ORIGINAL ARTICLE

WILEY

Copeptin is associated with mortality in elderly people

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Abstract

Background: Elevated copeptin, a marker for vasopressin release, has been associated with impaired prognosis in acute myocardial infarction (MI). The aim was to investigate whether this association extends beyond the acute phase and whether it is related to markers of stress (cortisol) and heart failure (NTproBNP).

Methods: Copeptin, cortisol and NTproBNP were measured in 926 participants (age: 76.0; male: 48.5%) in the ICELAND MI study whereof 246 had a previous MI (91 recognizable (RMI) and 155 previously unrecognizable (UMI) detected by cardiac magnetic resonance imaging). The primary endpoint was cardiovascular events (CVEs), and secondary endpoints were total mortality, heart failure and MI (median follow-up was 9.1 years). The relation between copeptin and prognosis was assessed with the Cox proportional hazard regression (unadjusted, adjusted for cortisol and NTproBNP, respectively, and a multiple model: copeptin, cortisol, NTproBNP, age, sex, serum creatinine, heart failure).

Results: Copeptin was higher in participants with MI (8.9 vs. 6.4 pmol/L; $P < .01$), with no difference between RMI vs. UMI. Increased copeptin correlated with evening cortisol ($r = .11$; $P < .01$) and NTproBNP ($r = .07$; $P = .04$). Copeptin was associated with CVE and total mortality after adjusting for cortisol and NTproBNP separately, and remained significantly associated with total mortality in the multiple model.

Conclusions: Copeptin was higher in subjects with previous MI regardless whether previously recognized or not. Copeptin correlated weakly with cortisol and NTproBNP, and was independently associated with total mortality. This indicates that the prognostic implications of copeptin are not only mediated by heart failure or stress, supporting the assumption that copeptin is a marker of general vulnerability.

KEYWORDS
copeptin, cortisol, myocardial infarction, NTproBNP, unknown myocardial infarction, vasopressin

1 | INTRODUCTION

Copeptin, a 39-amino acid glycopeptide originating from the C-terminal part of pre-pro-vasopressin is more stable in the circulation and easier to measure than vasopressin and may therefore be used as surrogate marker for vasopressin release.[1] Elevated copeptin levels have been reported in patients with acute myocardial infarction (MI) and heart failure and have furthermore been associated with an impaired cardiovascular prognosis.[2-5]

It has been speculated that vasopressin may be involved in the pathophysiology of heart failure and/or atherosclerotic disease since it plays an important role in body fluid homeostasis and also acts on other mechanisms, such as platelet aggregation and release of von Willebrand factor.[6,7] On the other hand, since vasopressin is also considered to be a stress hormone the increased copeptin levels in such situations may be reflecting increased physiological stress.[8] The observational AGES-Reykjavik study [9] offers an opportunity to study whether copeptin is increased in people who have had an earlier MI, previously known or newly detected MI by means of cardiac magnetic resonance, and hence are in a more stable phase than in most previous reports comprising patients with acute conditions.

An additional way to elucidate whether the increased levels of copeptin in patients with cardiovascular disease (CVD) are related to stress or heart failure per se is to study copeptin in relation to other biomarkers such as the stress marker cortisol and heart failure marker N-terminal pro–B-type natriuretic peptide (NTproBNP).

The aims of the present report were (a) to explore whether copeptin levels differ between people with and without previous MI and to compare the levels in people with UMI to those with clinically recognized MI (RMI), and (b) to explore the prognostic implication of copeptin, and whether it is associated with markers of stress (cortisol) and/or heart failure (NTproBNP).

2 | METHODS

2.1 | Data source

The present study cohort is based on the Imaging Cardiac Evaluation to Locate Areas of Necrosis and Detect MI (ICELAND MI), a substudy of the population-based Age, Gene/Environment Susceptibility (AGES)-Reykjavik study (n = 5764; Figure S1).[9] The AGES-Reykjavik included survivors from the original Icelandic Reykjavik study, a randomly selected population-based cohort of Icelandic people living in the greater Reykjavik area born between 1907 and 1935 and followed since 1967. The recruitment for the ICELAND MI study was done in two phases from AGES-Reykjavik.

The first phase included 670 randomly selected participants from the total AGES-Reykjavik cohort, and in the second phase, 266 participants with T2DM from the same cohort were selected. The participants were enrolled from January 2004 to January 2007. The 936 study participants were examined by means of a questionnaire, blood sampling, blood pressure measurement, ECG and cardiac magnetic resonance (CMR) imaging at three occasions.[9,10] Blood samples for copeptin analysis were available in 926 of the participants while samples from ten participants, excluded from further analysis, could not be analysed due to insufficient amounts of blood or formation of blood clots.

2.2 | Definitions

Participants were classified as having a RMI if they had a history of MI supported by hospital or surveillance records.[10] An UMI was defined as myocardial damage disclosed by the CMR as a late gadolinium enhancement in the subendocardial myocardium in the absence of any hospital or surveillance records indicating MI.[11,12]

Participants were allocated to two main groups: no previous MI (n = 680) and previous MI (n = 246), and two subgroups from the latter: UMI (n = 155) and RMI (n = 91) based on their baseline characteristics and CMR findings.

T2DM was defined as the presence of a positive case history, a fasting glucose >7.0 mmol/L or a prescription of glucose-lowering drugs at the baseline visit.

Hypercholesterolemia was considered present in participants on statins or with a total cholesterol >6.0 mmol/L at baseline.

The presence of hypertension was considered if there was a positive case history, a blood pressure ≥140/90 mm Hg or prescription of blood pressure-lowering drugs at baseline.

Previous heart failure was, based on findings in hospital records, specified as two major or one major and two minor criteria for diagnosis: *major criteria*: (a) new onset of dyspnoea on exertion and (b) pulmonary oedema on chest film that clears with diuresis; and *minor criteria:* (a) weight gain >5% of baseline over a 2-week period, (b) new appearance of jugular vein distension >3 cm above the sternal manubrial angle, filling from below, (c) pleural effusion not of extracardiac aetiology and (d) reduction in left ventricular ejection fraction by at least 20%.

2.3 | Laboratory analyses

Blood samples were stored at −70°C at the Icelandic Heart Association in Kópavogur, Iceland. They were subsequently transferred to the Cardiology Unit, Department of Medicine, Karolinska Institutet, Solna, Sweden, for

analysis of copeptin in plasma by means of a fully automated, immunofluorescent assay (BRAHMS KRYPTOR Compact Plus, Hennigsdorf, Germany). The method has an analytical detection limit of 0.7 pmol/L and functional assay sensitivity <1.08 pmol/L.[13]

Two cortisol saliva samples were collected with the Salivette device (Sarstedt, Rommelsdorf, Germany), participants were instructed to collect the first sample prior going to sleep the evening before the clinic visit and the latter was collected 45 minutes after waking up.[14] The samples were analysed with a time-resolved immunoassay with fluorescence detection with intra-assay variability <10% and inter-assay variability <12%[15] with a lower detection limit was 0.43 nmol/L for a 50 μL sample. NTproBNP was measured using a fully automated Cobas e411 analyzer utilizing Immunoassay, the sandwich principle (Roche Diagnostics).

2.4 | Outcomes

Copeptin was studied in relation to four endpoints during 9.1 years of follow-up: (a) cardiovascular events (CVE; cardiovascular death, stroke, MI, percutaneous coronary intervention [PCI], coronary artery bypass grafting [CABG]); (b) total mortality; (c) heart failure; and (d) re-infarction or first MI. Endpoints were based on hospital record information and a national mortality register with authentication of all death certificates.[9] The end of follow-up was 28 February 2010 for heart failure and 31 December 2014 for all other events.

2.5 | Statistical methods

Continuous variables are presented as median and interquartile ranges (IQRs), and categorical variables as number and percentages unless otherwise stated. A two-tailed P-value of <.05 was accepted as indication of statistically significant difference between groups.

Fisher's exact test (dichotomous variables) and Wilcoxon's rank-sum test (continuous variables) were used to assess differences in baseline characteristics between the different groups and subgroups. The Wilcoxon rank-sum test was furthermore used to study differences in copeptin levels in the subsets stratified by dichotomous variables (sex, coronary heart disease, hypercholesterolemia, hypertension, heart failure, stroke and T2DM) at baseline for participants. Spearman rank's correlation test was used to explore potential association between copeptin and morning cortisol, evening cortisol and NTproBNP.

Because of skewed distributions, the copeptin values were log-transformed prior to analysis.

The Cox proportional hazard regression analysis was applied to estimate hazard ratios (HR) with 95% confidence intervals (CI) for CVE, total mortality, heart failure and myocardial infarction by an increase of one standard deviation (SD) of copeptin. Furthermore, morning cortisol, evening cortisol and NTproBNP were analysed separately in univariable analyses. Copeptin was then adjusted for morning/evening cortisol and NTproBNP respectively. Finally, a stepwise model included copeptin, morning/evening cortisol, NTproBNP, age, sex, serum creatinine and previous heart failure. These covariates were selected based on results from the Spearman and Wilcoxon analyses in the present study cohort and available literature.[3,13,16] All analyses were done using SAS version 9.3 (SAS Institute).

2.6 | Ethical considerations

The National Bioethics Committee of Iceland approved the AGES-Reykjavik study and subsequently the ICELAND MI substudy (VSN:00-063-V6/VSN:00-063-V6+3/VSN:14-00-35). Written, informed consent was obtained from all participants prior to participation.

3 | RESULTS

3.1 | Participants characteristics

Important characteristics in the total cohort as well as different groups, that is without (n = 680) and with MI (n = 246), and subgroups of the latter divided into RMI (n = 91) or UMI (n = 155) are presented in Table 1. For the total cohort, the median age was 76 years and 51.5% were women. The median BMI was 27.3 kg/m^{2}, and the median serum creatinine was 85.0 μmol/L. A majority, 83.2%, had hypertension, 58.0% had hypercholesterolemia, and 35.8% had established T2DM.

3.2 | Copeptin levels

The median copeptin level for the total cohort was 6.8 pmol/L (IQR 4.1-11.7 pmol/L). The median copeptin level was significantly higher for participants with (8.9 pmol/L) compared to those without previous MI (6.4 pmol/L; P <.01) but did not differ between those with RMI and UMI (9.2 pmol/L vs. 8.8 pmol/L; P =.68; Table 1).

A gender difference was found in the total cohort with significantly lower copeptin levels in women than men (5.5 pmol/L vs. 8.7 pmol/L; P <.01), and also in subjects with and without previous MI (6.8 vs. 10.1 (P <.01) and 5.3 vs 8.4 (P <.01), respectively) with a similar pattern in those with UMI but not RMI (data not shown).

TABLE 1 Baseline characteristics of the total cohort, as well as participants with and without myocardial infarction (MI) and for the subgroups: recognized MI (RMI) and unrecognized MI (UMI)

		Myocardial infarction			Myocardial infarction		
	Total cohort	No	Yes	*P*	Recognized	Unrecognized	*P*
Number	926	680	246		91	155	
Age (y)	76.0 (72.0-81.0)	76.0 (72.0-80.0)	77.0 (74.0-82.0)	<.01	78.0 (74.0-82.0)	77.0 (74.0-83.0)	.73
Females	477 (51.5%)	388 (57.1%)	89 (36.2%)	<.01	32 (35.2%)	57 (36.8%)	.89
Body mass index	27.3 (24.6-30.0)	27.3 (24.5-30.0)	27.5 (25.0-30.1)	.59	27.3 (24.3-30.6)	27.6 (25.3-29.9)	.60
Cardiovascular risk factors							
Currently smoking	105 (11.3%)	73 (10.7%)	32 (13.0%)	.35	9 (9.9%)	23 (14.8%)	.33
Type 2 diabetes mellitus	331 (35.8%)	223 (32.8%)	108 (43.9%)	<.01	37 (40.7%)	71 (45.8%)	.51
Hypercholesterolemia	537 (58.0%)	363 (53.4%)	174 (70.7%)	<.01	74 (81.3%)	100 (64.5%)	<.01
Hypertension	770 (83.2%)	542 (79.7%)	228 (92.7%)	<.01	88 (96.7%)	140 (90.3%)	.08
Pharmacological treatment							
ACE inhibitor	148 (17.4%)	108 (17.6%)	40 (16.8%)	.84	15 (16.5%)	25 (17.0%)	1.00
Loop diuretics	85 (10.0%)	48 (7.8%)	37 (15.5%)	<.01	23 (25.3%)	14 (9.5%)	<.01
Statins	271 (29.3%)	149 (21.9%)	122 (49.6%)	<.01	66 (72.5%)	56 (36.1%)	<.01
Laboratory results							
Serum creatinine μmol/L	85.0 (73.0-100.0)	84.0 (71.0-97.0)	92.0 (80.0-108.0)	<.01	93.0 (82.0-112.0)	90.0 (76.0-106.0)	.06
Total cholesterol mmol/L	5.4 (4.6-6.3)	5.6 (4.8-6.3)	4.9 (4.2-6.0)	<.01	4.6 (4.0-5.3)	5.2 (4.3-6.2)	<.01
HDL[a] cholesterol mmol/L	1.5 (1.2-1.8)	1.5 (1.2-1.8)	1.4 (1.1-1.6)	<.01	1.3 (1.1-1.5)	1.4 (1.2-1.6)	.05
LDL[b] cholesterol mmol/L	3.3 (2.6-4.1)	3.5 (2.8-4.20)	2.8 (2.2-3.7)	<.01	2.6 (2.0-3.3)	3.1 (2.4-4.1)	<.01
Triglycerides mmol/L	1.1 (0.9-1.5)	1.1 (0.8-1.5)	1.2 (0.9-1.7)	<.01	1.2 (0.8-1.7)	1.2 (0.9-1.7)	.75
Fasting blood glucose mmol/L	5.7 (5.3-7.0)	5.7 (5.3-6.6)	6.0 (5.4-7.5)	<.01	6.0 (5.3-7.2)	6.1 (5.5-7.6)	.39
CRP[c] mg/L	1.8 (1.0-3.8)	1.8 (0.9-3.7)	2.1 (1.1-4.1)	.08	1.8 (1.0-3.8)	2.1 (1.1-4.5)	.55
Morning cortisol levels nmol/L	17.4 (10.4-26.4)	18.0 (10.7-26.9)	15.9 (9.4-25.5)	.160	16.6 (9.3-25.6)	15.3 (9.4-25.5)	.74
Evening cortisol levels nmol/L	2.3 (1.4-3.9)	2.1 (1.3-3.5)	2.6 (1.6-4.9)	<.01	2.4 (1.4-4.6)	2.8 (1.8-5.0)	.13
NTproBNP pg/mL	141.4 (80.8-285.4)	122.4 (69.9-224.6)	228.5 (117.9-492.1)	<.01	273.5 (125.6-563.6)	217.8 (110.1-443.9)	.17
Copeptin pmol/L	6.8 (4.1-11.7)	6.4 (3.9-10.8)	8.9 (5.1-14.4)	<.01	9.2 (5.1-17.2)	8.8 (5.1-13.3)	.43
CMR[d] characteristics							
Left ventricle ejection fraction	62.2 (56.0-66.8)	63.2 (58.3-67.3)	56.7 (48.4-63.7)	<.01	53.2 (41.8-61.3)	59.6 (51.1-64.7)	<.01

Note: For categorical variables, n (%), and for continuous variables, median (lower quartile-upper quartile) are presented.

Abbreviation: NA, Not applicable.

[a]High-density lipoprotein.

[b]Low-density lipoprotein.

[c]C-reactive protein.

[d]Cardiac magnetic resonance.

Participants with previous heart failure (n = 25) had higher median levels of copeptin than those without (15.0 vs. 6.8 pmol/L; *P* <.01) in the total cohort but not in the subgroups (data not shown).

The median copeptin levels were higher in participants with T2DM than those without (8.0 pmol/L vs. 6.3 pmol/L; *P* <.01). The pattern was similar in the group without MI (7.8 pmol/L vs. 5.7 pmol/L; *P* <.01), but not in those with MI (data not shown).

TABLE 2 Unadjusted and adjusted predictive ability of log copeptin (increase in one standard deviation) assessed by the Cox proportional hazard regression analyses and presented as hazard ratio (HR) and 95% confidence intervals (CI) for the total cohort

	Total cohort		No myocardial infarction		Myocardial infarction	
Event	**HR (95%CI)**	**P**	**HR (95%CI)**	**P**	**HR (95%CI)**	**P**
Cardiovascular event						
n = 392						
Copeptin[univariable]	1.16 (1.05-1.29)	<.01	1.06 (0.93-1.20)	.42	1.10 (0.94-1.29)	.22
Morning cortisol[univariable]	0.99 (0.89-1.10)	.87	1.04 (0.93-1.16)	.49	0.84 (0.67-1.05)	.12
Evening cortisol[univariable]	0.99 (0.90-1.09)	.87	1.01 (0.90-1.13)	.91	0.92 (0.78-1.09)	.34
NTproBNP[univariable]	1.29 (1.22-1.37)	<.01	1.32 (1.21-1.44)	<.01	1.22 (1.09-1.36)	<.01
Stepwise model[a]	1) NTproBNP 1.24 (1.17-1.32)	<.01	1) NTproBNP 1.31 (1.19-1.45)	<.01	1) NTproBNP 1.22 (1.10-1.36)	<.01
Total mortality						
n = 368						
Copeptin[univariable]	1.31 (1.18-1.45)	<.01	1.21 (1.06-1.38)	<.01	1.32 (1.10-1.57)	<.01
Morning cortisol[univariable]	1.01 (0.92-1.11)	.82	1.04 (0.93-1.15)	.53	0.96 (0.80-1.12)	.68
Evening cortisol[univariable]	1.07 (0.94-1.11)	.69	1.02 (0.92-1.14)	.65	1.02 (0.87-1.19)	.83
NTproBNP[univariable]	1.34 (1.27-1.41)	<.01	1.40 (1.29-1.51)	<.01	1.31 (1.18-1.45)	<.01
Stepwise model[a]	2) NTproBNP 1.23 (1.16-1.31)	<.01	2) NTproBNP 1.37 (1.24-1.51)	<.01	2) Copeptin 1.49 (1.23-1.79)	<.01
	3) Copeptin 1.21 (1.08-1.35)	<.01				
Heart failure						
n = 82						
Copeptin[univariable]	1.04 (0.85-1.27)	.72	1.05 (0.81-1.38)	.71	1.02 (0.75-1.38)	.92
Morning cortisol[univariable]	0.93 (0.36-2.40)	.88	0.47 (0.06-3.63)	.47	1.07 (0.72-1.58)	.76
Evening cortisol[univariable]	1.09 (0.40-2.97)	.87	1.27 (0.18-8.80)	.81	1.00 (0.64-1.58)	.99
NTproBNP[univariable]	1.02 (0.88-1.19)	.77	1.01 (0.83-1.23)	.93	1.05 (0.77-1.41)	.77
Stepwise model[a]	No effects met the 0.05 level for entry into the model		No effects met the 0.05 level for entry into the model		No effects met the 0.05 level for entry into the model	
Myocardial infarction						
n = 119						
Copeptin[univariable]	1.29 (1.08-1.55)	<.01	1.20 (0.93-1.54)	.17	1.15 (0.89-1.50)	.28
Morning cortisol[univariable]	1.04 (0.92-1.19)	.52	1.10 (0.95-1.26)	.20	0.92 (0.67-1.26)	.62
Evening cortisol[univariable]	1.06 (0.97-1.17)	.22	1.11 (1.00-1.23)	.06	0.73 (0.46-1.16)	.18
NTproBNP[univariable]	1.27 (1.14-1.40)	<.01	1.20 (0.97-1.48)	.09	1.21 (1.01-1.44)	.04
Stepwise model[a]	1) NTproBNP 1.19 (1.06-1.33)	<.01	3) Evening cortisol 1.12 (1.01-1.26)	.04		

[a]Including copeptin, morning cortisol, evening cortisol, NTproBNP, age, sex, serum creatinine and previous heart failure (only presenting significant results of the three biomarkers).

Copeptin did not correlate with left ventricular ejection fraction (data not shown).

3.3 | Cortisol and NTproBNP levels

For the total cohort, the median morning cortisol and evening cortisol level was 17.4 μg/dL (IQR: 10.4-26.4 μg/dL) respective 2.3 μg/dL (IQR: 1.4-3.9 μg/dL). The evening cortisol was significantly higher for participants with previous MI than for those without (2.6 μg/dL [IQR: 1.6-4.9 μg/dL] respective 2.1 μg/dL [IQR: 1.3-3.5 μg/dL]; P <.01), but the morning cortisol levels did not differ in these groups (Table 1). No significant difference was found for morning or evening cortisol levels in the subgroups RMI and UMI (Table 1).

Copeptin correlated in the total cohort with evening cortisol ($r = .11$, $P < .01$) but not morning cortisol ($r = -0.01$, $P = .85$), this was also seen in those with no previous MI ($r = 0.10$, $P = .02$) (data not shown).

In the total cohort, the median NTproBNP was 141.4 pg/mL (IQR: 80.8-285.4 pg/mL). The NTproBNP was significantly higher for participants with previous MI than for those without (228.5 pg/mL [IQR: 117.9-492.1 pg/mL] respective 122.4 pg/ml [IQR: 69.9-225.6]; $P <.01$). There was no significant difference in NTproBNP levels in the subgroups RMI and UMI ($P = .17$). Copeptin correlated with NTproBNP only in the total cohort ($r = .07$, $P = .04$) (data not shown).

3.4 | Prognostic influence of copeptin

The total time of follow-up was 9.1 years during which 392 participants had a CVE (cardiovascular death/stroke/MI/PCI/CABG). The number of total deaths was 368, while 82 were diagnosed with heart failure and 119 suffered a re-infarction or developed a first MI.

In unadjusted Cox regression analyses, copeptin was significantly associated with CVE in the total cohort (HR: 1.16, 95% CI: 1.05-1.29; $P < .01$), but not in the groups with or without previous MI. Copeptin continued to associate with CVE after adjustments for morning and evening cortisol separately (data not shown). In the model including copeptin and NTproBNP, both biomarkers remained significantly associated with prognosis (Table 2). In the stepwise model, it was only NTproBNP that remained significantly associated with CVE.

Copeptin was significantly associated with total mortality for the total cohort (HR: 1.31 [1.18-1.45]; $P < .01$), as well for those with and without previous MI (Table 2) in unadjusted analysis. Copeptin continued to associate with total mortality after separate adjustments for morning cortisol, evening cortisol and NTproBNP for the total cohort as well as the groups with and without previous MI (data not shown). Copeptin was furthermore associated with total mortality in the final stepwise model for the total cohort and for those with previous MI.

Neither copeptin nor morning cortisol, evening cortisol or NTproBNP was associated with heart failure in unadjusted analyses.

Increasing copeptin levels were associated with an increased risk of MI in the total cohort (HR: 1.29 [1.08-1.55]; $P < .01$) in unadjusted Cox regression analysis (Table 2) and also after separate adjustments for morning and evening cortisol and NTproBNP (data not shown). This association with MI did not remain in the stepwise model.

4 | DISCUSSION

In this cohort of elderly individuals, copeptin levels were highest for those with previous MI, regardless whether it had been previously recognized or not. Even though copeptin correlated with evening cortisol, only copeptin was associated with total mortality after adjustments, indicating that copeptin elevation at least partly is related to physiological stress. Furthermore, copeptin correlated weakly with NTproBNP and continued to associate with cardiovascular events, MI and total mortality after adjustments for NTproBNP. Thus, the present findings shed further light on the role of copeptin as a prognostic marker, suggesting it relates to multifactorial reasons, that is a marker of general vulnerability rather than being specifically related to such as heart failure.

The present findings where copeptin was elevated in participants with evidence of a previous MI expands the knowledge of vasopressin activation in stable phases of coronary artery disease. Several studies have shown that copeptin is increased during the acute phase of MI. Patients with acute MI without previously known glucose abnormalities had significantly higher copeptin levels than population-based, age- and sex-matched controls without MI (10.5 pmol/L vs 5.9 pmol/L; $P < .01$) in the Glucose in Acute Myocardial Infarction (GAMI) study.[2] Furthermore, in the Leicester Acute Myocardial Infarction Peptide (LAMP) study copeptin levels were highest at hospital admission reaching a lower plateau 3-5 days later, however, still with levels above the normal range.[3] The present findings suggests that the activation of vasopressin in individuals with previous MI is persistent, which are in line with study by Sabatine et al that explored the prognostic capability of copeptin in 3717 patients with stable coronary artery disease of whom 56% had a previous MI.[17] In addition, the present study revealed that the copeptin levels were similarly elevated in participants with a previously known diagnosis of MI (ie RMI) and newly detected by CMR (ie UMI). This may reasonably be seen as an expression for a similar degree of vasopressin activation, mirroring stress and/or a pathophysiological mechanism in a stable phase post-MI, irrespective of the presence or absence of any previously recognized clinical manifestations, an assumption supported by the fact that participants with UMI and RMI have a similar prognosis as described previously.[10]

Since vasopressin is considered as a stress hormone,[8,18] it has been speculated that elevated copeptin levels in patients with acute MI are a reflection of physiological stress.[2,19] Indeed, in 101 critically ill patients copeptin correlated positively with the stress marker cortisol ($r = .42$, $P < .01$).[20] This relation was further explored in the current study in a stable phase as copeptin correlated with evening cortisol in participants in the total cohort, however, only in subgroup without previous MI and not in those with a previous MI.

Katan et al studied copeptin and cortisol levels in situations with different degrees of acute stress; a) healthy controls without apparent stress, b) hospitalized medical patients with moderate stress and c) surgical patients with maximal stress. As copeptin was already elevated in moderate stress and cortisol not, it was suggested that copeptin is more sensitive and a better mirror of stress than cortisol.[8] This gains support by the current results where copeptin had a stronger association with CVE, total mortality and MI than cortisol. Individuals with previous MI had higher evening cortisol levels compared to those without, while no difference was found in this respect in morning cortisol levels. However, neither morning nor evening cortisol was associated with clinical events. Furthermore, there was no association between copeptin and cortisol in those with previous MI, suggesting that there may also be other explanations for the increased copeptin levels in the study participants with myocardial damage.

Another potential explanation for the elevated copeptin levels in patients with previous MI may be that vasopressin activation is involved in the pathophysiology behind MI or its complications, for example heart failure. To explore the relation to heart failure, copeptin was studied in relation to the biomarker NTproBNP. Increased copeptin levels have previously been reported in heart failure and with a correlation to NTproBNP and prognosis.[21,22] Furthermore, in a recent study by Molvin et al, in 286 patients hospitalized with newly diagnosed or exacerbated heart failure, elevated levels of NTproBNP and copeptin, were associated with higher mortality after discharge. However, it was only NTproBNP that showed an association with re-hospitalization due to cardiac causes.[23]

The present study participants with previous heart failure had higher copeptin levels and NTproBNP showed a weak correlation to copeptin in the total cohort. However, neither copeptin nor NTproBNP was associated with heart failure which is probably explained by the low number of heart failure events. Interestingly, copeptin remained significantly associated with CVE, total mortality and MI after adjusting for NTproBNP in the total cohort, implying that the prognostic implications of copeptin are not fully explained by the development of heart failure. In addition, there was a sex difference in copeptin levels and patients with diabetes had higher levels suggesting that the elevated copeptin levels have a multifactorial explanation and reflect a general vulnerability where physiological stress might contribute. This assumption is further supported by the fact that elevated levels of copeptin continued to associate with total mortality after multiple adjustments. Therefore, the present study has shown that vasopressin activation, measured by copeptin, is raised in the chronic phase of post-MI patients and that this elevation is associated with prognostic implications. The prognostic relevance of vasopressin activation is not related only to heart failure or stress but presumably also to general vulnerability.

4.1 | Limitations

Potential limitations with the present report are that the copeptin, NTproBNP and cortisol measurements were not performed at the same time as the CMR, and furthermore, the time of the MI in relation to the investigations were not known. Cortisol measurements were collected at one occasion, and to reduce measurement error, multiple samples or even a hair sample might be an advantage. Another limitation is that the duration of follow-up was shorter for heart failure compared with the other outcomes. The relatively few heart failure events might explain why copeptin, which has been shown to predict development of heart failure after an AMI and 1-year mortality in those with acute heart failure,[24] was not associated with heart failure events in the present cohort. The median age was high, and therefore, the results may not be applicable to younger age groups. One way to further analyse copeptin as a stress marker would be to include measurements from the participants during the acute phase of a MI, a stressful condition, and after follow-up in more a stable condition.

In conclusion, in the present cohort of elderly individuals in the ICELAND MI study copeptin levels were higher in elderly people with previous MI whether previously recognized or not. Copeptin correlated with evening cortisol levels, not morning levels, and was independently associated with total mortality in the total cohort. Copeptin only correlated weakly with NTproBNP but continued to associate with events after adjustments for NTproBNP. The present study supports the assumption that the increase in copeptin is multifactorial, supporting the assumption that copeptin is a marker of general vulnerability.

CONFLICT OF INTEREST
There are no economical conflicts of interest related to this work.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.