



**HAL**  
open science

## Clinical determinants and prognostic implications of renin and aldosterone in patients with symptomatic heart failure

Masatake Kobayashi, Susan Stienen, Jozine M ter Maaten, Kenneth Dickstein, Nilesh J Samani, Chim C Lang, Leong L Ng, Stefan D Anker, Macro Metra, Gregoire Preud'Homme, et al.

### ► To cite this version:

Masatake Kobayashi, Susan Stienen, Jozine M ter Maaten, Kenneth Dickstein, Nilesh J Samani, et al.. Clinical determinants and prognostic implications of renin and aldosterone in patients with symptomatic heart failure. *ESC Heart Failure*, 2020, 7 (3), pp.953-963. 10.1002/ehf2.12634 . hal-02557196

**HAL Id: hal-02557196**

**<https://hal.univ-lorraine.fr/hal-02557196>**

Submitted on 28 Apr 2020

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

Masatake Kobayashi <sup>1</sup>; Susan Stienen <sup>1</sup>; Jozine M. ter Maaten <sup>2</sup>; Kenneth Dickstein <sup>3,4</sup>; Nilesh J. Samani <sup>5</sup>; Chim C. Lang <sup>6</sup>; Leong L. Ng <sup>5</sup>; Stefan D. Anker <sup>7</sup>; Macro Metra <sup>8</sup>; Gregoire Preud'homme <sup>1</sup>; Kevin Duarte <sup>1</sup>; Zohra Lamiral <sup>1</sup>; Nicolas Girerd <sup>1</sup>; Patrick Rossignol <sup>1</sup>; Dirk J. van Veldhuisen <sup>2</sup>; Adriaan A. Voors <sup>2</sup>; Faiez Zannad <sup>1</sup>; João Pedro Ferreira <sup>1</sup>

1. Université de Lorraine, INSERM, Centre d'Investigations Cliniques Plurithématique 1433, Inserm U1116, CHRU de Nancy and F-CRIN INI-CRCT, Nancy, France.
2. University of Groningen, Department of Cardiology, University Medical Center Groningen, Hanzeplein, Groningen, The Netherlands.
3. Department of Internal Medicine, University of Bergen, Bergen, Norway.
4. Department of Cardiology, Stavanger University Hospital, Stavanger, Norway.
5. Department of Cardiovascular Sciences, University of Leicester, NIHR Leicester Biomedical Research Centre, Glenfield Hospital, Leicester, UK.
6. Division of Molecular and Clinical Medicine, School of Medicine, University of Dundee, Ninewells Hospital & Medical School, Dundee, UK.
7. Department of Cardiology (CVK); and Berlin Institute of Health Center for Regenerative Therapies (BCRT); German Centre for Cardiovascular Research (DZHK) partner site Berlin; Charité Universitätsmedizin Berlin, Germany.
8. Cardiology. University and Civil hospitals of Brescia. Italy.

**Running title:** Renin and aldosterone in patients with symptomatic heart failure

**Corresponding Author:** João Pedro Ferreira

Centre d'Investigation Clinique 1433 module Plurithématique, CHRU Nancy - Hopitaux de Brabois, Institut Lorrain du Coeur et des Vaisseaux Louis Mathieu, Nancy, 54500, France

Email: [j.ferreira@chru-nancy.fr](mailto:j.ferreira@chru-nancy.fr)

**Total number of tables and figures:** tables 4 figures 2

## **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 EPHEBUS trial and in an acute HF cohort (PORTO).

### **Results**

In BIOSTAT-CHF study, median renin and aldosterone levels were 85.3 (percentile<sub>25-75</sub>=28-247)  $\mu$ IU/mL and 9.4 (percentile<sub>25-75</sub>=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 EPHEBUS 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<sup>1,2</sup>. Renin and aldosterone, as markers of RAAS activation, have been associated with poor prognosis in previous studies<sup>3-7</sup>. 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<sup>1,8,9</sup>.

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 implications<sup>10</sup>. 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) trial<sup>11</sup> and in a cohort of acute HF patients from Porto, Portugal<sup>12</sup>.

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<sup>10,13</sup>. 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<sup>14</sup>.

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<sup>11, 15</sup>. 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<sup>12</sup>. 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<sup>16</sup>. 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<sup>17-19</sup>. 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  $\chi^2$  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<sup>20</sup>], 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 EPHEBUS 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 <sup>21</sup>. 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 $\mu$ 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)/( $\mu$ 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 EPHEBUS 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 aldosterone<sup>22-24</sup>. Angiotensin II and aldosterone may also play a crucial role in promoting kidney damage by regulating inflammation and reparative processes that follow the tissue fibrosis<sup>25-27</sup>. These mechanisms may explain our observations that high renin and aldosterone levels were associated with lower SBP, lower sodium levels and poorer renal function<sup>3-5, 8, 28</sup>. 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<sup>29, 30</sup>. 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 remodeling<sup>31-33</sup>, resulting in a higher degree of (excessive) RAAS activation<sup>1, 34</sup>.

Circulating levels of renin and aldosterone are also influenced by HF treatment. Renin is upregulated in response to activation of the sympathetic nervous system<sup>35</sup>, hence explaining the association between beta blocker treatment and lower renin and aldosterone levels<sup>36</sup>. Moreover, the current analysis also showed the association of higher doses of ACEi/ARB with lower aldosterone, suggesting that despite the aldosterone “escape” phenomenon<sup>37, 38</sup>, 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<sup>4, 5, 39, 40</sup>. 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<sup>28, 41, 42</sup>. 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  $\mu$ IU/mL) and aldosterone (9.4 ng/dL) in this cohort were lower than in other recent reports<sup>3, 5, 28, 43, 44</sup>, 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%<sup>3</sup>. 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 AHF<sup>5</sup>. 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 arms<sup>4</sup>. Here, increasing renin levels were associated with poorer prognosis. In the Valsartan Heart Failure Trial (Val-HeFT)<sup>45</sup>, 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<sup>6, 7, 46</sup>. 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<sup>47, 48</sup>. However, renin level in this study was lower than that in previous reports<sup>18, 28, 43, 44</sup>, 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).

## Funding

This project was funded by a grant from the European Commission (FP7-242209-BIOSTAT-CHF; EudraCT 2010–020808–29). JPF, NG, PR and FZ are supported by a public grant overseen by the French National Research Agency (ANR) as part of the second “Investissements d’Avenir” program FIGHT-HF (reference: ANR-15-RHU-0004) and by the French PIA project “Lorraine Université d’Excellence”, reference ANR-15-IDEX-04-LUE. And by Contrat de Plan Etat-Lorraine and FEDER Lorraine.

## Disclosures

MK and JPF have no conflicts of interest to disclose with regard to the present manuscript. PR: Personal fees (consulting) from Novartis, Relypsa, AstraZeneca, Grünenthal, Stealth Peptides, Fresenius, Idorsia, Vifor Fresenius Medical Care Renal Pharma, Vifor and CTMA; lecture fees from Bayer and CVRx; cofounder of CardioRenal

## Reference

1. Weber KT. Aldosterone in congestive heart failure. *N Engl J Med.* 2001;345:1689-97.
2. Schrier RW and Abraham WT. Hormones and hemodynamics in heart failure. *N Engl J Med.* 1999;341:577-85.
3. Girerd N, Pang PS, Swedberg K, Fought A, Kwasny MJ, Subacius H, Konstam MA, Maggioni A, Gheorghide M, Zannad F and investigators E. Serum aldosterone is associated with mortality and re-hospitalization in patients with reduced ejection fraction hospitalized for acute heart failure: analysis from the EVEREST trial. *Eur J Heart Fail.* 2013;15:1228-35.
4. Vaduganathan M, Cheema B, Cleveland E, Sankar K, Subacius H, Fonarow GC, Solomon SD, Lewis EF, Greene SJ, Maggioni AP, Bohm M, Zannad F, Butler J and Gheorghide M. Plasma renin activity, response to aliskiren, and clinical outcomes in patients hospitalized for heart failure: the ASTRONAUT trial. *Eur J Heart Fail.* 2018;20:677-686.
5. Mentz RJ, Stevens SR, DeVore AD, Lala A, Vader JM, AbouEzzeddine OF, Khazanie P, Redfield MM, Stevenson LW, O'Connor CM, Goldsmith SR, Bart BA, Anstrom KJ, Hernandez AF, Braunwald E and Felker GM. Decongestion strategies and renin-angiotensin-aldosterone system activation in acute heart failure. *JACC Heart Fail.* 2015;3:97-107.
6. Vergaro G, Emdin M, Iervasi A, Zyw L, Gabutti A, Poletti R, Mammini C, Giannoni A, Fontana M and Passino C. Prognostic value of plasma renin activity in heart failure. *Am J Cardiol.* 2011;108:246-51.

7. Ueda T, Kawakami R, Nishida T, Onoue K, Soeda T, Okayama S, Takeda Y, Watanabe M, Kawata H, Uemura S and Saito Y. Plasma renin activity is a strong and independent prognostic indicator in patients with acute decompensated heart failure treated with renin-angiotensin system inhibitors. *Circ J*. 2015;79:1307-14.
8. Rossi F, Mascolo A and Mollace V. The pathophysiological role of natriuretic peptide-RAAS cross talk in heart failure. *Int J Cardiol*. 2017;226:121-125.
9. McMurray J and Pfeffer MA. New therapeutic options in congestive heart failure: Part I. *Circulation*. 2002;105:2099-106.
10. Voors AA, Anker SD, Cleland JG, Dickstein K, Filippatos G, van der Harst P, Hillege HL, Lang CC, Ter Maaten JM, Ng L, Ponikowski P, Samani NJ, van Veldhuisen DJ, Zannad F, Zwinderman AH and Metra M. A systems BIOlogy Study to TAIlored Treatment in Chronic Heart Failure: rationale, design, and baseline characteristics of BIOSTAT-CHF. *European journal of heart failure*. 2016;18:716-26.
11. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J and Gatlin M. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*. 2003;348:1309-21.
12. Ferreira JP, Santos M, Almeida S, Marques I, Bettencourt P and Carvalho H. Mineralocorticoid receptor antagonism in acutely decompensated chronic heart failure. *Eur J Intern Med*. 2014;25:67-72.
13. Ouwerkerk W, Voors AA, Anker SD, Cleland JG, Dickstein K, Filippatos G, van der Harst P, Hillege HL, Lang CC, Ter Maaten JM, Ng LL, Ponikowski P, Samani NJ, van Veldhuisen DJ, Zannad F, Metra M and Zwinderman AH. Determinants and clinical outcome of uptitration of ACE-inhibitors and beta-blockers in patients with heart failure: a prospective European study. *European heart journal*. 2017;38:1883-1890.
14. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Stromberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG and Swedberg K. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur J Heart Fail*. 2008;10:933-89.
15. Pitt B, Williams G, Remme W, Martinez F, Lopez-Sendon J, Zannad F, Neaton J, Roniker B, Hurley S, Burns D, Bittman R and Kleiman J. The EPHESUS trial: eplerenone in patients with heart failure due to systolic dysfunction complicating acute myocardial infarction. Eplerenone Post-AMI Heart Failure Efficacy and Survival Study. *Cardiovasc Drugs Ther*. 2001;15:79-87.
16. Ter Maaten JM, Voors AA, Damman K, van der Meer P, Anker SD, Cleland JG, Dickstein K, Filippatos G, van der Harst P, Hillege HL, Lang CC, Metra M, Navis G, Ng L, Ouwerkerk W, Ponikowski P, Samani NJ, van Veldhuisen DJ, Zannad F, Zwinderman AH and de Borst MH. Fibroblast growth factor 23 is related to profiles indicating volume overload, poor therapy optimization and prognosis in patients with new-onset and worsening heart failure. *Int J Cardiol*. 2018;253:84-90.
17. Morganti A. A comparative study on inter and intralaboratory reproducibility of renin measurement with a conventional enzymatic method and a new chemiluminescent assay of immunoreactive renin. *J Hypertens*. 2010;28:1307-12.

18. Tsutamoto T, Sakai H, Tanaka T, Fujii M, Yamamoto T, Wada A, Ohnishi M and Horie M. Comparison of active renin concentration and plasma renin activity as a prognostic predictor in patients with heart failure. *Circ J*. 2007;71:915-21.
19. Hartman D, Sagnella GA, Chesters CA and Macgregor GA. Direct renin assay and plasma renin activity assay compared. *Clin Chem*. 2004;50:2159-61.
20. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T and Coresh J. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604-12.
21. Voors AA, Ouwerkerk W, Zannad F, van Veldhuisen DJ, Samani NJ, Ponikowski P, Ng LL, Metra M, Ter Maaten JM, Lang CC, Hillege HL, van der Harst P, Filippatos G, Dickstein K, Cleland JG, Anker SD and Zwinderman AH. Development and validation of multivariable models to predict mortality and hospitalization in patients with heart failure. *European journal of heart failure*. 2017;19:627-634.
22. Verbrugge FH, Steels P, Grieten L, Nijst P, Tang WH and Mullens W. Hyponatremia in acute decompensated heart failure: depletion versus dilution. *J Am Coll Cardiol*. 2015;65:480-92.
23. Schrier RW. Role of diminished renal function in cardiovascular mortality: marker or pathogenetic factor? *J Am Coll Cardiol*. 2006;47:1-8.
24. Schrier RW and De Wardener HE. Tubular reabsorption of sodium ion: influence of factors other than aldosterone and glomerular filtration rate. 2. *N Engl J Med*. 1971;285:1292-303.
25. Brewster UC and Perazella MA. The renin-angiotensin-aldosterone system and the kidney: effects on kidney disease. *Am J Med*. 2004;116:263-72.
26. Wolf G. Angiotensin II as a mediator of tubulointerstitial injury. *Nephrol Dial Transplant*. 2000;15 Suppl 6:61-3.
27. Weber KT, Swamynathan SK, Guntaka RV and Sun Y. Angiotensin II and extracellular matrix homeostasis. *The international journal of biochemistry & cell biology*. 1999;31:395-403.
28. Pavo N, Goliash G, Wurm R, Novak J, Strunk G, Gyongyosi M, Poglitsch M, Saemann MD and Hulsman M. Low- and High-renin Heart Failure Phenotypes with Clinical Implications. *Clinical chemistry*. 2018;64:597-608.
29. Lastra G and Sowers JR. Obesity and cardiovascular disease: role of adipose tissue, inflammation, and the renin-angiotensin-aldosterone system. *Hormone molecular biology and clinical investigation*. 2013;15:49-57.
30. Engeli S, Negrel R and Sharma AM. Physiology and pathophysiology of the adipose tissue renin-angiotensin system. *Hypertension*. 2000;35:1270-7.
31. Gheorghiade M, De Luca L, Fonarow GC, Filippatos G, Metra M and Francis GS. Pathophysiologic targets in the early phase of acute heart failure syndromes. *Am J Cardiol*. 2005;96:11G-17G.
32. Assomull RG, Prasad SK, Lyne J, Smith G, Burman ED, Khan M, Sheppard MN, Poole-Wilson PA and Pennell DJ. Cardiovascular magnetic resonance, fibrosis, and prognosis in dilated cardiomyopathy. *J Am Coll Cardiol*. 2006;48:1977-85.
33. Schuster A, Morton G, Chiribiri A, Perera D, Vanoverschelde JL and Nagel E. Imaging in the management of ischemic cardiomyopathy: special focus on magnetic resonance. *J Am Coll Cardiol*. 2012;59:359-70.

34. Hirsch AT, Pinto YM, Schunkert H and Dzau VJ. Potential role of the tissue renin-angiotensin system in the pathophysiology of congestive heart failure. *Am J Cardiol.* 1990;66:22D-30D; discussion 30D-32D.
35. Berl T, Henrich WL, Erickson AL and Schrier RW. Prostaglandins in the beta-adrenergic and baroreceptor-mediated secretion of renin. *The American journal of physiology.* 1979;236:F472-7.
36. Buhler FR, Laragh JH, Baer L, Vaughan ED, Jr. and Brunner HR. Propranolol inhibition of renin secretion. A specific approach to diagnosis and treatment of renin-dependent hypertensive diseases. *N Engl J Med.* 1972;287:1209-14.
37. Zannad F. Angiotensin-converting enzyme inhibitor and spironolactone combination therapy. New objectives in congestive heart failure treatment. *Am J Cardiol.* 1993;71:34a-39a.
38. Cleland JG, Dargie HJ, Hodsman GP, Ball SG, Robertson JI, Morton JJ, East BW, Robertson I, Murray GD and Gillen G. Captopril in heart failure. A double blind controlled trial. *British heart journal.* 1984;52:530-5.
39. Ferreira JP, Santos M, Almeida S, Marques I, Bettencourt P and Carvalho HC. High-dose spironolactone changes renin and aldosterone levels in acutely decompensated heart failure. *Cor et Vasa.* 2014;56:463-70.
40. Rousseau MF, Gurne O, Duprez D, Van Mieghem W, Robert A, Ahn S, Galanti L and Ketelslegers JM. Beneficial neurohormonal profile of spironolactone in severe congestive heart failure: results from the RALES neurohormonal substudy. *J Am Coll Cardiol.* 2002;40:1596-601.
41. Rousseau MF, Konstam MA, Benedict CR, Donckier J, Galanti L, Melin J, Kinan D, Ahn S, Ketelslegers JM and Pouleur H. Progression of left ventricular dysfunction secondary to coronary artery disease, sustained neurohormonal activation and effects of ibopamine therapy during long-term therapy with angiotensin-converting enzyme inhibitor. *Am J Cardiol.* 1994;73:488-93.
42. Eudy RJ, Sahasrabudhe V, Sweeney K, Tugnait M, King-Ahmad A, Near K, Loria P, Banker ME, Piotrowski DW and Boustany-Kari CM. The use of plasma aldosterone and urinary sodium to potassium ratio as translatable quantitative biomarkers of mineralocorticoid receptor antagonism. *Journal of translational medicine.* 2011;9:180.
43. Kanno Y, Yoshihisa A, Watanabe S, Takiguchi M, Yokokawa T, Sato A, Miura S, Shimizu T, Nakamura Y, Abe S, Sato T, Suzuki S, Oikawa M, Saitoh S and Takeishi Y. Prognostic Significance of Insomnia in Heart Failure. *Circ J.* 2016;80:1571-7.
44. Meijers WC, van der Velde AR, Muller Kobold AC, Dijck-Brouwer J, Wu AH, Jaffe A and de Boer RA. Variability of biomarkers in patients with chronic heart failure and healthy controls. *Eur J Heart Fail.* 2017;19:357-365.
45. Latini R, Masson S, Anand I, Salio M, Hester A, Judd D, Barlera S, Maggioni AP, Tognoni G, Cohn JN and Val-He FTI. The comparative prognostic value of plasma neurohormones at baseline in patients with heart failure enrolled in Val-HeFTI. *Eur Heart J.* 2004;25:292-9.
46. Nijst P, Verbrugge FH, Martens P, Bertrand PB, Dupont M, Francis GS, Tang WW and Mullens W. Plasma renin activity in patients with heart failure and reduced ejection fraction on optimal medical therapy. *J Renin Angiotensin Aldosterone Syst.* 2017;18:1470320317729919.
47. Kley HK and Rick W. [The effect of storage and temperature on the analysis of steroids in plasma and blood]. *Journal of clinical chemistry and clinical biochemistry Zeitschrift fur klinische Chemie und klinische Biochemie.* 1984;22:371-8.

48. Hillebrand JJ, Heijboer AC and Endert E. Effects of repeated freeze-thaw cycles on endocrine parameters in plasma and serum. *Annals of clinical biochemistry*. 2017;54:289-292.

**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 BIOSAT-CHF study

	Global (N=2039)	Renin levels			p-value	Aldosterone levels			p-value
		Low, 0-40 $\mu$ IU/ml (N=684)	Intermediate, 41-170 $\mu$ IU/ml (N=679)	High, >171 $\mu$ IU/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 $\pm$ 12.1	69.2 $\pm$ 12.2	68.7 $\pm$ 12.5	67.4 $\pm$ 11.5	<b>0.005</b>	69.7 $\pm$ 12.1	68.6 $\pm$ 11.9	67.0 $\pm$ 12.1	<b>&lt;0.001</b>
Male, N (%)	1481 (72.6 %)	468 (68.4 %)	477 (70.3 %)	536 (79.3 %)	<b>&lt;0.001</b>	481 (70.6 %)	492 (71.3 %)	508 (76.0 %)	0.052
Body mass index, kg/m <sup>2</sup>	27.8 $\pm$ 5.5	27.5 $\pm$ 5.5	27.6 $\pm$ 5.2	28.3 $\pm$ 5.6	0.07	27.5 $\pm$ 5.5	27.9 $\pm$ 5.5	28.0 $\pm$ 5.4	0.15
<b>Medical history</b>									
Hypertension, N (%)	1259 (61.7 %)	472 (69.0 %)	419 (61.7 %)	368 (54.4 %)	<b>&lt;0.001</b>	426 (62.6 %)	458 (66.4 %)	375 (56.1 %)	<b>&lt;0.001</b>
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 %)	<b>&lt;0.001</b>	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 %)	<b>0.007</b>	137 (20.1 %)	99 (14.3 %)	110 (16.5 %)	<b>0.02</b>
Prior HF hospitalization, N (%)	649 (31.8 %)	182 (26.6 %)	220 (32.4 %)	247 (36.5 %)	<b>&lt;0.001</b>	177 (26.0 %)	235 (34.1 %)	237 (35.5 %)	<b>&lt;0.001</b>
HF etiology					<b>&lt;0.001</b>				<b>0.004</b>
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 %)	
<b>Clinical profile</b>									
NYHA III+IV, N (%)	1234 (62.3 %)	397 (59.7 %)	387 (58.7 %)	450 (68.4 %)	<b>&lt;0.001</b>	450 (68.4 %)	403 (60.4 %)	381 (58.0 %)	<b>&lt;0.001</b>
Orthopnea, N (%)	715 (35.1 %)	233 (34.1 %)	221 (32.6 %)	261 (38.8 %)	<b>0.045</b>	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 $\pm$ 21.8	133.2 $\pm$ 22.2	123.9 $\pm$ 19.6	116.6 $\pm$ 20.2	<b>&lt;0.001</b>	127.4 $\pm$ 22.6	126.5 $\pm$ 21.9	119.8 $\pm$ 19.9	<b>&lt;0.001</b>
Heart rate, bpm	80.1 $\pm$ 19.7	82.1 $\pm$ 21.6	79.1 $\pm$ 19.0	78.9 $\pm$ 18.2	<b>0.03</b>	81.5 $\pm$ 21.7	79.8 $\pm$ 19.1	78.9 $\pm$ 18.0	0.44
LVEF, %	31.1 $\pm$ 10.8	32.7 $\pm$ 10.6	31.4 $\pm$ 11.5	29.0 $\pm$ 9.8	<b>&lt;0.001</b>	32.8 $\pm$ 11.4	30.6 $\pm$ 10.3	29.8 $\pm$ 10.4	<b>&lt;0.001</b>
LVEF <40%, N (%)	1623 (88.7 %)	539 (85.6 %)	535 (88.1 %)	549 (92.7 %)	<b>&lt;0.001</b>	509 (84.6 %)	569 (90.3 %)	545 (91.3 %)	<b>&lt;0.001</b>
<b>Medication</b>									
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 %)	<b>&lt;0.001</b>
ACEi/ARB target dose, N (%)	259 (12.7 %)	110 (16.1 %)	80 (11.8 %)	69 (10.2 %)	<b>0.003</b>	96 (14.1 %)	99 (14.3 %)	64 (9.6 %)	<b>0.02</b>
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 %)	<b>&lt;0.001</b>	334 (49.0 %)	330 (47.8 %)	412 (61.7 %)	<b>&lt;0.001</b>
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)	<b>0.03</b>	40.0 (20.0 – 80.0)	40.0 (20.0 – 75.0)	40.0 (25.0 – 100.0)	<b>0.02</b>
<b>Laboratory</b>									

<b>Hemoglobin, g/dl</b>	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	<b>&lt;0.001</b>
<b>Blood urea nitrogen, mg/dl</b>	41.4 ± 33.1	34.7 ± 30.7	39.7 ± 29.9	50.1 ± 36.4	<b>&lt;0.001</b>	40.7 ± 32.2	41.4 ± 35.6	42.1 ± 31.1	0.13
<b>eGFR, ml/min/1.73m<sup>2</sup></b>	62.0 ± 24.3	66.2 ± 24.1	61.7 ± 25.9	58.1 ± 22.0	<b>&lt;0.001</b>	63.3 ± 24.8	62.4 ± 23.2	60.3 ± 24.9	<b>0.03</b>
<b>Sodium, mmol/l</b>	139.2 ± 4.0	140.5 ± 3.6	139.6 ± 3.6	137.5 ± 4.2	<b>&lt;0.001</b>	139.4 ± 3.9	139.7 ± 3.9	138.5 ± 4.2	<b>&lt;0.001</b>
<b>Potassium, mmol/l</b>	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	<b>0.003</b>
<b>BNP, pg/ml</b>	773 (424 - 1353)	786 (457 - 1186)	687 (320 - 1353)	793 (451 - 1485)	0.89	1009 (598 - 1457)	590 (283 - 923)	892 (338 - 1678)	<b>&lt;0.001</b>
<b>Renin, μIU/ml</b>	83.9 (27.4 - 246.1)	17.6 (10.4 - 27.8)	84.6 (60.8 - 117.2)	386.3 (246.6 - 1535.4)	<b>&lt;0.001</b>	54.9 (19.7 - 163.6)	71.7 (24.8 - 203.9)	154.3 (55.7 - 415.5)	<b>&lt;0.001</b>
<b>Aldosterone, ng/dl</b>	9.3 (4.3 - 19.3)	6.6 (3.4 - 12.7)	9.4 (4.4 - 18.0)	13.8 (5.8 - 29.9)	<b>&lt;0.001</b>	3.0 (1.8 - 4.3)	9.4 (7.3 - 11.9)	27.2 (19.6 - 44.2)	<b>&lt;0.001</b>

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

Variable	Renin			Aldosterone		
	$\beta$	95%CI	$R^2 = 0.26$ p-Value	$\beta$	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 <sup>2</sup> (per 5kg/m <sup>2</sup> )	0.14	0.07 - 0.20	<0.001			
<b>Medical history</b>						
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			
<b>HF etiologies*</b>						
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			
<b>Physical examination</b>						
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
<b>Laboratory</b>						
Hemoglobin, g/dl				0.14	0.10 - 0.17	<0.001
eGFR, ml/min/1.73m <sup>2</sup> (per 5 ml/min/1.73m <sup>2</sup> )	-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
<b>Medication</b>						
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
<b>Renin</b>	<b>Continuous</b>		1.20 (1.16 - 1.25)	<b>&lt;0.001</b>	1.11 (1.06 - 1.15)	<b>&lt;0.001</b>
	<b>Tertiles</b>	<b>Low</b>	(reference)		(reference)	
		<b>Intermediate</b>	1.34 (1.12 - 1.61)	<b>0.001</b>	1.17 (0.98 - 1.41)	0.08
		<b>High</b>	2.01 (1.70 - 2.38)	<b>&lt;0.001</b>	1.48 (1.25 - 1.76)	<b>&lt;0.001</b>
<b>Aldosterone</b>	<b>Continuous</b>		1.01 (0.96 - 1.07)	0.58	1.02 (0.97 - 1.07)	0.53
	<b>Tertiles</b>	<b>Low</b>	(reference)		(reference)	
		<b>Intermediate</b>	0.96 (0.82 - 1.13)	0.65	1.10 (0.93 - 1.29)	0.28
		<b>High</b>	1.05 (0.89 - 1.24)	0.55	1.09 (0.92 - 1.28)	0.32
<b>Interaction between renin and aldosterone</b>		<b>Continuous</b>		0.06		0.14
		<b>Categorical</b>		0.08		0.13

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

		<b>c-index (95% CI)</b>	<b>p-Value</b>	<b>Increased c-index</b>	<b>p-Value</b>
<b>Renin model</b>	<b>BIOSTAT-CHF risk model</b>	76.5 (74.5 to 78.6)	<b>&lt;0.001</b>		
	<b>+ Renin</b>	76.8 (74.7 to 78.8)	<b>&lt;0.001</b>	0.27 (-0.33 to 0.87)	0.37
<b>Aldosterone model</b>	<b>BIOSTAT-CHF risk model</b>	76.5 (74.5 to 78.6)	<b>&lt;0.001</b>		
	<b>+ Aldosterone</b>	76.5 (74.5 to 78.6)	<b>&lt;0.001</b>	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**

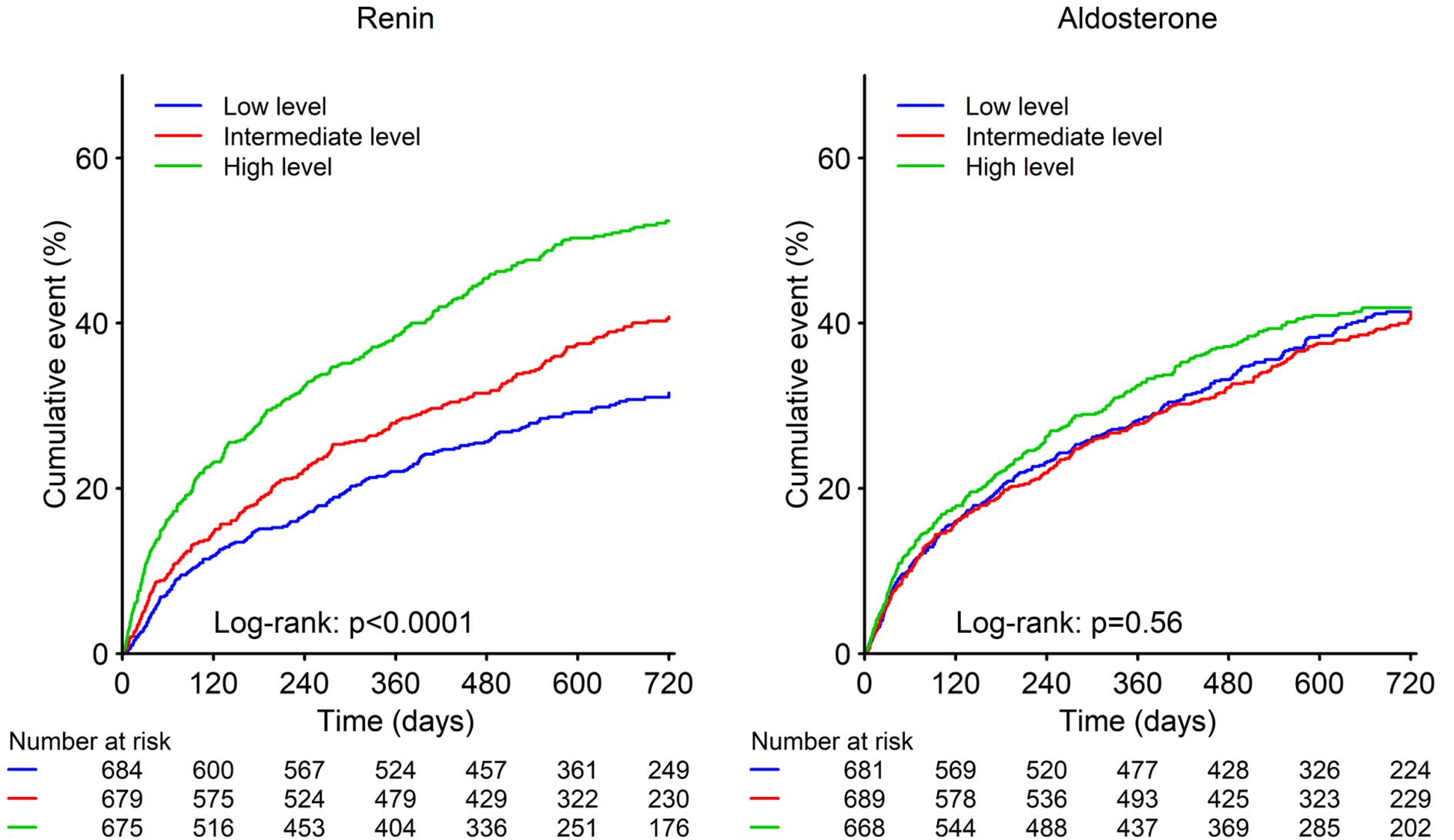
Renin level: Lower tertile, 0-40  $\mu\text{IU/ml}$ ; Intermediate tertile, 41-170  $\mu\text{IU/ml}$ ; Higher tertile,  $>171 \mu\text{IU/ml}$ .

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

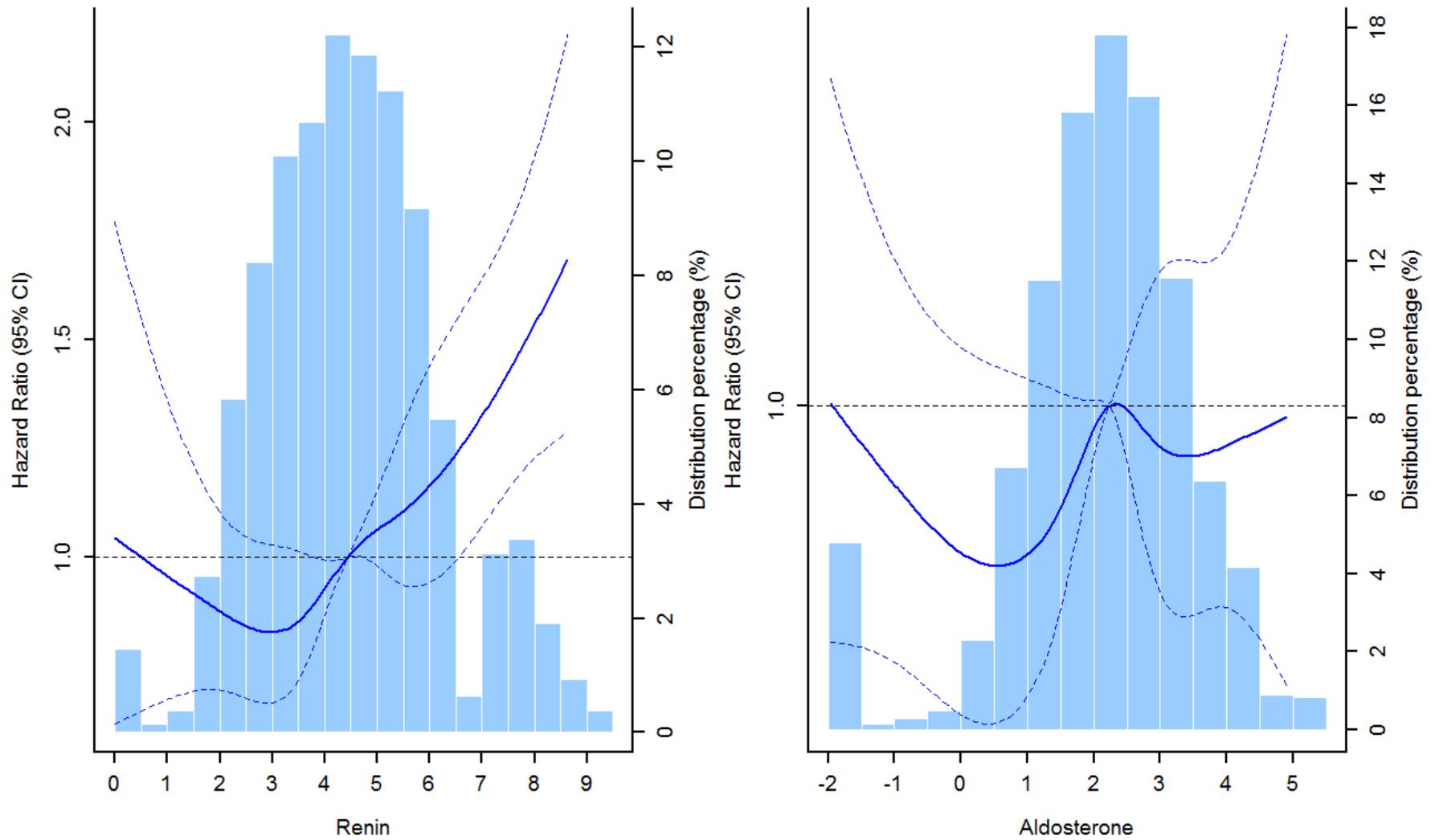
**Figure 2. Restricted Cubic Spline Regression for the Associations of Renin or Aldosterone with the Primary Outcome in BIOSTAT-CHF study**

(A)Renin; (B) aldosterone. Solid line - hazard ratio; dashed line - 95% confidence interval. Knots were placed at the 5<sup>th</sup>, 27.5<sup>th</sup>, 50<sup>th</sup>, 72.5<sup>th</sup> and 95<sup>th</sup> 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 ( $\mu$ 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 ( $\mu$ 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  $\mu$ IU/ml; Intermediate tertile, 34-130  $\mu$ IU/ml; Higher tertile, >131  $\mu$ 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			
<b>HF etiologies*</b>						
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/m <sup>2</sup>	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	
<b>Renin, μIU/ml</b>	69.75 (23.17 - 180.88)	122.13 (39.87 - 326.84)	70.56 (22.63 - 198.68)	79.29 (24.48 - 316.07)	<b>&lt;0.001</b>
<b>Aldosterone, ng/dl</b>	8.40 (4.07 - 17.83)	12.15 (4.70 - 26.10)	6.90 (3.55 - 12.75)	9.45 (4.50 - 17.50)	<b>&lt;0.001</b>

**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	
<b>Renin</b>	<b>Continuous</b>	600	189	1.12 (1.02 - 1.22)	<b>0.02</b>	1439	658	1.11 (1.06 - 1.16)	<b>&lt;0.001</b>	0.62
				(reference)				(reference)		
	<b>Tertiles</b>									
	<b>Intermediate</b>	208	67	1.31 (0.89 - 1.91)	0.17	471	207	1.14 (0.93 - 1.39)	0.22	0.77
	<b>High</b>	179	76	1.60 (1.10 - 2.33)	<b>0.01</b>	497	281	1.50 (1.23 - 1.82)	<b>&lt;0.001</b>	
<b>Aldosterone</b>	<b>Continuous</b>	600	189	1.11 (0.98 - 1.26)	0.09	1439	658	1.01 (0.96 - 1.07)	0.70	0.90
				(reference)				(reference)		
	<b>Tertiles</b>									
	<b>Intermediate</b>	226	79	1.68 (1.16 - 2.44)	<b>0.01</b>	464	201	1.00 (0.83 - 1.21)	0.97	0.55
	<b>High</b>	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		
<b>North European area (N=689)</b>													
<b>Continuous Tertiles</b>	<b>Low</b>	78.5 [24.6 - 219.8]	1.10 (1.03 - 1.18)	<b>0.006</b>	0.34 (-0.54 - 1.21)	0.45	7.8 [3.5 - 16.9]	0.99 (0.92 - 1.08)	0.92	-0.02 (-0.06 - 0.02)	0.36		
	<b>Intermediate</b>		(reference)		0.46 (-0.48 - 1.41)			0.34		(reference)		-0.02 (-0.08 - 0.05)	0.66
	<b>High</b>		1.20 (0.89 - 1.61)		0.23			1.01 (0.77 - 1.33)		0.94		0.97 (0.74 - 1.28)	0.84
<b>Centre European area (N=665)</b>													
<b>Continuous Tertiles</b>	<b>Low</b>	64.6 [22.1 - 190.1]	1.12 (1.04 - 1.21)	<b>0.002</b>	0.36 (-0.82 - 1.54)	0.55	9.2 [4.6 - 18.1]	1.01 (0.92 - 1.10)	0.87	0.02 (-0.06 - 0.10)	0.67		
	<b>Intermediate</b>		(reference)		0.31 (-0.60 - 1.23)			0.50		(reference)		0.02 (-0.10 - 0.15)	0.69
	<b>High</b>		1.11 (0.81 - 1.51)		0.51			1.12 (0.84 - 1.50)		0.44		1.04 (0.76 - 1.40)	0.82
<b>South European area (N=684)</b>													
<b>Continuous Tertiles</b>	<b>Low</b>	121.5 [38.5 - 341.7]	1.12 (1.04 - 1.12)	<b>0.002</b>	0.53 (-0.75 - 1.81)	0.42	11.2 [5.0 - 22.9]	1.07 (0.98 - 1.18)	0.12	0.07 (-0.59 - 0.73)	0.84		
	<b>Intermediate</b>		(reference)		0.59 (-0.64 - 1.82)			0.35		(reference)		0.07 (-0.83 - 0.97)	0.88
	<b>High</b>		1.21 (0.87 - 1.69)		0.25			1.28 (0.94 - 1.74)		0.12		1.39 (1.03 - 1.87)	<b>0.03</b>
<b>P-value for interaction with region of site allocations</b>													
<b>Continuous</b>										0.91			
<b>Tertiles</b>										0.84			

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

	<b>N</b>	<b>Event (%)</b>	<b>Baseline risk model</b>	<b>c-index</b>	<b>p-value</b>	<b>Increased c-index</b>	<b>p-value</b>
<b>Overall</b>	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
<b>ACEi/ARB use</b>							
<b>Yes</b>	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
<b>No</b>	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
<b>MRA use</b>							
<b>Yes</b>	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
<b>No</b>	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

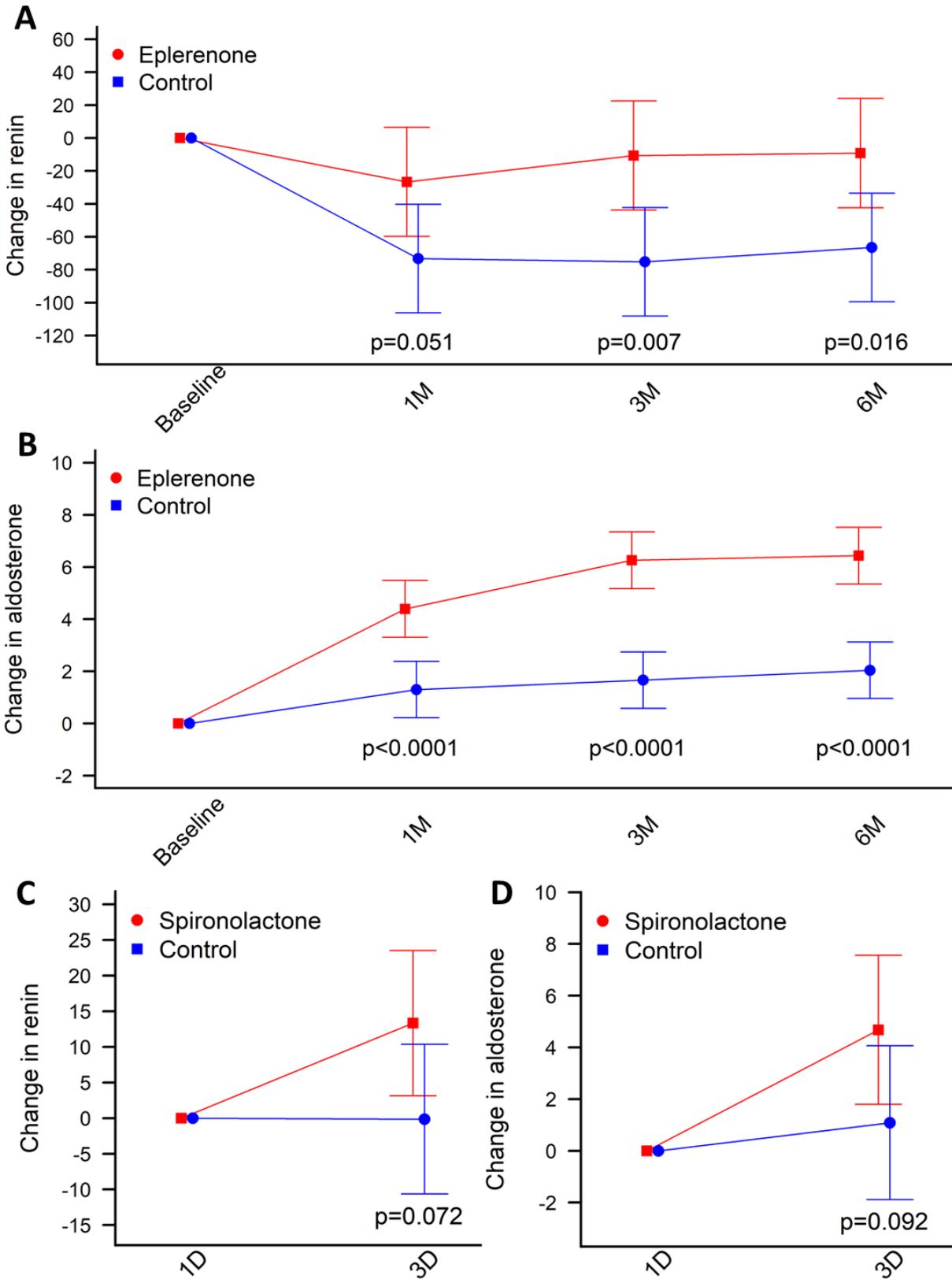
Supplementary table 7. Patients' Characteristics according to Aldosterone-to-Renin Ratio (Tertiles)

	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 %)	<b>0.02</b>
BMI, kg/m <sup>2</sup>	27.8 ± 5.5	27.9 ± 5.6	27.9 ± 5.4	27.6 ± 5.3	0.76
<b>Medical history</b>					
Hypertension, N (%)	1259 (61.7 %)	402 (59.6 %)	393 (58.1 %)	464 (67.5 %)	<b>&lt;0.001</b>
Diabetes mellitus, N (%)	656 (32.2 %)	248 (36.7 %)	217 (32.1 %)	191 (27.8 %)	<b>0.002</b>
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 %)	<b>&lt;0.001</b>
PAD, N (%)	239 (11.7 %)	103 (15.3 %)	70 (10.3 %)	66 (9.6 %)	<b>0.002</b>
COPD, N (%)	346 (17.0 %)	137 (20.3 %)	118 (17.4 %)	91 (13.2 %)	<b>0.002</b>
Prior HF hospitalization, N (%)	649 (31.8 %)	221 (32.7 %)	233 (34.4 %)	195 (28.4 %)	<b>0.047</b>
<b>Clinical profile</b>					
NYHA III+IV, N (%)	1234 (62.3 %)	466 (71.6 %)	395 (59.8 %)	373 (55.6 %)	<b>&lt;0.001</b>
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	<b>&lt;0.001</b>
Heart rate, bpm	80.1 ± 19.7	79.7 ± 19.5	80.0 ± 20.2	80.5 ± 19.4	0.50
<b>Echocardiogram</b>					
LVEF, %	31.1 ± 10.8	29.8 ± 10.2	31.1 ± 10.8	32.2 ± 11.1	<b>&lt;0.001</b>
MR ≥ moderate, N (%)	924 (47.9 %)	289 (46.0 %)	297 (46.3 %)	338 (51.1 %)	0.12
<b>Medications</b>					
ACEi/ARB, N (%)	1467 (71.9 %)	516 (76.4 %)	483 (71.3 %)	468 (68.1 %)	<b>0.003</b>
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
<b>Laboratory</b>					
Hemoglobin, g/dl	13.2 ± 1.9	12.8 ± 2.0	13.3 ± 1.9	13.5 ± 1.8	<b>&lt;0.001</b>
Blood urea nitrogen, mg/dl	41.4 ± 33.1	48.7 ± 34.9	40.5 ± 33.3	35.4 ± 29.6	<b>&lt;0.001</b>
eGFR, mL/min/1.73m <sup>2</sup>	62.0 ± 24.3	59.1 ± 23.0	63.2 ± 24.4	63.7 ± 25.2	<b>&lt;0.001</b>
Sodium, mmol/l	139.2 ± 4.0	138.0 ± 4.4	139.3 ± 3.7	140.3 ± 3.6	<b>&lt;0.001</b>
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)	<b>0.01</b>
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)	<b>&lt;0.001</b>
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)	<b>&lt;0.001</b>

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

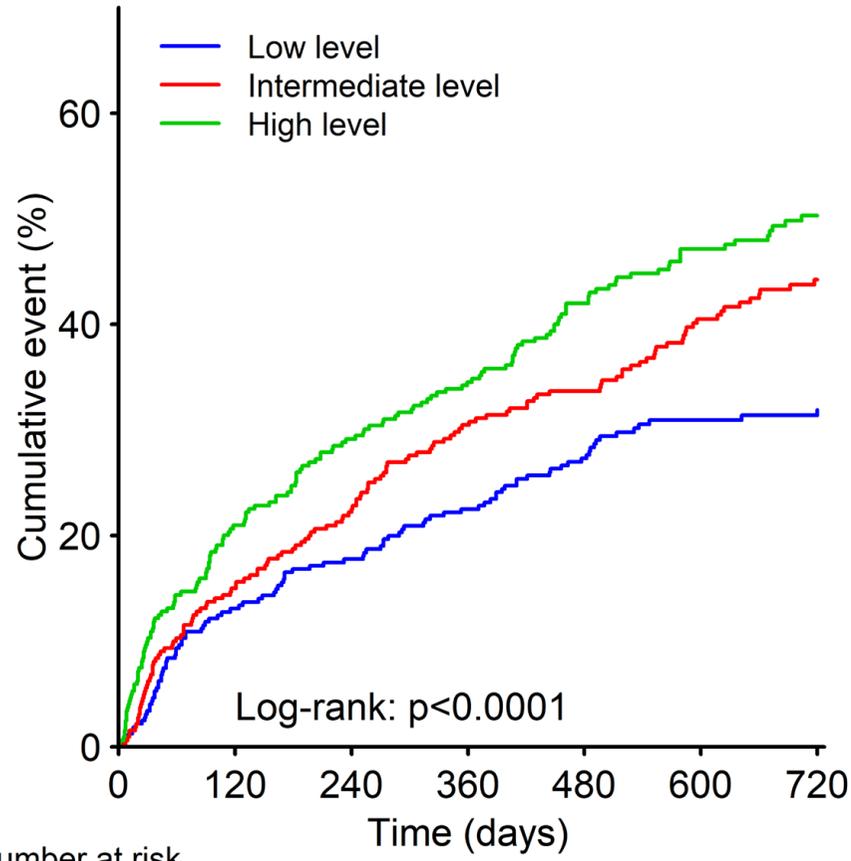
All-Cause mortality or HF re-hospitalization			Univariable model		Multivariable model	
			HR (95 % CI)	p-Value	HR (95 % CI)	p-Value
Aldosterone-to-renin ratio	Continuous		0.88 (0.85 - 0.91)	<0.001	0.93 (0.90 - 0.97)	<0.001
	Tertiles	Low	1.81 (1.54 - 2.14)	<0.001	1.31 (1.11 - 1.55)	0.002
		Intermediate	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
Aldosterone-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 EPHEBUS (A, B) and PORTO (C, D) Studies**



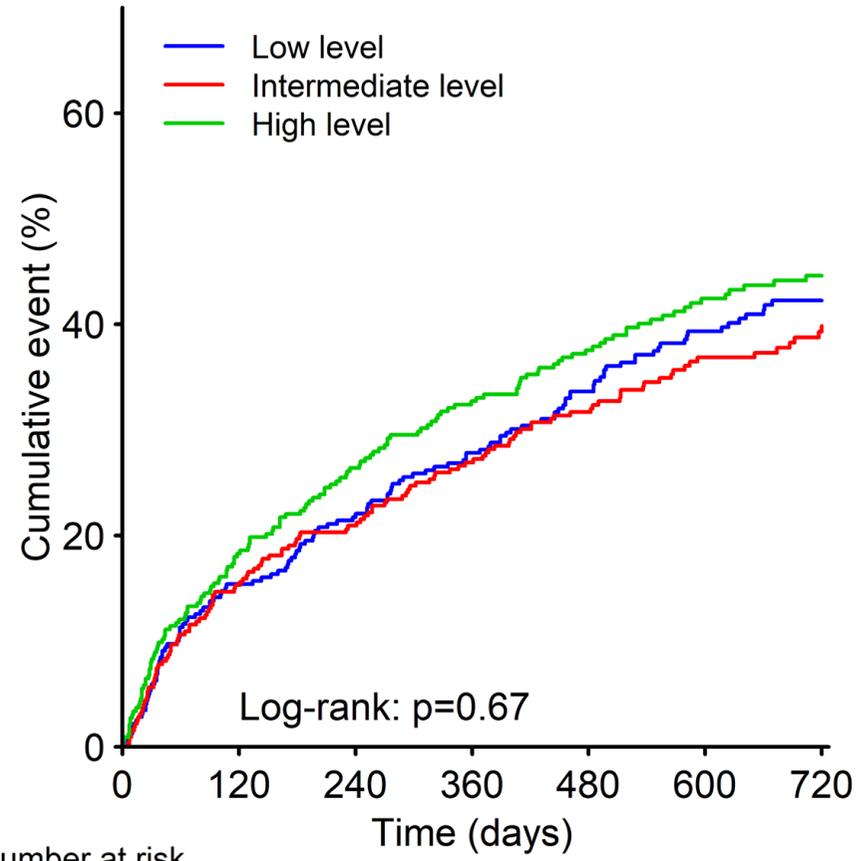
**Supplementary figure 2. Survival Curves for the Primary Outcome according to Renin and Aldosterone Levels in Patients without MRAs Prescription in BIOSTAT-CHF study**

### Renin



Number at risk							
	0	120	240	360	480	600	720
Low level	321	278	263	244	214	169	131
Intermediate level	321	271	248	216	199	157	113
High level	320	252	225	205	171	132	94

### Aldosterone



Number at risk							
	0	120	240	360	480	600	720
Low level	318	268	247	223	198	157	114
Intermediate level	321	271	253	231	202	159	109
High level	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**

