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Plasma renin activity has a complex prognostic role in patients with acute coronary syndromes

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ABSTRACT

Background: Plasma renin activity (PRA) has been related to all-cause mortality and cardiovascular events in patients with cardiovascular disease. However, data from patients with acute coronary syndromes (ACS) are sparse.
Methods: Determination of PRA was made in 550 patients with ACS, including a subgroup of 287 patients not on treatment with angiotensin converting enzyme inhibitors, angiotensin receptor blockers or diuretics, and without heart failure. We evaluated the relations between PRA and all-cause mortality after three years and long-term, and to cardiovascular events after median 8.7 years. Adjustments were made for variables that influenced the hazard ratio (HR) > 5% for the relation between PRA and outcome.
Results: Baseline PRA was associated with all-cause mortality during three-years (unadjusted HR 1.74 per 1 SD increase in logarithmically transformed PRA; 95% confidence interval (CI) 1.39–2.16, $p < 0.0001$) and long-term (HR 1.12, CI 1.00–1.25, $p = 0.046$). After adjustments, only the three-year association remained significant. In unadjusted analyses, PRA was associated with cardiovascular death, but not with nonfatal cardiovascular events. In the subgroup there was an inverse relation between PRA and long-term all-cause mortality.
Conclusion: Higher PRA was a significant independent predictor of all-cause mortality after three years, but not at long-term follow-up and not significantly associated with cardiovascular incidence. The renin-angiotensin-system pathophysiology is of great interest, not least due to its association with the COVID-19 pandemic. Our findings indicate a need for further research on the prognostic/predictive aspects of the renin-angiotensin-system in ACS.

1. Introduction

The possible usefulness of biochemical markers as tools for predicting future events in patients with cardiovascular (CV) disease is receiving considerable attention. Though markers of myocardial injury and inflammation have been of particular interest [1–4] — given the inflammatory hypothesis of atherothrombosis [5] — a variety of other potential markers have also been studied [6]. One such marker is renin, part of the classic renin-angiotensin-system (RAS) and the rate-limiting step in the production of angiotensin II (Ang II), the main effector peptide of the RAS [7]. Classic effects exerted by Ang II via the AT_1 receptor include arterial vasoconstriction, stimulation of sodium reabsorption, and increased release of noradrenaline, aldosterone and ADH. An association between renin and CV events was reported already fifty years ago [8].

To assess RAS activity and its effects on prognosis in patients with CV disease, measurement of plasma renin concentrations or plasma renin activity (PRA), the in vitro rate of formation of Ang I, has been the method of choice for many years. Many outcome studies have been undertaken in hypertension and heart failure (HF) [9–12], but studies have also been performed in general populations and in patients with various types of CV disease [13–19]. Meanwhile, data from patients with acute coronary events are sparse.

Cumulative results from published studies have been contradictory, and definite conclusions have been difficult to draw [20]. Drug use influences PRA with a decrease caused by beta-blockers and an increase by diuretics and angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) [21]. Further, when the RAS is blocked, the plasma level does not mirror the "effective" PRA [22].

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Therefore, differences in baseline medications between studies probably contribute to differences in results.

Increased PRA is part of the neurohormonal activation seen in connection with acute myocardial infarction (MI) [23]. Given the deleterious effects that the RAS can exert on the CV system, we hypothesized that a high PRA level might predict adverse outcomes in acute coronary syndromes (ACS). To test this hypothesis, we determined the circulating PRA level in patients consecutively hospitalized for ACS and followed them for 3 years and long-term to evaluate their risk of all-cause mortality in association with elevated PRA. Separate analyses were made in a subgroup without ACE inhibitors/ARBs, diuretics or HF. The risk of CV events was also assessed.

2. Materials and methods

2.1. Study sample

All patients under age 80 years who were admitted to the coronary care unit at Sahlgrenska University Hospital and diagnosed with ACS between September 1995 and March 2001 were included in a prospective study on prognosis and risk (PRACSIS) [24]. Altogether, 2335 patients were recruited. In a subsample of 550 patients who were alive and still hospitalized 4 days after admission, blood was drawn for determination of PRA. ACS diagnosis (ST elevation MI [STEMI], non-STEMI [NSTEMI], and unstable angina) was based on symptoms indicating myocardial ischemia, along with electrocardiographic (ECG) changes, elevation of biochemical markers of myocardial necrosis (as registered and evaluated according to standard procedures at the time of inclusion) and previously recognized coronary artery disease. Current hospital routines were followed for patient treatment and management. To evaluate whether the predictability of PRA was affected by the baseline use of ACE inhibitors/ARBs or diuretics, we also studied a subgroup of 287 patients not treated with these drugs prior to determination of PRA. No one in this group was diagnosed with previous HF or exhibited signs of HF at admission. The study was approved by the Regional Ethics Committee, Gothenburg University, and informed consent was obtained from all participants.

2.2. Data collection

Information on clinical history, risk factors, and hospital course and treatment were collected from the hospital medical records and by interview. The patients were prospectively classified by ECG changes at admission, Killip class at admission and during hospitalization, and treatment before and after admission. Hospital routines and laboratories were used to determine creatine kinase MB fraction (CKMB), troponin T (TnT), creatinine, leucocytes, and lipids. The glomerular filtration rate (GFR) was estimated using the Cockcroft–Gault formula.

Blood samples to determine PRA, C-reactive protein (CRP) and pro-B-type natriuretic peptide $(BNP)_{3-108}$ were obtained in the early morning, median 3 days after admission, with the patient in the supine position after a night's rest. All plasma and serum samples were stored at −80 °C before analysis. CRP was measured using an ultrasensitive immunoturbidimetric method (Orion Diagnostica, Espoo, Finland) on a Konelab 20 autoanalyzer (Thermo Fisher Scientific, Vantaa, Finland). To determine proBNP, an immunofluorescent assay calibrated with spiked plasma was used (Biosite Inc., San Diego, CA, USA). PRA was analyzed with a commercially available radioimmunoassay kit (Renin-RIA bead; Abbot Diagnostics Division, South Pasadena, CA, USA) [25]. The normal value was 0.85 + 0.6 pmol of Ang I (Ang I h^{-1} mL^{-1}) with a 95% confidence interval (CI) of 0.6–1.1 pmol of Ang I h^{-1} mL^{-1}. The interassay coefficient of variation was 8.8%.

Echocardiography was performed by an experienced investigator within five days after hospital admission.

2.3. Endpoint definitions

Outcomes were: all-cause mortality, at 3 years and median (25th–75th percentiles) 14.7 (7.6–17.3) years of follow-up, based on survival confirmation and date of death from the Swedish National Population Registry; CV mortality and the composite endpoint CV death/HF/MI from the Swedish National Cause of Death Register and the Swedish Hospital Discharge Register at 8.7 (7.1–9.9) years of follow-up.

2.4. Statistical analysis

Associations between PRA levels and patient characteristics were performed using Mann–Whitney *U* test for dichotomous variables and Spearman's rank correlation statistic for continuous variables. Actual PRA levels were used in these tests. Descriptive results are presented as stratified by PRA level quartiles. For analysis of various outcomes, Cox proportional hazard regression model was used. Since PRA levels were found to violate the linearity assumption, transformation by natural logarithm was used in this analysis and results are expressed by hazard ratios (HRs) of 1 standard deviation (SD) increase with corresponding 95% CIs. In the multivariable analysis, adjustments were made for confounders defined as those patient characteristic variables that altered the HR by >5%. All tests were two-sided and p values < 0.05 were considered statistically significant. All analyses were performed using SAS for Windows version 9.4.

3. Results

3.1. Basal characteristics

Table 1 shows the characteristics at admission according to PRA quartiles in overall sample of 550 patients. Those with a *higher PRA level* at baseline were significantly more likely to have a history of HF and diabetes, and to be registered with a Killip class > 1 at admission and during hospitalization. Accordingly, these patients more frequently had a lower left ventricular ejection fraction and were more frequently treated with ACE inhibitors and diuretics at admission, in hospital, and at discharge. They exhibited higher levels of CKMB and TnT, and had more frequent ECG Q-waves, lower systolic blood pressure, higher heart rate at admission, and had higher levels of CRP and leucocytes. Patients with *lower PRA* were more likely to be diagnosed with unstable angina, more frequently subjected to in-hospital nonprimary percutaneous coronary intervention, and more frequently treated with beta-blockers in hospital and at discharge. Lower PRA was associated with higher likelihood of being discharged alive.

In the subgroup of 287 patients without ACE inhibitor/ARBs or diuretics (Table 2), those with *higher PRA levels* were significantly more likely to be younger and lack a history of angina pectoris, and were less likely to be diagnosed with unstable angina. Consistent with the overall sample of 550 patients, these patients had higher levels of CKMB, TnT and leukocytes. A similar pattern was seen for estimated GFR, Q-wave at admission, treatment with thrombolysis, and lipid-lowering drugs at discharge. Their systolic blood pressure tended to be lower.

3.2. Complementary information on the overall ACS sample and its non-ACE inhibitor/ARB/diuretic/HF subgroup

The 550 (subgroup of 287 in parenthesis) patients had a mean age of 64.2 ± 9.9 years, 26.4% women (61.8 ± 9.9 years, 24.7% women). Their median PRA was 0.78 and 25th,75th percentile 0.32, 1.83 pmol of Ang I h^{-1} mL^{-1} (0.55 and 0.26, 1.21), while 32.4% (18.8%) were above the upper level of normal. Their diagnoses were STEMI in 35.3% (30.7%), NSTEMI 37.8% (38.7%), and unstable angina 26.9% (30.7%), with median PRA level per diagnostic group 0.90, 0.88, and 0.62 (0.52, 0.65 and 0.48)

Table 1
Patient characteristics at baseline in relation to PRA levels among overall sample (n = 550).

	PRA q1 <0.32 (n = 134)	PRA q2 0.32–0.77 (n = 141)	PRA q3 0.78–1.83 (n = 138)	PRA q4 >1.83 (n = 137)	p*	All (n = 550)
PRA, pmol h^{-1} mL^{-1}	0.18	0.51	1.23	3.51	–	0.78
Age, years (mean ± SD)	64 ± 9	65 ± 10	63 ± 11	64 ± 10	0.85	64 ± 10
Female	28	27	22	29	0.98	26
Previous MI	20	26	25	25	0.20	24
Previous angina	54	56	46	48	0.15	51
Previous HF	3	5	11	15	0.0003	9
Previous diabetes	12	20	16	28	0.006	19
Previous hypertension	47	41	36	40	0.50	41
Previous hypercholesterolemia	26	32	33	30	0.29	30
Current smoker	34	40	35	36	0.99	36
STEMI	36	31	33	42	0.37	35
NSTEMI	36	34	43	39	0.17	38
UAP	28	35	25	20	0.01	27
ST-elevation at admission	34	29	30	39	0.41	33
ST-depression at admission	13	12	11	12	0.96	12
Q-wave at admission	10	10	12	25	<0.0001	14
Systolic BP <100 mmHg at admission	2	4	1	4	0.51	3
Systolic BP at admission, mmHg	160	150	150	145	0.003	150
Diastolic BP at admission, mmHg	90[1]	88	90	90	0.09	90[1]
Heart rate at admission, bpm	70	70	73	77	0.03	72
CKMB max, μg/L	36	28	54	59	0.0004	43
TnT max, μg/L	0.2[4]	0.7[3]	0.8[3]	1.9[3]	<0.0001	0.9[3]
Estimated GFR, μmol/L	65	68	71	64	0.87	68
ProBNP, pg/mL	1640[2]	1803[1]	1268[2]	2228[1]	0.30	1672[1]
CRP, mg/L	10.0[2]	13.7[2]	12.7[1]	21.0[2]	0.0001	13.9[2]
Leukocytes 10^9/L	8.2[1]	8.8[2]	8.7[1]	9.4[2]	0.0003	8.8[2]
Total cholesterol, mmol/L	5.1[3]	5.5[3]	5.5[3]	5.5[3]	0.11	5.4[3]
LDL cholesterol, mmol/L	3.2[4]	3.5[3]	3.5[3]	3.5[3]	0.32	3.5[3]
BMI, kg/m^2	25.5	25.9	26.0	25.4	0.50	25.7
Killip class II–IV at admission	2	5	4	14	<0.0001	6
Max Killip class II–IV	7	11	8	39	<0.0001	16
Thrombolysis	12	15	13	22	0.08	15
Primary PCI	14	9	10	8	0.17	10
Other PCI	26	19	24	14	0.03	21
CABG	12	14	9	9	0.31	11
No thrombolysis or revascularization	42	48	46	53	0.06	47
LVEF, %	55[4]	56[3]	55[3]	50[3]	0.003	54[3]
Discharged alive	100	99	99	96	0.01	99
Cardiovascular medication						
Beta-blocker at admission	38	45	35	36	0.28	39
Aspirin at admission	31	37	30	36	0.71	34
ACE inhibitor at admission	9	5	14	17	0.004	11
ARB at admission	0	1	1	1	0.26	1
Diuretics at admission	7	7	10	17	0.007	10
Lipid-lowering drugs at admission	17	11	17	15	0.78	15
Beta-blocker in hospital	97	98	95	91	0.02	95
Aspirin in hospital	97	94	93	95	0.39	95
ACE inhibitor in hospital	19	25	26	60	<0.0001	33
Before PRA	12	15	22	47	<0.0001	24
After PRA	4	6	1	7	0.50	4
Unknown whether before PRA	4	4	4	6	0.41	4
ARB in hospital	0	1	1[1]	1	0.39	1
Diuretics in hospital	21	20	28	58	<0.0001	32
Beta-blocker at discharge	93	96	89	86	0.03	91
Aspirin at discharge	94	91	91	90	0.38	91
ACE inhibitor at discharge	19	25	26	55	<0.0001	31
ARB at discharge	0	0	1	0	0.53	0
Diuretics at discharge	15	16	20	42	<0.0001	23
Lipid-lowering drugs at discharge	40	42	51	44	0.13	44

Values are percentage or median unless otherwise given.
Abbreviations: PRA, plasma renin activity; q, quartile; MI, myocardial infarction; HF, heart failure; STEMI, ST-elevation myocardial infarction; NSTEMI, non-STEMI; UAP, unstable angina; BP, blood pressure; CK MB, creatine kinase MB fraction; TnT, troponin T; GFR, glomerular filtration rate; BNP, brain natriuretic peptide; CRP, C-reactive protein; LDL, low density lipoprotein; BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; LVEF, left ventricular ejection fraction; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker.
[1]1%–5% missing; [2]5%–10% missing; [3]10%–25% missing; [4]25%–50% missing.
* Actual PRA values were used in *p* value calculations.

pmol of Ang I h^{-1} mL^{-1}. The percentage with prior hypertension was 41.1 (36.2).

In the overall sample (n = 550) the highest proBNP level was seen in the 4th quartile of PRA (ns, Table 1) whereas an inverse trend was noted in the subgroup (ns, Table 2). There was a significant association between proBNP and outcome variables (not MI) at all time points studied in the overall sample. In the subgroup it was significant at 8.7 and 14.7 years (data not shown). Only a few patients in the subgroup were discharged

Table 2
Patient characteristics at baseline in relation to PRA levels in the subgroup (n=287) not treated with angiotensin converting enzyme inhibitors, angiotensin receptor blockers or diuretics before determination of PRA.

	PRA q1 <0.26 (n = 71)	PRA q2 0.26–0.54 (n = 72)	PRA q3 0.55–1.20 (n = 72)	PRA q4 >1.20 (n = 72)	p*	Subgroup (n = 287)
PRA, pmol h^{-1} mL^{-1}	0.15	0.36	0.77	1.76	–	0.55
Age, years (mean ± SD)	62 ± 9	64 ± 10	62 ± 11	59 ± 10	0.04	62 ± 10
Female	25	26	26	21	0.44	25
Previous MI	15	22	19	12	0.45	17
Previous angina	58	56	50	42	0.02	51
Previous HF	0	0	0	0	–	0
Previous diabetes	10	14	14	15	0.24	13
Previous hypertension	42	38	36	29	0.08	36
Previous hypercholesterolemia	23	40	40	35	0.18	34
Current smoker	35	32	46	35	0.59	37
STEMI	37	26	22	38	0.76	31
NSTEMI	30	38	47	40	0.11	39
UAP	34	36	31	22	<0.05	31
ST-elevation at admission	34	25	18	36	0.73	28
ST-depression at admission	11	14	12	10	0.72	12
Q-wave at admission	6	4	6	14	<0.05	7
Systolic BP <100 mmHg at admission	4	3	3	0	0.29	2
Systolic BP at admission, mmHg	160	150	150	145	0.01	150
Diastolic BP at admission, mmHg	90[1]	90[1]	92[1]	90[1]	0.36	90[1]
Heart rate at admission, bpm	70	73	72	70	0.84	72
CKMB max, μg/L	19	24	34	751	0.002	34
TnT max, μg/L	0.1[3]	0.3[3]	0.8[3]	0.9[3]	0.001	0.5[3]
Estimated GFR, μmol/L	69	68	71	83	0.02	72
ProBNP, pg/mL	1258[2]	1414[1]	1095[1]	952[2]	0.10	1200[2]
CRP, mg/L	9.4[2]	9.0[2]	8.0[1]	13.0[2]	0.24	10.0[2]
Leukocytes 10^9/L	8.0[1]	8.2[1]	8.8[1]	9.2[1]	0.0007	8.6[1]
Total cholesterol, mmol/L	5.2[3]	5.6[2]	5.5[3]	5.6[2]	0.07	5.5[3]
LDL cholesterol, mmol/L	3.3[4]	3.6[3]	3.4[3]	3.6[3]	0.39	3.5[3]
BMI, kg/m^2	25.5	25.6	26.0	26.0	0.56	25.7
Killip class II–IV at admission	0	0	0	0	1.00	0
Max Killip class II–IV	0	0	0	0	1.00	0
Thrombolysis	7	14	8	21	0.02	13
Primary PCI	18	7	6	10	0.06	10
Other PCI	28	25	22	22	0.22	24
CABG	10	17	15	10	0.69	13
No thrombolysis or revascularization	39	44	54	40	0.45	45
LVEF, %	57[3]	56[4]	58[3]	60[3]	0.40	57[3]
Discharged alive	100	100	99	100	0.54	100
Cardiovascular medication						
Beta-blocker at admission	35	49	36	35	0.41	39
Aspirin at admission	31	32	28	28	0.39	30
ACE inhibitor at admission	0	0	0	0	1.00	0
ARB at admission	0	0	0	0	1.00	0
Diuretics at admission	0	0	0	0	1.00	0
Lipid-lowering drugs at admission	14	17	18	11	0.79	15
Beta-blocker in hospital	100	100	100	100	1.00	100
Aspirin in hospital	100	94	96	97	0.49	97
ACE inhibitor in hospital	0	3	6	1	0.59	2
Before PRA	0	0	0	0	1.00	0
After PRA	0	3	6	1	0.59	2
Unknown whether before PRA	0	0	0	0	1.00	0
ARB in hospital	0	0	0	0	1.00	0
Diuretics in hospital	0	0	0	0	1.00	0
Beta-blocker at discharge	94	99	94	93	0.40	95
Aspirin at discharge	96	90	93	94	0.92	93
ACE inhibitor at discharge	0	3	7	0	0.94	2
ARB at discharge	0	0	0	0	1.00	0
Diuretics at discharge	0	1	0	3	0.17	1
Lipid-lowering drugs at discharge	42	43	56	56	<0.05	49

Values are percentage or median unless otherwise given.
Abbreviations: PRA, plasma renin activity; q, quartile; MI, myocardial infarction; HF, heart failure; STEMI, ST-elevation myocardial infarction; NSTEMI, non-STEMI; UAP, unstable angina; BP, blood pressure; CK MB, creatine kinase MB fraction; TnT, troponin T; GFR, glomerular filtration rate; BNP, brain natriuretic peptide; CRP, C-reactive protein; LDL, low density lipoprotein; BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; LVEF, left ventricular ejection fraction; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker.
[1]1–5% missing; [2]5–10% missing; [3]10–25% missing; [4]25–50% missing.
* Actual PRA values were used in *p* value calculations.

on ACE inhibitors/ARBs or diuretics (Table 2). Among all patients 8.4% (46/550) and in the subgroup 2.4% (7/287) were rehospitalized for HF, while 8.7% (48/550) and 8.7% (25/287) were rehospitalized for MI during the first three years of follow-up. All-cause mortality was 12.7% (69/550) and 5.9% (17/287) during this period (Table 3).

Table 3
Associations between PRA and 3-year and long-term all-cause mortalities, as well as composite and separate cardiovascular endpoints: incidence of death, acute myocardial infarction and heart failure.

	Unadjusted HR (95% CI)[a]	p	Adjusted HR (95% CI)[a]	p	Adjusted for	No. of endpoints/patients
All patients						
All-cause mortality						
3 years	1.74 (1.39–2.16)	<0.0001	1.39 (1.10–1.76)	0.006	Max Killip > 1, ACE inhibitor/ARB, diuretics	69/550
Long-term	1.12 (1.00–1.25)	0.046	1.00 (0.89–1.12)	0.94	Max Killip > 1, ACE inhibitor/ARB, diuretics	322/550
Endpoints[b]						
CV death/MI/HF	1.13 (0.99–1.30)	0.07	0.97 (0.84–1.12)	0.66	Max Killip > 1, ACE inhibitor/ARB, diuretics	204/550
CV mortality	1.29 (1.08–1.55)	0.005	1.06 (0.88–1.27)	0.57	Max Killip > 1, ACE inhibitor/ARB, diuretics	115/550
MI (recurrent)	1.02 (0.83–1.26)	0.85	0.99 (0.80–1.24)	0.95	Max Killip > 1, ACE inhibitor/ARB, diuretics	93/550
HF (readmission)	1.22 (0.99–1.51)	0.07	0.96 (0.77–1.19)	0.69	Max Killip > 1, ACE inhibitor/ARB, diuretics	82/550
Subgroup						
All cause mortality						
3 years	0.87 (0.54–1.41)	0.57	0.92 (0.55–1.53)	0.74	Age	17/287
Long-term	0.79 (0.66–0.93)	0.006	0.83 (0.69–0.99)	0.04	Age	138/287
Endpoints[b]						
CV death/MI/HF	0.88 (0.70–1.10)	0.27	0.94 (0.74–1.20)	0.64	Age, eGFR	75/287
CV mortality	0.78 (0.56–1.09)	0.15	0.88 (0.62–1.23)	0.45	Age, hypertension	36/287
MI (recurrent)	0.97 (0.73–1.30)	0.84	0.99 (0.72–1.34)	0.93	Age, CKMB, eGFR	45/287
HF (readmission)	0.86 (0.57–1.31)	0.49	1.09 (0.71–1.66)	0.70	Age, angina, hypertension, eGFR	22/287

Abbreviations: CV, cardiovascular; MI, myocardial infarction; HF, heart failure; HR, hazard ratio; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; CKMB, creatine kinase MB fraction.
[a] Hazard ratio and corresponding 95% confidence interval for 1 SD increase in the natural logarithm of PRA levels.
[b] Median 8.7 years.

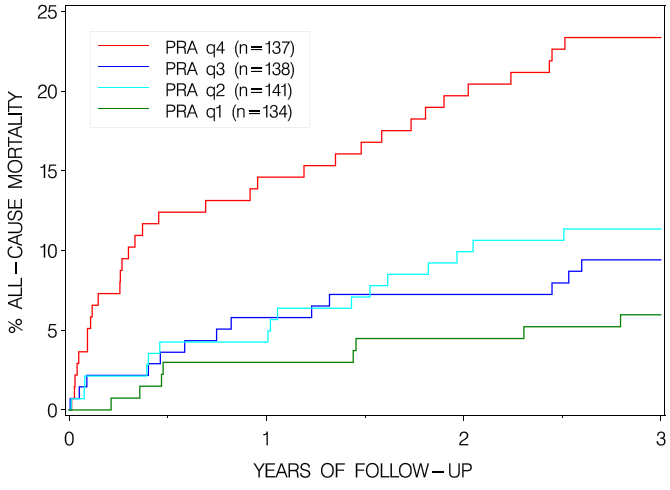

Fig. 1. Association between PRA quartiles and all-cause mortality in patients with acute coronary syndromes (n=550) at 3-year follow-up.

3.3. PRA level and prognosis

The association between PRA quartile and 3-year mortality is shown in Fig. 1. In univariate analysis, PRA was significantly associated with both 3-year and long-term all-cause mortality in the overall sample (Table 3). HR associated with a 1 SD increase in logarithmically transformed PRA levels at baseline was 1.74 (95% CI 1.39–2.16; $p < 0.0001$) after 3 years and 1.12 (95% CI 1.00–1.25; $p = 0.046$) long-term. The association between PRA and the composite endpoint of CV mortality, rehospitalization due to HF or MI, was not significant, while it was significant for the association with CV mortality alone (HR 1.29 (95% CI 1.08–1.55; $p = 0.005$). In the subgroup, PRA showed a significant inverse association with long-term all-cause mortality, with HR per 1-SD increase in logarithmically transformed PRA level 0.79 (95% CI 0.66–0.93; $p = 0.006$). No other significant association with outcome was observed in this subgroup.

Table 3 shows the association between PRA and outcomes *after adjustments* for confounders, yielding a significant adjusted association between PRA and 3-year all-cause mortality, with HR 1.39 (95% CI 1.10–1.76; $p = 0.006$). In the subgroup, the inverse long-term association between PRA and all-cause mortality remained significant after adjustment, with HR 0.83 (95% CI 0.69–0.99; $p = 0.04$).

4. Discussion

This study adds information about acute CV disease to the available data on PRA as a predictor of adverse outcomes. Among our patients with ACS, unadjusted PRA levels during the acute phase were significantly associated with all-cause mortality, both 3 years later and long-term. After adjustment for confounders the 3-year association between PRA and all-cause mortality remained significant. On follow-up after a median of 8.7 years, PRA showed a significant univariate association with CV mortality which, however, was no longer significant after adjustments. In the analysis of the subgroup without ACE inhibitors/ARBs or diuretics and no clinical HF, we observed an inverse relation between PRA and long-term all-cause mortality, even after adjustment for age.

In line with current knowledge about the effect of drugs on the PRA level [21], we found a negative association between PRA and ongoing therapy with beta-blockers (only in the overall sample) and a positive for ACE inhibitors and diuretics. The latter drugs, but not beta-blockers, also altered the relationship between PRA and outcomes. Adjustment for these therapies abolished the association, probably because patients with HF or hypertension and a worse prognosis were more often treated with ACE inhibitors. Of note is that the effective PRA level is overestimated in patients treated with ACE inhibitors, since blocking of the conversion of Ang I to Ang II means that no more than about one-tenth of the measured PRA level is effective [26].

The results from studies on renin as a prognostic factor in CV disease have varied considerably [27]. Studies on treatment naive patients are rare. Alderman et al. [9] found an independent association between renin before treatment and the subsequent risk of MI during 8.7 years of prospective follow-up in 1717 patients with mild-to-moderate hypertension. The findings were reinforced and extended in a second report after a further 8 years [28]. On the other hand, Meade et al. [16] reported no association between PRA and coronary events in a predominantly normotensive population with PRA without treatment and followed prospectively for many years. In the population-based prospective Framingham Heart Study with 3408 participants, only 957 of the 1413 included hypertensive subjects were on treatment at baseline [18]. The

results were similar to those obtained in our overall sample. Log-renin was associated with all-cause adjusted mortality at 2.5 years, but not beyond, and not with CV events. The results were the same among the hypertensive participants, with or without therapy.

Both consistent and contradictory reports are available from larger populations with different types of CV disease and on medication at baseline. In the Valsartan Heart Failure Trial (Val-Heft) baseline PRA predicted 2-year mortality in 4291 patients, even after adjustment for confounders, and in subgroups with or without beta-blockers or ACE inhibitors [10]. In the prospective Luric study plasma renin concentration in 3303 patients referred for coronary angiography, 30% with ACS, showed a strong association, independent of medication, between plasma renin concentration and CV mortality after almost 10 years [29]. No association was found between renin and fatal MI.

In a recent retrospective report from Japan on 878 patients with acute MI, and PRA measured within 48 h from admission, high PRA was an independent predictor of CV death and hospitalization for HF during a 4.5-year follow-up, but as in our study did not predict MI incidence [15]. Similar results were obtained in subsets of patients who had not previously been treated with ACE inhibitors/ARBs or beta-blockers. However, differences in outcome variables, treatment regimens, time for determination of PRA, and follow-up time, between this study and ours, make comparisons difficult.

It appears that studies assessing PRA as a predictor of future events have given more consistent and robust results in patients with more severe cardiac disease [10,17]. The diverging results between our subgroup and the overall sample support this notion. In the 4th PRA quartile in our overall sample 60% of the patients were on treatment with ACE inhibitors/ARBs or diuretics and, most probably, some individuals suffered from overt HF, which could explain high PRA and tendency towards high proBNP. We cannot exclude that excessive sodium-volume depletion contributed to high PRA levels among these patients despite the notion by Sealy et al. [26] that lower proBNP levels would be expected in connection with sodium-volume depletion.

In our subgroup (not on treatment with ACE inhibitors/ARBs or diuretics), with an inverse correlation between PRA and all-cause mortality, there was a tendency towards inverse relation between proBNP and PRA. These patients were also admitted to hospital due to ACS, and the proportion of diagnosed MI was almost the same as in the overall sample (69.4% vs 73.1%). As reflected by treatment at discharge only a few subjects in the subgroup developed HF during hospitalization, and after 3 years a much smaller proportion than in the overall sample had been rehospitalized due to HF. It is interesting that almost the same proportion as in the overall sample had been readmitted due to MI, both after 3 and 8.7 years.

Results in line with those in our subgroup were reported from a case-control analysis in the ASCOT trial (n = 9098, 91.2% on antihypertensive therapy at baseline, followed for >5.5 years), where among 377 cases and 823 controls, PRA showed a non-significant inverse association with risk of CV events [11]. Bhandari et al. [30], evaluated retrospectively PRA and 2-year prognosis in subjects (majority on antihypertensives) with elevated (≥140 mmHg) or controlled (<140 mmHg) systolic blood pressure. PRA was associated with increased risk for ischemic events and HF among hypertensive but not normotensive subjects suggesting higher PRA in normotension to reflect a physiological compensation. This suggestion might also be valid in our subgroup. Within this group, those with higher PRA were somewhat younger, had larger infarcts and inflammatory response but lower proBNP, lower systolic blood pressure and better renal function. However, although studies on PRA and prognosis have given most consistent results in HF-studies, associations between PRA and adverse events have also repeatedly been found in studies not including HF patients. It is therefore tempting to speculate that also other mechanisms than those involved in the classic RAS system might have been operating.

A number of negative effects exerted by Ang II via the AT_1 receptor (ACE/Ang II/AT_1 axis), in addition to those belonging to classic RAS, and related to oxidative stress, inflammation, endothelial dysfunction and tissue remodeling, have been identified [31,32]. It has gradually been recognized that, in addition to the circulating RAS, there are also tissue-based RASs in many organs (heart, brain, large arteries and arterioles, kidneys, etc.) [33]. Furthermore, systematic research has led to the discovery of a counter-regulatory RAS (ACE2/ANG-(1–7)/MAS axis) with protective effects on the CV system, and with ACE2 as a novel endogenous inhibitor [34]. Although speculative, it cannot be excluded that the balance between the two counter-regulatory arms of the RAS could have had cardioprotective effects in our non-ACE inhibitors/ARBs subgroup. In an experimental study, Burrell et al. [35] found an increased ACE2 expression after MI in the rat and in human failing hearts, and suggested that "increased cardiac ACE2 after MI may act as a counter-regulatory mechanism to limit the adverse effects of an elevated cardiac Ang II by increasing levels of the vasodilatory Ang 1-7". Information about cardiac ACE2 levels in our patients would, of course, have been of interest. Recently techniques for determining soluble ACE2 in humans have been developed. The extent to which these levels mirror ACE2 activity in the heart and their association with prognosis remains to be determined. Of note, ACE2 has emerged as the functional receptor for the coronavirus SARS-CoV-2 and has thus attracted widespread interest in connection with the currently ongoing COVID-19 pandemic [36,37].

Consistent with some reports [12], we demonstrated an association between PRA and CRP as well as leucocyte level. This association was present in both the overall sample and the subgroup. Inflammation is a key mechanism in the development and progression of atherosclerosis and RAS activation is involved in the inflammatory processes that lead to the development and also rupture of vulnerable plaque [38]. Further, the RAS is upregulated in association with the intense inflammatory reactions elicited by MI development [39]. It is well known that myocardial ischemia increases Ang II levels and that chronic treatment with ACE inhibitors or ARBs may reduce ischemia reperfusion injury [40]. Clinical data have demonstrated that the ARB ibesartan in patients at high risk for CV death reduces inflammation and oxidative stress, and exerts beneficial effects on metabolic syndrome [41].

Another interesting observation herein is the positive correlation between PRA levels and CKMB and troponin. The increase in the latter reflects infarct size but may simultaneously mirror the degree of inflammation. Sigurdsson et al. [23] observed a prolonged neurohormonal activation after acute MI. It occurred predominantly in patients with overt HF, but it was related to infarct size and seen also in patients without HF.

5. Strengths and limitations

The prospective design with long-term follow-up together with standardized procedures is an important strength of this single center study. Blood sampling for determination of PRA was standardized with respect to activity, time of the day, food intake and position. Blood pressures from this specific occasion were not available. We cannot exclude that such measurements would have had a larger impact on the association between PRA levels and outcomes than blood pressure from admission. Our patients were admitted due to ACS and pharmacological treatment for cardioprotection could not be withheld. However, in a subgroup there was no need for ACE inhibitors/ARBs or diuretics. The beneficial ACE2-angiotensin-(1–7) MAS axis of the RAS had not yet been recognized when this study was conducted, and PRA was the only component of the classic RAS available.

6. Conclusion

Higher PRA levels were independently associated with all-cause mortality at the 3-year follow-up in patients with ACS, but not with CV events or long-term. In a subgroup of patients without ongoing treatment with ACE inhibitors/ARBs or signs of HF, there was an inverse relation between PRA and long-term all-cause mortality. Our data support PRA as a predictor of death in high-risk patients with ACS, though

many questions remain and its use for risk stratification is questionable. The findings strongly support further investigations of RAS, including both its classical aspects and the more recently discovered counter-regulatory axis, in humans with various CV diseases. The extent to which the pathophysiological mechanisms and varying outcomes of COVID-19 may be explained by an imbalance in the RAS is currently the subject of much research.

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Declaration of Competing Interest

None.

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