

# Complementary and Incremental Mortality Risk Prediction by Cortisol and Aldosterone in Chronic Heart Failure

Gülmisal Güder, MD; Johann Bauersachs, MD; Stefan Frantz, MD; Dirk Weismann, MD; Bruno Allolio, MD; Georg Ertl, MD; Christiane E. Angermann, MD; Stefan Störk, MD, PhD

**Background**—In patients with systolic heart failure, high levels of circulating aldosterone are associated with an adverse prognosis, and mineralocorticoid receptor blockade improves survival. The prognostic significance of cortisol that may also bind and activate the mineralocorticoid receptor in chronic heart failure is unknown.

**Methods and Results**—Serum levels of cortisol and aldosterone were quantified in a prospective cohort study of 294 consecutive patients with chronic heart failure [48% were in New York Heart Association functional class III or IV; 58% had systolic heart failure]. During a median follow-up of 803 days (interquartile range, 314 to 1098), 79 patients died (27.3% mortality rate). Cortisol and aldosterone were independent predictors of increased mortality risk in Cox regression analyses adjusted for age, sex, New York Heart Association functional class, C-reactive protein, N-terminal pro-brain natriuretic peptide, sodium, and hypercholesterolemia. The hazard ratio for highest versus lowest tertile of cortisol was 2.72 [95% confidence interval [CI], 1.38 to 5.36;  $P=0.004$ ], and the hazard ratio for aldosterone was 2.19 (95% CI, 1.23 to 3.93;  $P=0.008$ ). Patients with both cortisol and aldosterone levels above the respective medians had a 3.4-fold higher mortality risk compared with subjects with both corticosteroids below the median (95% CI, 1.54 to 7.46;  $P=0.0001$ ). Addition of cortisol and aldosterone levels to the fully adjusted model significantly improved the discriminatory power [increase in Harrell's  $C$ -statistic from 0.80 (95% CI, 0.70 to 0.90) to 0.86 (95% CI, 0.79 to 0.94;  $P<0.001$  for change].

**Conclusions**—In patients with chronic heart failure, higher serum levels of both cortisol and aldosterone were independent predictors of increased mortality risk that conferred complementary and incremental prognostic value. (*Circulation*. 2007;115:1754-1761.)

**Key Words:** aldosterone ■ cortisol ■ heart failure ■ hormones ■ prognosis

Progression of chronic heart failure is mediated largely via persistent activation of various neuroendocrine systems.<sup>1</sup> Inhibition of the sympathoadrenergic system by  $\beta$ -blockers and of the renin-angiotensin-aldosterone system by angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and mineralocorticoid receptor (MR) antagonists is responsible for the marked prognostic improvement of patients with chronic heart failure over the last 2 decades.<sup>2,3</sup> Despite the combined administration of different neurohumoral antagonists, neuroendocrine activation remains incompletely blocked in many patients.<sup>4,5</sup> Higher serum aldosterone concentrations in patients on diuretics treated with or without angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers were associated with increased mortality and rehospitalization rates.<sup>5–8</sup> Nevertheless, these studies were restricted to patients in New York Heart Association (NYHA) functional classes III and IV with systolic heart failure after myocardial infarction.<sup>7</sup> So far, no data exist on the prognostic value of aldosterone in nonsystolic chronic heart failure.

## Clinical Perspective p 1761

Over the past several years, evidence has accumulated that cortisol may also contribute to the progression of cardiac damage in chronic heart failure. Because cardiomyocytes lack  $11\beta$ -hydroxysteroid dehydrogenase type II, MRs are normally occupied by cortisol in a tonic inhibitory fashion.<sup>9–11</sup> However, in the context of tissue damage and generation of reactive oxygen species, this inhibitory role of cortisol is transformed by the altered intracellular redox state, and cortisol may act as a MR agonist that mimics the physiological and pathophysiological effects of aldosterone.<sup>11–13</sup> Up to now, the prognostic value of cortisol levels in chronic heart failure, additive or complementary to aldosterone levels, has not been determined.

The present study investigated the independent and incremental association of serum cortisol and aldosterone concentrations with all-cause mortality risk in a consecutive cohort of patients across all NYHA classes with systolic as well as nonsystolic heart failure.

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From the Department of Internal Medicine I, Center for Cardiovascular Medicine, University of Würzburg, Würzburg, Germany.

Correspondence to Dr Stefan Störk, MD, PhD, University of Würzburg, Department of Internal Medicine I, Center for Cardiovascular Medicine, Klinikstrasse 6–8, D-97070 Würzburg, Germany. E-mail stoerk\_s@klinik.uni-wuerzburg.de

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## Methods

### Study Design and Subjects

A total of 300 patients who presented consecutively between June 2002 and July 2003 with either impaired left ventricular function [echocardiographic fractional shortening (FS) <24%] or typical heart failure symptoms with preserved left ventricular function (FS ≥24%) were enrolled if they were not on current corticosteroid therapy. Patients were eligible regardless of heart failure severity and mode of admission. In 6 patients, blood analyses on hormones were not feasible because of storage failure; therefore, the current report refers to 294 subjects. All patients underwent a detailed standardized clinical examination, and FS was measured according to standard recommendations. The study was approved by the Ethics Committee of the Medical Faculty of Würzburg University, and all patients provided written informed consent.

### Hormone Analysis and Laboratory Measurements

Serum samples for aldosterone and cortisol measurements were collected at study start between 8 and 11 AM after 30 minutes of rest. Cortisol was measured with an automated immunoassay (Immulite 2000, DPC Biermann, Bad Nauheim, Germany). Aldosterone was measured by radioimmunoassay with commercially available reagents (DPC Biermann, Bad Nauheim, Germany). All other laboratory parameters such as C-reactive protein (Roche Diagnostics GmbH, Basel, Switzerland) and N-terminal pro-brain natriuretic peptide (NT-proBNP; Roche Diagnostics GmbH) were measured as part of the clinical routine in the central laboratory of the University Hospital. For all assays, the intra- and interassay coefficients of variation were <8% and <12%, respectively.

### Outcome Ascertainment

Patient status (dead or alive) was ascertained between June and August 2005 by communication with the patient's general practitioner or by review of hospital discharge letters. Follow-up was 100% complete. The median follow-up time for survivors was 803 days.

### Data Analysis

Group comparisons between systolic (FS ≥24%) and nonsystolic (FS <24%) heart failure were made with Fisher exact test and the Mann-Whitney *U*-test, as appropriate. Comparisons within groups were made with the Kruskal-Wallis test. Univariate and multivariate determinants of naturally log-transformed aldosterone and cortisol levels were determined with linear backward regression (*P* value for exclusion was 0.05). Age and sex were forced into all regression models. The association of aldosterone and cortisol levels with all-cause mortality was determined by Cox proportional hazards regression with the corticosteroids as log-normalized continuous or categorized variables (tertiles, or dichotomized at the median). Univariately predictive variables (*P* <0.05) were backward eliminated in multivariable models with the likelihood ratio criterion, and hazard ratios (HRs) with 95% confidence intervals (CIs) were reported. Four multivariable Cox models were constructed: model 0 included all predictors except the corticosteroids; models 1 and 2, in addition to model 0, included information on cortisol or aldosterone, respectively; model 3 included combined information on both corticosteroids in addition to model 0. Interaction was assessed by the introduction of a product term. To assess the incremental prognostic value of the corticosteroids on top of variables included in model 0, Harrell's *C*-statistic was computed (comparable to the area under the receiver-operating characteristic curve).<sup>14</sup> To compare the difference between the *C*-statistics of models 0 and 3, a bootstrap procedure was used with 2000 repetitions. The empirical 1-sided *P* value was calculated as the number of differences <0. Statistical analysis was performed with SPSS 13.0.1 (SPSS Inc, Chicago, Ill) and S-plus software (Version 2000, Math-Soft Inc, Seattle, Wash).<sup>15</sup>

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

## Results

### Patient Characteristics

Table 1 summarizes the baseline characteristics of all subjects and subgroups according to systolic (58%) and nonsystolic (42%) heart failure. Women comprised 34% of the study population and were on average 5 years older than men. The distribution of NYHA classes was similar between groups. As expected, women were more frequently in the group with nonsystolic heart failure (28% versus 44%).<sup>16</sup>

### Hormone Concentrations and Inflammatory Markers

The median cortisol and aldosterone serum levels are shown in Table 2 together with levels of C-reactive protein and NT-proBNP. Levels of cortisol (*P*=0.036) and NT-proBNP (*P*<0.001) were higher in systolic heart failure, whereas levels of aldosterone and C-reactive protein were not different between groups. Table 3 summarizes the statistically significant univariate and multivariate associations of cortisol and aldosterone levels selected from the parameters listed in Tables 1 and 2. In multivariate analysis, the independent determinants of cortisol were body mass index, renal insufficiency, and atrial fibrillation; for aldosterone, the respective determinants were renal insufficiency, use of MR antagonists, and use of diuretics.

### Predictors of All-Cause Mortality

During a median follow-up of 803 days (interquartile range, 314 to 1098 days), 79 patients died (27.3% mortality rate). The crude mortality rate per aldosterone tertile was 19.4%, 21.2%, and 40.6% (from low to high; *P* for trend was 0.001). The association of all-cause death with cortisol tertiles was in the same direction and of similar strength, with a risk of death of 14.0%, 25.8% and 42.1%, respectively (from low to high; *P* for trend <0.001). Both corticosteroids were positively associated with all-cause mortality risk in univariate analysis (Figure 1) with a HR of 3.41 (95% CI, 1.85 to 6.29) for highest versus lowest tertile of cortisol and of 2.48 (95% CI, 1.43 to 4.30) for highest versus lowest tertile of aldosterone. Further univariate predictors of increased all-cause mortality risk were age, NYHA class, high C-reactive protein, low sodium, high potassium, absence of hypercholesterolemia, high NT-proBNP, reduced FS, hypotension, atrial fibrillation, renal insufficiency, and intake of angiotensin-converting enzyme inhibitors, β-blockers, and diuretics. Tables 4 and 5 shows the results of the multivariate Cox analysis after backward selection of univariate predictors other than the corticosteroids (model 0). To assess whether the protective effect of hypercholesterolemia was carried by intake of statins, we forced use of statins into the model and found an unchanged HR for hypercholesterolemia (HR, 0.36; 95% CI, 0.18 to 0.72; *P*=0.004) and no effect for statin use (HR, 0.73; 95% CI, 0.21 to 2.59; *P*=0.627). The corresponding test on multiplicative interaction was also negative (change in −2 log-likelihood 0.229, *P*=0.624).

### Complementary and Incremental Prognostic Value of Corticosteroids

To further elucidate the added value conferred by the corticosteroid hormones, we included cortisol and aldosterone

**TABLE 1. Baseline Characteristics of Study Participants**

	All Subjects (N=294)	Systolic Heart Failure (FS <24%; n=171)	Non-Systolic Heart Failure (FS ≥24%; n=123)	P
Age, y	66.2 (12.4)	65.4 (12.3)	67.2 (12.5)	0.221
Female sex	34.4	27.5	43.9	0.004
NYHA class				0.585
I/II	19.0/33.0	19.9/31.6	17.9/35.0	
III/IV	41.8/6.1	40.9/7.6	43.1/4.1	
Ischemic heart failure cause	44.2	47.4	37.3	0.234
Fractional shortening, %	23.1 (8.7)	17.2 (4.4)	31.3 (6.1)	<0.001
LVEDD, mm	60.1 (10.6)	64.5 (9.7)	53.4 (7.6)	<0.001
Comorbidities/risk factors				
BMI, kg/m <sup>2</sup>	27.8 (5.0)	27.9 (5.1)	27.6 (4.9)	0.965
Obesity	28.6	28.7	28.5	0.996
Hypercholesterolemia	56.5	57.3	55.3	0.812
Diabetes mellitus	30.6	29.8	31.7	0.798
Hypotension	11.3	9.8	12.4	0.576
Hypertension	62.2	57.3	69.1	0.051
Atrial fibrillation	24.9	24.7	25.2	0.998
Anemia	28.1	28.4	27.6	0.893
GFR-MDRD, mL · min <sup>-1</sup> per 1.73 m <sup>2</sup>	71.8 (25.7)	72.8 (27.4)	70.3 (23.2)	0.283
Renal dysfunction				0.193
Grade 1/2	24.3/43.0	26.5/41.0	21.2/45.8	
Grade 3/4	27.5/5.3	25.3/7.2	30.5/2.5	
Medication				
ACE inhibitor or ARB	81.6	82.5	78.9	0.455
ACE inhibitor	71.1	72.5	69.1	0.602
ARB	10.5	9.9	11.4	0.704
Spironolactone	28.3	31.6	23.6	0.149
Diuretic	82.0	84.2	78.9	0.282
β-Blocker	65.3	64.9	65.9	0.902
Statin	38.1	39.2	40.2	0.715
Cardiac glycoside	39.5	45.0	31.7	0.022

Values are mean (SD) or %. *P* values refer to Fisher exact test and Mann-Whitney *U* test, as appropriate. Obesity is defined as body mass index >30 kg/m<sup>2</sup>; hypercholesterolemia, total cholesterol >240 mg/dL or on lipid-lowering drugs; hypotension, systolic blood pressure <90 mm Hg; hypertension, systolic blood pressure >140/90 mm Hg or on antihypertensive drugs; and anemia, hemoglobin <12 g/dL in women, <13 g/dL in men. Renal dysfunction is graded according to the National Kidney Foundation Disease Outcomes Quality Initiative guidelines: Grade 1, GFR >90 mL · min<sup>-1</sup> per 1.73 m<sup>2</sup>; grade 2, GFR 60–89 mL · min<sup>-1</sup> per 1.73 m<sup>2</sup>; grade 3, GFR 30–59 mL · min<sup>-1</sup> per 1.73 m<sup>2</sup>; grade 4, GFR 15–29 mL · min<sup>-1</sup> per 1.73 m<sup>2</sup>; grade 5, <15 mL · min<sup>-1</sup> per 1.73 m<sup>2</sup> (not represented in the study cohort). LVEDD indicates left ventricular end-diastolic diameter; BMI, body mass index; GFR-MDRD, glomerular filtration rate estimated by the Modification of Diet in Renal Disease formula<sup>15</sup>; ACE, angiotensin converting enzyme; and ARB, angiotensin II type 1 receptor blocker.

separately (Tables 4 and 5, models 1 and 2) and in combination (Tables 4 and 5, model 3) into multivariable Cox models adjusted for the variables of model 0. The highest tertiles of both cortisol and aldosterone were associated with an increased mortality risk of 2.72 (95% CI, 1.38 to 5.36; model 1) and 2.19 (95% CI, 1.23 to 3.93; model 2), respectively. To assess the influence of NYHA class we performed subanalyses in strata of NYHA classes I–II and III–IV. For cortisol, the highest-versus-lowest tertile in NYHA class I–II was associated with a HR of 5.00 (95% CI, 1.31 to 13.89; *P*=0.020), and in NYHA III–IV with a HR of 2.44 (95% CI, 1.27 to 4.62; *P*=0.034).

The corresponding HRs for aldosterone were 4.20 (95% CI, 1.34 to 12.11; *P*=0.011) for NYHA I–II, and 1.82 (95% CI, 1.13 to 3.20; *P*=0.042) for NYHA III–IV. Further subanalyses were performed in groups with systolic and nonsystolic heart failure. For cortisol, the highest-versus-lowest tertile in patients with systolic heart failure was associated with a HR of 2.29 (95% CI, 1.15 to 4.92; *P*=0.032), and in nonsystolic heart failure with a HR of 7.19 (95% CI, 1.47 to 15.23; *P*=0.015). The corresponding HRs for aldosterone were 2.02 (95% CI, 1.12 to 4.02; *P*=0.034) for systolic and 2.40 (95% CI, 1.28 to 7.83; *P*=0.022) for nonsystolic heart failure.

**TABLE 2. Median Hormone Concentrations and Inflammatory Markers at Different Percentiles**

	All Subjects (N=294)	Systolic Heart Failure (FS <24%; n=171)	Nonsystolic Heart Failure (FS ≥24%; n=123)	Normal Range	P
Cortisol, μg/dL	13.0 (6.3, 9.7, 17.0, 24.9)	13.7 (6.9, 10.2, 17.1, 25.8)	12.4 (6.1, 9.3, 16.0, 22.0)	5–25	0.036
Aldosterone, pg/mL	100 (25, 56, 191, 377)	106 (25, 56, 215, 468)	95 (25, 59, 168, 332)	10–160	0.299
NT-proBNP, pg/mL	1020 (178, 412, 2941, 13572)	1803 (131, 568, 4148, 23265)	864 (57, 282, 2058, 6227)	NA	<0.001
C-reactive protein, mg/dL	0.66 (0.09, 0.27, 1.59, 7.72)	0.71 (0.09, 0.28, 1.59, 7.01)	0.63 (0.09, 0.25, 1.80, 9.94)	0–0.5	0.976

Values in parentheses are mean concentrations, in order, at the 2.5, 25, 75, and 97.5 percentiles of the study cohort. P values refer to comparison between groups of systolic vs nonsystolic heart failure (Mann-Whitney U-test).

NT-proBNP indicates N-terminal pro-brain natriuretic peptide; NA, not applicable. Conversion factor for cortisol from μg/dL to nmol/L is 27.59.

If both corticosteroids were added to model 0, the highest tertiles of both cortisol and aldosterone remained independently predictive, with only small reductions in their respective HRs (model 3). The test on multiplicative interaction was not statistically significant, but showed a trend: change in -2 log likelihood 3.62 (P=0.092).

To examine whether use of the information on corticosteroids allows identification of a high-risk subgroup, cortisol and aldosterone were entered into model 0 with levels dichotomized at their median (see Table 2 for median levels).

Compared with subjects who had low levels of both cortisol and aldosterone, patients with high levels of both corticosteroids had a 4.5-fold higher mortality risk in unadjusted analysis (HR, 4.48; 95% CI, 1.81 to 6.77; P<0.0001) (Figure 2) and a 3.4-fold higher mortality risk (HR, 3.37; 95% CI, 1.54 to 7.46; P=0.0001) in multivariable analysis. All analyses were rerun with log-normalized instead of trichotomized values and yielded very similar results (Table 5).

To estimate the incremental prognostic value of corticosteroids, we compared the C-statistics of models 0 and 3 with

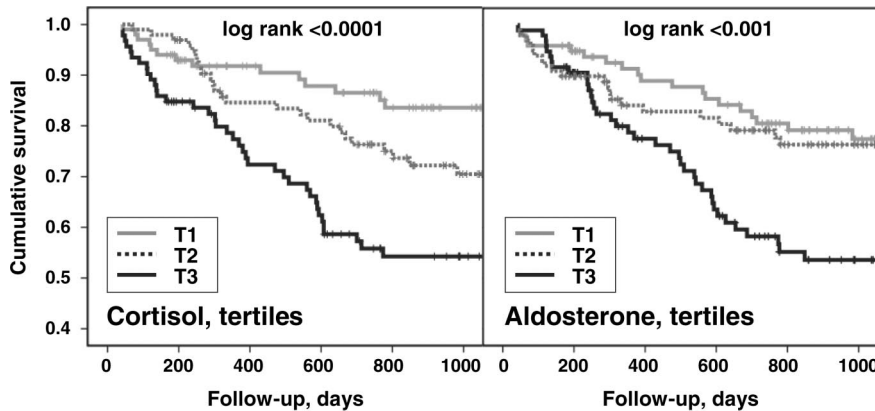
**TABLE 3. Univariate and Multivariate Determinants (Standardized Beta Coefficients, β) of Serum Log Aldosterone and Cortisol Concentrations**

	Univariate Analysis*			Multivariate Analysis*		
	β	T	P	β	T	P
Log cortisol						
FS <24%, yes vs no	0.127	2.17	0.031	...	...	...
BMI, per tertile	-0.221	-3.82	<0.001	-0.183	-3.19	0.002
Hypotension, yes vs no	0.133	2.27	0.024	...	...	...
Atrial fibrillation, yes vs no	0.216	3.75	<0.001	0.156	2.74	0.007
Renal dysfunction, per grade	0.241	4.14	<0.001	0.196	3.28	0.001
ARB, yes vs no	-0.126	-2.16	0.032	...	...	...
Spironolactone, yes vs no	0.119	2.03	0.043	...	...	...
Diuretic, yes vs no	0.152	2.60	0.010	0.114	1.97	0.050
Cardiac glycoside, yes vs no	0.132	2.25	0.025	...	...	...
NT-proBNP, per tertile	0.210	3.64	<0.001	...	...	...
Aldosterone, per tertile	0.118	2.02	0.044	...	...	...
Log aldosterone						
NYHA class, per class	0.158	2.72	0.007	...	...	...
Hypotension, yes vs no	0.209	3.64	<0.001	...	...	...
Renal dysfunction, per grade	0.170	2.90	0.004	0.197	3.29	0.001
Cardiac glycoside, yes vs no	0.147	2.53	0.012	...	...	...
Spironolactone, yes vs no	0.393	7.29	<0.001	0.371	6.89	<0.001
Diuretics, yes vs no	0.214	3.73	<0.001	0.152	2.73	0.007
Cortisol, per tertile	0.176	3.03	0.003	...	...	...
Sodium, per tertile	-0.135	-2.28	0.024	...	...	...

Abbreviations as in Tables 1 and 2. The T statistic denotes the relative importance of a variable in each model: the larger the absolute value, the larger the contribution. Cut-off values for tertiles (T) were: cortisol T1 <10.9 μg/dL, T2 10.9–15.5 μg/dL, T3>15.5 μg/dL; sodium T1 <140 mmol/L, T2 140–142 mmol/L, T3 >142 mmol/L; BMI: T1 <25.1 kg/m<sup>2</sup>, T2 25.1–28.7 kg/m<sup>2</sup>, T3 >28.7 kg/m<sup>2</sup>; NT-proBNP: T1 <600 pg/mL, T2 600–2261 pg/mL, T3 >2261 pg/mL; aldosterone: T1 <66.7 pg/mL, T2 66.7–150.8 pg/mL, T3 >150.8 pg/mL. P values for trend across categories.

\*Age and sex were forced into all models.





**Figure 1.** Cortisol (left) and aldosterone (right) serum concentrations predict all-cause mortality risk in patients with chronic heart failure (Kaplan-Meier plot). Hazard ratio (95% CI) for highest versus lowest tertile of cortisol: 3.41 (1.85 to 6.29); for highest versus lowest tertile of aldosterone: 2.48 (1.43 to 4.30). Cut-off values for tertiles (T) were: cortisol T1 <10.9 μg/dL, T2 10.9 to 15.5 μg/dL, T3 >15.5 μg/dL; aldosterone T1 <66.7 pg/mL, T2 66.7 to 150.8 pg/mL, T3 >150.8 pg/mL.

both approaches (ie, trichotomized and log-normalized variables as detailed in Tables 4 and 5). For the trichotomized approach, we found that in model 0,  $C=0.80$  (95% CI, 0.70 to 0.90), whereas in model 3,  $C=0.86$  (95% CI, 0.79 to 0.94), for a difference between the 2 models of 0.057 (95% CI, 0.029 to 0.083);  $P<0.001$ . For the log-normalized approach, we found that in model 0,  $C=0.80$  (95% CI, 0.70 to 0.90),

whereas in model 3,  $C=0.85$  (95% CI, 0.78 to 0.93), for a difference between the 2 models of 0.050 (95% CI, 0.020 to 0.081);  $P=0.004$ .

**TABLE 4. Multivariable Cox Regression Analysis of Risk Factors at Baseline For All-Cause Mortality Risk, Approach A: Laboratory Markers Entered as Tertiles**

	HR	95% CI	Wald	P
<b>Model 0*</b>				
Age group, per decade	1.04	1.02–1.07	13.12	<0.001
Male sex	1.57	0.94–2.62	2.98	0.084
NYHA class, per class	2.65	1.89–3.73	31.64	<0.001
Hypercholesterolemia, yes vs no	0.40	0.24–0.65	13.86	<0.001
C-reactive protein, per tertile	1.38	1.01–1.84	3.92	0.042
Sodium, per tertile	0.63	0.46–0.86	8.46	0.002
NT-proBNP, per tertile	2.16	1.53–3.05	19.01	<0.001
<b>Model 1†</b>				
Cortisol, tertile 1	1.00 <sup>§</sup>		11.34	0.003
Cortisol, tertile 2	1.33	0.65–2.68	0.61	0.434
Cortisol, tertile 3	2.72	1.38–5.36	8.37	0.004
<b>Model 2†</b>				
Aldosterone, tertile 1	1.00‡		7.83	0.020
Aldosterone, tertile 2	1.32	0.68–2.56	0.65	0.420
Aldosterone, tertile 3	2.19	1.23–3.93	6.98	0.008
<b>Model 3†</b>				
Cortisol, tertile 1	1.00*		10.47	0.005
Cortisol, tertile 2	1.24	0.61–2.50	0.35	0.557
Cortisol, tertile 3	2.55	1.29–5.03	7.31	0.007
Aldosterone, tertile 1	1.00*		6.43	0.040
Aldosterone, tertile 2	1.49	0.76–2.88	1.35	0.246
Aldosterone, tertile 3	2.22	1.26–3.98	6.92	0.008

Abbreviations as in Table 2. Tertiles are in the order from low to high; for cut-off values please refer to Table 3. Tertiles for C-reactive protein were: T1 <0.38 mg/dL, T2 0.38–1.17 mg/dL, T3 >1.17 mg/dL.

\*Model 0: Cortisol and aldosterone excluded from analysis; age and sex forced into the model.

†Models 1–3 include all parameters listed in Model 0.

‡Referent. P values for trend across categories.

**Effect of Spironolactone**

Intake of spironolactone was strongly associated with aldosterone levels and weakly with cortisol levels (Table 3) but was not a predictor of mortality risk. When use of spironolactone was forced into models 1 to 3, the HR and CI values for aldosterone and cortisol did not change materially (data not shown).

**Discussion**

The present study identified higher serum levels of cortisol and aldosterone as independent, complementary, and incremental predictors of all-cause mortality risk in consecutively enrolled patients with chronic heart failure of any cause and severity.

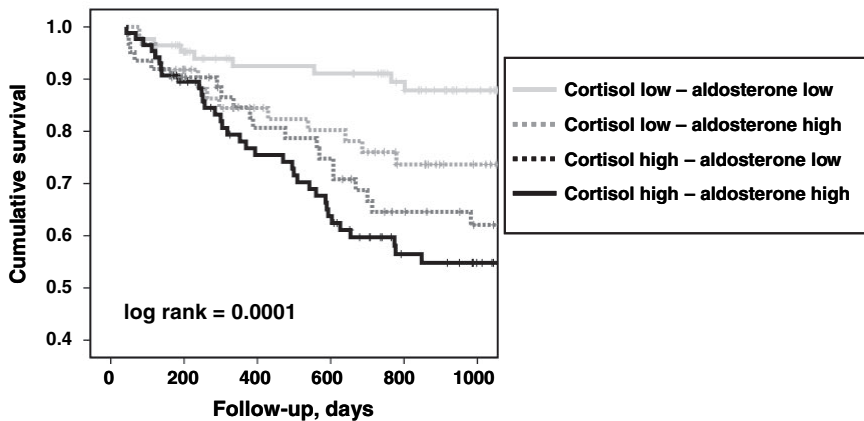
**TABLE 5. Multivariable Cox Regression Analysis of Risk Factors at Baseline for All-Cause Mortality Risk, Approach B: Laboratory Markers Entered as Continuous (Log-Normalized) Variables**

	HR	95% CI	Wald	P
<b>Model 0*</b>				
Age group, per decade	1.04	1.021–1.067	14.75	<0.001
Male sex	1.61	0.961–2.687	3.27	0.070
NYHA class, per class	2.38	1.710–3.312	26.42	<0.001
Hypercholesterolemia, yes vs no	0.41	0.248–0.672	12.43	<0.001
Log C-reactive protein, per SD	1.32	1.044–1.671	5.39	0.020
Log sodium, per SD	0.89	0.720–0.92	4.22	0.041
Log NT-proBNP, per SD	1.61	1.248–2.118	12.95	<0.001
<b>Model 1† log cortisol, per SD</b>	1.54	1.16–2.06	8.79	0.003
<b>Model 2† log aldosterone, per SD</b>	1.29	1.05–1.61	4.99	0.025
<b>Model 3†</b>				
Log cortisol, per SD	1.51	1.12–2.03	7.45	0.006
Log aldosterone, per SD	1.28	1.03–1.56	3.92	0.046

Abbreviations as in Table 2. The standard deviations for the log-normalized variables were: aldosterone, 0.842; cortisol, 0.420; NT-proBNP, 1.547; C-reactive protein, 1.299; sodium, 0.024.

\*Model 0: Cortisol and aldosterone excluded from analysis; age and sex forced into the model

†Models 1–3 include all parameters listed in Model 0.



**Figure 2.** Prognostic utility of the combination of aldosterone and cortisol serum concentrations (Kaplan-Meier plot with levels of corticosteroid hormones dichotomized at their median). Hazard ratio (95% CI) for comparison with the referent (ie, “cortisol low–aldosterone low”): for “cortisol low–aldosterone high”: 2.38 (1.03 to 5.51); for “cortisol high–aldosterone low”: 3.46 (1.58 to 7.61); for “cortisol high–aldosterone high”: 4.54 (2.18 to 9.43).

We demonstrated for the first time the independent prognostic utility of serum cortisol in unselected patients with heart failure. Cortisol is known to unfavorably affect classic cardiovascular risk factors such as hypertension and insulin resistance, which in turn adversely influence survival.<sup>17,18</sup> However, there is increasing evidence that cortisol may also interfere directly with the pathological processes that lead to heart failure progression by binding to and activating cardiac MRs.<sup>11,19</sup> According to a hypothesis proposed by J.W. Funder, cortisol may be the dominant agonist that activates cardiac and vascular MRs under conditions of chronic heart failure.<sup>12,20</sup> Blockade of the MR was effective in the reduction of cardiovascular damage in experimental models with low aldosterone and renin levels and also in patients with low to normal aldosterone levels.<sup>13,21,22</sup> Cortisol and aldosterone exhibit a similar affinity to the MR, and free cortisol circulates at systemic concentrations 2 orders of magnitude higher than aldosterone, which suggests that the beneficial effect of MR blockade in these studies may result from inhibition of cortisol binding to the MR. Under physiological conditions, specific intracellular inhibitory systems counteract cortisol-mediated activation of the MR.

In typical aldosterone targets such as renal, tubular, or vascular smooth muscle cells,  $11\beta$ -hydroxysteroid dehydrogenase type II inactivates cortisol to cortisone and thus mediates specificity of the MR for aldosterone. In contrast, in several nonepithelial cells such as cardiomyocytes, expression of  $11\beta$ -hydroxysteroid dehydrogenase type II is negligibly low. Hence, under physiological conditions most MR are presumably occupied by cortisol.<sup>12</sup> In situations of inflammation and hypoxia, generation of reactive oxygen species and changes in the intracellular redox state may interfere with the cortisol–MR complex and trigger cortisol-mediated activation of the MR.<sup>11</sup> However, despite the powerful prognostic value of cortisol in the present study, it remains uncertain whether the observed increases in cortisol concentration significantly alter cardiac MR activation.

Activation of the hypothalamus-pituitary-adrenal axis is often considered to be a nonspecific indicator of stress or systemic inflammation, which calls into question any causative role of cortisol as a mediator of poor prognosis in cardiac failure. Higher cortisol concentrations have been reported in acute heart failure, cardiac cachexia, and systemic inflammation.<sup>23–25</sup> How-

ever, no such increase in cortisol levels has been found in chronic heart failure. Inclusion of catabolic markers such as low cholesterol in our models did not alter the strength and direction of the observed associations, and no difference existed in cortisol concentrations between NYHA classes. Finally, in our data, C-reactive protein was not a determinant of cortisol levels, neither in crude nor in sex- and age-adjusted analyses. This suggests that the observed association is not merely an indicator of disease severity, cardiac cachexia, or a general inflammatory response. Of note, serum cortisol levels were well within the normal range and were comparable to morning cortisol concentrations in samples of healthy subjects.<sup>26</sup> Thus, no major activation of the hypothalamus-pituitary-adrenal axis during morning hours was evident in our study, a finding that supports the concept that normal circulating cortisol concentrations are sufficient to predominantly activate cardiac MRs in heart failure.

Furthermore, we report a complementary prognostic value of cortisol and aldosterone levels. In contrast to cortisol, the prognostic and pathophysiological role of aldosterone in systolic heart failure is well characterized. Aldosterone participates in numerous detrimental procedures that lead to heart failure progression such as cardiovascular inflammation and fibrosis, endothelial dysfunction, hypertension, and arrhythmia.<sup>27–29</sup> Elevated aldosterone levels serve as a prognostic marker in systolic heart failure and acute ST-elevation myocardial infarction and also correlate inversely with survival.<sup>6,30</sup> In the present study, the prognostic value of both higher aldosterone and cortisol levels remained robust even after multivariable adjustment (Tables 4 and 5). As shown in Figure 2, the combined information on high concentrations of both corticosteroids had an intriguing impact on mortality risk prediction. Moreover, the concurrence of high cortisol and high aldosterone serum levels was an independent prognostic marker for all-cause mortality and increased the HRs of each of the individual corticosteroid hormones. Addition of both corticosteroids to a model that comprised the main multivariate predictors significantly improved the C-statistic, which also implies an incremental prognostic utility of corticosteroids. Hence, it is tempting to speculate that both aldosterone and cortisol play an important role in heart failure progression.

Our results are in line with previously published data and show that the highest tertile of aldosterone is associated with an adverse outcome. In the Randomized Aldactone Evaluation Study (RALES), the Eplerenone Post-AMI Heart Failure Effi-

cacy and Survival Study (EPHESUS), and the 4E Left Ventricular Hypertrophy study,<sup>22,31,32</sup> the beneficial effects of aldosterone blockade were observed despite normal plasma levels of aldosterone, a finding that supports the concept that other ligands also activate the MR under pathological conditions. Cortisol is considered the ideal candidate because it binds to the MR, activates it under certain circumstances, and exceeds plasma aldosterone concentrations by several orders of magnitude. In our study, only patients in the highest aldosterone tertile (ie, plasma levels at a median concentration of 244 pg/mL) showed an association with mortality risk. Thus, the benefit of MR blockade in the trials mentioned above may indeed have resulted from blockade of both cortisol and aldosterone.

Current treatment guidelines emphasize the role of MR blockers in patients with severe chronic systolic heart failure or in patients after myocardial infarction with impaired ejection fraction.<sup>2</sup> We found that the association between higher aldosterone serum levels and all-cause mortality was also observed in subjects with nonsystolic heart failure to a similar degree. This may support the use of MR antagonists in patients with nonsystolic heart failure.<sup>33</sup> For a firm recommendation, however, we look forward to the results of the randomized, double-blind, placebo-controlled TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial) and ALDO-DHF (MR Blockade in Diastolic Heart Failure) trials. TOPCAT will recruit 4500 subjects with left ventricular ejection fraction  $\geq 45\%$ . The primary end point is a composite of cardiovascular mortality, aborted cardiac arrest, or hospitalization for heart failure. ALDO-DHF will recruit 420 subjects with ejection fraction  $\geq 50\%$ . The primary end points are the changes in maximum exercise capacity (spirometry) and diastolic dysfunction.

Other significant predictors of mortality in our analysis were older age, increasing NYHA class, high amino-terminal pro-brain natriuretic protein and C-reactive protein levels, and low sodium and low cholesterol levels, all of which have consistently been related to worse outcome in patients with heart failure.<sup>34–38</sup> In multivariable models, intake of medication was not predictive. In particular, the protective effect of higher cholesterol levels (total cholesterol levels  $\geq 240$  mg/dL) was not modified by statin intake.

Certain limitations need to be considered in the interpretation of the present findings. We investigated a consecutive heterogeneous cohort of patients with chronic heart failure across all NYHA classes who exhibited preserved as well as reduced ejection fraction and who were treated with various drug therapies. In addition, the modest sample size may limit the power of the analyses performed in subgroups. Serum levels of both cortisol and aldosterone were determined only once at baseline. Although the blood samples were drawn in a standardized manner during morning hours, a single sample may inadequately reflect the average adrenal hormone release. However, the determinants of corticosteroid levels as well as the main predictors of mortality risk found in this study were consistent with previous reports.<sup>21, 34–36, 38–40</sup> The investigated cohort represents a typical real-world heart failure population. Our findings may thus be applicable to the heart failure population in general. It remains to be determined whether our study extends to other end points of

clinical relevance in chronic heart failure such as sudden cardiac death, cardiovascular death, or rehospitalization rate. Obviously, conclusions about a specific role of cortisol cannot be drawn on the basis of the present study. Such a role needs to be defined in further studies.

In conclusion, serum levels of both cortisol and aldosterone appeared to be equally strong independent predictors of all-cause mortality risk in patients with systolic and nonsystolic chronic heart failure of any cause. The highest serum concentrations of both cortisol and aldosterone identified a subgroup of chronic heart failure patients with a particularly high mortality risk.

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### Disclosures

None.

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### CLINICAL PERSPECTIVE

Mineralocorticoid receptor (MR) blockade exerts beneficial effects in systolic heart failure even when aldosterone levels are within the normal range, and the MR antagonist spironolactone has become standard in the pharmacotherapy of patients with moderate-to-severe heart failure. Under certain conditions that are part of the heart failure syndrome, such as tissue damage and generation of reactive oxygen species, cortisol may also bind to and agonistically activate MRs in the heart and vasculature and thus mimic the pathophysiological effects of aldosterone. If both corticosteroids induce similar deleterious effects, they might also have a similar prognostic role. The present prospective cohort study in consecutively recruited patients with chronic heart failure of any cause and severity demonstrates the complementary and incremental prognostic value of both cortisol and aldosterone plasma levels in the prediction of all-cause death. Although the study design precludes causal inferences on mechanistic processes, the present study proposes that elevated cortisol levels even within the high normal range are associated with worse outcome. The data support the use of MR antagonists in chronic heart failure to block not only aldosterone but also the putative stimulatory effects of cortisol on MRs in the cardiovascular system.