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Clinical Determinants and Prognostic Implications of Renin and Aldosterone in Patients with Symptomatic Heart Failure

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Abstract

Background

Activation of the renin-angiotensin-aldosterone system (RAAS) plays an important role in the pathophysiology of heart failure (HF) and has been associated with poor prognosis. There is limited data on the associations of renin and aldosterone levels with clinical profiles, treatment response and study outcomes in patients with HF.

Methods

We analyzed 2,039 patients with available baseline renin and aldosterone levels in BIOSTAT-CHF (a systems BIOlogy study to Tailored Treatment in Chronic Heart Failure). The primary outcome was the composite of all-cause mortality or HF hospitalization. We also investigated changes in renin and aldosterone levels after administration of mineralocorticoid receptor antagonists (MRAs) in a subset of the EPHESUS trial and in an acute HF cohort (PORTO).

Results

In BIOSTAT-CHF study, median renin and aldosterone levels were 85.3 (percentile₂₅₋₇₅=28-247) μ IU/mL and 9.4 (percentile₂₅₋₇₅=4.4-19.8) ng/dL, respectively. Prior HF admission, lower blood pressure, sodium, poorer renal function and MRA treatment were associated with higher renin and aldosterone. Higher renin was associated with an increased rate of the primary outcome [highest vs. lowest renin tertile: adjusted-HR(95% CI)=1.47 (1.16-1.86), $p=0.002$], whereas higher aldosterone was not [highest vs. lowest aldosterone tertile: adjusted-HR (95% CI)=1.16 (0.93-1.44), $p=0.19$]. Renin and/or aldosterone did not improve the BIOSTAT-CHF prognostic models. The rise in aldosterone with the use of MRAs was observed in EPHESUS and PORTO studies.

Conclusions

Circulating levels of renin and aldosterone were associated with both the disease severity and use of MRAs. By reflecting both the disease and its treatments, the prognostic discrimination of these biomarkers was poor. Our data suggest that the “point” measurement of renin and aldosterone in HF is of limited clinical utility.

Keywords: Heart failure; Renin; Aldosterone; prediction model; prognosis

Introduction

Activation of the renin-angiotensin aldosterone system (RAAS) plays a pivotal role in the development and subsequent progression of heart failure (HF); excessive and inappropriate RAAS activation may increase myocardial fibrosis and favor the adverse myocardial remodeling^{1,2}. Renin and aldosterone, as markers of RAAS activation, have been associated with poor prognosis in previous studies³⁻⁷. However, several clinical parameters such as severity of congestion, cardiac and renal function, and HF treatments, *e.g.* angiotensin converting enzyme inhibitor/angiotensin receptor blocker (ACEi/ARBs), beta-blockers and mineralocorticoid receptor antagonist (MRAs) may also influence the RAAS activation^{1,8,9}.

The systems BIOlogy study to Tailored Treatment in Chronic Heart Failure (BIOSTAT-CHF), is a multicenter international European project, that assessed the factors associated with under-prescription of life-saving therapies in HF and the respective prognostic implications¹⁰. The BIOSTAT-CHF study allows for the unique opportunity to explore both the prognostic value and the factors associated with activation of the RAAS, reflected here by the determination of the circulating levels of renin and aldosterone. We also measured renin and aldosterone in a subset of patients of the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) trial¹¹ and in a cohort of acute HF patients from Porto, Portugal¹².

The aims of the present study **are** to investigate; 1) the clinical determinants of renin and aldosterone levels; 2) the association of renin and aldosterone with clinical outcomes; and 3) the discriminative prognostic value of renin and aldosterone on top of the “best” clinical model.

Methods

Patient Population

The description of the BIOSTAT-CHF cohort has been previously published^{10,13}. In brief, BIOSTAT-CHF was an investigator-driven multi-center clinical study being consisted of 2,516 patients from 69 centers in 11 European countries with symptoms of HF, which was confirmed by left ventricular ejection fraction $\leq 40\%$ and/or brain natriuretic peptide >400 pg/mL or N-terminal pro BNP (NT-

proBNP) >2000 pg/mL and treatment of furosemide. From this cohort, we analyzed 2,039 patients with available data on renin and aldosterone at baseline. Patients were receiving <50% of the target doses of at least one of ACEi/ARBs and beta-blockers at the time of inclusion. The first 3 months of treatment were a treatment optimization phase. During the optimization phase, initiation or up-titration of ACEi/ARB and/or beta-blocker was done according to the routine clinical practice of the treating physicians, who were encouraged to follow the European Society of Cardiology guideline ¹⁴.

All patients recruited in BIOSTAT-CHF gave written informed consent to participate in the study. BIOSTAT-CHF was conducted in concordance with the declaration of Helsinki, national ethics and legal requirements, as well as relevant EU legislation. The study was approved by national and local ethics committees. All patients recruited in BIOSTAT-CHF gave written informed consent to participate in the study.

EPHESUS was designed to assess the effects of eplerenone on morbidity and mortality in patients with an left ventricular ejection fraction (LVEF) $\leq 40\%$ after acute myocardial infarction who had signs and symptoms of HF or diabetes as previously published ^{11, 15}. Among 6,632 patients in the EPHESUS trial, 360 and 366 patients had respectively available renin and aldosterone measurements at screening, 1-month, 3-month and 6-month visits.

The PORTO study was a prospective, single-center, non-randomized, open-label and interventional study ¹². Patients presenting with acute HF (AHF) were assigned to either oral spironolactone plus standard AHF care or standard AHF care alone in a Portuguese tertiary hospital. We analyzed 97 patients with available renin and aldosterone measurements in the first 24 hours and at day 3 after admission. Spironolactone was administrated after the first sample was collected.

Biomarkers

Plasma samples were measured at baseline, *i.e.* when patients with HF visited a medical service in a decompensated state in BIOSTAT-CHF study. Patients could have come at any time during the day and they have had food before the blood samples had been collected. All patients rested for at least 15 min before collecting the samples. Renin and aldosterone were both measured using a RadioImmunoAssay (Renin: CisBio International; Aldosterone: IBL International) in plasma samples

that had previously undergone two freeze/thaw cycles as previously published ¹⁶. For renin, the dynamic range for this assay is 1.0 $\mu\text{IU/mL}$ to 11,160 $\mu\text{IU/mL}$ and interassay coefficients of variation were 5.0%. The direct renin assay has been demonstrated to yield measurements that have a high correlation with plasma renin activity and high reproducibility ¹⁷⁻¹⁹. The dynamic range for the aldosterone assay is 0.14 ng/dL to 150 ng/dL and interassay coefficients of variation were <7.5%. All the biomarkers were measured either at local hospital site or within the BIOSTAT-CHF central laboratory.

Statistical Analysis

Categorical variables are described as frequencies (percentages) and continuous variables are described as means \pm standard deviation or median (25th and 75th percentiles) depending on the variable distributions. Comparisons of demographic, clinical and biological parameters among tertiles of renin and aldosterone levels were analyzed using χ^2 tests for categorical variables and Kruskal-Wallis test for continuous variables.

Linear regression analyses were performed to assess the associations of clinical variables with renin and aldosterone levels. Clinical variables were entered in the multivariable model with forward selection. Covariates considered to be of potential prognostic impact were: age, sex, body mass index (BMI), medical history (diabetes mellitus, atrial fibrillation, previous myocardial infarction, prior HF admission and chronic obstructive pulmonary disease), HF etiologies (ischemic, hypertensive, valvular heart disease, dilated cardiomyopathy and other), presence of signs and symptoms of congestion (orthopnea, III heart sound, leg edema and hepatomegaly), systolic blood pressure (SBP), heart rate, LVEF, laboratory findings [hemoglobin, sodium, potassium, blood urea nitrogen and estimated glomerular filtration rate (eGFR) by the Chronic Kidney Disease Epidemiology Collaboration formula ²⁰], and treatments (use of ACEi/ARB, beta-blockers and MRA). These variables had a small proportion of missing values (<10%), and no multiple imputation was performed.

To assess the changes in renin and aldosterone levels after the initiation of MRAs, repeated-measures ANCOVA models were fit in terms of treatment group in the EPHEsus and Porto studies

(eplerenone in the EPHESUS sub-study and spironolactone in PORTO study). Changes at each time point were adjusted for baseline values and compared between treatment groups.

The primary outcome was the composite of hospitalization for HF or all-cause mortality. Secondary outcomes were all-cause mortality and cardiovascular mortality. Survival probabilities were estimated using the Kaplan-Meier method. The covariates used for adjustment were chosen from demographic (age and sex), clinical (prior HF admission, use of beta-blockers and SBP), and laboratory (NT-proBNP, blood urea nitrogen, hemoglobin, high-density lipoprotein cholesterol, eGFR, and sodium) parameters as previously published ²¹. All parameters used to build the BIOSTAT-CHF risk models are depicted herein (<https://biostat-chf.shinyapps.io/calc/>). Interactions between renin and aldosterone on clinical outcomes were assessed using both continuous and categorical variables. Curvilinear associations between log transformed baseline renin, aldosterone levels and outcome were tested using Cox models with unadjusted and adjusted for the BIOSTAT-CHF risk models in a restricted cubic spline with 5 knots. The added value of baseline renin and aldosterone levels on the BIOSTAT-CHF risk model was assessed by means of the increased c-index.

All analyzes were performed using R version 3.4.0 (R Development Core Team, Vienna, Austria). A two-sided p-value <0.05 was considered statistically significant.

Results

Baseline Characteristics according to Renin and Aldosterone Levels

Among the 2,039 patients included in BIOSTAT-CHF study, 73% were male, mean age was 69±12 years and mean LVEF was 31±11% (**Table 1**). In the total cohort, median renin and aldosterone levels were 85.3 (IQR 28-247) µIU/mL and 9.4 (IQR 4.4-19.8) ng/dL, respectively. The correlation between renin and aldosterone was weak (Spearman Rho=0.28).

Patients with higher renin and aldosterone levels were younger, more often male, had more often a prior HF admission, lower SBP, lower LVEF, poorer renal function, were less likely to receive target doses of ACEi/ARB and were more often prescribed MRAs (**Table 1**).

Clinical Determinants of Renin and Aldosterone Levels

In the linear regression models, lower SBP, eGFR, sodium, prior HF admission, no use of beta-blocker and MRA use were the factors that were associated with both higher levels of both renin and aldosterone (**Table 2**). Higher renin levels alone were associated with higher BMI, previous myocardial infarction, chronic obstructive pulmonary disease and dilated cardiomyopathy. Higher aldosterone levels alone were associated with no use of ACEi/ARB. The clinical variables associated with the highest tertiles of renin and aldosterone are shown in **Supplementary table 1**. The associations of renin and aldosterone levels by the different doses of ACEi/ARBs or MRAs are depicted in **Supplementary table 2**. Renin and aldosterone levels were higher with the use of MRAs and lower with increasing doses of ACEi/ARBs.

Effects of Mineralocorticoid Receptor Antagonists on Renin and on Aldosterone Levels in EPHESUS and PORTO Cohort Studies

In the EPHESUS sub-study, eplerenone increased aldosterone levels, and patients receiving eplerenone had higher renin levels compared to placebo (**Supplementary figure 1**). Both changes persisted thereafter. In addition, we observed that both renin and aldosterone levels tended to increase after the initiation of spironolactone in PORTO study (**Supplementary figure 1**).

Survival Analysis

During a median follow up of 21 months, the primary outcome occurred more frequently in patients with higher renin levels (per each tertile increase; **Figure 1**). Similar results were found in patients without MRA prescription (**Supplementary figure 2**). Compared with the lowest tertile, the highest renin tertile was associated with an increased rate of the primary outcome [adjusted-HR (95%CI)=1.48 (1.25-1.76), $p<0.001$] (**Table 3**). Concordantly, highest renin levels were associated with increased rates of all-cause mortality and cardiovascular mortality (**Supplementary table 3**). The association of renin levels with the primary outcome after adjustment for the BIostat-CHF risk models using restricted cubic spline regression analysis is shown in **Figure 2**. A log-normalized renin above 6.55 (=700 μ IU/mL) was associated with a higher incidence of the primary outcome.

Higher aldosterone levels were not associated with the primary outcome [adjusted-HR (95% CI)=1.09 (0.92-1.28), $p=0.32$] (**Table 3**). Similar results were found for all-cause and cardiovascular mortality (**Supplementary figure 3**).

There was no interaction between renin and aldosterone on the primary outcome (p -Value >0.1). As a sensitivity analysis, the associations of renin and aldosterone levels with the primary outcome in ambulatory and hospitalized patients are shown in **Supplementary table 4**. Furthermore, survival analyses for the primary outcome across European regions are also presented in **Supplementary table 5**.

Renin and Aldosterone on Top of the BIOSTAT-CHF Risk Model

Renin and aldosterone levels did not improve risk stratification on top of the BIOSTAT-CHF risk model [for renin: increased c-index (95% CI)=0.28 (-0.33-0.87), $p=0.37$; for aldosterone; 0.03 (-0.05-0.102), $p=0.51$] (**Table 4**). The discriminative value of renin and aldosterone across baseline HF treatment strata is shown in **Supplementary table 6**. A consistent absence of discriminative value of renin and aldosterone was observed across treatment strata.

Aldosterone-to-Renin Ratio

The median aldosterone-to-renin ratio (ARR) was 0.11 (IQR 0.03-0.31) (ng/dL)/(μ IU/mL). Patients with lower ARR (driven by higher renin levels) were more often male, had more often cardiovascular comorbidities, lower SBP, LVEF, sodium concentrations, poorer renal function, and were more often prescribed ACEi/ARBs (**Supplementary table 7**). Compared with the highest tertile, the lowest ARR was associated with an increased rate of the primary outcome [adjusted-HR (95% CI)=1.31 (1.11-1.55), $p=0.002$] (**Supplementary table 8**), but did not improve risk stratification on top of the BIOSTAT-CHF risk model [increased c-index (95% CI)=0.15 (-0.25-0.55), $p=0.47$].

Discussion

In patients with symptomatic HF, we assessed the clinical determinants and prognostic implications of baseline renin and aldosterone levels. Our main findings are: 1) higher baseline renin and aldosterone levels were associated with HF severity, worse symptoms, poorer renal function and were influenced by treatment with ACEi/ARBs, beta-blockers and MRAs; 2) higher renin but not aldosterone was independently associated with poor prognosis; 3) renin and aldosterone levels did not improve risk stratification on top of the “best” BIOSTAT-CHF prognostic models, 4) initiation of MRAs was associated with increased levels of renin and aldosterone in the EPHESUS substudy and in an AHF cohort (PORTO).

Clinical Determinants of Renin-Angiotensin Aldosterone System Activation

In response to a decrease in baroreceptor stretch, a rise in renin levels ultimately result in sodium and water retention by triggering sequential activation of peptides in the RAAS cascade such as angiotensin II and aldosterone²²⁻²⁴. Angiotensin II and aldosterone may also play a crucial role in promoting kidney damage by regulating inflammation and reparative processes that follow the tissue fibrosis²⁵⁻²⁷. These mechanisms may explain our observations that high renin and aldosterone levels were associated with lower SBP, lower sodium levels and poorer renal function^{3-5, 8, 28}. In addition, previous studies have shown that renin was overexpressed in visceral and perivascular adipose tissue in an obese population which may explain the association between renin and BMI in the present study^{29, 30}. A prior HF admission and specific HF etiologies, *e.g.*, patients with an ischemic etiology or dilated cardiomyopathy (particularly the latter), may partly contribute to progression of ventricular remodeling³¹⁻³³, resulting in a higher degree of (excessive) RAAS activation^{1, 34}.

Circulating levels of renin and aldosterone are also influenced by HF treatment. Renin is upregulated in response to activation of the sympathetic nervous system³⁵, hence explaining the association between beta blocker treatment and lower renin and aldosterone levels³⁶. Moreover, the current analysis also showed the association of higher doses of ACEi/ARB with lower aldosterone, suggesting that despite the aldosterone “escape” phenomenon^{37, 38}, a chronic decrease of aldosterone levels in patients taking ACEi/ARB therapy may occur. On the other hand, increased renin and

aldosterone levels in patients treated with MRAs are consistent with previous reports^{4, 5, 39, 40}. This is likely related to an increase in angiotensin II via feedback mechanisms of the RAAS cascade or by direct regulation of aldosterone synthase by MRA treatment^{28, 41, 42}. Indeed, the present analysis showed continuous increases in renin and aldosterone after administration with MRAs.

Association of Renin and Aldosterone with Outcomes

Median baseline levels of renin (85.3 μ IU/mL) and aldosterone (9.4 ng/dL) in this cohort were lower than in other recent reports^{3, 5, 28, 43, 44}, potentially being influenced by the relative clinical stability and insufficient blockage of RAAS cascade in the current study. We show that renin (but not aldosterone) was associated with the primary outcome (all-cause mortality and/or HF admission). Studies examining the prognostic value of these biomarkers in the field of HF have yielded conflicting results. In a post-hoc analysis of EVEREST, aldosterone levels were assessed in 1,850 placebo-treated patients with AHF and a LVEF \leq 40%³. During a median follow-up of 9.9 months (during which 19.0% of patients died), the highest quartile of aldosterone was significantly associated with higher incidence of all-cause mortality. A post-hoc analysis of Diuretic Optimization Strategies in Acute Heart Failure (DOSE-AHF) and Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) assessed renin and aldosterone at baseline in 427 patients with AHF⁵. Within 60 days, 6% patients died and 30% were hospitalized. Renin and aldosterone were not associated with the composite outcome of death or HF re-hospitalization. A recent report of the Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT) assessed baseline renin in 1,306 patients in both the aliskiren and placebo arms⁴. Here, increasing renin levels were associated with poorer prognosis. In the Valsartan Heart Failure Trial (Val-HeFT)⁴⁵, baseline renin level was associated with a higher incidence of mortality, while aldosterone was not. This is in line with findings of several smaller observational studies^{6, 7, 46}. To the best of our knowledge, our study is first to assess the (lack of) prognostic value of renin and aldosterone on top of a well calibrated risk model. By demonstrating a lack of discriminatory prognostic improvement, our findings suggest a limited prognostic utility of renin and aldosterone.

Clinical Implications

In the present analysis, we demonstrated that renin and aldosterone levels were mainly associated with the patients' clinical severity (e.g. prior HF admission, lower SBP, sodium concentration, poorer renal function) and by the used therapies (e.g. ACEi/ARB and MRAs) in consistency with the existing literature. Importantly, these biomarkers do not improve risk prediction on top of an already well-performing clinical risk score. Furthermore, there was a consistent lack of discriminative value of renin and aldosterone levels across HF treatment regimens or different European regions.

Consequently, a “point” measurement of renin and aldosterone levels in patients with decompensated HF should be of clinically limited utility.

Limitations

Our study has several limitations. This is a post-hoc analysis of the BIOSTAT-CHF, hence the limitations inherent to observational data are present herein and causality cannot be inferred. By design, BIOSTAT-CHF enrolled patients not on optimal guideline medical therapy. Although this condition is frequent, results may not be generalizable to patients on optimal therapy. All renin and aldosterone samples were frozen and thawed with a same number of freeze/thaw cycles. It may be associated with increased level of renin^{47, 48}. However, renin level in this study was lower than that in previous reports^{18, 28, 43, 44}, the effect of freeze/thaw cycles therefore may be limited.

Conclusions

Renin and aldosterone activation were associated with both the patients' poor clinical condition (neurohormonal activation) and HF treatments (feedback mechanism). Renin and/or aldosterone did not improve risk-stratification. These findings suggest that the “point” measurement of these biomarkers in patients with HF is of limited utility, both for ascertaining the patients' clinical condition and prognosis (as they may reflect both the disease severity and the use of life-saving therapies).

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Table 1. Patients' Characteristics according to Renin and Aldosterone Levels (Tertiles) in BIOSTAT-CHF study

Values are Mean \pm SD, n (%) or median (25th to 75th percentile)

COPD, chronic obstructive pulmonary disease; HF, heart failure; NYHA, New York Heart Association; BP, blood pressure; LVEF, left ventricular ejection fraction; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide.

Table 2. Multivariable Model for the Associations of Clinical Profiles with Renin and Aldosterone Levels in BIOSTAT-CHF study

Renin and aldosterone levels were expressed by natural logarithm transformation.

*Other etiology was considered as the reference group among HF etiologies

CI, confidence interval; HF, heart failure; BP, blood pressure; eGFR, estimated glomerular filtration rate; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist.

Table 3. Cox Proportional Hazards Models of Renin and Aldosterone Levels for the Primary Outcome in BIOSTAT-CHF study

HR, hazard ratio; CI, confidence interval.

Renin and aldosterone levels as continuous variables were expressed by natural logarithm transformation.

Table 4. Discrimination of Renin and Aldosterone Levels for the Primary Outcome in BIOSTAT-CHF study

CI, confidence interval.

C-statistic was calculated to compare the discriminatory power to predict primary outcome of baseline renin and aldosterone levels on top of the BIOSTAT-CHF risk model. Renin and aldosterone levels as continuous variables are expressed by natural logarithm transformation

Table 1. Patients' Characteristics according to Renin and Aldosterone Levels (Tertiles) in BIOSTAT-CHF study

	Global (N=2039)	Renin levels			p-value	Aldosterone levels			p-value
		Low, 0-40 μIU/ml (N=684)	Intermediate, 41-170 μIU/ml (N=679)	High, >171 μIU/ml (N=675)		Low, 0-5 ng/dl (N=681)	Intermediate, 6-14 ng/dl (N=690)	High, >15 ng/dl (N=668)	
Age, yrs	68.5 ± 12.1	69.2 ± 12.2	68.7 ± 12.5	67.4 ± 11.5	0.005	69.7 ± 12.1	68.6 ± 11.9	67.0 ± 12.1	<0.001
Male, N (%)	1481 (72.6 %)	468 (68.4 %)	477 (70.3 %)	536 (79.3 %)	<0.001	481 (70.6 %)	492 (71.3 %)	508 (76.0 %)	0.052
Body mass index, kg/m²	27.8 ± 5.5	27.5 ± 5.5	27.6 ± 5.2	28.3 ± 5.6	0.07	27.5 ± 5.5	27.9 ± 5.5	28.0 ± 5.4	0.15
Medical history									
Hypertension, N (%)	1259 (61.7 %)	472 (69.0 %)	419 (61.7 %)	368 (54.4 %)	<0.001	426 (62.6 %)	458 (66.4 %)	375 (56.1 %)	<0.001
Diabetes mellitus, N (%)	656 (32.2 %)	207 (30.3 %)	216 (31.8 %)	233 (34.5 %)	0.24	230 (33.8 %)	224 (32.5 %)	202 (30.2 %)	0.37
Atrial fibrillation, N (%)	932 (45.7 %)	316 (46.2 %)	300 (44.2 %)	316 (46.7 %)	0.61	305 (44.8 %)	325 (47.1 %)	302 (45.2 %)	0.66
Myocardial infarction, N (%)	750 (36.8 %)	205 (30.0 %)	243 (35.8 %)	302 (44.7 %)	<0.001	260 (38.2 %)	242 (35.1 %)	248 (37.1 %)	0.48
COPD, N (%)	346 (17.0 %)	95 (13.9 %)	114 (16.8 %)	137 (20.3 %)	0.007	137 (20.1 %)	99 (14.3 %)	110 (16.5 %)	0.02
Prior HF hospitalization, N (%)	649 (31.8 %)	182 (26.6 %)	220 (32.4 %)	247 (36.5 %)	<0.001	177 (26.0 %)	235 (34.1 %)	237 (35.5 %)	<0.001
HF etiology					<0.001				0.004
Ischemic heart disease, N (%)	881 (44.1 %)	249 (37.1 %)	295 (44.5 %)	337 (50.9 %)		301 (45.5 %)	286 (42.1 %)	294 (44.8 %)	
Hypertensive heart disease, N (%)	204 (10.2 %)	111 (16.5 %)	60 (9.0 %)	33 (5.0 %)		76 (11.5 %)	74 (10.9 %)	54 (8.2 %)	
Valvular heart disease, N (%)	150 (7.5 %)	50 (7.5 %)	53 (8.0 %)	47 (7.1 %)		50 (7.6 %)	50 (7.4 %)	50 (7.6 %)	
Dilated cardiomyopathy, N (%)	458 (22.9 %)	148 (22.1 %)	143 (21.6 %)	167 (25.2 %)		116 (17.5 %)	171 (25.2 %)	171 (26.1 %)	
Other, N (%)	303 (15.2 %)	113 (16.8 %)	112 (16.9 %)	78 (11.8 %)		118 (17.9 %)	98 (14.4 %)	87 (13.3 %)	
Clinical profile									
NYHA III+IV, N (%)	1234 (62.3 %)	397 (59.7 %)	387 (58.7 %)	450 (68.4 %)	<0.001	450 (68.4 %)	403 (60.4 %)	381 (58.0 %)	<0.001
Orthopnea, N (%)	715 (35.1 %)	233 (34.1 %)	221 (32.6 %)	261 (38.8 %)	0.045	250 (36.8 %)	242 (35.1 %)	223 (33.4 %)	0.43
Leg edema, N (%)	1711 (84.0 %)	573 (83.8 %)	573 (84.4 %)	565 (83.7 %)	0.93	576 (84.7 %)	585 (84.8 %)	550 (82.3 %)	0.38
Systolic BP, mmHg	124.6 ± 21.8	133.2 ± 22.2	123.9 ± 19.6	116.6 ± 20.2	<0.001	127.4 ± 22.6	126.5 ± 21.9	119.8 ± 19.9	<0.001
Heart rate, bpm	80.1 ± 19.7	82.1 ± 21.6	79.1 ± 19.0	78.9 ± 18.2	0.03	81.5 ± 21.7	79.8 ± 19.1	78.9 ± 18.0	0.44
LVEF, %	31.1 ± 10.8	32.7 ± 10.6	31.4 ± 11.5	29.0 ± 9.8	<0.001	32.8 ± 11.4	30.6 ± 10.3	29.8 ± 10.4	<0.001
LVEF <40%, N (%)	1623 (88.7 %)	539 (85.6 %)	535 (88.1 %)	549 (92.7 %)	<0.001	509 (84.6 %)	569 (90.3 %)	545 (91.3 %)	<0.001
Medication									
ACEi/ARB, N (%)	1467 (71.9 %)	497 (72.7 %)	476 (70.1 %)	494 (73.1 %)	0.42	514 (75.5 %)	518 (75.1 %)	435 (65.1 %)	<0.001
ACEi/ARB target dose, N (%)	259 (12.7 %)	110 (16.1 %)	80 (11.8 %)	69 (10.2 %)	0.003	96 (14.1 %)	99 (14.3 %)	64 (9.6 %)	0.02
Beta-blocker, N (%)	1694 (83.1 %)	572 (83.6 %)	568 (83.7 %)	554 (82.0 %)	0.63	566 (83.1 %)	584 (84.6 %)	544 (81.4 %)	0.29
Beta-blocker target dose, N (%)	117 (5.7 %)	44 (6.4 %)	39 (5.7 %)	34 (5.0 %)	0.54	39 (5.7 %)	48 (7.0 %)	30 (4.5 %)	0.15
MRA, N (%)	1076 (52.8 %)	320 (46.8 %)	340 (50.1 %)	416 (61.5 %)	<0.001	334 (49.0 %)	330 (47.8 %)	412 (61.7 %)	<0.001
Loop diuretics dose, mg	40.0 (20.0 – 80.0)	40.0 (20.0 – 80.0)	40.0 (20.0 – 80.0)	40.0 (20.0 – 100.0)	0.03	40.0 (20.0 – 80.0)	40.0 (20.0 – 75.0)	40.0 (25.0 – 100.0)	0.02
Laboratory									

Hemoglobin, g/dl	13.2 ± 1.9	13.3 ± 1.8	13.2 ± 2.0	13.1 ± 1.9	0.09	12.7 ± 2.0	13.4 ± 1.8	13.4 ± 1.9	<0.001
Blood urea nitrogen, mg/dl	41.4 ± 33.1	34.7 ± 30.7	39.7 ± 29.9	50.1 ± 36.4	<0.001	40.7 ± 32.2	41.4 ± 35.6	42.1 ± 31.1	0.13
eGFR, ml/min/1.73m²	62.0 ± 24.3	66.2 ± 24.1	61.7 ± 25.9	58.1 ± 22.0	<0.001	63.3 ± 24.8	62.4 ± 23.2	60.3 ± 24.9	0.03
Sodium, mmol/l	139.2 ± 4.0	140.5 ± 3.6	139.6 ± 3.6	137.5 ± 4.2	<0.001	139.4 ± 3.9	139.7 ± 3.9	138.5 ± 4.2	<0.001
Potassium, mmol/l	4.3 ± 0.6	4.2 ± 0.5	4.3 ± 0.6	4.3 ± 0.6	0.19	4.2 ± 0.6	4.3 ± 0.6	4.3 ± 0.6	0.003
BNP, pg/ml	773 (424 - 1353)	786 (457 - 1186)	687 (320 - 1353)	793 (451 - 1485)	0.89	1009 (598 - 1457)	590 (283 - 923)	892 (338 - 1678)	<0.001
Renin, µIU/ml	83.9 (27.4 – 246.1)	17.6 (10.4 – 27.8)	84.6 (60.8 – 117.2)	386.3 (246.6 – 1535.4)	<0.001	54.9 (19.7 – 163.6)	71.7 (24.8 – 203.9)	154.3 (55.7 – 415.5)	<0.001
Aldosterone, ng/dl	9.3 (4.3 – 19.3)	6.6 (3.4 – 12.7)	9.4 (4.4 – 18.0)	13.8 (5.8 – 29.9)	<0.001	3.0 (1.8 – 4.3)	9.4 (7.3 – 11.9)	27.2 (19.6 – 44.2)	<0.001

Table 2. Multivariable Model for the Associations of Clinical Profiles with Renin and Aldosterone Levels in BIoSTAT-CHF study

Variable	Renin			Aldosterone		
	β	95%CI	R ² = 0.26 p-Value	β	95%CI	R ² = 0.10 p-Value
(Constant)	21.69	19.28 - 24.09	<0.001	5.79	3.54 - 8.04	<0.001
Age, yrs (per 5yrs)				-0.04	-0.07 - -0.01	0.004
Male	0.21	0.05 - 0.36	0.010			
Body mass index, kg/m ² (per 5kg/m ²)	0.14	0.07 - 0.20	<0.001			
Medical history						
Myocardial infarction	0.33	0.14 - 0.53	0.001			
Diabetes				-0.14	-0.27 - -0.03	0.018
Prior HF hospitalization	0.21	0.07 - 0.36	0.005	0.26	0.13 - 0.39	<0.001
Chronic obstructive pulmonary disease	0.28	0.10 - 0.46	0.003			
HF etiologies*						
Other		(reference)				
Ischemic heart disease	0.24	-0.003 - 0.48	0.053			
Hypertensive heart disease	-0.13	-0.41 - 0.15	0.37			
Valvular heart disease	0.27	-0.03 - 0.57	0.08			
Dilated cardiomyopathy	0.31	0.08 - 0.54	0.007			
Physical examination						
III heart sound				0.24	0.03 - 0.44	0.025
Systolic BP, mmHg (per 10mmHg)	-0.20	-0.23 - -0.16	<0.001	-0.06	-0.09 - -0.04	<0.001
Laboratory						
Hemoglobin, g/dl				0.14	0.10 - 0.17	<0.001
eGFR, ml/min/1.73m ² (per 5 ml/min/1.73m ²)	-0.04	-0.06 - -0.03	<0.001	-0.03	-0.05 - -0.02	<0.001
Sodium, mmol/l	-0.11	-0.13 - -0.09	<0.001	-0.03	-0.04 - -0.01	0.001
Medication						
ACEi/ARB				-0.27	-0.41 - -0.13	<0.001
Beta-blocker	-0.33	-0.51 - -0.14	<0.001	-0.21	-0.37 - -0.04	0.014
MRA	0.33	0.19 - 0.53	0.001	0.23	0.11 - 0.36	<0.001

Table 3. Cox Proportional Hazards Models of Renin and Aldosterone Levels for the Primary Outcome in BIOSTAT-CHF study

			Univariable model		Multivariable model	
			HR (95 % CI)	p-Value	HR (95 % CI)	p-Value
Renin	Continuous		1.20 (1.16 - 1.25)	<0.001	1.11 (1.06 - 1.15)	<0.001
	Tertiles	Low	(reference)		(reference)	
		Intermediate	1.34 (1.12 - 1.61)	0.001	1.17 (0.98 - 1.41)	0.08
		High	2.01 (1.70 - 2.38)	<0.001	1.48 (1.25 - 1.76)	<0.001
Aldosterone	Continuous		1.01 (0.96 - 1.07)	0.58	1.02 (0.97 - 1.07)	0.53
	Tertiles	Low	(reference)		(reference)	
		Intermediate	0.96 (0.82 - 1.13)	0.65	1.10 (0.93 - 1.29)	0.28
		High	1.05 (0.89 - 1.24)	0.55	1.09 (0.92 - 1.28)	0.32
Interaction between renin and aldosterone		Continuous		0.06		0.14
		Categorical		0.08		0.13

Table 4. Discrimination of Renin and Aldosterone Levels for the Primary Outcome in BIOSTAT-CHF study

		c-index (95% CI)	p-Value	Increased c-index	p-Value
Renin model	BIOSTAT-CHF risk model	76.5 (74.5 to 78.6)	<0.001		
	+ Renin	76.8 (74.7 to 78.8)	<0.001	0.27 (-0.33 to 0.87)	0.37
Aldosterone model	BIOSTAT-CHF risk model	76.5 (74.5 to 78.6)	<0.001		
	+ Aldosterone	76.5 (74.5 to 78.6)	<0.001	0.03 (-0.05 to 0.102)	0.51

Figure 1. Survival Curves for the Primary Outcome according to Renin and Aldosterone Levels in BIOSTAT-CHF study

Renin level: Lower tertile, 0-40 $\mu\text{IU/ml}$; Intermediate tertile, 41-170 $\mu\text{IU/ml}$; Higher tertile, $>171 \mu\text{IU/ml}$.

Aldosterone level: Lower tertile, 0-5 ng/dl ; Intermediate tertile, 6-14 ng/dl ; Higher tertile, $>15 \text{ ng/dl}$

Figure 2. Restricted Cubic Spline Regression for the Associations of Renin or Aldosterone with the Primary Outcome in BIOSTAT-CHF study

(A)Renin; (B) aldosterone. Solid line - hazard ratio; dashed line - 95% confidence interval. Knots were placed at the 5th, 27.5th, 50th, 72.5th and 95th percentiles. The models were adjusted for the BIOSTAT-CHF risk model. Renin and aldosterone levels are expressed by natural logarithm transformation.

Figure 1. Survival Curves for the Primary Outcome according to Renin and Aldosterone Levels in BIOSTAT-CHF study

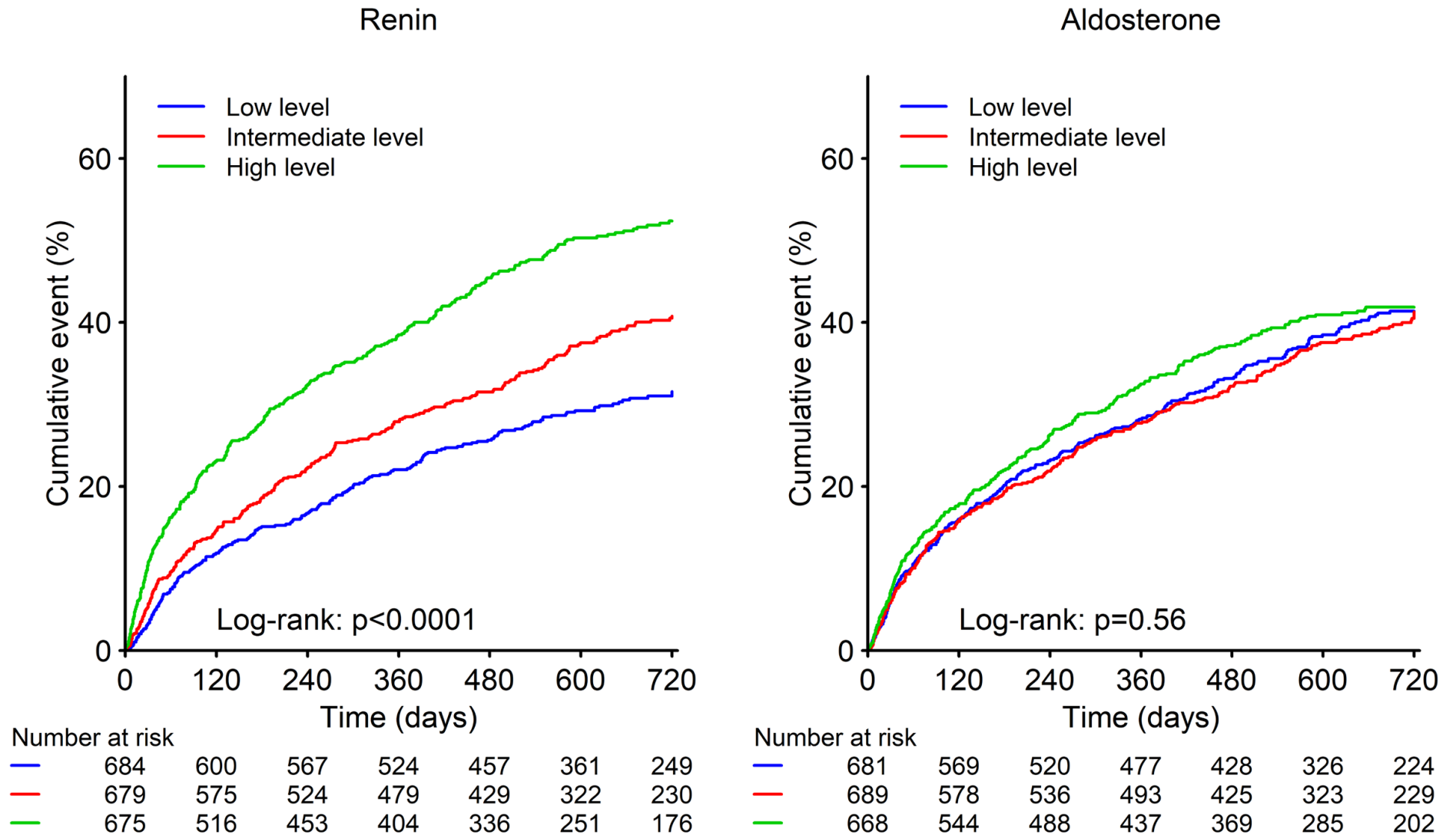
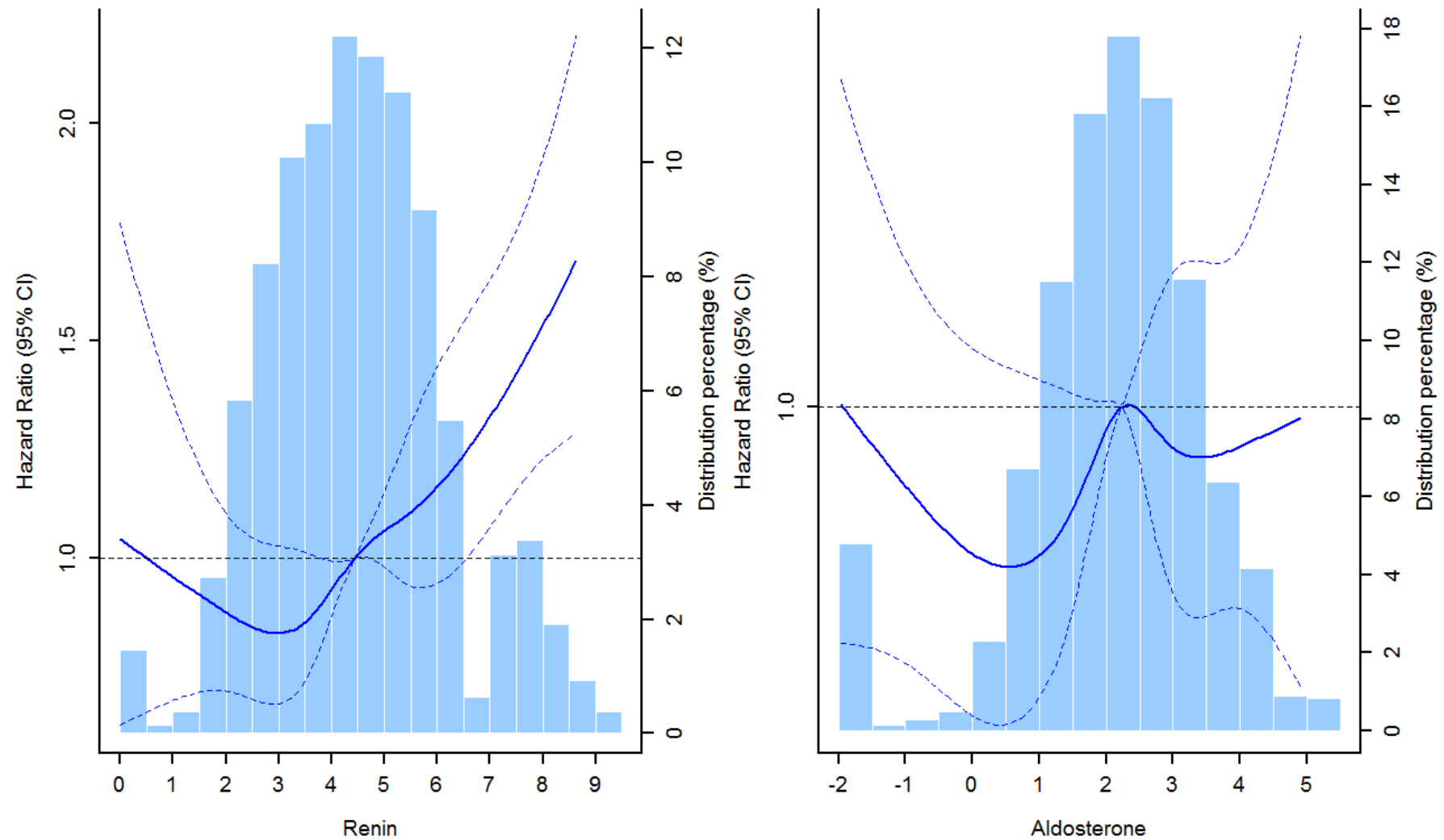


Figure 2. Restricted Cubic Spline Regression for the Associations of Renin or Aldosterone with the Primary Outcome in BIOSTAT-CHF study



Supplementary table 1. Multivariable Model for the Associations of Clinical Profiles with the Highest Tertile of Renin and Aldosterone Levels in BIOSTAT-CHF study

Depending variables were defined as highest levels of renin tertile ($>171\mu\text{IU/ml}$) and aldosterone tertile ($>15\text{ng/dl}$), respectively.

*Other etiology was considered as the reference group among HF etiologies.

OR, odd ratio; CI, confidence interval; BP, blood pressure; eGFR, estimated glomerular filtration rate; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist.

Supplementary table 2. Associations of ACEi/ARB and MRA with Renin and Aldosterone Levels at Baseline in BIOSTAT-CHF study

Values are median (IQR)

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist.

Supplementary table 3. Cox Hazard Models of Renin and Aldosterone Levels for the Clinical Outcomes in BIOSTAT-CHF study

HR, hazard ratio; CI, confidence interval.

Renin and aldosterone levels as continuous variables are expressed by natural logarithm transformation.

Supplementary table 4. Cox Hazard Models of Renin and Aldosterone Levels for the Primary Outcome in Ambulant and Hospitalized Patients in BIOSTAT-CHF study

Supplementary table 5. Survival Analyses for the Primary Outcome according to Different European Regions in the BIOSTAT-CHF Study

Cox model after adjustment for BIOSTAT-CHF risk model.

Increased c-index showed the improvement of risk-stratification on top of the BIOSTAT-CHF risk model.

Supplementary table 6. Discrimination of Renin and Aldosterone Levels for the Primary Outcome in BIOSTAT-CHF study across Heart Failure Treatment Regimens

Supplementary table 7. Patients' Characteristics according to Aldosterone-to-Renin Ratio (Tertiles)

Values are Mean \pm SD, n (%) or median (25th to 75th percentile)

BMI, body mass index; PAD, peripheral artery disease; COPD, chronic obstructive pulmonary disease; HF, heart failure; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide.

Supplementary table 8. Cox Hazard Models of Aldosterone-to-Renin Ratio for the Clinical Outcomes

HR, hazard ratio; CI, confidence interval.

Ratio of aldosterone to renin as continuous variables was expressed by natural logarithm transformation

Supplementary figure 1. Changes in Renin and Aldosterone by Mineralocorticoid Receptor Antagonist (Eplerenone and Spironolactone) in EPHESUS and PORTO Studies

A, Renin (μ IU/ml) kinetics between treatment groups in the EPHESUS sub-study. B, Aldosterone (ng/dl) kinetics between treatment groups in the EPHESUS sub-study. C, Renin (μ IU/ml) and aldosterone (ng/dl) kinetics between treatment groups in PORTO study.

* Spironolactone was administered after the blood sample was collected (day 1) in PORTO study.

M, month; D, day.

Supplementary figure 2. Survival Curves for the Primary Outcome according to Renin and Aldosterone Levels in Patients without MRAs Prescription in BIOSTAT-CHF study

Renin level: Lower tertile, 0-33 μ IU/ml; Intermediate tertile, 34-130 μ IU/ml; Higher tertile, >131 μ IU/ml; Aldosterone level: Lower tertile, 0-5 ng/dl; Intermediate tertile, 6-12 ng/dl; Higher tertile, >13 ng/dl.

Supplementary figure 3. Associations of Renin and Aldosterone with Composite Outcome, All-Cause Mortality and Cardiovascular Mortality in BIOSTAT-CHF study

Renin and aldosterone levels were expressed by natural logarithm transformation

Supplementary table 1. Multivariable Model for the Associations of Clinical Profiles with the Highest Tertile of Renin and Aldosterone Levels in BIOSTAT-CHF study

	Renin (highest tertile)			Aldosterone (highest tertile)		
	OR	95%CI	p-Value	OR	95%CI	p-Value
Age <70 yrs				0.66	0.49 – 0.88	0.005
Male	1.51	1.13 – 2.02	0.006			
HF etiologies*						
Other		(reference)				
Ischemic heart disease	1.61	1.03 – 2.53	0.04			
Hypertensive heart disease	0.69	0.38 – 1.22	0.21			
Valvular heart disease	1.44	0.82 – 2.52	0.21			
Dilated cardiomyopathy	2.03	1.34 – 3.12	0.001			
Systolic BP <100 mmHg	3.03	1.90 – 4.88	<0.001	1.77	1.04 – 3.001	0.034
Sodium <135 mEq/l	3.68	2.51 – 5.45	<0.001	1.53	1.001 – 2.33	0.048
eGFR <45ml/min/m²	1.60	1.20 – 2.12	0.001			
ACEi/ARB				0.63	0.46 – 0.85	0.002
Beta-blocker				0.67	0.47 – 0.97	0.035
MRA	1.59	1.24 – 2.04	<0.001	1.62	1.22 – 2.14	0.001

Supplementary table 2. Associations of ACEi/ARB and MRA with Renin and Aldosterone Levels at Baseline in BIOSTAT-CHF study

	ACEi/ARB <50% of recommended dose		ACEi/ARB ≥50% of recommended dose		p
	No MRA	MRA prescription	No MRA	MRA prescription	
Renin, µIU/ml	69.75 (23.17 - 180.88)	122.13 (39.87 - 326.84)	70.56 (22.63 - 198.68)	79.29 (24.48 - 316.07)	<0.001
Aldosterone, ng/dl	8.40 (4.07 - 17.83)	12.15 (4.70 - 26.10)	6.90 (3.55 - 12.75)	9.45 (4.50 - 17.50)	<0.001

Supplementary table 3. Cox Hazard Models of Renin and Aldosterone Levels for the Clinical Outcomes in BIOSTAT-CHF study

All-Cause mortality			Univariable model		Multivariable model	
			HR (95%CI)	p-Value	HR (95%CI)	p-Value
Renin	Continuous		1.21 (1.15 - 1.27)	<0.001	1.11 (1.05 - 1.17)	<0.001
	Tertiles	Low	(reference)		(reference)	
		Intermediate	1.22 (0.97 - 1.53)	0.09	0.99 (0.79 - 1.25)	0.95
		High	1.91 (1.55 - 2.36)	<0.001	1.32 (1.07 - 1.64)	0.01
Aldosterone	Continuous		0.98 (0.92 - 1.05)	0.61	1.01 (0.95 - 1.07)	0.88
	Tertiles	Low	(reference)		(reference)	
		Intermediate	0.94 (0.76 - 1.15)	0.55	1.11 (0.90 - 1.36)	0.34
		High	1.01 (0.82 - 1.24)	0.94	1.09 (0.88 - 1.34)	0.43
Interaction between renin and aldosterone		Continuous		0.07		0.15
		Categorical		0.18		0.56
Cardiovascular mortality			Univariable model		Multivariable model	
			HR (95 %CI)	p-Value	HR (95 %CI)	p-Value
Renin	Continuous		1.26 (1.18 - 1.33)	<0.001	1.16 (1.09 - 1.23)	<0.001
	Tertiles	Low	(reference)		(reference)	
		Intermediate	1.28 (0.96 - 1.71)	0.09	1.05 (0.78 - 1.40)	0.76
		High	2.29 (1.76 - 2.97)	<0.001	1.58 (1.21 - 2.07)	<0.001
Aldosterone	Continuous		1.06 (0.98 - 1.14)	0.18	1.07 (0.99 - 1.16)	0.07
	Tertiles	Low	(reference)		(reference)	
		Intermediate	0.97 (0.75 - 1.26)	0.84	1.15 (0.89 - 1.49)	0.29
		High	1.14 (0.89 - 1.47)	0.30	1.23 (0.96 - 1.59)	0.10
Interaction between renin and aldosterone		Continuous		0.35		0.32
		Categorical		0.44		0.43

Supplementary table 4. Cox Hazard Models of Renin and Aldosterone Levels for the Primary Outcome in Ambulant and Hospitalized Patients in BIOSTAT-CHF study

		Ambulant Patients				Hospitalized Patients				P-value for Interaction with ambulatory/ hospitalization
		N	Event (%)	HR (95%CI)	P-value	N	Event (%)	HR (95%CI)	P-value	
Renin	Continuous	600	189	1.12 (1.02 - 1.22)	0.02	1439	658	1.11 (1.06 - 1.16)	<0.001	0.62
	Low	213	46	(reference)		471	170	(reference)		
	Tertiles Intermediate	208	67	1.31 (0.89 - 1.91)	0.17	471	207	1.14 (0.93 - 1.39)	0.22	0.77
	High	179	76	1.60 (1.10 - 2.33)	0.01	497	281	1.50 (1.23 - 1.82)	<0.001	
Aldosterone	Continuous	600	189	1.11 (0.98 - 1.26)	0.09	1439	658	1.01 (0.96 - 1.07)	0.70	0.90
	Low	153	46	(reference)		528	241	(reference)		
	Tertiles Intermediate	226	79	1.68 (1.16 - 2.44)	0.01	464	201	1.00 (0.83 - 1.21)	0.97	0.55
	High	221	64	1.26 (0.86 - 1.85)	0.23	447	216	1.12 (0.94 - 1.35)	0.21	

Supplementary table 5. Survival Analyses for the Primary Outcome according to Different European Regions in the BIOSTAT-CHF Study

		Renin				Aldosterone					
		Median [IQR], μIU/mL	adjusted HR (95%CI)	p	Increased c-index	p	Median [IQR], ng/dl	adjusted HR (95%CI)	p	Increased c-index	p
North European area (N=689)											
Continuous Tertiles		78.5 [24.6 - 219.8]									
	Low		1.10 (1.03 - 1.18) (reference)	0.006	0.34 (-0.54 - 1.21) 0.46 (-0.48 - 1.41)	0.45 0.34	7.8 [3.5 - 16.9]	0.99 (0.92 - 1.08) (reference)	0.92	-0.02 (-0.06 - 0.02) -0.02 (-0.08 - 0.05)	0.36 0.66
	Intermediate		1.20 (0.89 - 1.61)	0.23			1.01 (0.77 - 1.33)	0.94			
	High		1.51 (1.13 - 2.02)	0.006			0.97 (0.74 - 1.28)	0.84			
Centre European area (N=665)											
Continuous Tertiles		64.6 [22.1 - 190.1]									
	Low		1.12 (1.04 - 1.21) (reference)	0.002	0.36 (-0.82 - 1.54) 0.31 (-0.60 - 1.23)	0.55 0.50	9.2 [4.6 - 18.1]	1.01 (0.92 - 1.10) (reference)	0.87	0.02 (-0.06 - 0.10) 0.02 (-0.10 - 0.15)	0.67 0.69
	Intermediate		1.11 (0.81 - 1.51)	0.51			1.12 (0.84 - 1.50)	0.44			
	High		1.43 (1.06 - 1.93)	0.02			1.04 (0.76 - 1.40)	0.82			
South European area (N=684)											
Continuous Tertiles		121.5 [38.5 - 341.7]									
	Low		1.12 (1.04 - 1.12) (reference)	0.002	0.53 (-0.75 - 1.81) 0.59 (-0.64 - 1.82)	0.42 0.35	11.2 [5.0 - 22.9]	1.07 (0.98 - 1.18) (reference)	0.12	0.07 (-0.59 - 0.73) 0.07 (-0.83 - 0.97)	0.84 0.88
	Intermediate		1.21 (0.87 - 1.69)	0.25			1.28 (0.94 - 1.74)	0.12			
	High		1.55 (1.14 - 2.11)	0.006			1.39 (1.03 - 1.87)	0.03			
P-value for interaction with region of site allocations											
Continuous				0.91					0.31		
Tertiles				0.84					0.13		

Supplementary table 6. Discrimination of Renin and Aldosterone Levels for the Primary Outcome in BIOSTAT-CHF study across Heart Failure Treatment Strata

	N	Event (%)	Baseline risk model		c-index	p-value	Increased c-index	p-value
Overall	2,039	847	BIOSTAT-CHF model		76.5 (74.5 to 78.6)	<0.001		
				+Renin	76.8 (74.7 to 78.8)	<0.001	0.27 (-0.33 to 0.87)	0.37
				+Aldosterone	76.5 (74.5 to 78.6)	<0.001	0.03 (-0.05 to 0.10)	0.51
ACEi/ARB use								
Yes	1,467	560	BIOSTAT-CHF model		76.1 (73.6 to 78.6)	<0.001		
				+Renin	76.5 (74.0 to 79.0)	<0.001	0.38 (-0.35 to 1.11)	0.31
				+Aldosterone	76.1 (73.6 to 78.6)	<0.001	0.01 (-0.09 to 0.10)	0.88
No	572	287	BIOSTAT-CHF model		75.5 (71.5 to 79.4)	<0.001		
				+Renin	75.7 (71.8 to 89.6)	<0.001	0.22 (-0.98 to 1.42)	0.71
				+Aldosterone	75.5 (71.6 to 79.5)	<0.001	0.07 (-0.07 to 0.22)	0.32
MRA use								
Yes	1,076	430	BIOSTAT-CHF model		77.5 (74.7 to 80.3)	<0.001		
				+Renin	77.9 (75.1 to 80.6)	<0.001	0.41 (-0.46 to 1.27)	0.36
				+Aldosterone	77.7 (74.9 to 80.4)	<0.001	0.17 (-0.09 to 0.43)	0.20
No	963	417	BIOSTAT-CHF model		75.4 (72.3 to 78.4)	<0.001		
				+Renin	75.6 (72.5 to 78.6)	<0.001	0.21 (-0.66 to 1.08)	0.64
				+Aldosterone	75.4 (72.3 to 78.5)	<0.001	0.03 (-0.06 to 0.12)	0.56

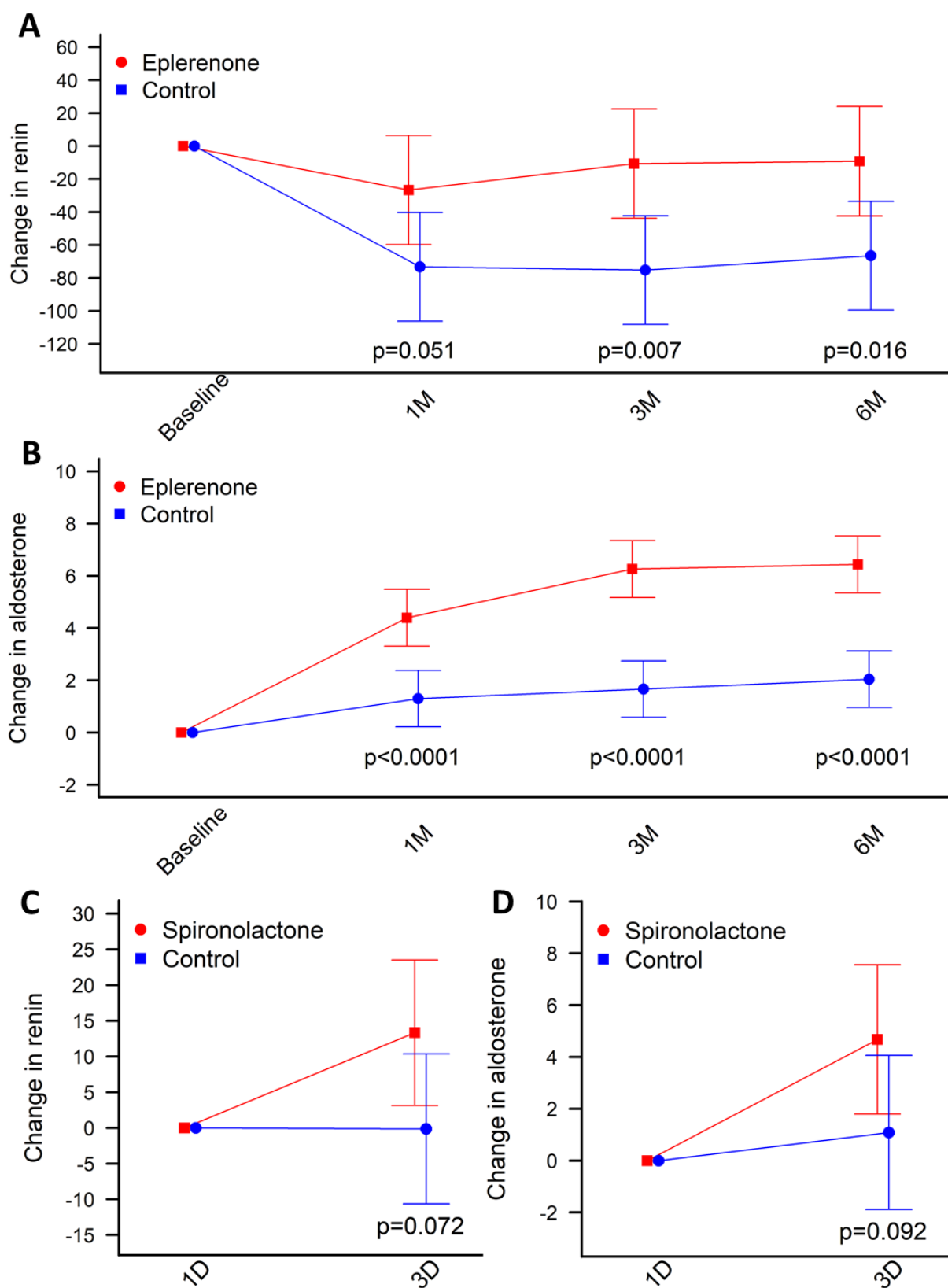
Supplementary table 7. Patients' Characteristics according to Aldosterone-to-Renin Ratio (Tertiles)

	Global (N=2039)	Aldosterone-to-renin ratio [(ng/dl)/(μIU/ml)]			p-value
		Low, 0-0.05 (N=675)	Intermediate, 0.05-0.21 (N=677)	High, >0.21 (N=687)	
Age, yrs	68.5 ± 12.1	68.7 ± 11.9	68.2 ± 12.3	68.5 ± 12.1	0.87
Male, N (%)	1481 (72.6 %)	516 (76.4 %)	481 (71.0 %)	484 (70.5 %)	0.02
BMI, kg/m ²	27.8 ± 5.5	27.9 ± 5.6	27.9 ± 5.4	27.6 ± 5.3	0.76
Medical history					
Hypertension, N (%)	1259 (61.7 %)	402 (59.6 %)	393 (58.1 %)	464 (67.5 %)	<0.001
Diabetes mellitus, N (%)	656 (32.2 %)	248 (36.7 %)	217 (32.1 %)	191 (27.8 %)	0.002
Atrial fibrillation, N (%)	932 (45.7 %)	308 (45.6 %)	307 (45.3 %)	317 (46.1 %)	0.96
Myocardial infarction, N (%)	750 (36.8 %)	298 (44.1 %)	234 (34.6 %)	218 (31.7 %)	<0.001
PAD, N (%)	239 (11.7 %)	103 (15.3 %)	70 (10.3 %)	66 (9.6 %)	0.002
COPD, N (%)	346 (17.0 %)	137 (20.3 %)	118 (17.4 %)	91 (13.2 %)	0.002
Prior HF hospitalization, N (%)	649 (31.8 %)	221 (32.7 %)	233 (34.4 %)	195 (28.4 %)	0.047
Clinical profile					
NYHA III+IV, N (%)	1234 (62.3 %)	466 (71.6 %)	395 (59.8 %)	373 (55.6 %)	<0.001
Orthopnea, N (%)	715 (35.1 %)	259 (38.5 %)	227 (33.6 %)	229 (33.3 %)	0.08
Rales > 1/3 up lung fields, N (%)	207 (19.6 %)	90 (21.8 %)	59 (17.6 %)	58 (18.8 %)	0.31
Leg edema, N (%)	1711 (84.0 %)	566 (84.0 %)	570 (84.2 %)	575 (83.7 %)	0.97
Systolic blood pressure, mmHg	124.6 ± 21.8	119.6 ± 21.3	123.7 ± 20.7	130.4 ± 21.9	<0.001
Heart rate, bpm	80.1 ± 19.7	79.7 ± 19.5	80.0 ± 20.2	80.5 ± 19.4	0.50
Echocardiogram					
LVEF, %	31.1 ± 10.8	29.8 ± 10.2	31.1 ± 10.8	32.2 ± 11.1	<0.001
MR ≥ moderate, N (%)	924 (47.9 %)	289 (46.0 %)	297 (46.3 %)	338 (51.1 %)	0.12
Medications					
ACEi/ARB, N (%)	1467 (71.9 %)	516 (76.4 %)	483 (71.3 %)	468 (68.1 %)	0.003
ACEi/ARB target dose, N (%)	259 (12.7 %)	88 (13.0 %)	71 (10.5 %)	100 (14.6 %)	0.08
Beta-blocker, N (%)	1694 (83.1 %)	556 (82.4 %)	575 (84.9 %)	563 (82.0 %)	0.28
Beta-blocker target dose, N (%)	117 (5.7 %)	40 (5.9 %)	39 (5.8 %)	38 (5.5 %)	0.95
MRA, N (%)	1076 (52.8 %)	367 (54.4 %)	363 (53.6 %)	346 (50.4 %)	0.29
Loop diuretics dose, mg	40.0 (20.0 – 80.0)	40.0 (20.0 – 80.0)	40.0 (22.5 – 80.0)	40.0 (20.0 – 80.0)	0.97
Digoxin, N (%)	380 (18.6 %)	135 (20.0 %)	110 (16.2 %)	135 (19.7 %)	0.15
Laboratory					
Hemoglobin, g/dl	13.2 ± 1.9	12.8 ± 2.0	13.3 ± 1.9	13.5 ± 1.8	<0.001
Blood urea nitrogen, mg/dl	41.4 ± 33.1	48.7 ± 34.9	40.5 ± 33.3	35.4 ± 29.6	<0.001
eGFR, mL/min/1.73m ²	62.0 ± 24.3	59.1 ± 23.0	63.2 ± 24.4	63.7 ± 25.2	<0.001
Sodium, mmol/l	139.2 ± 4.0	138.0 ± 4.4	139.3 ± 3.7	140.3 ± 3.6	<0.001
Potassium, mmol/l	4.3 ± 0.6	4.3 ± 0.6	4.3 ± 0.6	4.3 ± 0.6	0.97
BNP, pg/ml	773 (424 - 1353)	876 (512 - 1457)	582 (250 - 1043)	910 (457 - 1879)	0.01
Renin, μIU/ml	83.9 (27.4 - 246.1)	310.9 (132.1 - 1519.2)	92.7 (43.4 - 184.6)	23.0 (11.0 - 52.9)	<0.001
Aldosterone, ng/dl	9.3 (4.3 - 19.3)	5.0 (2.1 - 11.6)	9.5 (5.0 - 18.4)	14.0 (7.5 - 28.2)	<0.001

Supplementary table 8. Cox Hazard Models of Aldosterone-to-Renin Ratio for the Clinical Outcomes

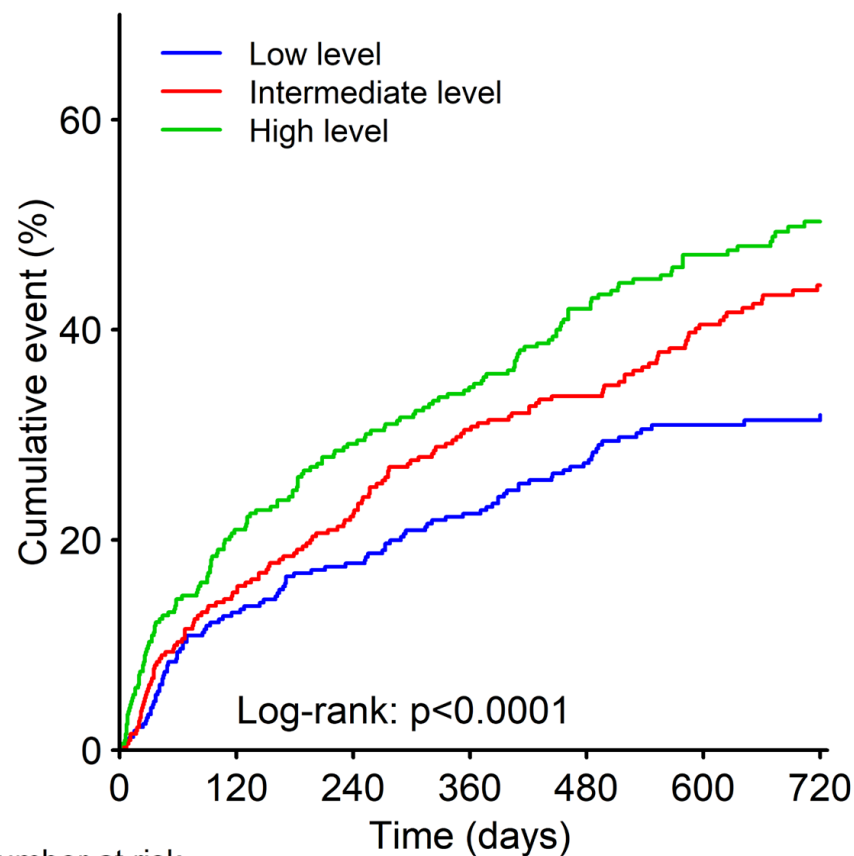
All-Cause mortality or HF re-hospitalization			Univariable model		Multivariable model	
			HR (95 % CI)	p-Value	HR (95 % CI)	p-Value
Aldosterone-to-renin ratio	Continuous		0.88 (0.85 - 0.91)	<0.001	0.93 (0.90 - 0.97)	<0.001
	Tertiles	Low	1.81 (1.54 - 2.14)	<0.001	1.31 (1.11 - 1.55)	0.002
		Intermediate	1.23 (1.03 - 1.47)	0.02	1.08 (0.90 - 1.29)	0.42
		High	(reference)		(reference)	
All-Cause mortality			Univariable model		Multivariable model	
			HR (95 % CI)	p-Value	HR (95 % CI)	p-Value
Aldosterone-to-renin ratio	Continuous		0.86 (0.82 - 0.90)	<0.001	0.93 (0.89 - 0.97)	0.001
	Tertiles	Low	1.83 (1.49 - 2.25)	<0.001	1.25 (1.02 - 1.55)	0.04
		Intermediate	1.11 (0.89 - 1.39)	0.36	0.97 (0.77 - 1.21)	0.78
		High	(reference)		(reference)	
Cardiovascular mortality			Univariable model		Multivariable model	
			HR (95 % CI)	p-Value	HR (95 % CI)	p-Value
ldosterone-to-renin ratio	Continuous		0.86 (0.82 - 0.91)	<0.001	0.93 (0.88 - 0.98)	0.01
	Tertiles	Low	1.86 (1.44 - 2.41)	<0.001	1.27 (0.98 - 1.65)	0.07
		Intermediate	1.18 (0.89 - 1.55)	0.25	1.02 (0.77 - 1.35)	0.88
		High	(reference)		(reference)	

Supplementary figure 1. Changes in Renin and Aldosterone by Mineralocorticoid Receptor Antagonist (Eplerenone and Spironolactone) in EPHESUS (A, B) and PORTO (C, D) Studies



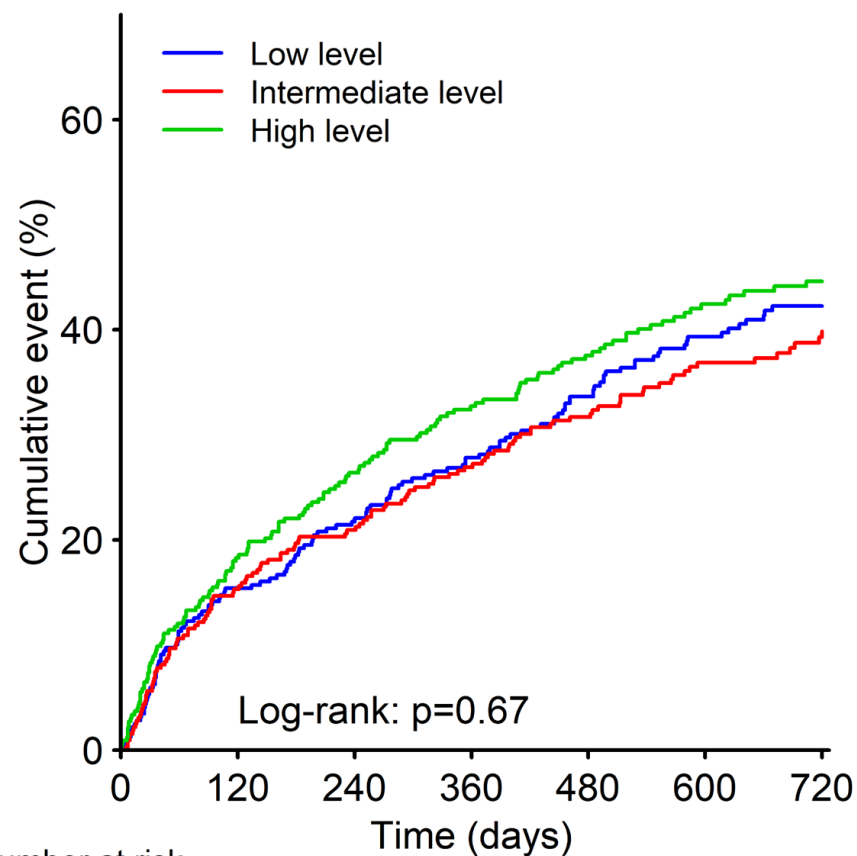
Supplementary figure 2. Survival Curves for the Primary Outcome according to Renin and Aldosterone Levels in Patients without MRAs Prescription in BIOSTAT-CHF study

Renin



Number at risk							
—	321	278	263	244	214	169	131
—	321	271	248	216	199	157	113
—	320	252	225	205	171	132	94

Aldosterone



Number at risk							
—	318	268	247	223	198	157	114
—	321	271	253	231	202	159	109
—	323	262	236	211	184	142	115

Supplementary figure 3. Associations of Renin and Aldosterone with Composite Outcome, All-Cause Mortality and Cardiovascular Mortality in BIOSTAT-CHF study

