Online Supplementary Materials

for the following *Heart* article

TITLE: Prognostic Value of Plasma B-Type Natriuretic Peptide Levels After Exercise in Patients with Severe Asymptomatic Aortic Stenosis

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SUPPLEMENTARY FIGURE LEGENDS

SUPPLEMENTARY FIGURE S1: Comparison of the event-free survival curves for tertiles of peak-exercise BNP level and tertiles of delta BNP levels in the whole cohort (n=211).

Caption: This figure shows the event-free survival curves for the composite end-point of death or aortic valve replacement according to tertiles of peak exercise BNP level (Panel A) and tertiles of delta BNP levels (Panel B) in the whole cohort (n=211). The symbols indicate the significant differences between groups: * $p<0.05$ versus "Tertile1"; ¶ $p<0.05$ versus "Tertile2". The numbers at the bottom of the graph represent the number of patients at risk at each follow-up year. The p value is that of the log-rank test.

SUPPLEMENTARY FIGURE S2: Comparison of the event-free survival curves for median peak-exercise BNP level in the subsets of patients with high and low resting BNP level in the whole cohort (n=211).

Caption: This figure shows the event-free survival curves in the whole cohort (n=211) for the composite end-point of death or aortic valve replacement in the subset of patients with low vs. high resting BNP level (full vs. dotted lines, respectively), according to low vs. high peak-exercise BNP (red vs. blue curves, respectively). The symbols indicate the significant difference between groups: * $p<0.05$ versus "Low resting – Low peak-exercise BNP level"; ¶ $p<0.05$ versus "Low resting – High peak-exercise BNP level"; § $p<0.05$ versus "High resting – Low peak-exercise BNP level". The numbers at the bottom of the graph represent the number of patients at risk at each follow-up year. The p value is that of the log-rank test.

SUPPLEMENTARY TABLE S1: Impact of BNP Level on Event-Free Survival in the Whole Cohort (n=211)

	Individual		Multivariate Models #1		Multivariate Models #2	
	HR (95% CI)	**p value**	**HR** (95% CI)	**p value**	**HR** (95% CI)	**p value**
Resting BNP level						
Resting BNP level (per 100 pg/ml increase)	**1.6** (1.3-1.9)	<0.0001	**1.4** (1.1-1.7)	0.004	–	–
Peak-exercise BNP level						
Peak-exercise BNP level (per 100 pg/ml increase)	**1.6** (1.4-1.8)	<0.0001	**1.4** (1.2-1.6)	<0.0001	–	–
Tertiles of peak-exercise BNP level						
Tertile 1 (6 to 42 pg/ml)	**1.0** (referent)	–	**1.0** (referent)	–	**1.0** (referent)	–
Tertile 2 (43 to 92 pg/ml)	**2.6** (1.5-4.7)	0.0007	**2.3** (1.3-4.4)	0.005	**2.3** (1.3-4.3)	0.007
Tertile 3 (92 to 956 pg/ml)	**5.9** (3.5-10.5)	<0.0001	**4.8** (2.7-9.0)	<0.0001	**4.5** (2.3-9.0)	<0.0001
Resting BNP level (per 100 pg/ml increase)	**1.6** (1.3-1.9)	<0.0001	–	–	**1.1** (0.8-1.4)	0.63
Delta of BNP levels						
Absolute difference of BNP levels (per 100 pg/ml increase from rest)	**3.4** (2.5-4.7)	<0.0001	–	–	**2.7** (1.7-4.1)	<0.0001
Resting BNP level (per 100 pg/ml increase)	**1.6** (1.3-1.9)	<0.0001	–	–	**1.1** (0.8-1.3)	0.69

Tertiles of delta BNP levels						
Tertile 1 *(-54 to 3)*	**1.0** (referent)	_	**1.0** (referent)	_	**1.0** (referent)	_
Tertile 2 *(4 to 19)*	**2.7** (1.5-5.1)	0.0009	**2.7** (1.4-5.6)	0.002	**2.7** (1.4-5.5)	0.002
Tertile 3 *(19 to 337)*	**6.4** (3.6-12.1)	<0.0001	**5.9** (3.1-12.1)	<0.0001	**5.3** (2.7-11.0)	<0.0001
Resting BNP level *(per 100 pg/ml increase)*	**1.6** (1.3-1.9)	<0.0001	_	_	**1.2** (0.9-1.5)	0.10

Legend: BNP: B-type natriuretic peptides; HR: hazard ratio; CI: confidence interval. Models #1 included age, gender, mean transvalvular gradient, valvulo-arterial impedance, indexed left atrial area, and exercise-induced increase in heart rate, mean transvalvular gradient, and valvulo-arterial impedance; Models #2 were Models #1 plus resting BNP level.

SUPPLEMENTARY TABLE S2: Impact of tertiles of resting BNP Level on Event-Free Survival in Severe AS patients (n=157; 74%)

	Individual		**Multivariate Model #1**		**Multivariate Model #2**	
	HR (95% CI)	**p value**	**HR (95% CI)**	**p value**	**HR (95% CI)**	**p value**
Tertiles of resting BNP level						
Tertile 1 *(4 to 35 pg/ml)*	**1.0** (referent)	_	**1.0** (referent)	_	**1.0** (referent)	_
Tertile 2 *(36 to 67 pg/ml)*	**1.8** (1.0-3.3)	0.06	**1.8** (0.9-3.4)	0.08	**1.6** (0.8-3.0)	0.16
Tertile 3 *(68 to 843 pg/ml)*	**3.7** (2.1-6.6)	<0.0001	**3.0** (1.6-6.0)	0.001	**2.0** (1.0-4.2)	0.06
Peak-ex BNP level *(per 100 pg/ml increase)*	**1.5** (1.4-1.7)	<0.0001	_	_	**1.4** (1.1-1.6)	0.002

Legend: BNP: B-type natriuretic peptides; HR: hazard ratio; CI: confidence interval. Model #1 included age, gender, mean transvalvular gradient, valvulo-arterial impedance, indexed left atrial area, and exercise-induced increase in heart rate, mean transvalvular gradient, and valvulo-arterial impedance; Model #2 was Model #1 plus resting BNP level.

SUPPLEMENTARY TABLE S3: Reclassification of Patients with Severe AS (n=157) for 1-Year Events using Model with Peak-Ex BNP in a 2-Category Net Reclassification Improvement Analysis

		Model with established risk factors and peak-ex BNP	
		<28% Risk	≥28% Risk
Participants with events at 1 year (n=42)			
Model with established risk factors	<28% Risk	10	4
	≥28% Risk	4	24
Participants without events at 1 year (n=92)			
Model with established risk factors	<28% Risk	60	1
	≥28% Risk	17	14

Legend: BNP: B-type natriuretic peptides; peak-ex: peak-exercise; NRI: net reclassification improvement. Established risk factors included age, gender, mean transvalvular gradient, valvulo-arterial impedance, indexed left atrial area, and exercise-induced changes in heart rate, mean transvalvular gradient and valvulo-arterial impedance.

SUPPLEMENTARY TABLE S4: Reclassification of Patients with Severe AS (n=157) for 1-Year Events using Model with Peak-Ex BNP in a 3-Category Net Reclassification Improvement Analysis

		Model with established risk factors and peak-ex BNP		
		<19% Risk	19-35% Risk	≥35% Risk
Participants with events at 1 year (n=42)				
Model with established risk factors	<19% Risk	6	0	1
	19-35% Risk	0	5	5
	≥35% Risk	1	5	19
Participants without events at 1 year (n=92)				
Model with established risk factors	<19% Risk	31	6	0
	19-35% Risk	19	15	1
	≥35% Risk	1	10	9

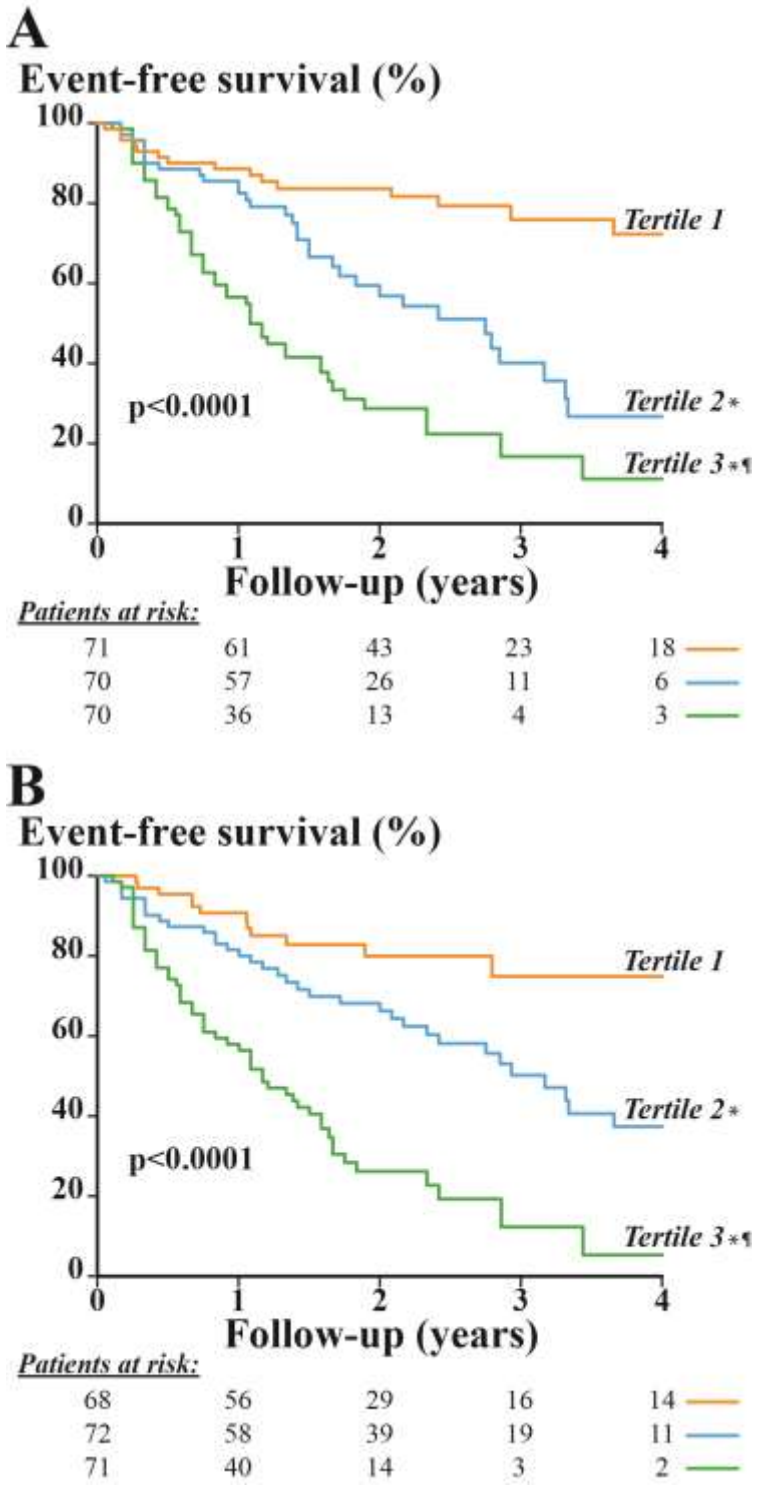
Legend: BNP: B-type natriuretic peptides; peak-ex: peak-exercise; NRI: net reclassification improvement. Established risk factors included age, gender, mean transvalvular gradient, valvulo-arterial impedance, indexed left atrial area, and exercise-induced changes in heart rate, mean transvalvular gradient, and valvulo-arterial impedance.

SUPPLEMENTARY TABLE S5: Impact of the best cut-point values for resting and peak-ex BNP Levels on Event-Free Survival in Patients with Severe AS (n=157)

	Individual		Multivariate Model	
	HR (95% CI)	**p value**	**HR** (95% CI)	**p value**
Best cut-point values				
Resting BNP level	**3.0**	<0.0001	**1.1**	0.86
> 58 pg/ml	(1.9-4.7)		(0.4-2.7)	
Peak-exercise BNP level	**4.1**	<0.0001	**3.5**	0.01
> 86 pg/ml	(2.6-6.5)		(1.3-9.2)	

Legend: BNP: B-type natriuretic peptides; HR: hazard ratio; CI: confidence interval. Multivariate model included age, gender, mean transvalvular gradient, valvulo-arterial impedance, indexed left atrial area, and exercise-induced increase in heart rate, mean transvalvular gradient, and valvulo-arterial impedance.

SUPPLEMENTARY FIGURE S1



SUPPLEMENTARY FIGURE S2