資料７

電子カルテ情報活用型
多施設症例データベースを利用した
糖尿病に関する大規模な
臨床情報収集に関する基盤的研究

診療録直結型全国糖尿病データベース事業

Japan Diabetes compREhensive database project based on an Advanced electronic Medical record System, **J-DREAMS**

研究概要

- 国立国際医療研究センター（NCGM）が主体となって実施
  - 平成26年から3ヵ年の研究費
  - 平成27年度追加予算（AMED調整費）で加速、充実
- 日本糖尿病学会と共同、連携
- 多施設共同、糖尿病全例調査

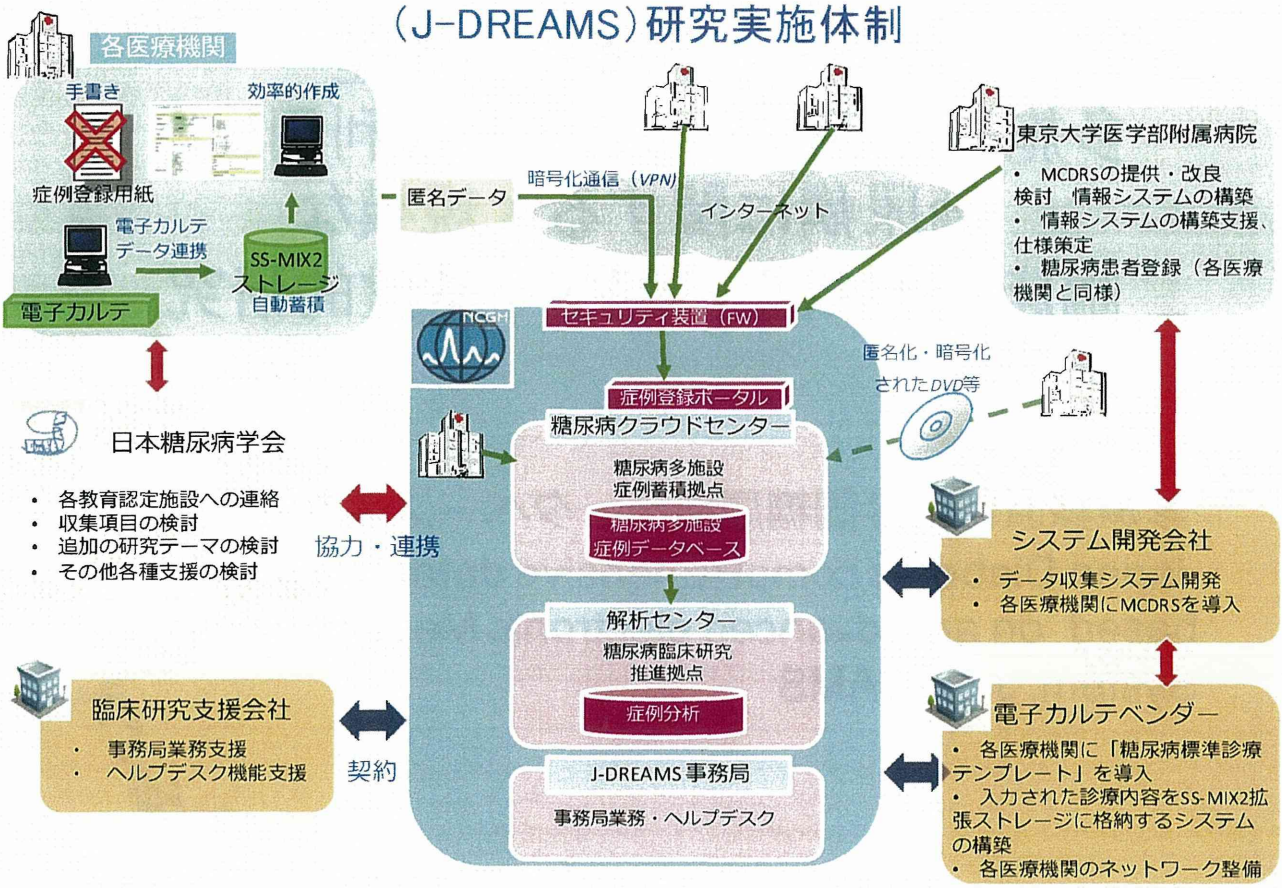
（平成27年度…約30施設、3万人目標）

→5年間で対象施設を増やし100施設を目指す

- 電子カルテ上の糖尿病標準診療テンプレートに入力
  - SS-MIX2を活用した自動蓄積
  - 多目的臨床データ登録システム(MCDRS)を使用してデータ抽出と送信
- 個人情報は匿名化
- 被験者の同意はポスター同意を原則とする（オプトアウト）

資料7

診療録直結型全国糖尿病データベース事業
（J-DREAMS）研究実施体制



別紙４

研究成果の刊行に関する一覧表

発表者氏名	論文タイトル名	発表誌名	巻(号)	ページ	出版年
Ueda T, Kawakami R, Nishida T, Onoue K, Soeda T, Okayama S, Takeda Y, Watanabe M, Kawata H, Uemura S, Saito Y.	Plasma renin activity is a strong and independent prognostic indicator in patients with acute decompensated heart failure treated with renin-angiotensin system inhibitors.	Circ J.	79(6)	1307-14	2015
Ueda T, Kawakami R, Nishida T, Onoue K, Soeda T, Okayama S, Takeda Y, Watanabe M, Kawata H, Uemura S, Saito Y.	Left Ventricular Ejection Fraction (EF) of 55% as Cutoff for Late Transition From Heart Failure (HF) With Preserved EF to HF With Mildly Reduced EF.	Circ J.	79(10)	2209-15	2015
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ORIGINAL ARTICLE
Heart Failure

Plasma Renin Activity Is a Strong and Independent Prognostic Indicator in Patients With Acute Decompensated Heart Failure Treated With Renin-Angiotensin System Inhibitors

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Background: The renin-angiotensin system (RAS) is activated in heart failure (HF) as a compensatory mechanism, being related to cardiac remodeling and poor prognosis. Although RAS inhibitors are used as first-line drugs for HF, plasma renin activity (PRA) is upregulated by RAS inhibitors via a negative feedback mechanism. The clinical significance of PRA during RAS inhibitor therapy is poorly understood in acute decompensated HF (ADHF). Therefore we examined the impact of PRA in HF patients already receiving RAS inhibitors.

Methods and Results: Of 611 consecutive patients with ADHF and emergency admission to hospital, we studied the impact of PRA on the prognosis of ADHF in 293 patients already receiving RAS inhibitors before admission. The patients were divided into 2 groups according to median PRA (≥ vs. <3.4 $ng \cdot ml^{-1} \cdot h^{-1}$). During a mean follow-up of 29.0 months, there were 124 deaths from all causes. Kaplan-Meier analysis showed that all-cause and cardiovascular mortality were significantly higher in patients with high PRA than low PRA (log-rank P=0.0002 and P<0.0001, respectively). Log PRA was an independent predictor of all-cause and cardiovascular death (HR, 1.194; 95% CI: 1.378–2.678, P<0.0001; and HR, 2.559; 95% CI: 1.610–4.144, P<0.0001, respectively).

Conclusions: PRA was associated with an increased risk of all-cause and cardiovascular mortality in ADHF patients already receiving RAS inhibitors, suggesting that PRA would be a useful biomarker during ADHF treatment. (*Circ J* 2015; **79:** 1307–1314)

Key Words: Acute decompensated heart failure; Plasma renin activity; Prognosis; Renin-angiotensin system blocker

In spite of great advances in the management of acute decompensated heart failure (ADHF), morbidity and mortality are still high and patient quality of life is impaired.[1–3] To improve the prognosis of ADHF, more sensitive and accurate diagnostic tools and more effective therapeutic approaches are necessary. The renin-angiotensin system (RAS) is fundamentally involved in the development and progression of heart failure (HF), which is initially upregulated in HF[4,5] to maintain cardiac output in order to maintain sufficient perfusion of vital organs. Overactivation of the RAS, however, ultimately results in increased afterload and body fluid retention, which leads to a vicious cycle of decompensated HF. Given that renin is the rate-limiting enzyme of the RAS, it is reasonable that measurement of plasma renin activity (PRA) helps to determine the degree of RAS activation in the clinical setting of HF. In fact, some earlier studies reported a strong inverse correlation between survival and PRA.[6–8]

Editorial p1206

After seminal clinical trials demonstrating that angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB) and β-adrenergic receptor blockers can effectively improve the prognosis of HF,[9–12] however, they have been routinely used as first-line treatment for HF. During RAS inhibitor therapy, PRA is elevated due to decreased production of angiotensin II, which negatively regulates renin release.

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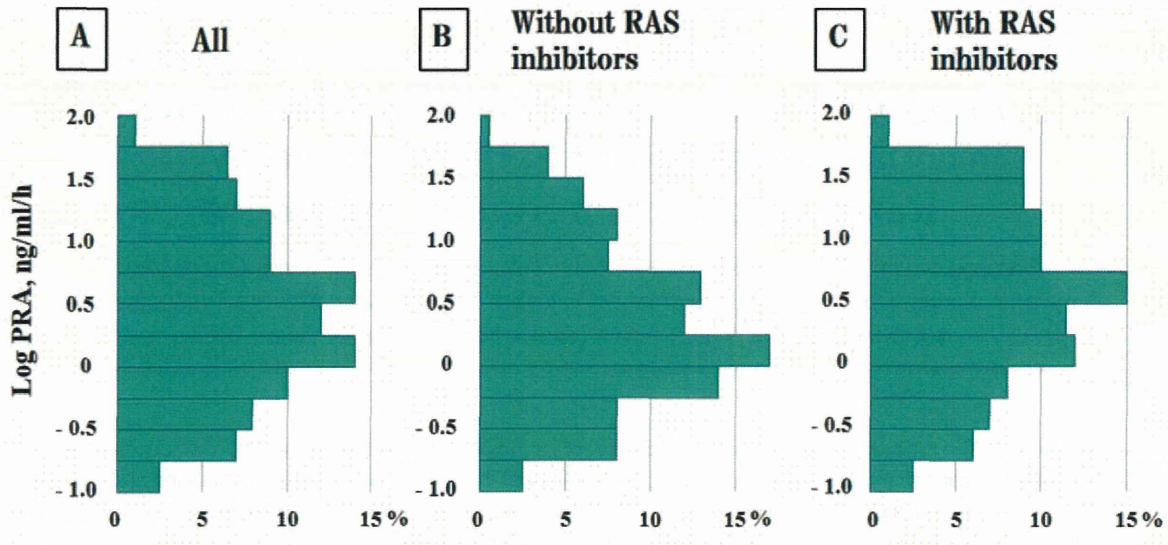

Figure 1. Distribution of log plasma renin activity (PRA) for (**A**) all patients (n=505), (**B**) patients without renin-angiotensin system (RAS) inhibitors (n=212), and (**C**) patients with RAS inhibitors (n=293).

β-blockers directly suppress PRA via inhibition of renal sympathetic activity. Moreover, loop diuretics, which block the Na+/K+/2Cl− co-transporter and stimulate renin release, are widely used to treat HF. Therefore, PRA is considerably altered by HF treatment. There is a paucity of data on the clinical interpretation of PRA as a biomarker in ADHF and its implications, although renin is the rate-limiting step in RAS activation. Compared to the large body of literature concerning brain natriuretic peptide (BNP) or BNP-related peptide as a prognostic marker of ADHF, very little is known about PRA.

Here we show for the first time the clinical impact of PRA on prognosis in patients with ADHF, all of whom were already being treated with ACEI, ARB, or both in the Nara Registry and Analyses for Heart Failure 2 (NARA-HF 2 study) cohort study.

Methods

Patient Selection

The NARA-HF study is a dynamic cohort study.[13] The NARA-HF 2 study recruited 611 consecutive patients with emergency admission to the internal medicine or cardiology wards or the coronary care unit at Nara Medical University Hospital with documented ADHF (either acute new-onset or acute-on-chronic HF) between January 2007 and December 2012. The diagnosis of HF was based on the Framingham criteria for HF.[14] Patients with acute myocardial infarction (AMI), acute myocarditis, and acute HF with acute pulmonary embolism were excluded.

Of the 611 patients, 505 patients had PRA measurement on admission. Among them, 293 patients had already received ACEI, ARB, or a combination of RAS inhibitors before admission but the remaining 212 patients had not been previously treated. We investigated the impact of PRA on the prognosis of ADHF in the 293 patients who had already received RAS inhibitors, but not direct renin inhibitors. Patients were divided into low PRA (n=147) and high PRA (n=146) groups based on median PRA ($3.4\,ng \cdot ml^{-1} \cdot h^{-1}$). For each patient, baseline data included age, sex, body mass index (BMI), cause of HF, medical history, vital signs, laboratory and echocardiographic data, and medications on admission and at discharge.

Outcomes

The primary endpoints were all-cause and cardiovascular mortality. Cardiovascular death was defined as death due to HF, myocardial infarction, sudden death, stroke, and vascular disease such as aortic dissection. We checked medical records to determine vital status and the cause of death. When this information was unavailable in the medical record, we telephoned patients or their families. Information regarding cardiovascular events such as non-fatal AMI, stroke, and rehospitalization due to recurrence of ADHF was also obtained.

Statistical Analysis

Continuous variables are expressed as mean±SD and were compared using Student's t-test. Categorical variables are summarized with frequency percentages and were analyzed using chi-squared test. Cumulative event-free rates during follow-up were derived using the Kaplan-Meier method. Univariate and multivariate analyses of mortality were performed using Cox proportional hazards models. We utilized 4 models for the adjustment of covariates: model 1, unadjusted; model 2, adjusted for age and sex; model 3, adjusted for all factors in model 2 plus hemoglobin concentration (Hb), estimated glomerular filtration rate (eGFR), and sodium and BNP; and model 4, adjusted for all factors in model 3 plus left ventricular ejection fraction (LVEF) and systolic blood pressure (SBP). Multiple linear regression was performed to determine the variables that affected PRA.

Results are reported as hazard ratios (HR), coefficients, 95% confidence intervals (95% CI), and P-value. The HR for outcomes in the high PRA group was compared with those for

Table 1. Baseline HF Patient Characteristics

Characteristics	Total (n=293)	Low PRA (n=147)	High PRA (n=146)	P-value
Demographic				
Age (years)	73.4±11.9	75.4±9.9	71.4±13.3	0.0303
Female	38.2	42.2	34.2	0.1625
BMI (kg/m^2)	23.7±4.1	23.6±4.0	23.9±4.2	0.3491
Cause of HF				
Ischemic	43.3	40.1	46.6	0.2661
Valvular	17.1	17.7	16.4	0.7763
Dilated cardiomyopathy	16.0	12.9	19.2	0.1448
Hypertensive	6.1	8.8	3.4	0.0534
Medical history				
Diabetes mellitus	49.2	44.2	54.1	0.0904
Dyslipidemia	44.3	44.8	43.8	0.8750
Old MI	36.9	34.0	39.7	0.3109
Dialysis	5.5	6.1	4.8	0.6169
Procedures				
PCI	31.9	27.9	35.9	0.1438
CABG	5.1	4.1	6.2	0.4186
CRT/ICD	3.1	2.0	4.1	0.3048
NYHA class on admission				
III or IV	88.4	89.8	87.0	0.4528
Vital sign on admission				
SBP (mmHg)	145.0±36.5	155.9±34.5	134.0±35.2	<0.0001
DBP (mmHg)	80.4±21.9	85.3±23.2	75.3±19.4	<0.0001
Heart rate (beats/min)	92.1±25.6	89.4±26.1	94.8±24.9	0.0416
Echocardiographic parameters				
LVEF (%)	46.6±16.7	50.5±15.4	42.6±17.0	<0.0001
EF ≥50%	45.4	52.4	38.2	0.0151
LVEDD (mm)	55.7±10.6	53.8±8.8	57.7±12.0	0.0064
Laboratory data on admission				
Hemoglobin (g/dl)	11.1±2.3	10.8±2.3	11.4±2.3	0.0072
eGFR (ml/min/1.73 m^2)	38.6±23.3	38.7±24.1	38.4±22.5	0.9291
CKD stage 4 or 5	38.9	38.8	39.4	0.9628
Sodium (mmol/L)	139.3±4.4	140.3±3.4	138.4±5.0	0.0003
Potassium (mmol/L)	4.23±0.83	4.13±0.77	4.33±0.88	0.1273
PRA (ng·ml^{-1}·h^{-1})	3.4 (1.0–12.1)	1.0 (0.5–1.9)	12.1 (5.4–25.5)	<0.0001
Aldosterone (pg/ml)	63.2 (35.9–108.6)	56.4 (31.3–81.0)	84.1 (44.4–148.6)	<0.0001
Plasma BNP (pg/ml)	892 (457–1,658)	972 (518–1,706)	757 (364–1,569)	0.1007
Medication				
Admission				
ACEI	47.1	40.1	54.1	0.0166
ARB	66.6	71.4	61.6	0.0759
ACEI or ARB	100	100	100	1.0000
β-blockers	35.2	38.1	32.2	0.2900
Loop diuretics	60.1	56.5	63.7	0.2060
MR blockers	21.8	17.0	26.7	0.0444
Ca channel blockers	42.0	48.3	35.6	0.0278
Statin	28.7	27.9	29.5	0.7677
Discharge				
ACEI	54.5	53.7	55.2	0.7972
ARB	52.1	56.5	47.6	0.1289
ACEI or ARB	91.4	94.6	88.1	0.0505
β-blockers	54.5	51.7	57.3	0.3348
Loop diuretics	77.6	78.2	76.9	0.7894
MR blockers	30.0	28.6	31.5	0.5904
Ca channel blockers	34.1	40.8	27.3	0.0150

Data given as %, mean±SD, or median (25th–75th percentile). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; Ca, calcium; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; EDD, end-diastolic diameter; EF ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter defibrillator; LV, left ventricular; MI, myocardial infarction; MR, mineralocorticoid receptor; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PRA, plasma renin activity; SBP, systolic blood pressure.

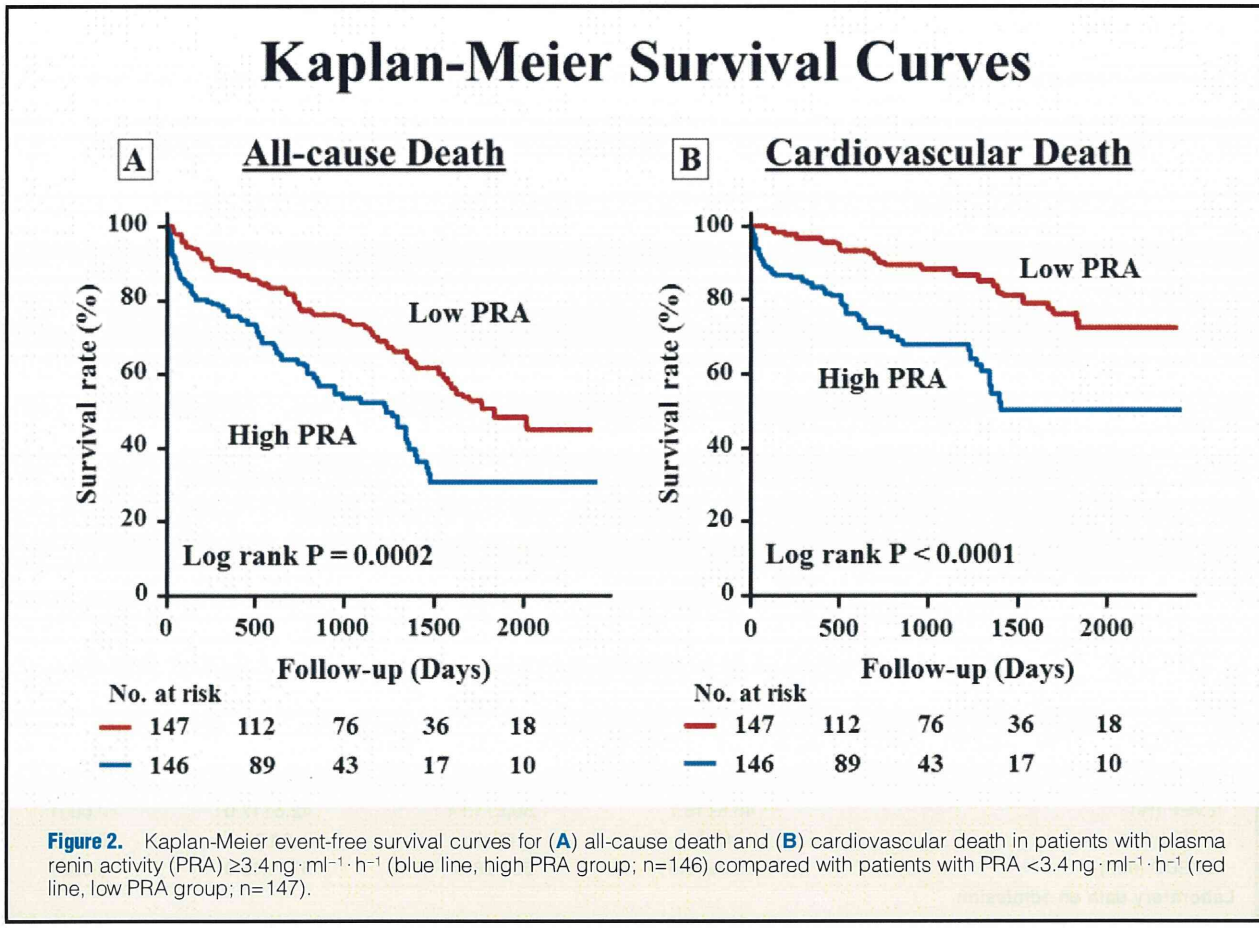

Figure 2. Kaplan-Meier event-free survival curves for (**A**) all-cause death and (**B**) cardiovascular death in patients with plasma renin activity (PRA) ≥3.4 ng·ml^{-1}·h^{-1} (blue line, high PRA group; n=146) compared with patients with PRA <3.4 ng·ml^{-1}·h^{-1} (red line, low PRA group; n=147).

the low PRA group, which served as the reference group. Variables with P<0.05 were retained in the model. JMP version 10 for Windows (SAS Institute, Cary, NC, USA) was used for all statistical analyses.

Results

PRA and RAS Inhibitor Therapy

Among the 611 patients who participated in this registry study, PRA was measured in 505 patients at the time of admission. Among them, 293 patients had already been treated with ACEI, ARB, or both, but 212 had not been on RAS inhibitors. Both PRA and logarithmically transformed PRA were significantly higher in patients treated with ACEI, ARB, or both than those who were not (mean±SD, 9.1±12.6 ng·ml^{-1}·h^{-1} vs. 6.0±10.3 ng·ml^{-1}·h^{-1}, P=0.0011; and 0.51±0.69 ng·ml^{-1}·h^{-1} vs. 0.31±0.64 ng·ml^{-1}·h^{-1}, P=0.0011, respectively). As shown in **Figure 1**, the histogram of logarithmically transformed PRA was shifted up in patients treated with RAS inhibitors. Age, proportion of women, proportion of New York Heart Association (NYHA) class III or IV patients, LVEF, and plasma BNP were similar between the groups. We investigated whether or not PRA at admission is associated with all-cause or cardiovascular mortality in the group of 293 patients who were already being treated with RAS inhibitors.

Baseline Characteristics

Mean age of the 293 patients was 73.4±11.9 years, and the proportion of women was 38.2% (**Table 1**). To investigate the impact of PRA on prognosis of ADHF, we divided patients into 2 groups according to median PRA on admission. **Table 1** lists baseline clinical characteristics vs. high and low PRA. Compared with patients in the low PRA group, the patients in the high PRA group were significantly younger, but the proportion of men and women and BMI were similar. There were no significant differences in the cause of HF or the proportion of comorbidities between the 2 groups. Laboratory findings except Hb, sodium, and aldosterone were similar between the groups, as shown in **Table 1**. Although NYHA functional class and plasma BNP were similar between the groups, patients with high PRA had significantly lower SBP and diastolic blood pressure (DBP), larger left ventricular end-diastolic diameter (LVEDD), and lower LVEF compared with those with low PRA.

The proportion of patients treated with β-blockers or loop diuretics was similar in the 2 groups both on admission and at discharge. Calcium (Ca) channel blockers were less frequently used in the high PRA group on admission and at discharge. Mineralocorticoid receptor blockers were more frequently used in the high PRA group on admission but the rates of use were similar between the groups at discharge.

Prognosis and Outcome

During the mean follow-up period of 29.0 months, 124 patients (42.3%) died; 68 (23.2%) from cardiovascular causes. As shown in the Kaplan-Meier survival curves, the high PRA

Table 2. Effect of PRA on Adverse Outcome

	PRA <3.4 ng·ml^{-1}·h^{-1} (n=147)	PRA ≥3.4 ng·ml^{-1}·h^{-1} (n=146)	P-value
All-cause death			
Unadjusted HR (95% CI)	1	1.965 (1.375–2.830)	0.0002
Adjusted HR (95% CI)	1	2.259 (1.530–3.353)	<0.0001
Cardiovascular death			
Unadjusted HR (95% CI)	1	3.243 (1.950–5.597)	<0.0001
Adjusted HR (95% CI)	1	3.668 (2.120–6.547)	<0.0001

The Cox proportional hazards model adjusted for the following covariates: age, sex, hemoglobin, eGFR, LVEF, BNP, and sodium. CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.

Table 3. Significant Factors in All-Cause and CV Death

	All-cause death		CV death	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Model 1				
Log PRA (ng·ml^{-1}·h^{-1})	1.803 (1.373–2.380)	<0.0001	2.660 (1.815–3.960)	<0.0001
Model 2				
Log PRA (ng·ml^{-1}·h^{-1})	2.059 (1.550–2.752)	<0.0001	2.917 (1.953–4.433)	<0.0001
Age (years)	1.036 (1.020–1.054)	<0.0001	1.022 (1.002–1.044)	0.0300
Male	1.284 (0.887–1.880)	0.1862	1.233 (0.742–2.100)	0.4235
Model 3				
Log PRA (ng·ml^{-1}·h^{-1})	2.175 (1.604–2.964)	<0.0001	3.242 (2.100–5.095)	<0.0001
Age (years)	1.034 (1.018–1.052)	<0.0001	1.018 (0.998–1.040)	0.0755
Male	1.308 (0.894–1.932)	0.1673	1.295 (0.769–2.229)	0.3343
Hemoglobin (g/dl)	0.914 (0.833–1.004)	0.0602	0.87 (0.771–0.984)	0.0271
eGFR (ml/min/1.73 m^2)	0.998 (0.988–1.006)	0.5593	1.006 (0.993–1.017)	0.3649
Sodium (mmol/L)	0.971 (0.929–1.017)	0.2079	0.959 (0.907–1.020)	0.1760
Plasma BNP (100 pg/ml)	1.016 (1.003–1.028)	0.0159	1.022 (1.004–1.038)	0.0161
Model 4				
Log PRA (ng·ml^{-1}·h^{-1})	1.914 (1.378–2.678)	<0.0001	2.559 (1.610–4.144)	<0.0001
Age (years)	1.033 (1.015–1.052)	0.0001	1.015 (0.994–1.038)	0.1595
Male	1.326 (0.900–1.974)	0.1546	1.390 (0.821–2.407)	0.2229
Hemoglobin (g/dl)	0.913 (0.826–1.007)	0.0699	0.881 (0.773–1.002)	0.0535
eGFR (ml/min/1.73 m^2)	0.995 (0.986–1.004)	0.2974	1.002 (0.990–1.013)	0.7809
Sodium (mmol/L)	0.972 (0.930–1.019)	0.2380	0.958 (0.906–1.019)	0.1689
Plasma BNP (100 pg/ml)	1.015 (1.001–1.028)	0.0310	1.022 (1.004–1.039)	0.0191
LVEF (%)	1.002 (0.988–1.016)	0.8224	1.008 (0.989–1.026)	0.4185
SBP (mmHg)	0.992 (0.987–0.998)	0.0080	0.989 (0.981–0.997)	0.0042

CV, cardiovascular. Other abbreviations as in Tables 1,2.

group had a much higher rate of all-cause death (log-rank P=0.0002) and cardiovascular death (log-rank P<0.0001; **Figure 2**). **Table 2** shows unadjusted and adjusted HR for outcomes in the 2 groups. Compared with the low PRA group, the unadjusted HR for all-cause and cardiovascular death were significantly higher in the high PRA group (HR, 1.965; 95% CI: 1.375–2.830, P=0.0002; and HR, 3.243; 95% CI: 1.950–5.597, P<0.0001, respectively). Even after adjustment for covariates (age, sex, Hb, eGFR, LVEF, BNP, and Na) in multivariate Cox proportional hazard models, these findings remained significant (**Table 2**). In addition, rehospitalization due to HF recurrence was significantly higher in the high PRA group (P=0.0369). There were no differences, however, in the frequency of non-fatal acute MI or stroke between the 2 groups.

As shown in **Table 3**, PRA predicted all-cause death and cardiovascular death (P<0.0001 and P<0.0001, respectively). Even after adjusting for age, sex, and cardiovascular risk factors, these findings remained significant (**Table 3**). These results were similar when patients on chronic dialysis were excluded.

Factors Affecting PRA

We also performed multiple linear regression to identify factors affecting PRA. As shown in **Table 4**, PRA was associated with age, sodium, SBP, and LVEF, but not sex, Hb, BNP, aldosterone, or medication.

Table 4. Variables Affecting PRA

	Coefficient	95% CI	P-value
Age (years)	−0.161	−0.278 to −0.044	0.0073
Male	2.373	−0.481 to 5.227	0.1028
Hemoglobin (g/dl)	−0.023	−0.698 to 0.652	0.9468
Sodium (mmol/L)	−0.381	−0.687 to −0.076	0.0145
Plasma BNP (100pg/ml)	−0.060	−0.176 to 0.055	0.3061
Aldosterone (pg/ml)	0.005	−0.001 to 0.010	0.0559
SBP (mmHg)	−0.085	−0.124 to −0.046	<0.0001
LVEF (%)	−0.102	−0.200 to −0.004	0.0407
β-blocker	−1.972	−4.866 to 0.922	0.1808
Loop diuretic	2.159	−0.668 to 4.985	0.1338
Calcium channel blocker	−1.487	−4.365 to 1.390	0.3098

If a patient was male or treated with medicine, the variable was assigned a value of 1; otherwise, 0 was assigned. Abbreviations as in Tables 1,2.

Discussion

Earlier studies showed that PRA is a risk factor for poor prognosis in patients with essential hypertension or chronic HF,[15–18] but they do not stratify patients according to RAS inhibitor status. In the present study, we demonstrate for the first time that PRA is a strong risk factor associated with all-cause and cardiovascular mortality in patients with ADHF already being treated with RAS inhibitors. This risk was still significant after adjustment for other risk factors such as age, anemia, eGFR, LVEF, and BNP. As with eGFR or BNP, PRA is a stronger predictor of all-cause and cardiovascular mortality. In contrast to earlier works, however, in the NARA-HF2 study, we could show only that high PRA tended to be associated with poor prognosis in ADHF patients who had not been treated with RAS blockers (log rank P=0.0841, data not shown). Current guidelines for the management of HF strongly recommend RAS inhibitors and β-blockers as first-line drugs with the goal of improving prognosis.[19–21] Most patients with HF receive RAS inhibitors and β-blockers if they do not have any contraindications. In this context, studying biomarkers, which are possibly altered by the use of these drugs, is becoming more important, to better understand the meaning of biomarkers.

In this study, we compared two groups based on median PRA (3.4 ng·ml^{-1}·h^{-1}), but it is not clear which cut-off point is clinically proper. We therefore also examined two other criteria: the upper reference value of PRA (2.0 ng·ml^{-1}·h^{-1}) and the best cut-off point according to receiver operating characteristic curve analysis (8.2 ng·ml^{-1}·h^{-1}). As shown in the Kaplan-Meier survival curves in **Figures S1,S2**, the higher PRA group had a much higher rate of all-cause death and cardiovascular death for both evaluations (log-rank P<0.0001 for both) as well as for median PRA, indicating that higher PRA is an predictor of poorer outcome in ADHF patients being treated with RAS blockers. Moreover, as shown in **Figure 2**, patients in the high PRA group were lost mostly at 100–200 days after admission. Within 200 days after admission, the proportion of cardiovascular death was higher in patients with high PRA than in those with low PRA (19.2% vs. 8.8%, P=0.0100). It is possible, therefore, that high PRA is more related to severe HF.

Although PRA is generally upregulated in HF as a reflection of RAS activation, there was a wide distribution of PRA, ranging from 0.1 to >60 ng·ml^{-1}·h^{-1} in patients with ADHF who were already being treated with RAS inhibitors. To date it has not been well investigated as to which factors determine the higher PRA in patients who were treated with RAS inhibitors. Generally, expression and secretion of renin is upregulated by decreases in arterial pressure detected by baroreceptors, decreases in sodium chloride influx into the juxtaglomerular apparatus through the Na+/K+/2Cl− co-transporter, and activation of renal sympathetic nerve activity, and downregulated by angiotensin II in a negative feedback loop. Thus, β-blockers lower PRA, but RAS inhibitors and loop diuretics increase PRA. In the setting of HF, RAS regulation is more complex. For example, negative feedback is blunted[22] and alternative pathways such as the chimase-dependent pathway are activated.[23]

As shown in **Table 1**, there was no significant difference in the proportion of β-blockers or loop diuretics used. LVEDD was significantly larger, whereas LVEF, blood pressure, and serum sodium were significantly lower in the high vs. low PRA group. Moreover, on multivariate regression analysis SBP, LVEF, and serum sodium concentration were inversely related to PRA (**Table 4**). These findings suggest that LV remodeling was more advanced in the high PRA group. Significantly lower serum sodium may be the result of high doses of loop diuretics in the high PRA group, despite similar numbers of patients on loop diuretics in both groups. To confirm this hypothesis, loop diuretics other than furosemide were converted to furosemide equivalent doses: 4 mg of torasemide and 30 mg of azosemide were considered equivalent to 20 mg of furosemide. After conversion, there were no significant differences in furosemide equivalent dose between the high and low PRA groups. In patients with PRA ≥12.1 ng·ml^{-1}·h^{-1} (top quartile), the furosemide equivalent dose was significantly higher than in the remaining patients (55.7±37.9 mg vs. 40.8±24.2 mg; P=0.0298). Although more detailed study is needed, the present findings suggest that high PRA may be correlated with the severity of HF itself rather than the effect of drugs used to treat it.

Aldosterone, an end-product of RAS, is involved in the pathophysiology of HF, as evidenced by recent clinical trials demonstrating that aldosterone blockers reduce mortality rates in patients with moderate–severe chronic HF and acute HF.[24–26] In this study, plasma aldosterone was significantly higher in the high PRA group compared with the low PRA group, suggesting insufficient suppression of RAS in the present patients. Another explanation is so called aldosterone