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Authors
Vaduganathan, Muthiah
Cheema, Baljash
Cleveland, Erin
et al.

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Plasma renin activity, response to aliskiren, and clinical outcomes in patients hospitalized for heart failure: the ASTRONAUT trial

Muthiah Vaduganathan[1], **Baljash Cheema**[2], **Erin Cleveland**[2], **Kamya Sankar**[2], **Haris Subacius**[2], **Gregg C. Fonarow**[3], **Scott D. Solomon**[1], **Eldrin F. Lewis**[1], **Stephen J. Greene**[4], **Aldo P. Maggioni**[5], **Michael Böhm**[6], **Faiez Zannad**[7], **Javed Butler**[8], **Mihai Gheorghiade**[9,*]

[1]Brigham and Women's Hospital Heart & Vascular Center and Harvard Medical School, Boston, MA, USA

[2]Northwestern University, Feinberg School of Medicine, Chicago, IL, USA

[3]Ahmanson-UCLA Cardiomyopathy Center, University of California Los Angeles, Los Angeles, CA, USA

[4]Division of Cardiology, Duke University Medical Center, Durham, NC, USA

[5]ANMCO Research Center, Florence, Italy

[6]Klinik für Innere Medizin III, Universitätsklinikum des Saarlandes, Homburg, Germany

[7]INSERM, CHRU Nancy, Université de Lorraine, Centre d'Investigation Clinique CIC1433, Nancy, France

[8]Stony Brook University, Stony Brook, NY, USA

[9]Center for Cardiovascular Innovation, Northwestern University, Feinberg School of Medicine, Chicago, IL, USA

Abstract

Aims—The direct renin inhibitor, aliskiren, is known to reduce plasma renin activity (PRA), but whether the efficacy of aliskiren varies based on an individual's baseline PRA in patients hospitalized for heart failure (HF) is presently unknown. We characterized the prognostic value of PRA and determined if this risk is modifiable with use of aliskiren.

Methods and results—This pre-specified neurohormonal substudy of ASTRONAUT analysed all patients hospitalized for HF with ejection fraction (EF) ≤40% with available baseline PRA data (*n* = 1306, 80.9%). Risk associated with baseline PRA and short-term changes in PRA from baseline to 1 month was modelled with respect to 12-month clinical events. Median baseline PRA was 3.0 (interquartile range 0.6–16.4) ng/mL/h. Aliskiren significantly reduced PRA early after

*Corresponding author. Center for Cardiovascular Innovation, Northwestern University, Feinberg School of Medicine, 201 East Huron, Galter 3-150, Chicago, IL 60611, USA. Tel: +1 312 695-0051, Fax: +1 312 926-7260, m-gheorghiade@northwestern.edu.

treatment initiation through 12-month follow-up compared with placebo ($P < 0.001$). The lowest baseline PRA quartile (<0.6 ng/mL/h) was independently predictive of lower all-cause mortality [adjusted hazard ratio (HR) 0.50, 95% confidence interval (CI) 0.31–0.81] and the composite of cardiovascular mortality and HF hospitalization (adjusted HR 0.57, 95% CI 0.40–0.79). Delta log-normalized PRA (from baseline to 1 month) was not predictive of either primary endpoint at 12 months (P 0.43). The prognostic value of baseline PRA and short-term changes in PRA did not vary by randomization to aliskiren or placebo (interaction P 0.13).

Conclusions—Plasma renin activity is reduced early and durably by aliskiren, but this did not translate into improved clinical outcomes in ASTRONAUT. Baseline PRA or short-term reduction in PRA do not identify a subgroup who may preferentially benefit from direct renin inhibition.

Keywords

Clinical outcomes; Heart failure; Neurohormones; Renin

Introduction

Secondary perturbations of the neurohormonal axis have traditionally been the major target for drug development in heart failure (HF). Renin, a 37kDa enzyme released from the kidney's juxtaglomerular apparatus, orchestrates the renin–angiotensin–aldosterone system (RAAS), alters systemic vasomotor tone, and may contribute to progression of HF. Several studies have suggested that high levels of plasma renin activity (PRA) correlate with adverse cardiovascular (CV) outcomes,[1-5] however therapeutic trials[6,7] have failed to demonstrate clinical benefits with direct renin inhibition in patients with HF. Limited mechanistic data, including whether PRA was adequately suppressed with aliskiren, are available to better understand the lack of success of incremental RAAS modulation in this population. This pre-specified analysis of neurohormonal data from ASTRONAUT (Aliskiren Trial on Acute Heart Failure Outcomes) dissects the complex interplay between measured neurohormones, their response to aliskiren, and clinical outcomes. We specifically aimed to: (i) characterize the patient-level characteristics that are associated with PRA; (ii) track the effects of aliskiren on PRA levels over time; (iii) assess the prognostic utility of baseline and short-term changes in PRA on post-discharge clinical outcomes; and (iv) determine whether baseline or short-term changes in PRA identify a subgroup who preferentially benefit from direct renin inhibition.

Methods

ASTRONAUT: patient selection and study flow

The study design and primary results of the ASTRONAUT trial have been previously described.[8] In brief, the ASTRONAUT trial was an international, prospective, double-blind, randomized placebo-controlled study investigating the effect of aliskiren, a direct renin inhibitor, on clinical outcomes in haemodynamically stable patients hospitalized for HF. Patients were randomized a median of 5 days after admission. The trial studied patients who were 18 years or older, with left ventricular ejection fraction (EF) of 40%, who had elevated natriuretic peptide levels [B-type natriuretic peptide (BNP) 400pg/mL or N-

terminal pro-B-type natriuretic peptide (NT-proBNP) 1600pg/mL] at admission, with signs and symptoms of fluid overload. The investigation conforms with the principles outlined in the Declaration of Helsinki.

Plasma renin activity

Our primary variable of interest was log-transformed PRA. PRA was measured by radioimmunoassay using the GammaCoat Plasma Renin Activity Assay (DiaSorin Inc., Stillwater, MN, USA) and analysed in a central core laboratory (Quest Diagnostics, Valencia, CA USA). PRA was determined by quantification of angiotensin I in the presence of certain enzyme inhibitors. The dynamic range for this assay is 0.1 ng/mL/h to 50 ng/mL/h, intra-assay variation is 4.6–10%, and inter-assay variation is 5.6–7.6%. Laboratory personnel handling these samples were blinded to treatment assignment. All biomarker samples were obtained in the morning in a fasting state with patients in seated positions with their legs extended. To minimize the influence of outliers, the sponsor set the extremes of PRA recorded in the database to set values: <0.2 (set to 0.1) and >30 (set to 45). PRA was measured at the following time-points: baseline (time of randomization), 1 month, 6 months, 9 months, and 12 months.

Plasma aldosterone

Plasma aldosterone was only available in a select sample of patients. Plasma aldosterone was measured using the Coat-a-Count assay (Siemens Healthcare Diagnostics, Tarrytown, NY, USA) and analyzed in a central core laboratory (CRL-USA Lenexa, KS, USA). Aldosterone-to-renin ratio was calculated at baseline, 6 months, and 12 months, and expressed as ng/dL per ng/mL/h.

Study endpoints and definitions

The two primary endpoints for the present analysis were all-cause mortality (ACM) and a composite of CV mortality and HF hospitalization within 12-month follow-up. Select secondary endpoints were cause-specific CV mortality, all-cause rehospitalization, myocardial infarction, stroke, and individual components of the primary composite endpoint. All clinical endpoints were independently adjudicated by a clinical events committee at Brigham and Women's Hospital (Boston, MA USA) in a blinded manner. Select safety endpoints were mild hyperkalaemia (serum potassium 5.5 and <6.0 mmol/L), severe hyperkalaemia (serum potassium 6.0 mmol/L), and worsening renal function [decrease in estimated glomerular filtration rate (eGFR) to <30 mL/min/1.73 m^2]. These definitions were based on the maximum potassium level at any time-point within the first year and the minimum eGFR recorded within the first year. eGFR was calculated using the Modification of Diet in Renal Disease formula.

Statistical analyses

We included all patients in both treatment arms with available baseline PRA levels. Although aliskiren is known to influence PRA baseline PRA was measured at time of randomization, prior to aliskiren exposure. The primary variable was analysed as quartiles and as a continuous function, since specific parameters for 'normal' values in this cohort

have not been defined. Continuous variables were expressed as mean ± standard deviation (SD) if normally distributed and median [interquartile range (IQR)] if not normally distributed. Categorical variables were expressed as a number (percentage). Demographic characteristics, medical history, vital signs, laboratory data, and baseline medication therapies were compared across quartiles of baseline PRA levels using chi-square and analysis of variance tests.

Kaplan–Meier curves by baseline PRA quartiles were constructed for both primary endpoints and compared using log-rank tests. Outcomes were assessed using univariable and multivariable Cox proportional hazard models to calculate hazard ratios (HR) and 95% confidence intervals (CI) for the primary predictor. Proportional hazards and linearity assumptions were met for log-normalized PRA as a predictor of both primary endpoints. For the quartile-based analysis, the reference group was quartile 4. For the continuous analysis, HR was calculated per one SD decrease in log-normalized PRA. Interaction analyses were performed by aliskiren/placebo (treatment status) and diabetes mellitus. [9] We also identified the 'optimal' cut-point for risk prediction, by conducting a series of univariable Cox regression models with various cut-points and identifying the minimal point estimate of hazard for each of the primary endpoints. Non-linear associations between log-normalized PRA and the two primary endpoints were tested and characterized by applying restricted cubic spline terms with three knots.

Multivariate models account for 38 covariates determined at the time of randomization: age, sex, race, geographic region, ischemic HF aetiology, New York Heart Association functional class, left ventricular EF, systolic blood pressure, heart rate, weight, body mass index, NT-proBNP, serum sodium, serum haemoglobin, serum troponin, serum creatinine, serum blood urea nitrogen, aliskiren randomization, medical history (hypertension, coronary artery disease, atrial fibrillation, diabetes, hyperlipidaemia, chronic obstructive pulmonary disease, chronic kidney disease, prior percutaneous coronary intervention, prior coronary bypass arterial graft surgery, prior stroke or transient ischaemic attack, prior myocardial infarction, prior HF hospitalization), and baseline therapies [loop diuretics, angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB), β-blockers, mineralocorticoid receptor antagonist (MRA), digoxin, implantable cardioverter-defibrillator, cardiac resynchronization therapy, and/or pacemaker].

The association between PRA at randomization and plasma aldosterone level was tested. The response of plasma aldosterone to aliskiren therapy was assessed through 12-month follow-up. To assess the prognostic effects of short-term changes in PRA, the difference between the 1-month and baseline log-normalized PRA levels was calculated for each patient. The 1-month time-point was selected to minimize patient attrition. Baseline log-normalized PRA, delta log-normalized PRA, aliskiren, and the delta log-normalized PRA by aliskiren treatment interaction were included in left-truncated analyses in predicting the two co-primary endpoints. In addition, intra-class correlation (ICC) analyses were used to assess the amount of change in PRA across the follow-up time-frame relative to the variability at each time-point.

Data imputation or correction for multiple statistical testing was not performed. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA).

Results

Of the overall ASTRONAUT trial cohort ($n = 1615$), 1306 patients (80.9%) had available PRA levels at the time of randomization. The median PRA level in ASTRONAUT was 3.0 (IQR 0.6–16.4) ng/mL/h (see Supplementary material online, Figure S1). Patients were divided into quartiles based on baseline PRA levels with the following ranges: Q1 ($n = 317$; <0.6 ng/mL/h); Q2 ($n = 332$; 0.6-2.9 ng/mL/h); Q3 ($n = 332$; 3.0–16.3 ng/mL/h); Q4 ($n = 325$; 16.4 ng/mL/h).

Patient-level variation in plasma renin activity

Patients in the lowest quartile of PRA (<0.6 ng/mL/h) were more likely to be female and non-white and have higher rates of hypertension, but less likely to have chronic kidney disease or coronary artery disease compared to patients in the other quartiles (P 0.04 for all comparisons; Table 1). There was marked variability in mean PRA levels at randomization across geographic regions ranging from North America ($n = 105$; 3.9 ng/mL/h) to Western Europe ($n = 298$; 13.8 ng/mL/h; $P < 0.001$). At randomization, these patients had higher median systolic blood pressures, serum sodium levels, NT-pro-BNP levels, and eGFR values (P 0.02 for all comparisons). A greater proportion of patients in the lowest quartile of PRA were receiving β-blockers, while fewer were receiving MRAs and digoxin at the time of randomization (P 0.008 for all comparisons). While 42.3% of patients in the lowest quartile of PRA were co-treated with ACEi/ARB and MRA, 53.5% received dual RAAS therapy in the highest quartile of PRA ($P = 0.03$). Patients in the lowest PRA quartile were also less likely to have implantable cardioverter-defibrillator or cardiac resynchronization therapy than the other quartiles (P 0.006 for all comparisons). Overall, patients in the lower PRA quartiles experienced slightly shorter total hospital length of stays compared to the highest quartile ($P = 0.008$; Table 1).

Response to aliskiren

Aliskiren significantly reduced PRA early after treatment initiation compared with placebo, and continued to suppress PRA through 12-month follow-up ($P < 0.001$; Figure 1). PRA levels slightly increased from randomization through 12-month follow-up. In patients treated with aliskiren, after initial large reductions in PRA levels from randomization to 1 month, there was a slight regression to randomization levels from 1-month to 12-month follow-up. The effect of aliskiren on PRA levels over time does not appear to vary by geographic region (region-by-visit interaction P 0.21 for both time intervals).

Prognostic value of plasma renin activity

At 12-month follow-up, rates of ACM and the composite of CV mortality and HF hospitalization were significantly lower in the lowest PRA quartile compared with the other three quartiles (P 0.03 for both primary endpoints; Table 2 and Figure 2). After accounting for baseline risk predictors, compared to the highest quartile, the lowest quartile of PRA at randomization (which corresponded to PRA <0.6 ng/mL/h) was independently predictive of

improved ACM (adjusted HR 0.50, 95% CI 0.31–0.81; $P = 0.005$) and the composite endpoint (adjusted HR 0.57, 95% CI 0.40–0.79; $P < 0.001$). Lower log-normalized PRA (per 1 SD), when treated as a continuous function, was independently associated with a decrease in risk of ACM (adjusted HR 0.80, 95% CI 0.67–0.95; $P = 0.01$) and the composite endpoint (adjusted HR 0.83, 95% CI 0.74–0.94; $P = 0.003$) (Table 3). The relationship between log-normalized PRA and the co-primary endpoints is visually displayed in Figure S2 (see Supplementary material online) using adjusted restricted cubic splines. When individual cut-points were analysed, the lowest point estimate of hazard function was associated with a PRA <0.7 (as compared to PRA ⩾ 0.7: HR 0.60 for ACM and HR 0.65 for the composite endpoint). Interaction terms with PRA (as a continuous function) and aliskiren treatment randomization (interaction P ⩾ 0.13 for both primary endpoints) and history of diabetes mellitus (interaction P ⩾ 0.16 for both primary endpoints) were negative, and thus were not included in the final multivariable models. As such, the treatment effects of aliskiren (vs. placebo) on the co-primary endpoints did not vary by baseline PRA. Rates of hyperkalaemia and worsening renal function were not significantly different across baseline PRA levels (Table 2).

Change in plasma renin activity

Complete data through 1-month follow-up were available in 1029 patients and the spread of log-normalized delta PRA values maintained a normal distribution. The median change in log-normalized PRA from randomization to 1-month follow-up was 0.68 (−2.20 to 0.45). In left-truncated analysis, delta log-normalized PRA was not predictive of 12-month ACM (HR 1.03, 95% CI 0.89–1.19, $P = 0.72$ for aliskiren arm and HR 0.96, 95% CI 0.85–1.10, $P = 0.57$ for placebo arm) and the composite endpoint (HR 1.02, 95% CI 0.92–1.12, $P = 0.76$ for aliskiren arm and HR 0.97, 95% CI 0.89–1.05, $P = 0.43$ for placebo arm) after accounting for baseline log-normalized PRA level. The lack of prognostic value of delta log-normalized PRA did not vary by randomization to aliskiren or placebo (interaction P ⩾ 0.39). After initial changes to 1-month post-randomization (ICC term 0.51), log-normalized PRA levels remained relatively stable through 12-month follow-up. Baseline log-normalized PRA quartiles maintained separation and stability from 1 month to 6 months (ICC term 0.65) and from 6 months to 12 months (ICC term 0.71), after accounting for the treatment interaction term (see Supplementary material online, Figure S3).

Plasma aldosterone

Plasma aldosterone levels were available in a subset of ASTRONAUT patients ($n = 613$; 38.0%). At baseline, PRA levels modestly correlated with plasma aldosterone ($r = 0.31$). Aliskiren diminished post-discharge increases in plasma aldosterone, which continued to increase in the placebo arm up to 12 months post-randomization (see Supplementary material online, Figure S4). However, aliskiren's effects on plasma aldosterone appeared to be more modest than its direct effects on PRA, such that the aldosterone-to-renin ratio was significantly increased by aliskiren compared with placebo at 6-month and 12-month follow-up ($P < 0.001$ at both time intervals).

Discussion

In this large neurohormonal substudy of a phase III clinical trial of patients hospitalized for HF and reduced EF, we highlight a number of important findings: (i) PRA levels >0.7 ng/mL/h prior to hospital discharge identify a high-risk cohort for subsequent mortality and CV events; (ii) PRA is reduced early and durably by aliskiren; and (iii) PRA at the time of randomization or short-term reductions in PRA do not identify a subgroup which may preferentially benefit from direct renin inhibition.

ASTRONAUT is well-suited to study neurohormonal status. The present analysis is one the largest neurohormonal substudies among patients hospitalized for HF with reduced EF, and PRA-based analysis was pre-specified in the study protocol. All enrolled patients were stabilized after initial haemodynamic and congestive perturbations, which may represent a relative 'steady-state'. Serial measurements of PRA were available through 12 months post-discharge, tracking neurohormonal status well beyond the initial 'vulnerable phase'. Finally, the study is uniquely positioned to inform whether aliskiren influences PRA trajectory and clinical outcomes in patients well treated with background neurohormonal blockers.

Renin—the 'gatekeeper' neurohormone

The RAAS system has historically been an important target of pharmacotherapies in chronic HF. Renin, involved in the rate-limiting step of this complex axis, is upregulated in response to a decrease in baroreceptor stretch from low arterial blood pressure, a decrease in sodium chloride flux into the juxtaglomerular apparatus, and activation of the sympathetic nervous system, and is downregulated by angiotensin II through feedback inhibition. Renin levels are known to increase in patients treated with RAAS modulating drugs, the so-called 'renin escape', [10] raising interest in pharmacologically blocking renin in patients with HF.[11]

Variation in plasma renin activity in a global trial

Average baseline levels of PRA in this cohort (3.0ng/mL/h) were lower than other recent in-hospital trial-based experiences (~5.0 ng/mL/h), [3] potentially reflecting the relative clinical stability of ASTRONAUT patients. We further demonstrate marked regional variation in PRA levels measured during hospitalization for HF. In addition to region-based variation in protocol execution, drug compliance, and background therapies, our data provide evidence of variation in neurohormonal status across geographic regions in a global HF program. Differences in PRA across geographic regions may reflect variation in diet, race/ethnic composition, environmental exposures, and background disease severity and neurohormonal antagonist use. Despite this regional heterogeneity, aliskiren appears to reduce PRA similarly across geographic regions. In light of recent trial experiences of potential regional departures from trial protocols,[12] these data are reassuring of consistent drug exposure and effects across regions.

Prognostic significance of plasma renin activity

Unlike other markers of the neurohormonal axis, [13] PRA appears to be steadily elevated in placebo-treated patients even late after the 'vulnerable phase' of hospitalization for HF. Early separations in PRA levels during hospitalization appear to persist up to 1 year post-

discharge. As such, PRA may represent a stable biomarker of neurohormonal status. High PRA measured shortly prior to discharge appears to identify a high-risk cohort for subsequent CV events. The risk associated with elevated PRA persisted after accounting for imbalances in region and background neurohormonal therapies.

Why was direct renin inhibition unsuccessful in heart failure?

Although PRA appears to be an independent marker of risk and aliskiren (at a dose of 150 mg to 300 mg once daily) reliably reduces PRA levels, direct renin inhibition did not translate to improved post-discharge clinical outcomes in ASTRONAUT. As such, this experience represents another cautionary example in drug development in which lowering of a target surrogate marker by an investigational therapy fails to reliably predict treatment effects with respect to definitive clinical endpoints. There are several potential explanations for this apparent disconnect. First, PRA levels were relatively low in this stabilized HF cohort with a large fraction of patients with baseline values at the lower reporting limit, potentially compromising our ability to demonstrate treatment benefit with aliskiren. Furthermore, PRA was subject to significant inter-individual variability and single time-point estimates of PRA during and soon after hospitalization may be altered by shifts in volume and haemodynamics, and transitions in medications, limiting its reliability. Second, PRA may represent an important marker of HF disease severity at a population level, but this conferred risk may not be modifiable despite reductions in measured levels for each individual patient. Renin is differentially absorbed in coronary and cardiac tissue beds, locally catalyzing angiotensin production.[14] As such, there may be inter-individual variation in plasma vs. local renin activity. Third, downstream compensatory mechanisms may overcome upstream direct renin inhibition over time. For instance, tissue chymase may be an important non-renin-dependent mediator of angiotensin II production in the failing heart. These mechanisms may lend to non-linear associations between renin, angiotensin intermediates, and aldosterone in HF.[15] Indeed, in our study, aliskiren appeared to reduce PRA levels more robustly than aldosterone levels. This magnitude of angiotensin and aldosterone modulation with add-on direct renin inhibition may not be sufficient to modify target pathways (including renal blood flow)[16] and subsequent clinical outcomes. Finally, the potential benefits from direct renin inhibition may be counterbalanced by adverse safety signals, especially in certain high-risk subgroups such as patients with diabetes.[9,17] Further modulation of the RAAS system may not confer incremental clinical benefit (ceiling effect in RAAS inhibition),[7] but may only augment risk for adverse effects such as hypotension, hyperkalaemia, and worsening renal function. However, in prior experiences of RAAS inhibition, the treatment-related occurrence of these adverse effects did not negate the overall survival benefit conferred by these agents in carefully monitored patients.[18] As such, excess risks of adverse effects alone are unlikely to account for all the lack of success of direct renin inhibition. Novel strategies to optimize RAAS modulation in a safe and effective manner in this population are necessary.[19] The recent clinical testing of adjunctive potassium binders[20-22] and potentially safer non-steroidal MRAs [23] has shown initial promise.

Study limitations

Despite the retrospective nature of the study design, these analyses were pre-specified and the measurement of neurohormones was protocol-driven. PRA and aldosterone levels were only available in a subset of patients and serial neurohormonal marker sampling and follow-up for endpoint analyses were limited to 12 months. Although PRA was subject to significant regional variation, the assay was handled in a central laboratory. Despite efforts to standardize collection, PRA measurement may be prone to significant diurnal variation and biological variability, and may vary substantially based on timing and posture of sampling and ambient temperature of storage.[24] These intervening factors may limit the reliability and reproducibility of these neurohormonal measurements during hospitalization, [25] and strict standardization of blood sampling conditions remains challenging in a global, multicenter trial. Residual measured and unmeasured confounding may influence these findings. Our findings may not be generalizable to patients with chronic stable HF, patients with preserved EF (although elevations in renin levels may be comparable to that observed in patients with reduced EF[26]), and those outside the immediate inclusion and exclusion criteria of the ASTRONAUT trial.

Conclusions

Plasma renin activity levels were relatively low and were subject to significant patient-level and regional variation in this cohort of patients stabilized after hospitalization for HF. Despite this, PRA represents an independent marker of disease severity, and elevated levels during hospitalization for HF with reduced EF predict subsequent risk for mortality and rehospitalization. The direct renin inhibitor, aliskiren, successfully reduced PRA in a broad range of hospitalized patients with HF in a global phase III trial. Baseline PRA or short-term changes in PRA did not identify a subgroup of patients who preferentially respond to direct renin inhibition. Taken together, successful therapeutic modulation of PRA was achieved with aliskiren in the ASTRONAUT trial, but this did not appear to translate into improved clinical outcomes. Further confirmatory studies are needed to clarify the role of PRA in risk stratification during this period of stabilization after hospitalization for HF with reduced EF. The dynamic nature of the plasma angiotensin peptide system is only recently becoming recognized, and more complete metabolic profiling of key angiotensin intermediates may be required to better understand the therapeutic effects of RAAS inhibitors.[15] Future drug development[27] will need to identify potentially safer strategies to attenuate secondary neurohormonal perturbations or re-focus attention on primary cardiac abnormalities. The potential for precision CV approaches in the application of novel or existing therapeutics in patients with HF requires further testing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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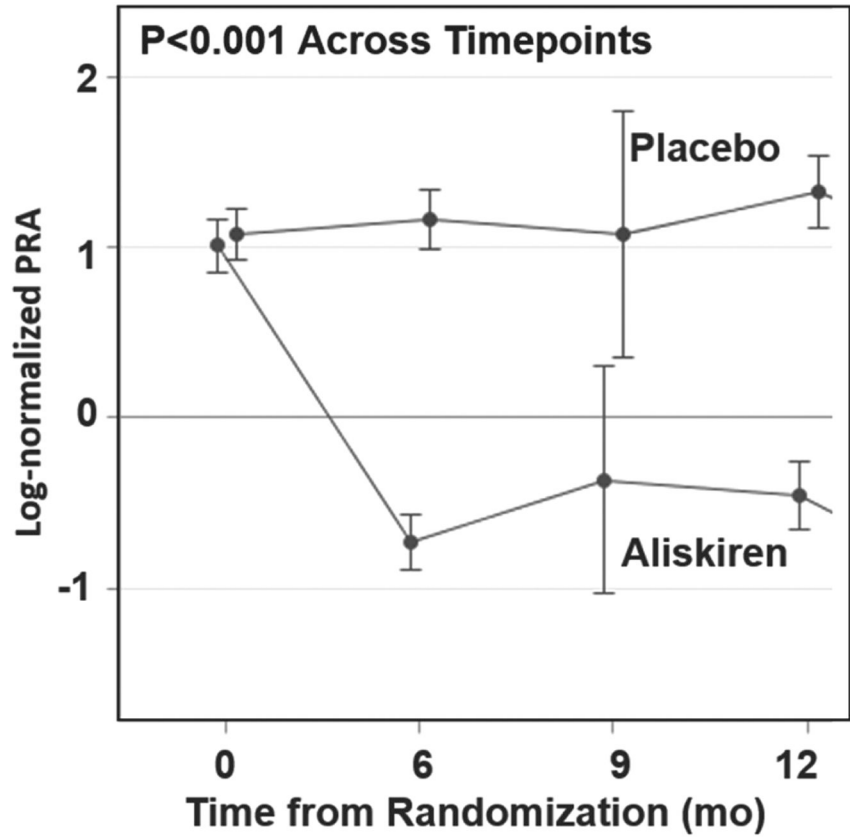
Figure 1.

Log-normalized plasma renin activity (PRA) by treatment arm through 12-month follow-up.
Log-normalized PRA levels (and 95% confidence interval bars) over time in the placebo
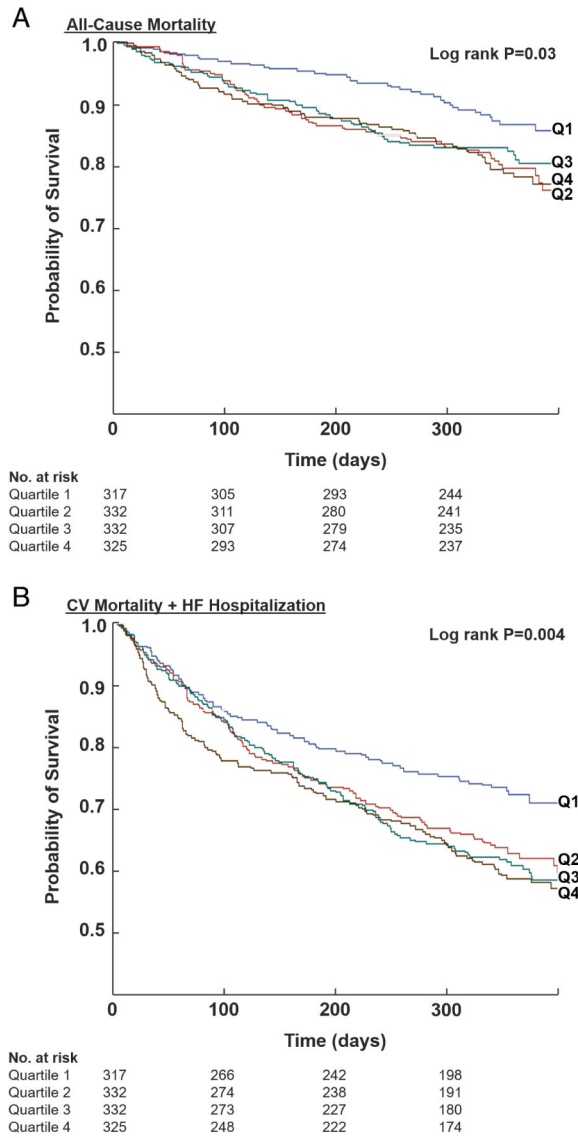group and in response to aliskiren

Figure 2.
Kaplan–Meier curves for all-cause mortality (*A*) and cardiovascular (CV) mortality or rehospitalization for heart failure (HF) (*B*) at 12-month follow-up by quartiles of baseline plasma renin activity. Times to events were compared using log-rank tests

Table 1

Baseline characteristics by quartiles of plasma renin activity

	Quartiles of PRA (ng/mL/h)				P-value
	Q1 (<0.6) n=317	Q2 (0.6–2.9) n=332	Q3 (3.0–16.3) n=332	Q4 (≥16.4) n=325	
Aliskiren (%) PRA (ng/mL/h)	175 (55.2)	154 (46.4)	161 (48.5)	166 (51.1)	0.20
Mean ± SD	0.2±0.1	1.5±0.6	7.8±3.9	35.9±10.9	
Median, IQR	0.2 (0.1–0.4)	1.3 (0.9–1.9)	6.8 (4.5–10.6)	45 (25.4–45)	
Demographics					
Age (years), median (IQR)	65 (56–74)	65 (56–74)	66 (55–74)	64	0.08
Male (n, %)	225 (71)	260 (78.3)	259 (78)	(56–71) 269 (82.8)	0.004
Race (n, %)					<0.001
White	202 (63.7)	221 (66.6)	240 (72.3)	236 (72.6)	
Black	31 (9.8)	16 (4.8)	14 (4.2)	4 (1.2)	
Asian	68 (21.5)	84 (25.3)	73 (22)	76 (23.4)	
Other	16 (5)	11 (3.3)	5 (1.5)	9 (2.8)	
Region (n, %) North America	41 (12.9)	34 (10.2)	23 (6.9)	6 (1.8)	<0.001
Latin America	35 (11)	28 (8.4)	26 (7.8)	17 (5.2)	
Western Europe	55 (17.4)	71 (21.4)	77 (23.2)	90 (27.7)	
Eastern Europe	101 (31.9)	93 (28)	104 (31.3)	114 (35.1)	
Asia/Pacific	85 (26.8)	106 (31.9)	102 (30.7)	98 (30.2)	
Time intervals (days), median (IQR) Time from admission to randomization	4 (2–6)	4 (2–6)	5 (2–7)	5 (2–8)	<0.001
Hospital length of stay	8 (4–12)	8 (5–12)	8 (5–12)	9 (5–14)	0.008
Medical history					
Ischaemic HF etiology (n, %)	193 (60.9)	216 (65.3)	223 (67.2)	213 (65.5)	0.36
NYHA class III/IV (n, %)	188 (59.3)	216 (65.1)	225 (67.8)	209 (64.3)	0.21
Prior HF hospitalization (n, %)	205 (64.7)	211 (63.6)	241 (72.6)	233 (71.7)	0.02
LV EF (%), mean±SD	28.3±7.4	27.8±7.7	27.4±7.3	27.4±7.1	0.38
Hypertension (n, %)	268 (84.5)	252 (75.9)	238 (71.7)	219 (67.4)	<0.001
Hyperlipidaemia (n, %)	73 (23.9)	75 (23.7)	110 (35.4)	80 (26.3)	0.005
Diabetes mellitus (n, %)	125 (39.4)	143 (43.1)	136 (41)	145 (44.6)	0.47

	Quartiles of PRA (ng/mL/h)				P-value
	Q1 (<0.6) n=317	Q2 (0.6–2.9) n=332	Q3 (3.0–16.3) n=332	Q4 (≥16.4) n=325	
Coronary artery disease (n, %)	152 (47.9)	182 (54.8)	200 (60.2)	180 (55.4)	0.01
Atrial fibrillation/flutter (n, %)	132 (41.6)	147 (44.3)	141 (42.5)	128 (39.4)	0.45
Chronic kidney disease (n, %)	50 (15.8)	74 (22.3)	68 (20.5)	81 (24.9)	0.04
Chronic obstructive pulmonary disease (n, %)	58 (18.3)	68 (20.5)	54 (16.3)	78 (24)	0.08
Prior PCI (n, %)	51 (16.1)	67 (20.2)	65 (19.6)	78 (24)	0.07
Prior CABG (n, %)	36 (11.4)	56 (16.9)	79 (23.8)	50 (15.4)	<0.001
Prior stroke (n, %)	32 (10.1)	40 (12)	29 (8.7)	27 (8.3)	0.40
Prior transient ischaemic attack (n, %)	9 (2.8)	14 (4.2)	10 (3)	10 (3.1)	0.60
Prior myocardial infarction (n, %)	111 (35)	137 (41.3)	160 (48.2)	147 (45.2)	0.002
Vital signs					
Weight (kg), median (IQR)	76.3 (64.3–90)	73.3 (62–86.1)	75 (62–85.7)	75 (64–89.6)	0.28
BMI (kg/m^2), median (IQR)	26.5 (23.3–30.6)	25.8 (22.7–29.7)	25.7 (22.7–29.6)	26.2 (22.8–30.5)	0.32
SBP (mmHg), median (IQR)	125 (118–138)	121 (115–130)	120 (112–130)	119 (111–125)	<0.001
Heart rate (b.p.m.), median (IQR)	75 (65–87)	76 (68–88)	77 (67–89)	77 (69–87)	0.36
Electrocardiogram					
Atrial fibrillation/flutter (n, %)	103 (33.4)	109 (33.3)	100 (30.4)	103 (32.1)	0.84
QRS duration (ms), median (IQR)	102 (88–140)	108 (90–130)	110 (92–143)	120 (93–152)	0.003
Laboratory data at randomization					
Haemoglobin (g/dL), median (IQR)	13.6 (12.2–14.8)	13.7 (12.4–15.1)	13.6 (12.2–14.9)	142 (12.5–15.5)	0.009
NT-proBNP admission (pg/mL), median (IQR) *	4697 (3000–8967)	4591 (2799–8675)	3973 (2671–7962)	3586.5 (2389–6966)	0.02
NT-proBNP at randomization (pg/mL), median (IQR) *	3141.5 (1742–6414)	2870.5 (1700–5374.5)	2631 (1369–5562)	2384 (1398–4423)	<0.001
Troponin I (ng/mL), median (IQR)	0 (0–0.1)	0 (0–0.1)	0 (0–0.1)	0 (0–0.1)	0.13
Sodium (mmol/L), median (IQR)	140 (138–142)	140 (138–141)	139 (137–141)	137 (134–139)	<0.001
Creatinine (μmol/L), median (IQR)	93 (78.1–107.8)	96.1 (79.6–113.5)	100.7 (83.2–120.5)	99 (82.4–116.6)	0.002
BUN (mmol/L), median (IQR)	7 (5.7–9.2)	8.2 (6.3–11.1)	8.7 (6.7–11.5)	9.3 (7.4–12.5)	<0.001
eGFR (mL/min/1.73m^2), median (IQR)	67.2 (55.8–78.7)	63.7 (53–81.9)	62.2 (50–75.8)	63.5 (52–78.6)	0.02
Baseline therapies					
Diuretics (n, %)	302 (95.3)	314 (94.6)	326 (98.2)	312 (96)	0.16
ACEi or ARB (n, %)	275 (86.8)	275 (82.8)	268 (80.7)	275 (84.6)	0.14

	Quartiles of PRA (ng/mL/h)				P-value
	Q1 (<0.6) n=317	Q2 (0.6–2.9) n=332	Q3 (3.0–16.3) n=332	Q4 (16.4) n=325	
β-blocker (n, %)	282 (89)	276 (83.1)	276 (83.1)	253 (77.8)	0.003
MRA (n, %)	155 (48.9)	180 (54.2)	190 (57.2)	208 (64)	0.003
ACEi/ARB + MRA (n, %)	134 (42.3)	146 (44)	149 (44.9)	174 (53.5)	0.03
Digoxin (n, %)	107 (33.8)	125 (37.7)	133 (40.1)	151 (46.5)	0.008
ICD (n, %)	26 (8.2)	37 (11.1)	56 (16.9)	80 (24.6)	<0 . 001
CRT (n, %)	12 (3.8)	17 (5.1)	26 (7.8)	33 (10.2)	0.006
Permanent pacemaker (n, %)	28 (8.8)	36 (10.8)	38 (11.4)	40 (12.3)	0.50

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BUN, blood urea nitrogen; CABG, coronary artery bypass grafting; CRT, cardiac resynchronization therapy; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; LV, left ventricular; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PRA, plasma renin activity; SBP, systolic blood pressure; SD, standard deviation.

*
Data available for 641 patients at admission and 1305 patients at baseline (randomization).

Table 2

Event rates by quartiles of plasma renin activity

	Quartiles of PRA (ng/mL/h)				P-value
	Q1 (<0.6) n=317	Q2 (0.6–2.9) n=332	Q3 (3.0–16.3) n=332	Q4 (16.4) n=325	
30-day events (n, %)					
All-cause mortality	3 (0.9)	3 (0.9)	8 (2.4)	6 (1.8)	0.32
All-cause rehospitalization	33 (10.4)	48 (14.5)	37 (11.1)	51 (15.7)	0.14
Rehospitalization for HF	13 (4.1)	19 (5.7)	13 (3.9)	28 (8.6)	0.04
6-month events (n, %)					
All-cause mortality	16 (5)	45 (13.6)	38 (11.4)	39 (12)	0.003
CV mortality or rehospitalization for HF	64 (20.2)	88 (26.5)	89 (26.8)	92 (28.3)	0.09
CV mortality	14 (4.4)	43 (13)	36 (10.8)	38 (11.7)	0.002
All-cause rehospitalization	106 (33.4)	132 (39.8)	125 (37.7)	127 (39.1)	0.37
Rehospitalization for HF	53 (16.7)	63 (19)	65 (19.6)	73 (22.5)	0.33
12-month events (n, %)					
All-cause mortality	39 (12.3)	66 (19.9)	59 (17.8)	66 (20.3)	0.03
CV mortality or rehospitalization for HF	87 (27.4)	124 (37.3)	129 (38.9)	131 (40.3)	0.003
CV mortality	32 (10.1)	61 (18.4)	54 (16.3)	62 (19.1)	0.008
Worsening HF	8 (2.5)	25 (7.5)	23 (6.9)	31 (9.5)	0.004
Sudden cardiac death	14 (4.4)	22 (6.6)	19 (5.7)	17 (5.2)	0.65
Presumed sudden death	3 (0.9)	2 (0.6)	1 (0.3)	3 (0.9)	0.72
All-cause rehospitalization	135 (42.6)	163 (49.1)	152 (45.8)	165 (50.8)	0.20
Rehospitalization for HF	69 (21.8)	87 (26.2)	95 (28.6)	102 (31.4)	0.04
Myocardial infarction	12 (3.8)	12 (3.6)	13 (3.9)	8 (2.5)	0.73
Stroke	5 (1.6)	13 (3.9)	11 (3.3)	5 (1.5)	0.13
Select safety endpoints (n, %)					
Hyperkalaemia					0.70
None	265 (86.3)	264 (82.2)	266 (84.2)	258 (83.0)	
Mild *	28 (9.1)	38 (11.8)	28 (8.9)	33 (10.6)	
Severe †	14 (4.6)	19 (5.9)	22 (7.0)	20 (6.4)	

	Quartiles of PRA (ng/mL/h)				*P*-value
	Q1 **(<0.6)** ***n*=317**	**Q2** **(0.6–2.9)** ***n*=332**	**Q3** **(3.0–16.3)** ***n*=332**	**Q4** **(16.4)** ***n*=325**	
Worsening renal failure *‡*	20 (6.5)	29 (9.0)	34 (10.8)	31 (10.0)	0.28

Laboratory data used to assess safety endpoints represent maximum post-baseline potassium and minimum post-baseline eGFR values.

CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; MDRD, modification of Diet in Renal Disease; PRA, plasma renin activity.

*
Mild hyperkalaemia defined as serum potassium   .5 and <6.0 mmol/L.

†
Severe hyperkalaemia defined as serum potassium   6.0 mmol/L.

‡
Worsening renal failure defined as a decrease in eGFR levels (calculated based on the abbreviated MDRD formula) to <30 mL/min/1.75m^2.

Table 3

Risk models for plasma renin activity (analysed as quartiles and as a continuous function) predicting the co-primary endpoints

	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)	P-value
All-cause mortality			
Quartile-based			
Q1	0.57 (0.38–0.85)	0.50 (0.31–0.81)	0.005
Q2	0.97 (0.69–1.37)	0.80 (0.54–1.18)	0.26
Q3	0.87 (0.61–1.23)	0.81 (0.55–1.19)	0.28
Q4	Reference	Reference	P(overall) =0.15
Continuous			
PRA (log-normalized)	0.85 (0.74–0.97)	0.80 (0.67–0.95)	0.01
Aliskiren treatment by PRA interaction term			0.13
CV mortality and rehospitalization for HF			
Quartile-based			
Q1	0.67 (0.51–0.88)	0.57 (0.40–0.79)	<0.001
Q2	0.89 (0.69–1.13)	0.80 (0.60–1.06)	0.11
Q3	0.93 (0.73–1.19)	0.86 (0.66–1.14)	0.29
Q4	Reference	Reference	P(overall) =0.03
Continuous			
PRA (log-normalized)	0.86 (0.78–0.95)	0.83 (0.74–0.94)	0.003
Aliskiren treatment by PRA interaction term			0.23

Data represent HR and 95% CI for risk of the primary co-endpoints. For quartile-based analyses, cut-offs for each quartile are included in Tables 1 and 2, and quartile 4 4 was used as the reference group. For continuous analyses, HR were estimated for 1 standard deviation decrease in log-normalized PRA. The proportional hazards and linearity assumptions were met for log-normalized PRA as a predictor of both co-primary endpoints. There was little evidence that quadratic polynomial improves on the linear model fit. Interactions with PRA (as a continuous function) and aliskiren treatment randomization and history of diabetes were negative, and thus were not included in the final multivariable models.

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; PRA, plasma renin activity.

*
Adjusted for age, sex, race, geographic region, body mass index, ischemic HF aetiology, New York Heart Association class III/IV, ejection fraction, systolic blood pressure, heart rate, N-terminal pro-B-type natriuretic peptide level, serum sodium, blood urea nitrogen, serum creatinine, QRS duration, aliskiren treatment randomization, past medical history (prior HF hospitalization, coronary artery disease, atrial fibrillation, diabetes, chronic obstructive pulmonary disease), and baseline therapies (angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, β-blocker, mineralocorticoid receptor antagonist, digoxin, implantable cardioverter-defibrillator, cardiac resynchronization therapy).