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RESEARCH ARTICLE

Is plasma renin activity associated with worse outcomes in acute heart failure? A secondary analysis from the BLAST-AHF trial

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Aims Neurohormonal activation characterizes chronic heart failure (HF) and is a well-established therapeutic target. Neurohormonal activation may also play a key role in acute HF (AHF). We aim to describe the association between plasma renin activity (PRA) and three AHF outcomes: (i) worsening HF or death through day 5 of hospitalization; (ii) HF rehospitalization or death through day 30; and (iii) all-cause death through day 30.

Methods and results A secondary analysis of the BLAST-AHF trial was performed. Eligible patients had a history of HF, elevated natriuretic peptides, signs and symptoms of HF, systolic blood pressure >120 mmHg, and an estimated glomerular filtration rate between 20–75 mL/min/1.73 m^2. The primary trial was neutral, with no differential effect of study drug by PRA levels. Baseline PRA levels were grouped into tertiles. Adjusted Cox proportional hazard model determined the association of PRA levels with outcomes (α set at $P < 0.05$). Of 618 randomized patients, 578 (93.5%) had a baseline PRA. PRA was modestly, but significantly, associated with each outcome without adjustment [worsening HF or death through day 5: hazard ratio (HR) 1.11, 95% confidence interval (CI) 1.01–1.23, $P = 0.04$; HF rehospitalization or death through day 30: HR 1.13, 95% CI 1.02–1.26, $P = 0.02$; all-cause death through day 30: HR 1.18, 95% CI 1.02–1.37, $P = 0.03$]. After multivariable adjustment, PRA was only significantly associated with HF rehospitalization or death through day 30 (HR 1.15, 95% CI 1.01–1.32, $P = 0.04$).

Conclusion Baseline PRA levels are associated with increased risk for the composite of 30-day HF rehospitalization or death in patients with AHF.

Keywords Acute heart failure • Plasma renin activity • Biased ligand

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Introduction

Neurohormonal (NH) activation is a fundamental physiologic and ultimately maladaptive response to the failing heart. Landmark studies in patients with chronic heart failure (HF) demonstrated that neurohormones – specifically, those involving the renin–angiotensin–aldosterone system (RAAS) – were associated with increased morbidity and mortality.[1–5] Therapies targeting RAAS significantly reduce morbidity and mortality in chronic HF with reduced ejection fraction.[6–8] RAAS activation plays a major role in the development and subsequent progression of chronic HF through retention of salt and water and systemic vasoconstriction.[9] This mechanism occurs in response to decreased cardiac output and helps to improve organ perfusion by restoring and maintaining intravascular volume and arterial tone. However, chronic RAAS activation leads to adverse ventricular remodelling and volume overload with associated haemodynamic derangements.[10]

RAAS activation may play a similar, but perhaps more accelerated, role in acute HF (AHF).[11] Whether it contributes to poor post-discharge outcomes is less well-established. Although renin is the rate-limiting enzyme of the RAAS system, its prognostic value in AHF has not been well studied.[12,13] Accordingly, we conducted this post-hoc analysis of the Biased Ligand of the Angiotensin II Type 1 Receptor in Patients with Acute Heart Failure (BLAST-AHF) trial (i) to describe RAAS activation in AHF patients, and (ii) to determine whether there is an association between plasma renin activity (PRA) levels and outcomes.

Methods

The rationale and design of the BLAST-AHF trial (NCT01966601) have been described previously.[14] Briefly, BLAST-AHF was a multicentre, international, randomized, double-blind, placebo-controlled, parallel-group, dose-finding trial designed to explore the short and long-term safety and efficacy of TRV027. TRV027 is a novel 'biased' ligand of the angiotensin II type 1 receptor (AT1R) designed to selectively block certain AT1R-mediated effects (vasoconstriction and reduced renal perfusion) while preserving the cardiac contractility effect attributed to AT1R stimulation. The BLAST-AHF trial was conducted according to the principles outlined in the Declaration of Helsinki.

Eligible patients were required to have a history of HF, elevated natriuretic peptides, signs and symptoms of HF, systolic blood pressure (SBP) >120 mmHg, and an estimated glomerular filtration rate (eGFR) between 20–75 mL/min/1.73 m^2. Patients using angiotensin II receptor blockers within 7 days of randomization were excluded. PRA levels were collected at baseline (from time of randomization) and 24, 48 and 96 h later.

As a confirmatory measure of plasma renin activation, plasma renin concentration (PRC) was measured using an automated sandwich immunochemiluminescent assay (LIAISON®, Diasorin, DiaSorin Ltd, Schiphol Rijk, The Netherlands), with a range of detection of 5–500 μU/mL.[15]

Endpoints

The primary objectives of this study were to describe the association between baseline PRA and three AHF outcomes: (i) worsening HF or death through day 5 of hospitalization; (ii) HF rehospitalization or death through day 30; and (iii) all-cause death through day 30. Events were not independently adjudicated.

Secondary objectives were to assess the correlation between: (i) PRA and PRC, and (ii) PRA and both SBP and left ventricular ejection fraction (LVEF). This last objective was performed to test the hypothesis that a lower SBP or lower LVEF is associated with a higher PRA level.

Statistical analysis

Subjects were categorized into three subgroups defined by tertiles of baseline PRA levels. Demographics and baseline characteristics are presented as mean and standard deviation, or frequency and percentage, as appropriate. For highly skewed continuous variables, results are presented as geometric mean and corresponding 95% confidence intervals (CI). Chi-squared test and ANOVA (with log-transformed data as appropriate) were utilized to determine baseline differences. Results are presented as frequency and percentage with *P*-values according to chi-squared test.

Cox proportional hazards models were created for each of the three clinical outcomes. For each outcome, a set of prognostic baseline variables was selected from well-established prognostic models for the same or similar endpoint,[16–18] further taking into account availability and number of events in BLAST-AHF (co-variates are listed in each table). Each selected baseline continuous variable was tested for non-linearity of its association with the corresponding endpoint by assessing the significance of the non-linear components of a restricted cubic spline transformation applied to it. If the association was found to be significantly non-linear, an appropriate non-linear transformation of the baseline variable was selected from a set of pre-specified transformations (such as quadratic, cubic, or linear spline transformations). The selection was based on values of Akaike's Information Criterion (AIC) and visual inspection of plotting the predicted outcome against the baseline values. Additional analyses were conducted where covariates were selected as the best subset of size approximately equal to the number of events divided by 10 using R package 'BeSS', and using backwards selection where the criterion for staying in the model was two-sided alpha of 0.10.[19]

The sets of prognostic baseline variables were used to form multivariable Cox proportional hazards models, not including biomarkers for each endpoint (Model 1), to which baseline values of troponin T and N-terminal pro-B-type natriuretic peptide (NT-proBNP) were added in a second step (Model 2), and finally baseline PRA levels in a third step (Model 3) to examine the prognostic value of PRA in models adjusted for known prognostic factors. Missing values in the database were imputed using multiple imputation assuming multivariate normality and creating 10 imputed data sets.[20] On each of the 10 imputed data sets, the univariable and multivariable models were run separately. Estimated effect sizes, CIs, and *P*-values were combined across the 10 imputed data sets using Rubin's algorithm.[21] Discrimination of the multivariable models (i.e. the tendency of a subject having experienced an event to have a higher predicted outcome probability than a subject without an event) was assessed using Harrell's C-indices for Cox proportional hazards models.[22] The resulting C-index values were then averaged across the 10 imputed data sets. Correlations were examined using Pearson's correlation coefficient based on log-transformed values of PRA or PRC as appropriate. Statistical analyses were performed using SAS® version 9.4 (SAS Institute, Cary, NC, USA) and R version 3.5.1.

Table 1 Baseline characteristics by baseline plasma renin activity tertiles

Parameter	PRA < 0.34 ng/mL/h ($n = 190$)	0.34 ng/mL/h ≤ PRA < 2.44 ng/mL/h ($n = 195$)	PRA ≥2.44 ng/mL/h ($n = 193$)	*P*-value*	Total ($n = 578$)
PRA, ng/mL/h, median	0.115	0.900	6.830		0.905
Age, years, mean (SD)	71 (9.6)	72 (9.3)	69 (9.3)	0.01	71 (9.5)
Male sex, *n* (%)	96 (51)	113 (58)	145 (75)	<0.01	354 (61)
White race, *n* (%)	186 (98)	192 (98)	190 (98)	0.89	568 (98)
Diabetes mellitus, *n* (%)	80 (42)	96 (49)	78 (40)	0.18	254 (44)
Left ventricular ejection fraction, %, mean (SD)	38 (11.7)	35 (11.0)	33 (12.5)	<0.01	36 (11.9)
Systolic blood pressure, mmHg, mean (SD)	140.2 (14.42)	134.6 (14.63)	127.9 (14.62)	<0.01	134.2 (15.38)
Atrial fibrillation/flutter, *n* (%)	115 (61)	99 (51)	101 (52)	0.12	315 (54)
eGFR, mL/min/1.73 m^2, mean (SD)	59.3 (21.42)	53.6 (18.69)	53.4 (17.61)	<0.01	55.4 (19.47)
NT-proBNP, ng/L, geom. mean (95% CI)	5492 (4841–6232)	5277 (4596–6058)	5152 (4565–5813)	0.78	5305 (4927–5712)
Plasma renin concentration, ng/L, geom. mean (95% CI)	5.26 (4.58–6.05)	16.89 (15.11–18.88)	81.94 (69.15–97.09)	<0.01	20.95 (18.35–23.92)
Medication (30 days prior to screening), *n* (%)					
ACE inhibitor	151 (79)	146 (75)	156 (81)	0.33	453 (78)
Beta-blocker	167 (88)	160 (82)	167 (87)	0.23	494 (85)
Aldosterone antagonist	52 (27)	73 (37)	81 (42)	<0.01	206 (36)
Oral loop diuretics	163 (86)	182 (93)	183 (95)	<0.01	528 (91)
Digoxin	37 (19)	28 (14)	30 (16)	0.37	95 (16)
Nitrates at randomization	18 (9)	15 (8)	9 (5)	0.19	42 (7)

ACE, angiotensin-converting enzyme; CI, confidence interval; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PRA, plasma renin activity; SD, standard deviation.
Analysis based on subjects in the full analysis set with observed baseline PRA ($n = 578$).
*P-value from ANOVA (F-test) for continuous variables, or from chi-squared test for categorical variables. For continuous variables with highly skewed distributions, the geometric mean and its 95% CI are presented together with *P*-value from ANOVA based on log-transformed values.

Results

Between December 2013 and May 2016, 621 patients were enrolled in the BLAST-AHF trial, of which 618 patients received study treatment (full analysis set).[14] Among the treated patients, 578 (93.5%) had a baseline PRA and were included in this analysis. In addition, 481 (77.8%) had baseline PRC measured, of which 446 had both PRC and PRA available for our secondary objectives.

Patient characteristics

Baseline PRA ranged from 0.04 to 42.66 ng/mL/h (median, 0.905 ng/mL/h). Patients were divided into groups based on baseline PRA tertiles: <0.34 ($n = 190$), ≥0.34 to <2.44 ($n = 195$), and ≥ 2.44 ng/mL/h ($n = 193$). Selected baseline characteristics for the PRA subset by tertile group are presented in *Table 1*. Baseline characteristics of the PRA cohort were similar to baseline characteristics of the full analysis set as previously reported.[14]

Between the PRA tertile groups, statistically significant differences were observed for age, sex, LVEF, SBP, and eGFR. Patients in the highest tertile group were more likely to be male, and have lower LVEF, SBP and eGFR ($P < 0.01$). There were no differences between groups in background angiotensin-converting enzyme inhibitor or beta-blocker use, though the proportion of patients on aldosterone antagonists increased by tertile group (*Table 1*). Although NT-proBNP levels decreased among increasing tertile groups, no statistically significant differences between groups were observed. PRA levels were repeatedly measured at 24, 48, and 96 h from baseline. The online supplementary *Figure S1* presents the overall distribution of PRA ratio to baseline per time-point of measurement. As shown, median PRA and interquartile range were similar across all time points.

Primary endpoints

There were 55 worsening HF episodes through day 5 of hospitalization (8.9%), 48 HF rehospitalizations through day 30 (7.8%), and 26 deaths through day 30 (4.2%). By univariate analysis, PRA levels (doubling of PRA) were significantly associated with worsening HF or death through day 5 of hospitalization [hazard ratio (HR) 1.11, 95% CI 1.01–1.23; $P = 0.04$], (*Table 2*). PRA levels were also significantly associated with HF rehospitalization through day 30 (HR 1.13, 95% CI 1.02–1.26; $P = 0.02$) (*Table 3*), as well as all-cause death though day 30 (HR 1.18, 95% CI 1.02–1.37; $P = 0.03$) (*Table 4*). After adjusting for other variables, PRA was only

Table 2 Univariable and multivariable associations of baseline parameters with worsening heart failure or death through day 5 of hospitalization

Parameter	Effect size for a change of	Univariable model		Multivariable Model 1		Multivariable Model 2		Multivariable Model 3	
		Effect size (95% CI)	*P*-value	Effect size (95% CI)	*P*-value	Effect size (95% CI)	*P*-value	Effect size (95% CI)	*P*-value
Left ventricular ejection fraction ≤41%[a]	1	0.95 (0.92–0.98)	<0.01	0.96 (0.92–0.99)	0.04	0.96 (0.93–0.99)	0.06	0.96 (0.93–1.00)	0.08
Left ventricular ejection fraction >41%[a]	1	1.04 (0.98–1.10)		1.03 (0.98–1.09)		1.04 (0.98–1.10)		1.04 (0.98–1.10)	
Systolic blood pressure, mmHg	10	0.84 (0.70–1.00)	0.05	0.87 (0.71–1.06)	0.17	0.86 (0.70–1.06)	0.16	0.89 (0.72–1.10)	0.27
Respiratory rate, breaths/min	5	1.63 (1.20–2.21)	<0.01	1.65 (1.18–2.31)	<0.01	1.67 (1.18–2.36)	<0.01	1.65 (1.17–2.33)	<0.01
Heart rate, bpm	5	1.07 (0.98–1.16)	0.11	1.05 (0.96–1.15)	0.30	1.05 (0.95–1.15)	0.33	1.05 (0.95–1.15)	0.33
Hospitalization for HF in past year	Yes vs. No	1.34 (0.78–2.31)	0.29	1.24 (0.72–2.16)	0.44	1.22 (0.70–2.13)	0.47	1.19 (0.69–2.08)	0.53
Diabetes mellitus	Yes vs. No	1.22 (0.72–2.07)	0.47	1.30 (0.75–2.25)	0.34	1.40 (0.80–2.46)	0.23	1.43 (0.82–2.51)	0.21
Albumin, g/L	1	0.94 (0.89–1.00)	0.04	0.97 (0.92–1.03)	0.40	0.98 (0.92–1.04)	0.47	0.98 (0.92–1.04)	0.43
Blood urea nitrogen, mmol/L	1	1.08 (1.03–1.14)	<0.01	1.06 (1.01–1.12)	0.02	1.07 (1.01–1.13)	0.02	1.06 (1.00–1.12)	0.06
Cholesterol, mmol/L	1	0.96 (0.77–1.20)	0.73	1.08 (0.86–1.36)	0.50	1.11 (0.88–1.40)	0.37	1.11 (0.89–1.40)	0.36
Sodium, mmol/L	3	0.97 (0.79–1.19)	0.75	1.09 (0.87–1.36)	0.47	1.09 (0.86–1.36)	0.48	1.14 (0.89–1.46)	0.30
Aldosterone antagonist	Yes vs. No	0.72 (0.40–1.29)	0.28	0.60 (0.33–1.10)	0.10	0.61 (0.33–1.10)	0.10	0.60 (0.33–1.09)	0.10
Troponin T, μg/L	Doubling	1.05 (0.85–1.30)	0.64			0.86 (0.66–1.13)	0.29	0.84 (0.64–1.11)	0.23
NT-proBNP, ng/L	Doubling	1.27 (1.04–1.56)	0.02			1.13 (0.88–1.46)	0.33	1.18 (0.91–1.53)	0.21
Plasma renin activity, ng/mL/h	Doubling	1.11 (1.01–1.23)	0.04					1.07 (0.95–1.21)	0.25
Observed C-index				0.7161		0.7246		0.7266	

CI, confidence interval; HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide.
Results from Cox proportional hazard regression model with effect sizes referring to hazard ratios. Clinical outcomes as defined in the Final Statistical Analysis Plan version 2.0 of this study.
[a]Non-linear association modelled as linear spline.

Table 3 **Univariable and multivariable associations of baseline parameters with heart failure rehospitalization or death through day 30**

Parameter	Effect size for a change of	Univariable model		Multivariable Model 1		Multivariable Model 2		Multivariable Model 3	
		Effect size (95% CI)	*P*-value	Effect size (95% CI)	*P*-value	Effect size (95% CI)	*P*-value	Effect size (95% CI)	*P*-value
Northern America	vs. Russia	1.92 (0.24–15.33)	0.88	1.14 (0.12–10.49)	0.64	1.51 (0.16–14.04)	0.26	2.02 (0.22–18.57)	0.23
Argentina	vs. Russia	1.39 (0.45–4.24)		1.40 (0.42–4.67)		1.21 (0.33–4.40)		1.44 (0.39–5.31)	
Israel	vs. Russia	3.33 (1.21–9.17)		2.62 (0.86–7.97)		3.67 (1.18–11.41)		4.08 (1.30–12.86)	
Western Europe	vs. Russia	2.81 (0.60–13.21)		2.27 (0.46–11.25)		3.53 (0.68–18.35)		3.07 (0.58–16.13)	
Eastern Europe	vs. Russia	1.08 (0.49–2.40)		1.34 (0.58–3.10)		1.44 (0.61–3.40)		1.43 (0.61–3.36)	
Age, years	10	0.94 (0.70–1.27)	0.71	0.93 (0.67–1.29)	0.66	0.85 (0.60–1.21)	0.37	0.89 (0.63–1.26)	0.51
Left ventricular ejection fraction ≤41%[a]	1	0.96 (0.92–0.99)	0.04	0.96 (0.92–1.00)	0.12	0.97 (0.93–1.02)	0.16	0.98 (0.94–1.02)	0.14
Left ventricular ejection fraction >41%[a]	1	1.06 (1.01–1.12)		1.05 (0.99–1.11)		1.06 (1.00–1.12)		1.06 (1.00–1.12)	
Systolic blood pressure, mmHg	10	0.89 (0.74–1.08)	0.24	0.94 (0.77–1.16)	0.58	0.94 (0.76–1.15)	0.53	0.99 (0.80–1.22)	0.93
Hospitalization for HF in past year	Yes vs. No	1.04 (0.57–1.87)	0.91	0.98 (0.54–1.80)	0.96	0.94 (0.51–1.74)	0.85	0.91 (0.49–1.70)	0.77
Oedema >2+	Yes vs. No	2.13 (1.20–3.79)	0.01	1.82 (0.99–3.32)	0.05	1.74 (0.95–3.20)	0.07	1.76 (0.96–3.24)	0.07
Albumin ≤43 g/L[a]	1	0.92 (0.86–0.98)	0.04	0.95 (0.88–1.02)	0.26	0.97 (0.90–1.05)	0.27	0.96 (0.89–1.04)	0.21
Albumin >43 g/L[a]	1	1.16 (0.93–1.44)		1.19 (0.94–1.51)		1.22 (0.96–1.54)		1.23 (0.97–1.57)	
Blood urea nitrogen, mmol/L	1	1.08 (1.02–1.13)	<0.01	1.05 (0.99–1.11)	0.10	1.02 (0.96–1.08)	0.49	1.00 (0.94–1.06)	0.96
Sodium, mmol/L	3	0.85 (0.68–1.05)	0.12	0.93 (0.74–1.16)	0.52	0.95 (0.77–1.18)	0.66	1.04 (0.82–1.32)	0.76
Aldosterone antagonist	Yes vs. No	0.35 (0.17–0.76)	<0.01	0.33 (0.15–0.72)	<0.01	0.34 (0.16–0.76)	<0.01	0.33 (0.15–0.73)	<0.01
Troponin T, μg/L	Doubling	1.39 (1.16–1.67)	<0.01			1.18 (0.94–1.48)	0.16	1.14 (0.90–1.44)	0.27
NT-proBNP, ng/L	Doubling	1.62 (1.30–2.03)	<0.01			1.40 (1.06–1.84)	0.02	1.51 (1.14–2.00)	<0.01
Plasma renin activity, ng/mL/h	Doubling	1.13 (1.02–1.26)	0.02					1.15 (1.01–1.32)	0.04
Observed C-index				0.7337		0.7766		0.7829	

CI, confidence interval; HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide.
Results from Cox proportional hazard regression model adjusted for geographical region with effect sizes referring to hazard ratios. Clinical outcomes as defined in the final statistical analysis plan version 2.0 of this study.
[a]Non-linear association modelled as linear spline.

Table 4 Univariable and multivariable associations of baseline parameters with all-cause death through day 30

Parameter	Effect size for a change of	Univariable model		Multivariable Model 1		Multivariable Model 2		Multivariable Model 3	
		Effect size (95% CI)	*P*-value	Effect size (95% CI)	*P*-value	Effect size (95% CI)	*P*-value	Effect size (95% CI)	*P*-value
Age, years	10	1.13 (0.74–1.71)	0.58	1.21 (0.76–1.93)	0.42	1.14 (0.70–1.86)	0.60	1.21 (0.74–1.99)	0.46
Systolic blood pressure, mmHg	10	0.80 (0.61–1.04)	0.10	0.84 (0.64–1.10)	0.21	0.83 (0.62–1.10)	0.19	0.89 (0.66–1.20)	0.46
Left ventricular ejection fraction, %	1	1.00 (0.96–1.03)	0.77	0.99 (0.96–1.03)	0.64	1.00 (0.96–1.03)	0.90	1.00 (0.97–1.04)	0.95
Albumin ≤43 g/L[a]	1	0.87 (0.80–0.94)	<0.01	0.87 (0.79–0.95)	<0.01	0.90 (0.81–0.98)	0.01	0.89 (0.81–0.98)	0.01
Albumin >43 g/L[a]	1	1.28 (1.00–1.64)		1.42 (1.07–1.87)		1.47 (1.11–1.93)		1.45 (1.11–1.90)	
Blood urea nitrogen, mmol/L	1	1.10 (1.03–1.17)	<0.01	1.00 (0.90–1.11)	0.95	0.99 (0.89–1.11)	0.92	0.98 (0.87–1.09)	0.68
Creatinine, μmol/L	1	1.01 (1.00–1.02)	<0.01	1.01 (1.00–1.02)	0.08	1.01 (0.99–1.02)	0.28	1.01 (0.99–1.02)	0.34
Sodium, mmol/L	3	0.82 (0.63–1.08)	0.15	0.85 (0.63–1.14)	0.28	0.88 (0.67–1.16)	0.38	0.95 (0.70–1.29)	0.76
Aldosterone antagonist	Yes vs. No	0.23 (0.07–0.76)	0.02	0.24 (0.07–0.81)	0.02	0.23 (0.07–0.80)	0.02	0.22 (0.06–0.76)	0.02
Troponin T, μg/L	Doubling	1.48 (1.18–1.84)	<0.01			1.23 (0.94–1.62)	0.14	1.19 (0.90–1.56)	0.22
NT-proBNP, ng/L	Doubling	1.71 (1.27–2.30)	<0.01			1.35 (0.97–1.88)	0.08	1.45 (1.03–2.06)	0.04
Plasma renin activity, ng/mL/h	Doubling	1.18 (1.02–1.37)	0.03					1.17 (0.97–1.42)	0.10
Observed C-index				0.7869		0.8124		0.8150	

CI, confidence interval; NT-proBNP, N-terminal pro-B-type natriuretic peptide.
Results from Cox proportional hazard regression model with effect sizes referring to hazard ratios. Clinical outcomes as defined in the final statistical analysis plan version 2.0 of this study.
[a]Non-linear association modelled as linear spline.

Figure 1 Association of plasma renin activity at baseline with heart failure rehospitalization or death through day 30. Shown is the effect size (hazard ratio) for heart failure rehospitalization or death through day 30 estimated from a Cox proportional hazards model adjusted for geographical region with baseline plasma renin activity modelled as a restricted cubic spline on logarithmic scale without further adjustment (black line), as well as adjusted for covariates of multivariable Model 3 in *Table 3* (red line). Short vertical lines at the bottom of the plot represent the observed distribution of baseline plasma renin activity.

significantly associated with HF rehospitalization or death through day 30 (HR 1.15, 95% CI 1.01–1.32; $P = 0.04$) (*Table 3*). *Figure 1* presents the association of baseline PRA with HF rehospitalization or death through day 30 modelled as a restricted cubic spline, supporting that higher values of baseline PRA are associated with higher HRs for HF rehospitalization or death through day 30 (relative to an 'average' subject). Similar results were obtained after adjustment for covariates found to be most highly associated with the outcomes in this study (online supplementary *Table S1*).

By univariate analysis, NT-proBNP levels (doubling of NT-proBNP) were significantly associated with worsening HF or death through day 5 of hospitalization (HR 1.27, 95% CI 1.04–1.56; $P = 0.02$) (*Table 2*), HF rehospitalization through day 30 (HR 1.62, 95% CI 1.30–2.03; $P < 0.01$) (*Table 3*), and all-cause death through day 30 (HR 1.71, 95% CI 1.27–2.30; $P < 0.01$) (*Table 4*). After adjusting for other variables, NT-proBNP was only significantly associated with HF rehospitalization or death through day 30 (HR 1.51, 95% CI 1.14–2.00; $P < 0.01$) (*Table 3*) and all-cause death through day 30 (HR 1.45, 95% CI 1.03–2.06; $P = 0.04$) (*Table 4*).

Secondary endpoints – correlation with plasma renin concentration, systolic blood pressure, and left ventricular ejection fraction

Baseline PRA levels were highly correlated with baseline PRC levels with correlation coefficients >0.8 (*Figure 2*). Modest inverse correlations were noted for both SBP and LVEF (for SBP at baseline,

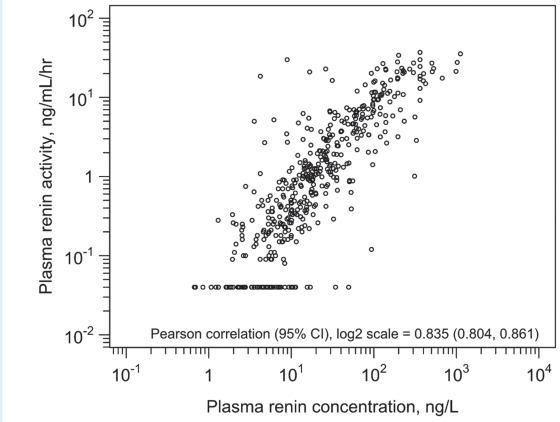

Figure 2 Scatterplot of plasma renin concentration vs. plasma renin activity at baseline. CI, confidence interval.

correlation coefficient of −0.3362, and for LVEF −0.1795; both $P < 0.0001$). The lower the SBP or LVEF, the higher the PRA level ($\log_2$ transformed).

Discussion

Despite the well-established pathophysiologic role of the RAAS system in chronic HF, scant data describe the relationship between NH activation and AHF outcomes. While there are clinical suggestions of exaggerated NH activation in AHF – as characterized by tachycardia, hypertension, increased vasoconstriction and volume overload – it is uncertain whether activation or amplification of NH leads to overt symptoms of HF or whether it is a secondary phenomenon.[23]

In this retrospective analysis from the BLAST-AHF trial, increased PRA was associated with greater risk of 30-day HF rehospitalization or death. Increased baseline PRA levels were observed despite greater use of aldosterone receptor antagonists. This suggests PRA, or perhaps NH activation in general, predicts adverse outcomes in AHF. Further, PRA may be a target in AHF, though this conclusion must be tempered by the large proportion of patients already on background RAAS inhibition therapies. However, it is unclear whether the association between increased PRA levels and adverse outcomes in AHF is related to increased renin-induced activation of the RAAS or whether the observed increase in PRA levels is simply reflective of greater HF severity at baseline. In a previous clinical trial, the addition of aliskiren, a direct renin inhibitor, to the standard treatment of AHF was not associated with decreased rehospitalization or cardiovascular death at 6 or 12 months following discharge.[24] Alternatively, previous studies have found higher PRA levels to be associated with more advanced disease in AHF as shown by increased morbidity and mortality.[12,13] The latter hypothesis is supported by the association between respiratory rate at baseline and worsening HF or death through day 5 of hospitalization (*Table 2*). Similar findings have been previously reported.[25,26] Such clinical severity markers may better identify short-term risks.

Comparison with previously published data

Prior to the standard use of NH blockers in HF with reduced ejection fraction, Francis *et al.*[11] demonstrated increased NH concentrations in patients with left ventricular dysfunction as compared to healthy volunteers, with highest levels observed in symptomatic patients. While NH activation occurs in asymptomatic left ventricular dysfunction, it is exaggerated in patients with overt HF as demonstrated by increased PRA levels.

Nijst *et al.*[12] demonstrated in a more contemporary cohort of patients on optimal NH blockade therapy that PRA levels were elevated in chronic HF. A contrarian finding, however, was the significantly higher PRA levels in patients with chronic HF compared to AHF. Further, there were no differences in PRA levels between patients presenting with AHF and healthy volunteers. Despite the high PRA levels observed in chronic HF, only in AHF and prior to decongestive therapy were PRA levels associated with rehospitalization and mortality.

Ueda *et al.*[13] studied the relationship between PRA levels and clinical outcomes in AHF patients on RAAS inhibitors prior to admission. After dividing their cohort by median PRA levels (3.4 ng/mL/h), patients with higher PRA levels had greater all-cause and cardiovascular mortality at 29-month follow-up. The latter finding is consistent with our results.

In a secondary analysis of the ASTRONAUT trial, authors found that patients with HF with reduced ejection fraction who were treated with the direct renin inhibitor aliskiren had an early and persistent decrease in PRA levels. Although lower PRA levels at baseline were associated with better outcomes, treatment with aliskiren did not translate into improved clinical outcomes at 12-month follow-up.[27]

A secondary analysis by Mentz *et al.*[28] explored the association between RAAS markers and decongestive therapy (i.e. diuretics and ultrafiltration), as well as worsening kidney function and 60-day clinical outcomes (i.e. HF rehospitalization or death). Unlike the Nijst study, Mentz et al. did not find an association between higher loop diuretic dose and RAAS activation. There was also no association between PRA levels at baseline and worsening kidney function or 60-day outcomes; a discordant finding compared to our study.

The online supplementary *Table S2* shows the central tendencies of PRA levels from other AHF trials, serving as a comparison. Although there are major limitations with such a comparison (especially with different assay characteristics), at face value, the PRA levels seen in BLAST-AHF appear relatively similar to other studies.

Mechanism of renin secretion and potential confounders

Renin is secreted by the juxtaglomerular cells in the kidney in response to decreased sodium delivery to the distal tubule, decreased arterial pressure sensed by intrarenal baroreceptors and sympathetic up-regulation via the beta-1 receptor; all in response to decreased cardiac output and subsequent ineffective

renal perfusion. Consistent with these mechanisms, BLAST-AHF patients with lower SBP and LVEF had increasingly higher PRA levels. Plasma renin is also regulated by angiotensin II via negative feedback. RAAS inhibitors (angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers) increase PRA levels by decreasing the production of angiotensin II, which negatively regulate the release of renin. Beta-blockers directly decrease PRA levels by suppressing renal sympathetic activity. Aldosterone receptor antagonists increase PRA levels, although the exact mechanism is less well-established.[29] Since an increasing number of patients with HF and reduced ejection fraction are treated with angiotensin-converting enzyme inhibitors, beta-blockers and aldosterone receptor antagonists, it was reasonable to account for the use of these medications in our analysis given their possible confounding of PRA levels. As noted earlier, the use of angiotensin II receptor blockers within 7 days of randomization was an exclusion criterion. Similar to previous studies, we found no difference in the angiotensin-converting enzyme inhibitor or beta-blocker use between PRA tertiles.[13,30] In contrast, there was a significant difference in the number of patients taking aldosterone receptor antagonists. After accounting for this factor on multivariate analysis, we found that PRA levels were related to outcomes.

Increased RAAS activation occurs in patients with diabetes mellitus. This observation has been attributed to increased p53 glycosylation, which in turn leads to increased transcription of angiotensinogen and subsequent production of angiotensin II.[31] This may confound our results, however, no difference in the number of diabetic patients was observed in our study between PRA tertiles.

NT-proBNP as a prognostic marker and its relation to renin–angiotensin–aldosterone system in acute heart failure

The prognostic value of NT-proBNP in AHF has been validated in multiple studies. NT-proBNP was the strongest predictor of 30-day rehospitalization and all-cause death in our analysis; a finding consistent with prior studies.[3,32] The use of biomarkers of RAAS activation to predict outcomes, however, is controversial since plasma levels can be influenced by multiple factors, particularly those related to HF therapy.[33] In our study, only the use of aldosterone receptor antagonists differed by baseline PRA levels. NT-proBNP and RAAS have counterregulatory roles in HF. However, our study – in line with Nakada's findings[30] – did not find baseline differences between NT-proBNP and PRA levels. Patients with lower, intermediate or higher PRA levels all had severely increased NT-proBNP. This suggests a potential disruption in the counterregulation mechanism in the setting of AHF.[30]

Limitations

As a retrospective analysis, any findings are hypothesis-generating only. Further, unmeasured confounders may have affected these findings. Because the numbers of clinical events were limited, any absence of a statistically significant association with PRA level after adjustment for clinical characteristics and commonly employed biomarkers may have been due to limited power rather than lack of a true association. As our study was restricted to acute settings, no comparisons were made between PRA levels in acute vs. chronic settings. This, in turn, could limit our interpretation of PRA level as a reliable marker of NH activation in AHF.

Measurement of PRA levels can be subjected to multiple confounding factors, including diurnal rhythms, level of activity, renal impairment, and dietary salt intake.[34] Thus, differences in PRA levels could be partly attributed to these confounders and not to a difference in RAAS activity only. Also, as mentioned earlier, PRA levels are affected by RAAS blocking drugs. In our analysis, we only accounted for the level of renal function and the use of medications.

PRA levels are determined indirectly by radioimmunologic measurement of angiotensin I levels following incubation of angiotensinogen with plasma renin from a sample. However, this method can lead to underestimation of plasma renin levels, particularly in patients with severe HF owing to their lower angiotensinogen levels resulting from liver congestion.[35] On the other hand, while PRC is also subject to the aforementioned limitations of PRA, it is measured using monoclonal antibodies against active renin independent of angiotensinogen levels. For this reason, PRC has been proposed as an alternative to PRA given better standardization of results. PRC has been suggested to be superior to PRA in predicting outcomes, in patients already treated with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers.[33] However, our results showed a high degree of correlation between PRA and PRC levels (*Figure 2*).

Conclusion

In this retrospective analysis from BLAST-AHF, PRA levels were associated with increased risk for the composite of 30-day HF rehospitalization or death in patients with AHF. Although the exact role of NH in AHF remains poorly understood, this analysis suggests NH activation may be a viable target in AHF.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Boxplots of plasma renin activity ratios to baseline by time-point of measurement with number of observations given below the plot.

Table S1. Candidate predictors for multivariable Model 1 for each endpoint.

Table S2. Central tendencies of plasma renin activity levels from other acute heart failure trials.

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