



# Relationship between B-type natriuretic peptide and invasive haemodynamics in patients with severe aortic valve stenosis

Micha T. Maeder<sup>1\*</sup>, Lukas Weber<sup>1,2</sup> , Peter Ammann<sup>1</sup>, Marc Buser<sup>1</sup>, Niklas F. Ehl<sup>1</sup>, Marc Gerhard<sup>1</sup> , Roman Brenner<sup>1</sup>, Philipp K. Haager<sup>1</sup>, Francesco Maisano<sup>3</sup> and Hans Rickli<sup>1</sup>

<sup>1</sup>Cardiology Division, Kantonsspital St. Gallen, Rorschacherstrasse 95, St. Gallen 9007, Switzerland; <sup>2</sup>Department of Internal Medicine, Spital Rorschach, St. Gallen, Switzerland; <sup>3</sup>Department of Cardiovascular Surgery, University Hospital Zürich, Zürich, Switzerland

## Abstract

**Aims** In patients with aortic stenosis (AS), B-type natriuretic peptide (BNP) is a prognostic marker. However, there is little information on the association between BNP and invasive haemodynamics in AS. The aim of the present study was to assess the hitherto not well-defined relationship between BNP and invasive haemodynamics in patients with severe AS undergoing aortic valve replacement (AVR) with a view to understand the link between high BNP and poor prognosis in these patients. In particular, we were interested in the association between BNP and combined pre-capillary and post-capillary pulmonary hypertension (CpcPH).

**Methods and results** BNP was measured in 252 patients (age  $74 \pm 10$  years, 58% male patients) with severe AS [indexed aortic valve area  $0.4 \pm 0.1$  cm<sup>2</sup>/m<sup>2</sup> and left ventricular ejection fraction (LVEF)  $57 \pm 12\%$ ] the day before cardiac catheterization. Patients were followed for a median (interquartile range) period of 3.1 (2.3–4.3) years after surgical ( $n = 157$ ) or transcatheter ( $n = 95$ ) AVR. The prevalence of CpcPH (mean pulmonary artery pressure  $\geq 25$  mmHg, mean pulmonary artery wedge pressure  $\geq 15$  mmHg, and pulmonary vascular resistance  $> 3$  Wood units) was 13%. The median BNP plasma concentration was 188 (78–452) ng/L. The indexed aortic valve area was similar across BNP quartiles ( $P = 0.21$ ). Independent predictors of higher BNP (ln transformed) included lower haemoglobin (beta =  $-0.18$ ;  $P < 0.001$ ), lower LVEF (beta =  $-0.20$ ;  $P < 0.001$ ), more severe mitral regurgitation (beta =  $0.20$ ;  $P < 0.001$ ), higher mean pulmonary artery wedge pressure (beta =  $-0.37$ ;  $P < 0.001$ ), and higher pulmonary vascular resistance (beta =  $0.21$ ;  $P < 0.001$ ). In a multivariate model with CpcPH rather than its haemodynamic components, CpcPH was independently associated with higher BNP ( $0.21$ ;  $P < 0.001$ ). Higher ln BNP was associated with higher mortality [hazard ratio 1.90 (95% confidence interval 1.33–2.71);  $P < 0.001$ ] in the univariate analysis. Patients in the third and fourth BNP quartiles had a more than six-fold risk of death compared with patients in the first and second quartiles [hazard ratio 6.29 (95% confidence interval 1.86–21.27);  $P = 0.003$ ]. In the multivariate analysis, lower LVEF [hazard ratio 0.96 (95% confidence interval 0.94–0.99) per 1% increase;  $P = 0.01$ ] and CpcPH [hazard ratio 4.58 (95% confidence interval 1.89–11.09);  $P = 0.001$ ] but not BNP were independently associated with mortality. The areas under the receiver operator characteristics curve for BNP for the prediction of CpcPH and mortality were 0.88 and 0.74, respectively.

**Conclusions** In patients with severe AS, higher BNP is a marker of the presence of CpcPH and its contributors. The association between BNP and such an adverse haemodynamic profile at least in part explains the ability of BNP to predict long-term post-AVR mortality.

**Keywords** Natriuretic peptide; Haemodynamics; Pulmonary hypertension; Aortic stenosis; Prognosis; Valve replacement

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\*Correspondence to: Micha T. Maeder, Cardiology Division, Kantonsspital St. Gallen Rorschacherstrasse 95, St. Gallen 9007, Switzerland. Tel: +41 71 494 10 39; Fax +41 71 494 61 42. Email: micha.maeder@kssg.ch

## Introduction

In patients with aortic stenosis (AS), B-type natriuretic peptide (BNP) and the N-terminal part of its precursor peptide, N terminal proBNP (NT-proBNP) are markers of prognosis.<sup>1–4</sup> This applies for both asymptomatic patients managed conservatively in whom BNP predicts the occurrence of symptoms and the need for aortic valve replacement (AVR)<sup>5</sup> and patients undergoing AVR in whom BNP and NT-proBNP predict clinical outcomes after surgical AVR (SAVR)<sup>6</sup> and transcatheter AVR (TAVR), respectively.<sup>2</sup> Higher BNP in AS is associated with lower left ventricular ejection fraction (LVEF) and higher left ventricular mass.<sup>4</sup> However, other information on the pathophysiological correlates of high BNP in AS is sparse. In general, the myocardial release of BNP is thought to be triggered primarily by stretch of left ventricular myocytes<sup>7</sup> and high wall stress.<sup>8,9</sup>

This concept underlies the idea that BNP might identify asymptomatic patients with AS in whom the compensatory mechanisms of the left ventricle start to become maladaptive with the consecutive development of left ventricular diastolic dysfunction and subtle systolic dysfunction leading to an increase in left ventricular end-diastolic pressure (LVEDP). Current guidelines state that a markedly elevated BNP value represents a IIa indication for AVR in asymptomatic subjects with severe AS.<sup>10</sup> However, the relationship between BNP and invasive haemodynamics in patients with severe AS has only been investigated in early small studies looking at a limited set of parameters.<sup>8,11,12</sup> Given the recently reported strong prognostic impact of invasive haemodynamics in patients with AS,<sup>13,14</sup> its relationship with BNP is clinically relevant however.

Therefore, the aim of this study was to assess the hitherto not well-defined relationship between BNP and invasive haemodynamics in patients with severe AS undergoing AVR with a view to understand the link between high BNP and poor prognosis in these patients. In particular, we investigated whether BNP is a marker of pulmonary hypertension and combined pre-capillary and post-capillary pulmonary hypertension (CpcPH), respectively, which both are markers of poor prognosis in AS.<sup>13,15</sup>

## Methods

### Study population

We studied 252 consecutive patients with severe AS undergoing cardiac catheterization in a single centre between January 2011 and January 2016 prior to AVR. This is a retrospective analysis of prospectively and systematically collected haemodynamic data. The study complies with the Declaration of Helsinki. The study was approved by the local ethics

committee. The present study population is a subgroup of a larger cohort we have previously reported on.<sup>13</sup>

### B-type natriuretic peptide measurement

On the day prior to cardiac catheterization, blood was drawn from an antecubital vein and collected in plastic tubes containing ethylene-diamine-tetra-acetate. BNP was measured using a commercially available and well characterized fluorescence immunoassay (Biosite Triage, Biosite Inc., San Diego, CA, USA). All analyses were performed in the clinical laboratory of the Kantonsspital St. Gallen by technicians unaware of any clinical data.

### Cardiac catheterization

Patients underwent coronary angiography using five or six French catheters by femoral or radial access and right heart catheterization using six French Swan Ganz catheters by femoral or brachial access. The mean pulmonary artery pressure (mPAP) and pulmonary artery wedge pressure (mPAWP) were measured. Measurements were obtained at end expiration; the mPAWP was calculated over the entire cardiac cycle, and V waves were included to determine mPAWP. In patients with atrial fibrillation, at least five cardiac cycles were used to assess mPAP and mPAWP. Cardiac output was assessed by the indirect Fick method. The transpulmonary gradient was calculated as mPAP (mPAP) – mPAWP. Pulmonary vascular resistance (PVR) was calculated as transpulmonary gradient/cardiac output. If the aortic valve was crossed, which was at the discretion of the invasive cardiologist, the LVEDP was recorded by a pig-tail catheter ( $n = 159$ ). Pulmonary hypertension was defined as mPAP  $\geq 25$  mmHg, and CpcPH was defined as mPAP  $\geq 25$  mmHg, mPAWP  $> 15$  mmHg, and PVR  $> 3$  Wood units.<sup>16</sup>

### Follow-up

All patients underwent SAVR ( $n = 157$ ) or TAVR ( $n = 95$ ). Information on long-term follow up was obtained from patients, general practitioner, and hospital or practice cardiologists. The clinical endpoint was all-cause mortality.

### Statistical analysis

Categorical data are presented as numbers and percentages, and continuous data are given as mean  $\pm$  standard deviation or median (interquartile range) as appropriate. The population was divided into BNP quartiles. Patient characteristics and non-invasive and invasive haemodynamic measurements were compared across BNP quartiles using  $\chi^2$ -tests, analysis of variance, or Kruskal–Wallis tests. For correlations of

interest, Pearson correlation coefficients were calculated (with ln-transformed BNP values given its skewed distribution). Multivariate linear regression was performed to identify independent predictors of plasma ln BNP. Survival of patients in different BNP quartiles was compared using Kaplan–Meier plots and log rank tests. Multivariate Cox regression was performed to assess independent predictors of mortality. Covariates associated with mortality in the univariate analysis ( $P$  value  $< 0.1$ ) were entered into the multivariate model. We also performed a multivariate logistic regression analysis with BNP in the highest quartiles as the dependent variable. Receiver operator characteristic curves were constructed for the ability of BNP and the BNP ratio to predict the presence of pulmonary hypertension and CpcPH and as well as mortality. Given that BNP depends on age and gender,<sup>17</sup> we also calculated the BNP ratio, i.e. the ratio of the measured BNP divided by the maximal normal value for age and gender.<sup>1</sup> The BNP ratio has previously shown to predict outcomes in patients with asymptomatic AS.<sup>1</sup> Therefore we report results for both BNP and the BNP ratio. A  $P$  value  $< 0.05$  was considered statistically significant. All analyses were performed using SPSS statistical package version 20.0 (SPSS Inc, Chicago, Illinois).

## Results

### Study population

The mean age of the study population ( $n = 252$ ) was  $74 \pm 10$  years, and 58% were male patients. The mean indexed aortic valve area was  $0.4 \pm 0.1$  cm<sup>2</sup>/m<sup>2</sup>, and the mean LVEF was  $57 \pm 12\%$ . The prevalence of pulmonary hypertension was 44% (111/252 patients), and 13% (32/252) of the entire population had CpcPH.

### Clinical characteristics and haemodynamics according to B-type natriuretic peptide quartiles

The median (interquartile) BNP plasma concentration in the entire population was 188 (78–452) ng/L. With increasing BNP quartile, patients were older, had lower estimated glomerular filtration rate, haemoglobin, and forced expiratory volume within the first second; were more symptomatic and more likely to have atrial fibrillation and had higher heart rate; and were more likely to use oral anticoagulants, loop diuretics, spironolactone, and digoxin (Table 1).

The indexed aortic valve area was similar across BNP quartiles (Table 2). However, with higher BNP quartile, left ventricular end-diastolic diameter was larger, LVEF was lower, left atrial area was larger, the prevalence of more severe mitral regurgitation was higher, and tricuspid annular

plane systolic excursion was lower (Table 2). With increasing BNP quartile, patients had a worse haemodynamic profile as reflected by higher right atrial pressure, right ventricular end-diastolic pressure, mPAP, mPAWP, LVEDP, and PVR, lower cardiac index, and stroke volume index, as well as higher prevalence of pulmonary hypertension and CpcPH (Table 2).

### Predictors of high B-type natriuretic peptide

Lower haemoglobin, lower LVEF, more severe mitral regurgitation, higher mPAWP, and higher PVR were independently associated with higher BNP (Table 3). The correlations between BNP and key haemodynamic variables are shown in Figure 1. If the presence of CpcPH rather than the single contributing haemodynamic parameters (mPAP, mPAWP, and PVR) was entered into the model, higher age ( $\beta = 0.21$ ), lower haemoglobin ( $\beta = -0.15$ ), lower forced expiratory volume within the first second ( $\beta = -0.16$ ), lower LVEF ( $\beta = -0.33$ ), more severe mitral regurgitation ( $\beta = 0.22$ ), and presence of CpcPH ( $\beta = 0.21$ ;  $P < 0.01$  for all) were independently associated with higher ln BNP.

If BNP was used as a categorical variable, lower haemoglobin, lower LVEF, and higher mPAWP were independently associated with BNP in the highest quartile (see Supporting Information, Table S1). If the presence of CpcPH rather than the single haemodynamic parameters was entered into the model, lower haemoglobin [odds ratio (OR) 0.95, 95% confidence interval (CI) 0.93–0.98] per 1-g/L increase;  $P < 0.001$ ], lower LVEF [OR 0.91 (95% CI 0.88–0.94) per 1% increase;  $P < 0.001$ ], and presence of CpcPH [OR 17.5 (6.2–49.6);  $P < 0.001$ ] were independently associated with BNP in the highest quartile.

### Clinical outcomes

After a median follow-up of 3.1 (interquartile range 2.3–4.3) years after AVR, there were 22 deaths. In the univariate analysis, BNP as a continuous (Table 4) or categorical (Figure 2) variable was associated with mortality. As shown in Figure 2, patients in the third and fourth BNP quartiles had a more than six-fold higher risk of death than patients in the first and second quartiles [hazard ratio (HR) 6.29 (95% CI 1.86–21.27);  $P = 0.003$ ].

In the multivariate analysis without invasive haemodynamic parameters, more severe mitral regurgitation [HR 1.88 (95% CI 1.04–3.40);  $P = 0.04$ ], presence of chronic obstructive lung disease [HR 3.13 (95% CI 1.26–7.81);  $P = 0.01$ ], and higher ln BNP [HR 1.74 (95% CI 1.16–2.61);  $P = 0.01$ ] were independently associated with higher mortality. In the multivariate analysis including invasive

**Table 1** Clinical characteristics according to B-type natriuretic peptide quartiles

	Q1 (n = 63)	Q2 (n = 63)	Q3 (n = 63)	Q4 (n = 63)	P value
Age (years)	68 ± 11	76 ± 8	78 ± 8	79 ± 10	<0.001
Gender (male)	38 (60%)	37 (59%)	29 (46%)	34 (54%)	0.37
Body mass index (kg/m <sup>2</sup> )	28.4 ± 4.5	28.7 ± 5.8	27.4 ± 5.4	27.0 ± 4.8	0.19
eGFR (mL/min/1.73m <sup>2</sup> )	85 ± 24	75 ± 26	69 ± 28	63 ± 30	<0.001
Haemoglobin (g/L)	142 ± 14	135 ± 15	135 ± 17	126 ± 20	<0.001
Diabetes	10 (16%)	13 (21%)	13 (21%)	17 (30%)	0.50
Stroke	4 (6%)	3 (5%)	6 (10%)	5 (8%)	0.75
Chronic obstructive lung disease	9 (14%)	7 (11%)	10 (16%)	11 (17%)	0.78
FEV1 (% predicted)	88 ± 23	94 ± 19	86 ± 20	76 ± 20	<0.001
Heart rhythm					0.01
Sinus rhythm	63 (100%)	53 (84%)	50 (79%)	48 (76%)	
Atrial fibrillation	0	6 (10%)	7 (11%)	12 (19%)	
Pacing	0	4 (6%)	5 (8%)	3 (5%)	
Other	0	0	1 (2%)	0	
Heart rate (bpm)	70 ± 12	70 ± 11	68 ± 13	75 ± 15	0.02
Medication					
Oral anticoagulation	5 (8%)	10 (16%)	17 (27%)	22 (35%)	0.001
Aspirin	39 (62%)	40 (63%)	38 (60%)	36 (57%)	0.9
Loop diuretics	21 (33%)	28 (44%)	32 (51%)	46 (73%)	<0.001
Beta-blocker	21 (33%)	32 (51%)	30 (48%)	29 (46%)	0.21
ACEI/ARB	34 (54%)	39 (62%)	28 (44%)	31 (49%)	0.24
Digoxin	0	1 (2%)	7 (11%)	13 (21%)	<0.001
Spironolactone	0	2 (3%)	3 (5%)	7 (11%)	0.03
Symptoms					<0.001
Dyspnoea NYHA class					
I	15 (24%)	17 (27%)	11 (17%)	6 (10%)	
II	35 (56%)	34 (54%)	30 (48%)	23 (37%)	
III	13 (21%)	11 (17%)	20 (32%)	20 (32%)	
IV	0	1 (2%)	2 (3%)	14 (22%)	
Mode of AVR					<0.001
SAVR	54 (86%)	43 (68%)	36 (57%)	24 (38%)	
TAVR	9 (14%)	20 (32%)	27 (43%)	39 (62%)	

ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; AVR, aortic valve replacement; eGFR, estimated glomerular filtration rate; FEV1, forced expiratory volume within the first second; NYHA, New York Heart Association; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

Data are given as numbers and percentages, mean ± standard deviation, or median (interquartile range).

haemodynamic parameters, lower LVEF and CpcPH but not BNP were independently associated with mortality (Table 4).

### Accuracy of B-type natriuretic peptide for the prediction of pre-capillary and post-capillary pulmonary hypertension and death

The areas under the receiver operator characteristics curve (AUC) for BNP for the prediction of pulmonary hypertension and CpcPH were 0.80 and 0.88, respectively (Figure 3). The optimal BNP cut-off for the prediction of pulmonary hypertension of 180 ng/L had a sensitivity of 77% and a specificity of 67%. The optimal cut-off for the prediction of CpcPH of 557 ng/L had a sensitivity of 75% and a specificity of 89%. The AUC for BNP for the prediction of death was 0.74 (Figure 3). The optimal BNP cut-off for the prediction of death of 361 ng/L had sensitivity of 73% and a specificity of 72%.

### B-type natriuretic peptide ratio

The BNP ratio quartiles were as follows: 0.47 ± 0.19, 1.35 ± 0.28, 2.87 ± 0.64, and 13.3 ± 11.1. In contrast to the analysis with absolute values, there were no statistically significant differences in age, estimated glomerular filtration rate, and haemoglobin across BNP ratio quartiles (Table S2). However, differences in symptoms and medication were similarly present across BNP ratio quartiles as for absolute BNP quartiles. The indexed aortic valve area was similar in the four BNP ratio quartiles. With increasing BNP ratio quartile, patients had larger left ventricular and left atrial dimensions, worse LVEF and right ventricular function, and a worse haemodynamic profile (Table S3). Independent predictors of higher BNP ratio included lower LVEF, more severe mitral regurgitation, and higher mPAP (Table S4). In the analysis with CpcPH, instead of single haemodynamic parameters as a covariate, lower LVEF and presence of CpcPH emerged as independent predictors of higher BNP ratio (data not shown). In the univariate analysis but not in the multivariate analysis, the BNP ratio was a predictor of mortality (Table S5). Patients

**Table 2** Data from echocardiography and cardiac catheterization according to B-type natriuretic peptide quartiles

	Q1 (n = 63)	Q2 (n = 63)	Q3 (n = 63)	Q4 (n = 63)	P value
<b>Echocardiography</b>					
Left ventricular end-diastolic diameter (mm)	44 ± 6	47 ± 9	47 ± 8	49 ± 7	0.005
Left ventricular ejection fraction (%)	64 ± 7	59 ± 11	58 ± 12	47 ± 13	<0.001
Left atrial area (cm <sup>2</sup> )	20 ± 3	22 ± 6	25 ± 5	31 ± 10	<0.001
Tricuspid annular plane systolic excursion (mm)	23 ± 4	22 ± 5	22 ± 5	19 ± 4	0.006
Mean aortic valve gradient (mmHg)	43 ± 12	44 ± 17	48 ± 17	46 ± 18	0.37
Aortic valve area (cm <sup>2</sup> )	0.85 ± 0.22	0.87 ± 0.26	0.77 ± 0.23	0.75 ± 0.23	0.01
Indexed aortic valve area (cm <sup>2</sup> /m <sup>2</sup> )	0.43 ± 0.10	0.44 ± 0.15	0.41 ± 0.13	0.40 ± 0.12	0.21
Mitral regurgitation					<0.001
No	48 (76%)	27 (43%)	20 (32%)	8 (13%)	
Mild	8 (13%)	25 (40%)	36 (57%)	38 (60%)	
Moderate	2 (3%)	3 (5%)	4 (6%)	12 (19%)	
Severe	0	1 (2%)	3 (5%)	2 (3%)	
Coronary artery disease					0.07
None	38 (60%)	29 (46%)	28 (44%)	26 (41%)	
1-vessel disease	15 (24%)	10 (16%)	10 (16%)	9 (14%)	
2-vessel disease	5 (8%)	8 (13%)	13 (21%)	14 (22%)	
3-vessel disease	5 (8%)	16 (25%)	11 (17%)	13 (21%)	
<b>Invasive haemodynamics</b>					
Mean right atrial pressure (mmHg)	5 ± 2	6 ± 3	6 ± 3	9 ± 5	<0.001
Right ventricular end-diastolic pressure (mmHg)	7 ± 3	7 ± 3	8 ± 3	11 ± 6	<0.001
mPAP (mmHg)	18 ± 5	22 ± 6	25 ± 7	36 ± 12	<0.001
mPAWP (mmHg)	10 ± 4	13 ± 6	16 ± 6	24 ± 8	<0.001
Pulmonary vascular resistance (Wood units)	1.7 ± 0.7	1.8 ± 0.7	2.2 ± 1.4	3.2 ± 1.9	<0.001
Left ventricular end-diastolic pressure (mmHg) (n = 159)	17 ± 6	21 ± 6	22 ± 7	25 ± 8	<0.001
Pulmonary hypertension	9 (14%)	21 (33%)	30 (48%)	51 (81%)	<0.001
Combined pre-capillary and post-capillary pulmonary hypertension	1 (2%)	1 (2%)	5 (8%)	25 (40%)	<0.001
Mean aortic pressure (mmHg)	99 ± 15	100 ± 15	97 ± 12	94 ± 15	0.09
Systemic vascular resistance (Wood units)	18.8 ± 3.8	20.1 ± 5.2	21.5 ± 5.5	21.6 ± 5.3	0.004
Cardiac output (L/min)	5.2 ± 0.8	4.9 ± 1.0	4.4 ± 1.0	4.0 ± 0.9	<0.001
Cardiac index (L/min/m <sup>2</sup> )	2.6 ± 0.4	2.5 ± 0.5	2.3 ± 0.7	2.2 ± 0.6	0.001
Stroke volume (mL)	76 ± 15	72 ± 17	66 ± 19	57 ± 17	<0.001
Stroke volume index (mL/m <sup>2</sup> )	38 ± 8	36 ± 8	35 ± 11	30 ± 10	<0.001

mPAP, mean pulmonary artery pressure; mPAWP, mean pulmonary artery wedge pressure.

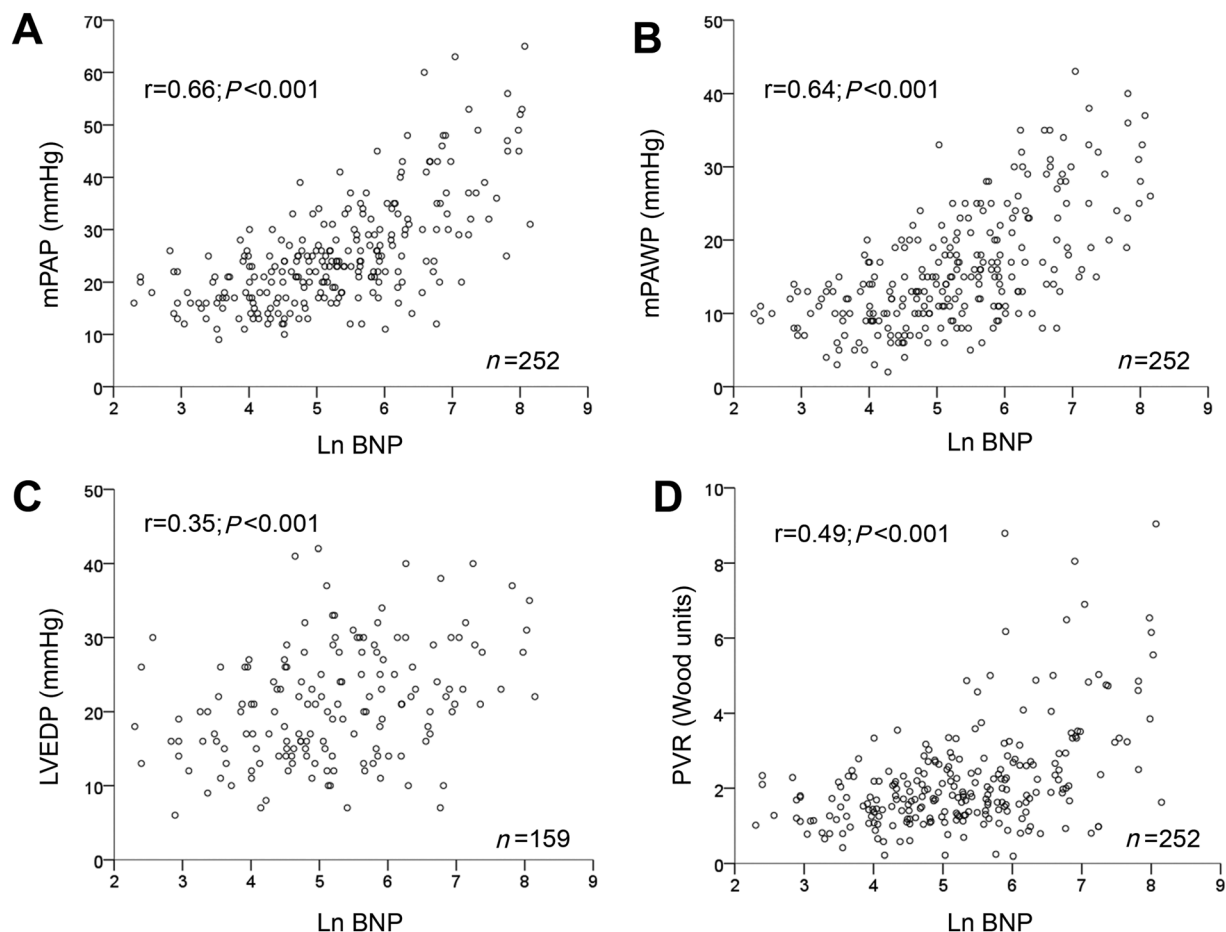
Data are given as numbers and percentages, mean ± standard deviation, and/or median (interquartile range).

**Table 3** Univariate and multivariate linear regression analyses with B-type natriuretic peptide (ln transformed) as the dependent variable ( $r^2 = 0.59$ )

	Univariate analysis		Multivariate analysis	
	$\beta$	P value	$\beta$	P value
Age	0.36	0.001		
eGFR	-0.29	<0.001		
Haemoglobin	-0.31	<0.001	-0.18	<0.001
FEV1	-0.24	<0.001		
Heart rhythm	0.21	0.001		
Heart rate	0.15	0.02		
Left ventricular ejection fraction	-0.49	<0.001	-0.20	<0.001
Tricuspid annular plane systolic excursion	-0.31	0.001		
Indexed aortic valve area	-0.17	0.01		
Mitral regurgitation severity	0.48	<0.001	0.21	<0.001
Coronary artery disease severity	0.14	0.03		
Mean right atrial pressure	0.40	<0.001		
Right ventricular end-diastolic pressure	0.36	<0.001		
mPAP	0.66	<0.001		
mPAWP	0.64	<0.001	0.37	<0.001
Pulmonary vascular resistance	0.49	<0.001	0.21	<0.001
Mean aortic pressure	-0.18	0.005		
Systemic vascular resistance	0.22	0.001		
Stroke volume index	-0.30	<0.001		
Cardiac index	-0.30	<0.001		

eGFR, estimated glomerular filtration rate; FEV1, forced expiratory volume within the first second; mPAP, mean pulmonary artery pressure; mPAWP, mean pulmonary artery wedge pressure.

**Figure 1** Scatter plots showing the correlations (Pearson correlation coefficients) between B-type natriuretic peptide (BNP; logarithmic scale) and mean pulmonary artery pressure (mPAP; panel A), mean pulmonary artery wedge pressure (mPAWP; panel B), left ventricular end-diastolic pressure (LVEDP; panel C), and pulmonary vascular resistance (PVR; panel D).

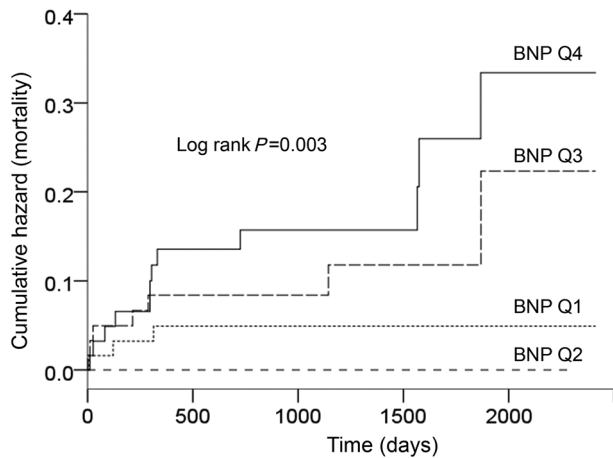


**Table 4** Univariate and multivariate Cox regression analyses with mortality as the dependent variable

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% confidence interval)	P value	Hazard ratio (95% confidence interval)	P value
Age	1.051 (0.999–1.106) per year	0.06		
Chronic obstructive lung disease	2.99 (1.22–7.34)	0.02		
Oral anticoagulation	2.73 (1.17–6.39)	0.02		
eGFR	0.98 (0.97–0.99) per mL/min/1.73 m <sup>2</sup>	0.048		
Left ventricular ejection fraction	0.95 (0.93–0.98) per %	<0.001	0.96 (0.94–0.99) per %	0.01
Combined pre-capillary and post-capillary pulmonary hypertension	6.51 (2.81–15.08)	<0.001	4.58 (1.89–11.09)	0.001
Mean aortic valve gradient	0.97 (0.94–1.00) per mmHg	0.06		
Mitral regurgitation	2.27 (1.41–3.67) per grade	0.001		
FEV1	0.97 (0.95–0.99) per %	0.003		
TAVR vs. SAVR	2.70 (1.15–6.36)	0.02		
ln BNP	1.90 (1.33–2.71)	<0.001		

BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; FEV1, forced expiratory volume within the first second; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

**Figure 2** Kaplan–Meier plots showing the cumulative incidence of death in the four B-type natriuretic peptide quartiles (BNP; Q1, lowest BNP values; and Q4, highest BNP values).



in the highest BNP ratio quartile had a more than four-fold risk of death compared with those in quartiles 1 to 3 [HR 4.03 (95% CI 1.84–10.09);  $P = 0.001$ ]. As shown in *Figure 3*, the AUCs for the BNP ratio for the prediction of pulmonary hypertension, CpcPH, and death were similar to BNP.

## Discussion

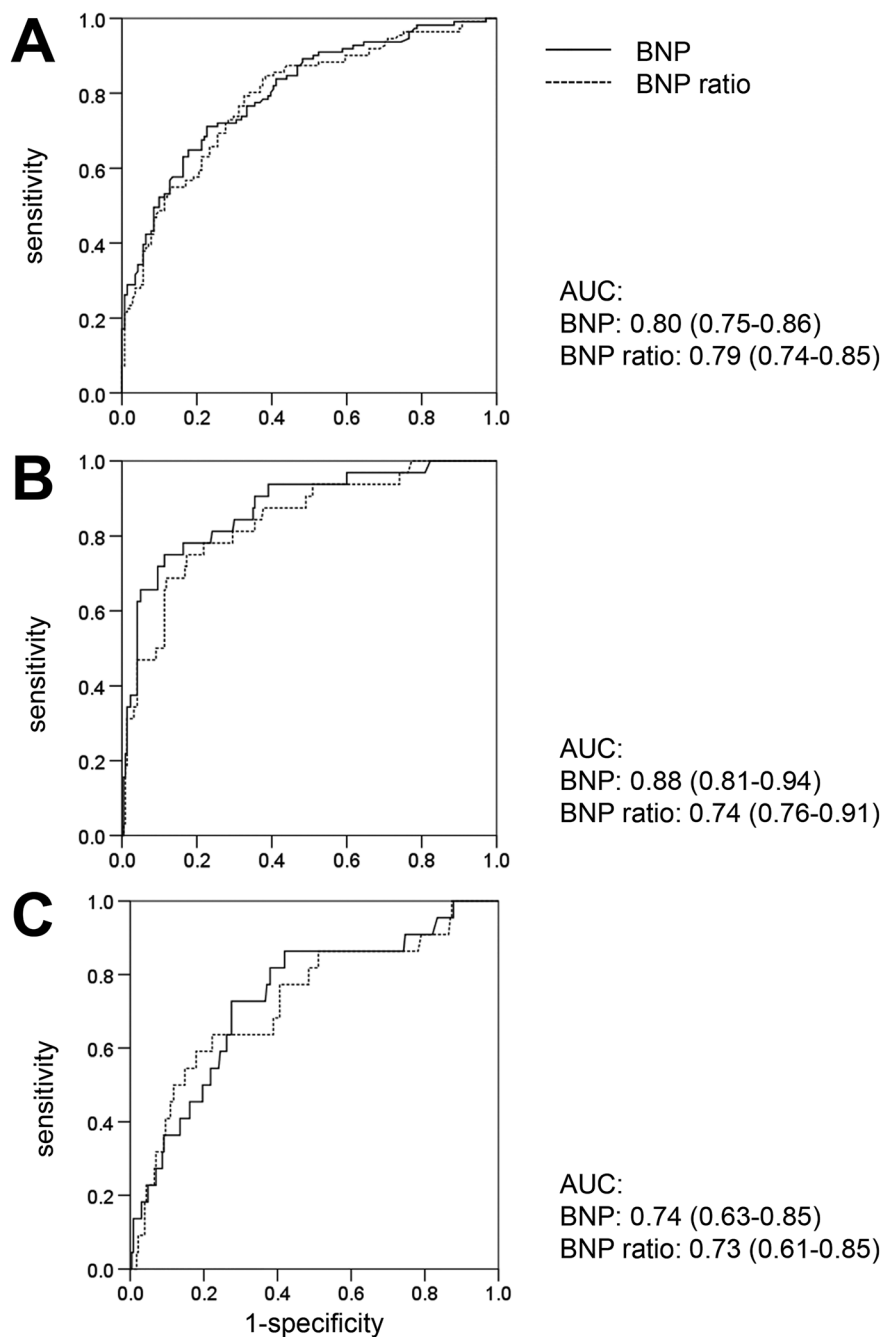
The present study provides the first detailed analysis of the invasive haemodynamic correlates of plasma BNP concentrations in a larger population of patients with severe AS. We showed that BNP is not a marker of the severity of AS *per se* but its consequences on the left ventricle and left atrium and the resulting effects on mPAWP and the pulmonary vasculature. Lower LVEF, more severe mitral regurgitation, higher mPAWP, and higher PVR were independently associated with higher BNP. While the correlations between BNP and single haemodynamic parameters were moderately strong, BNP was closely associated with the presence of CpcPH. We also confirmed the strong prognostic value of BNP as a predictor of long-term mortality after AVR. The present data suggest that the association between BNP and mortality is at least in part mediated by the fact that BNP is a marker of haemodynamics (*Figure 4*).

Natriuretic peptides are very frequently used biomarkers in clinical practice. Still, relatively little is known about the detailed mechanisms leading to the cardiac production and release of BNP and NT-proBNP. Myocyte stretch has, among other stimuli, been shown to lead to BNP release in experimental studies.<sup>7</sup> Human studies with measurements of BNP in arterial and coronary sinus plasma in patients with heart failure with reduced and preserved LVEF and healthy controls

have revealed a relationship between the transcardiac BNP gradient and left ventricular end-diastolic and end-systolic wall stress.<sup>9</sup> For patients with AS associations between higher BNP and higher New York Heart Association class, higher AS severity, higher left ventricular mass, and lower LVEF have been reported previously (summarized by Parikh *et al.*<sup>4</sup>). Small invasive studies in patients with AS had revealed associations between BNP and left ventricular end-systolic wall stress<sup>11</sup> and mPAWP.<sup>8</sup> Thus, despite a guideline recommendation for high BNP as trigger for AVR in asymptomatic patients with severe AS,<sup>10</sup> there has been very limited information as to whether BNP in AS really reflects haemodynamic parameters of interest. In the first larger and detailed invasive haemodynamic study on BNP in AS, we have shown that BNP in patients with severe AS is indeed a marker of the most important maladaptive effects of severe AS including reduced LVEF, significant mitral regurgitation, and elevated mPAWP and PVR.

While the associations between BNP and single haemodynamic parameters were moderately strong, the presence of CpcPH outperformed all these parameters in the multivariate analysis. The AUC for BNP for the prediction of CpcPH was 0.88, which is attractive for a blood biomarker because the non-invasive assessment of pulmonary hypertension and the underlying haemodynamic mechanisms are notoriously challenging,<sup>15</sup> and right heart catheterization only can definitely reveal the haemodynamic constellation. The definition of CpcPH is based on several parameters, i.e. mPAP, mPAWP, and PVR, and the presence CpcPH in AS represents an advanced disease stage with left ventricular and left atrial dysfunction, pulmonary vascular remodelling, and right ventricular dysfunction.<sup>13</sup> Because pulmonary hypertension and CpcPH, respectively, do not directly impose stress on the left ventricle, the right ventricle is likely to contribute to cardiac BNP release in patients with AS and CpcPH as suggested for patients with pulmonary arterial hypertension.<sup>18,19</sup> In patients with pulmonary arterial hypertension, BNP and NT-proBNP are established prognostic markers,<sup>16,20</sup> and several studies in patients with pulmonary arterial hypertension have shown a direct relationship between BNP and/or NT-proBNP and PVR,<sup>21,22</sup> which is in line with the present findings. A study from our research group has shown correlations between higher transcardiac BNP and NT-proBNP gradients (i.e. the difference between the natriuretic plasma concentrations in the coronary sinus and the natriuretic peptide plasma concentrations in the aorta, a measure of the cardiac release of BNP and NT-proBNP) and higher PVR, lower tricuspid annular plane systolic excursion, smaller left ventricular end-diastolic volume index, and higher left ventricular eccentricity index.<sup>19</sup> Although the coronary sinus does not receive the complete venous drainage of the right ventricle, increased BNP and NT-proBNP release from the right ventricle seems to be very likely. Taken together, these data collectively suggest that increased plasma concentrations of

**Figure 3** Receiver operator characteristics curves for B-type natriuretic peptide (BNP) and the BNP ratio for the prediction of pulmonary hypertension (panel A), combined pre-capillary and post-capillary pulmonary hypertension (panel B), and mortality (panel C). The areas under the curve (AUC) are reported.



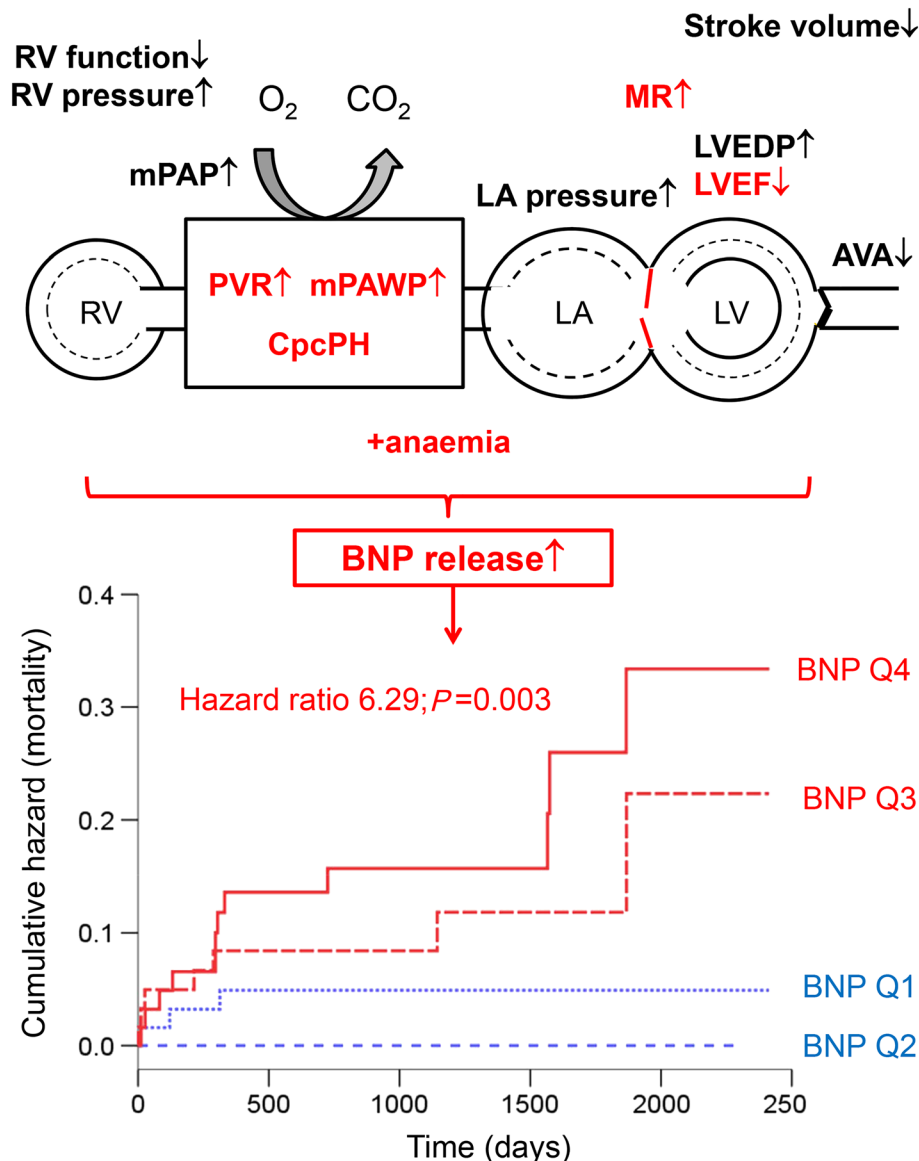
natriuretic peptides in pulmonary arterial hypertension and potentially also in CpcPH are due to increased release from the right ventricle due to increased right ventricular wall stress.

In accordance with previous studies,<sup>1-6</sup> we found a strong association between BNP and mortality after AVR. However, if invasive haemodynamic parameters were entered into the

multivariate model, BNP was not an independent predictor of death anymore. This suggests that the prognostic value of BNP in this setting is to a relevant degree mediated by the fact that BNP is a marker of haemodynamics. It is well known that pulmonary hypertension can persist after AVR and that such a constellation is associated with poor prognosis.<sup>15</sup> It is unknown but may be speculated that these



**Figure 4** Schematic representation of the key haemodynamic measures (red) reflecting the maladaptive effects of severe aortic stenosis associated with increased plasma concentrations of B-type natriuretic peptide (BNP; top) and the strong long-term prognostic impact of high BNP (bottom). The hazard ratio refers to the comparison of quartiles (Q) 4 and 3 (red, poor prognosis) vs. Q2 and 1 (blue, favourable prognosis).



are patients with a constellation of CpcPH prior to AVR. In such patients, AVR may not always lead to the desired clinical benefit, and importantly, persistent CpcPH after AVR does not respond to pulmonary arterial hypertension therapeutics.<sup>23</sup> Thus, high BNP in a patient with AS may trigger a more detailed assessment including left and right heart catheterizations, which are currently not recommended as a routine procedure in patients evaluated for AVR. Although AVR reduces the left ventricular afterload, natriuretic peptides are not always reduced after AVR.<sup>24</sup> In a recent study among 704 patients undergoing TAVR, there was a rise in NT-proBNP from pre-TAVR to discharge in nearly 50% of patients. Both

high pre-TAVR NT-proBNP and a post-TAVR rise in NT-proBNP predicted mortality.<sup>24</sup> The haemodynamic correlate of the post-TAVR rise in NT-proBNP remains unknown, but this observation clearly highlights that a more detailed non-invasive and invasive evaluation pre-AVR and post-AVR is required to understand the impact of AVR on haemodynamics and who will benefit most from AVR and/or additional medical therapy.

Several non-cardiac factors are known to affect plasma concentrations of circulating BNP including age, gender, body mass index, renal function, and haemoglobin.<sup>25</sup> It has therefore been suggested not to use absolute BNP values

but the so-called BNP ratio, i.e. the ratio between the effective BNP and the maximal normal BNP value for a given age category and sex.<sup>1</sup> In a previous study in a large population of patients with at least moderate AS, the BNP ratio was a strong predictor of mortality.<sup>1</sup> We therefore repeated the statistical analysis with the BNP ratio instead of absolute BNP values, and although this eliminated differences in age and estimated glomerular filtration rate across quartiles, the strong association between higher BNP quartile and worse haemodynamics persisted. We found an independent association between higher BNP and lower haemoglobin, which was not present anymore in the analysis with the BNP ratio. Thus, while interpreting absolute BNP values in patients with AS, extracardiac factors have to be taken into account, which is in line with the guideline recommendation where the use of age-corrected and sex-corrected BNP values is proposed for decision making regarding AVR in asymptomatic patients with severe AS.<sup>10</sup> However, the BNP ratio was not superior to absolute BNP for the prediction of CpcPH and mortality.

### Limitations

First, although this represents the first larger study on BNP and haemodynamics in AS patients, the number of patients was still moderate. In addition, selection of the mode of AVR was not randomized, and thus the prognostic impact of TAVR vs. SAVR (Table 4) must be interpreted carefully because the TAVR group was much sicker. Second, although all patients had an echocardiogram, not all parameters of interest were measured in a systematic manner. In particular, information on left ventricular dimensions (wall thickness and diameter) was not available in all patients; and therefore, wall stress could not be calculated. Third, there is an established impact of atrial fibrillation on BNP,<sup>26</sup> and this is also reflected by the present data (Tables 1 and 3). However, because we only labelled patients as having atrial fibrillation, if they had atrial fibrillation on admission and during cardiac catheterization, we probably have missed patients with paroxysmal atrial fibrillation. This speculation is supported by the fact that there were patients on oral anticoagulation but without atrial fibrillation. Patients in sinus rhythm and on oral anticoagulation had higher BNP levels than those in sinus rhythm without oral anticoagulation (data not shown), which is highlighting this limitation.

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### Conclusions

In patients with severe AS, higher BNP is a marker of the presence of CpcPH and its contributors. The association between BNP and such an adverse haemodynamic profile at least in part explains the ability of BNP to predict long-term post-AVR mortality.

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### Conflict of interest

None declared.

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None

### Supporting information

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

**Table S1.** Univariate and multivariate logistic regression analysis with BNP in Q4 as the dependent variable.

**Table S2.** Clinical characteristics according to B-type natriuretic peptide (BNP) ratio quartiles

**Table S3.** Data from echocardiography and cardiac catheterization according to B-type natriuretic peptide (BNP) quartiles

**Table S4.** Univariate and multivariate linear regression analysis with BNP ratio (ln-transformed) as the dependent variable ( $r^2 = 0.52$ ).

**Table S5.** Univariate and multivariate Cox regression analysis with mortality as the dependent variable.

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