to investigate whether copeptin would improve state-of-the-art risk scores (e.g. Framingham). Secondly, while the register of deaths could confirm the survival status of the patients, no information was available on the cause of death. There is also the possibility that the GPs have not seen their patients on a regular basis, or that the relatives did not remember their medical information. Therefore, we limited our analysis to all-cause mortality rather than to cause-specific mortality. Thirdly, we lack in comprehensive measurement of confounders. Thus, our results are biased by confounding we cannot control for. Finally, our sample was small in size with a follow-up rate of 78.5% and we observed only few events. We were therefore not able to look into short-term adverse outcomes in this study and a larger trial is needed.

Conclusions

In a sample of community-dwelling patients visiting their GP for a respiratory infection, copeptin was associated with a 10-year all-cause mortality. In conjunction with traditional risk factors, this marker may help to better direct preventive measures in this population. Still, further evidence must determine the role of copeptin in primary care as a marker of risk stratification, by evaluating whether preventive interventions help to reduce mortality risk in this population.

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the findings, read and revised the manuscript critically for important intellectual content, and approved the final version of the manuscript.

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