

# Baseline and Serial Brain Natriuretic Peptide Level Predicts 5-Year Overall Survival in Patients With Pulmonary Arterial Hypertension

Data From the REVEAL Registry

*Robert P. Frantz, MD; Harrison W. Farber, MD; David B. Badesch, MD; C. Greg Elliott, MD; Adaani E. Frost, MD; Michael D. McGoon, MD; Carol Zhao, MS; David R. Mink, MS; Mona Selej, MD; and Raymond L. Benza, MD*

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**e-Appendix 1.**

***REVEAL Sites – IRB Name (IRB Approval Number)***

University of Colorado HSC (Colorado Multiple IRB, 06-0235)

Columbia University (CUMC IRB, AAAC0789)

MAYO Clinic-Jackson (MAYO Clinic IRB, 06-002271 00)

Washington University (Washington University Human Research Protection Office (HRPO), 06-0753)

University of Minnesota Medical Center (University of Minnesota Research Subjects' Protection Programs IRB, 0607M89066)

Midwest Heart Foundation (Western IRB, 20060231)

Children's Research Institute at Ohio State (Nationwide Children's IRB, 06-00411)

Ohio State University (Biomedical Institutional Review Board, 2006H0177)

Cleveland Clinic Foundation (Cleveland Clinic Foundation IRB, 06-259)

Intermountain Medical Center and the University of Utah (Intermountain Healthcare IRB, # 1009009)

Boston University School of Medicine (Western IRB, 1081775)

MAYO Clinic College of Medicine, Rochester (MAYO Clinic IRB, 06-00227100)

Baylor College of Medicine (Baylor College of Medicine IRB, H-19065)

University of Chicago Hospitals (The University of Chicago IRB, 14917B)

Georgia's Health Sciences University (Human Assurance Committee [HAC], 06-05-288)

Virginia Commonwealth University (Western IRB, 1090150)

University of Iowas Hospitals & Clinics (The University of Iowa IRB, #200603714)

Johns Hopkins Medical Center (Western IRB, 1078595)

Medical University of South Carolina (Office of Research Integrity (ORI) Medical University of South Carolina IRB, 16617)

Tufts-New England Medical Center (Tufts Health Sciences Campus IRB, 7929)

Children's Hospital Department of Cardiology (Colorado Multiple IRB, 06-0500)

Rhode Island Hospital (Rhode Island Hospital IRB, 4075-06)

University Texas Health Science Center (University of Texas EIRB, HSC 20070383H)

Texas Children's Hospital (Baylor College of Medicine IRB, H-19569)

Legacy Clinic Northwest (1. Oregon Health & Science University, 00002436; 2. Western IRB, 1099977)

University of Pittsburgh School of Medicine (Western IRB, 1077291)

Kentuckiana Pulmonary Associates (Western IRB, 1086454)

UCSF Medical Center (UCSF Committee on Human Research, H46460-29039-01)

Children's Hospital at Vanderbilt (Vanderbilt University IRB, 061152)

University of Florida (Western IRB, 1097909)  
Allegheny General Hospital (Allegheny General Hospital IRB, RC -4088)  
Inova Heart and Vascular Institute (Western IRB, 1079519)  
LA Biomedical Research Institute at Harbor-UCLA (LABioMed, 12722-01)  
University of Maryland School of Medicine (University of Maryland For Human Subject Research IRB, H-28017)  
Vanderbilt University Medical Center (Vanderbilt University IRB, 070020)  
UCLA Medical Center (UCLA IRB, 06-06-118-02A)  
Wayne University (Wayne State University Human Investigation Committee, 064606MP4E)  
University Hospital of Cleveland (University Hospitals IRB, #07-06-28)  
VA Greater Los Angeles Health System (Department of Veterans Affairs IRB, PCC2008-11178)  
Beth Israel Medical Center (Beth Israel IRB, #013-08)  
Penn Lung Center at Penn Presbyterian Medical Center (University of Pennsylvania IRB, 804760)  
University of Alabama at Birmingham (Western IRB, 1078385)  
North Shore University-LIJ Medical Center (BioMedical Research Alliance of New York, 06-02-83-03)  
Duke University Medical Center (Duke University Health System IRB, 8650-06-6R0DB)  
UCSD Medical Center (UCSD Human Research Protection Program, #060466)  
St. Luke's Medical Center –Aurora (Aurora Health Care RSPP, L-06-74E)

**e-Appendix 2.****Results*****OS by PAH etiology***

BNP level was predictive of mortality risk regardless of PAH etiology. Of patients with PAH associated with congenital heart disease, those with a high baseline BNP had an increased mortality risk compared with those with a low baseline BNP (n = 124; HR, 3.7; 95% CI, 1.7-8.3; *P* = .0014). Similar results were observed for patients with connective tissue disease (n = 384; HR, 3.2; 95% CI, 2.3-4.5; *P* < .0001) and all other PAH etiologies (n = 918; HR, 3.4; CI, 2.6-4.4; *P* < .0001).

***BNP Score***

BNP scores were highly correlated with OS, with the highest OS observed in those with the lowest BNP scores and the lowest survival observed in those with the highest BNP scores (Fig 3 in the main text). This is consistent at any time interval (baseline, and at 1, 2, 3, 4, and 5 years). The risk of death correlated proportionally and significantly with the change in BNP score between baseline and post-baseline assessment within 5 years of enrollment (e-Table 2). The greater the increase/decrease in BNP score, the greater the increase/decrease in the risk of death, respectively.

***Sensitivity Analysis***

Comparisons between the four BNP groups were adjusted for prognostic factors that were significantly associated with OS. These included: age, 6MWD, systolic blood pressure, heart rate, PVR, mRAP, WHO Group I diagnosis, and NYHA/WHO FC at enrollment. An additional sensitivity analysis of survival in newly diagnosed patients was conducted. In this analysis, there was a lower risk of death in the low-low (n = 188, 37 events; HR, 0.19; 95% CI, 0.13-0.29; *P* < .0001), low-high (n = 23, 11 events; HR, 0.50; 95% CI, 0.26-0.96; *P* = .0373), and high-low (n = 47, 17 events; HR, 0.37; 95% CI, 0.21-0.63; *P* = .0003) groups when compared with the high-high group (n = 82; 56 events).

**e-Table 1.** Baseline Characteristics of Patients with PAH by BNP Change Group (N = 1426)

Variable	Low-Low (N = 908)	Low-High (N = 143)	P value	High-Low (N = 103)	High-High (N = 272)	P value	Total (N = 1426)
Age, year Mean $\pm$ SD Median	50.4 $\pm$ 14.5 50.8	54.2 $\pm$ 14.0 55.6	.0033	53.2 $\pm$ 14.2 54.7	58.5 $\pm$ 14.1 59.2	.0017	52.5 $\pm$ 14.7 53.3
Sex, n (%)			.2462			.8642	
Male	172 (18.9)	33 (23.1)		23 (22.3)	63 (23.2)		291 (20.4)
Female	736 (81.1)	110 (76.9)		80 (77.7)	209 (76.8)		1135 (79.6)
Race, n (%)			.8974			.5625	
White	671 (73.9)	107 (74.8)		73 (70.9)	203 (74.6)		1054 (73.9)
Black	105 (11.6)	17 (11.9)		20 (19.4)	39 (14.3)		181 (12.7)
Hispanic	83 (9.1)	14 (9.8)		7 (6.8)	19 (7.0)		123 (8.6)
Asian or Pacific Islander	30 (3.3)	4 (2.8)		3 (2.9)	4 (1.5)		41 (2.9)
Native American	6 (0.7)	1 (0.7)		0	1 (0.4)		8 (0.6)
Other	5 (0.6)	0		0	2 (0.7)		7 (0.5)
Unknown	8 (0.9)	0		0	4 (1.5)		12 (0.8)
BMI, kg/m <sup>2</sup> Mean $\pm$ SD Median	n = 896 29.0 $\pm$ 7.1 27.9	n = 141 27.3 $\pm$ 6.3 26.3	.0068	n = 101 28.8 $\pm$ 7.6 27.4	n = 263 26.8 $\pm$ 6.5 25.5	.0111	n=1401 28.4 $\pm$ 7.0 27.1
PAH etiology, n (%)			.0006			< .0001	
Idiopathic	463 (51.0)	57 (39.9)		45 (43.7)	116 (42.6)		681 (47.8)
Familial	28 (3.1)	9 (6.3)		0	8 (2.9)		45 (3.2)



PAH associated with							
CTD	195 (21.5)	51 (35.7)		27 (26.2)	111 (40.8)		384 (26.9)
CHD	93 (10.2)	10 (7.0)		4 (3.9)	17 (6.3)		124 (8.7)
Other	129 (14.2)	16 (11.2)		27 (26.2)	20 (7.4)		192 (13.5)
NYHA/WHO functional class, at diagnosis, n (%)			.6480			.6749	
I	21 (2.3)	6 (4.2)		0	2 (0.7)		29 (2.0)
II	135 (14.9)	20 (14.0)		12 (11.7%)	24 (8.8)		191 (13.4)
III	378 (41.6)	65 (45.5)		50 (48.5)	114 (41.9)		607 (42.6)
IV	68 (7.5)	11 (7.7)		15 (14.6)	43 (15.8)		137 (9.6)
Unknown <sup>a</sup>	306 (33.7)	41 (28.7)		26 (25.2)	89 (32.7)		462 (32.4)
Disease characteristics							
6MWD, m Mean ± SD Median	n = 809 385.3 ± 123.8 392.0	n = 124 365.0 ± 112.0 375.9	.0826	n = 86 332.0 ± 102.8 327.0	n = 219 267.5 ± 124.5 262.0	< .0001	n = 1238 358.7 ± 129.2 365.8
Resting mPAP, mmHg Mean ± SD Median	n = 900 49.0 ± 14.6 48.0	n = 143 48.7 ± 11.9 49.0	.8376	n = 102 52.1 ± 12.9 52.0	n = 271 51.9 ± 12.6 51.0	.8953	n = 1416 49.7 ± 13.9 49
mRAP, mmHg Mean ± SD Median	n = 855 8.1 ± 5.0 8.0	n = 136 9.3 ± 5.6 8.0	.0161	n = 98 11.6 ± 6.0 11.0	n = 248 11.4 ± 5.6 10.5	.7648	n = 1337 9.1 ± 5.4 8
Mixed venous oxygen saturation, % Mean ± SD Median	n = 627 66.0 ± 8.5 67.0	n = 103 63.3 ± 8.9 63.0	.0055	n = 69 58.8 ± 8.9 59.0	n = 158 58.4 ± 10.4 58.0	.7275	n = 957 63.9 ± 9.4 65



Resting PAWP, mmHg Mean ± SD Median	n = 877 9.8 ± 4.0 10.0	n = 139 10.0 ± 4.4 10.0	.5647	n = 99 9.5 ± 4.3 10.0	n = 266 10.3 ± 4.3 10.0	.0896	n = 1381 9.9 ± 4.2 10.0
Cardiac Index, L/min/m <sup>2</sup> Mean ± SD Median	n = 759 2.5 ± 0.9 2.4	n = 122 2.5 ± 0.8 2.4	.9990	n = 83 2.1 ± 0.6 1.9	n = 222 2.1 ± 0.7 2.0	.9871	n = 1186 2.4 ± 0.8 2.3
GFR, mL/min/1.73m <sup>2</sup> Mean ± SD Median	n = 806 80.0 ± 25.7 78.9	n = 127 71.4 ± 25.3 68.9	.0004	n = 98 69.1 ± 23.7 67.4	n = 249 63.1 ± 24.4 62.5	.0449	n = 1280 75.0 ± 26.1 73.5
IV/SC prostacyclin treatment, n (%)	79 (8.7)	12 (8.4%)	.9029	18 (17.5)	21 (7.7)	.0057	130 (9.1)

6MWD = 6-min walk distance; BMI = body mass index; BNP = brain natriuretic peptide; CTD = connective tissue disease; CHD = congenital heart disease; FC = Functional Class; GFR = glomerular filtration rate; IV, intravenous; mPAP = mean pulmonary arterial pressure; mRAP = mean right atrial pressure; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PAWP = pulmonary arterial wedge pressure; SC, subcutaneous; WHO = World Health Organization.  
<sup>a</sup>WHO FC may have been known at baseline but not in follow-up assessment.

**e-Table 2.** Kaplan-Meier Estimates of 5-Year Overall Survival by Baseline BNP Level and PAH Etiology

PAH Etiology	N	BNP ≤340 pg/mL, n (%)	BNP >340 pg/mL, n (%)	Hazard Ratio (95% CI)	P value
CHD	124	103 (83.1)	21 (16.9)	3.7 (1.7-8.3)	.0014
CTD	384	246 (64.1)	138 (35.9)	3.2 (2.3-4.5)	< .0001
Other	918	702 (76.5)	216 (23.5)	3.4 (2.6-4.4)	< .0001

BNP = brain natriuretic peptide; CHD = congenital heart disease; CI = confidence intervals; CTD = connective tissue disease; PAH = pulmonary arterial hypertension.

**e-Table 3.** Overall Survival by BNP Change Adjusted for Prognostic Factors at Enrollment

BNP Change Group	Comparison with Low-Low Group		Comparison with High-High Group	
	Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value
Low-Low	NA		0.22 (0.17-0.29)	<i>P</i> < .0001
Low-High	3.30 (2.41-4.51)	<i>P</i> < .0001	0.72 (0.53-0.99)	<i>P</i> = .0404
High-Low	1.59 (1.04-2.43)	<i>P</i> = .0327	0.35 (0.23-0.53)	<i>P</i> < .0001
High-High	4.58 (3.49-6.00)	<i>P</i> < .0001	NA	

BNP = brain natriuretic peptide; CI = confidence intervals.



**e-Table 4.** Risk of Death According to BNP Score Change from Baseline

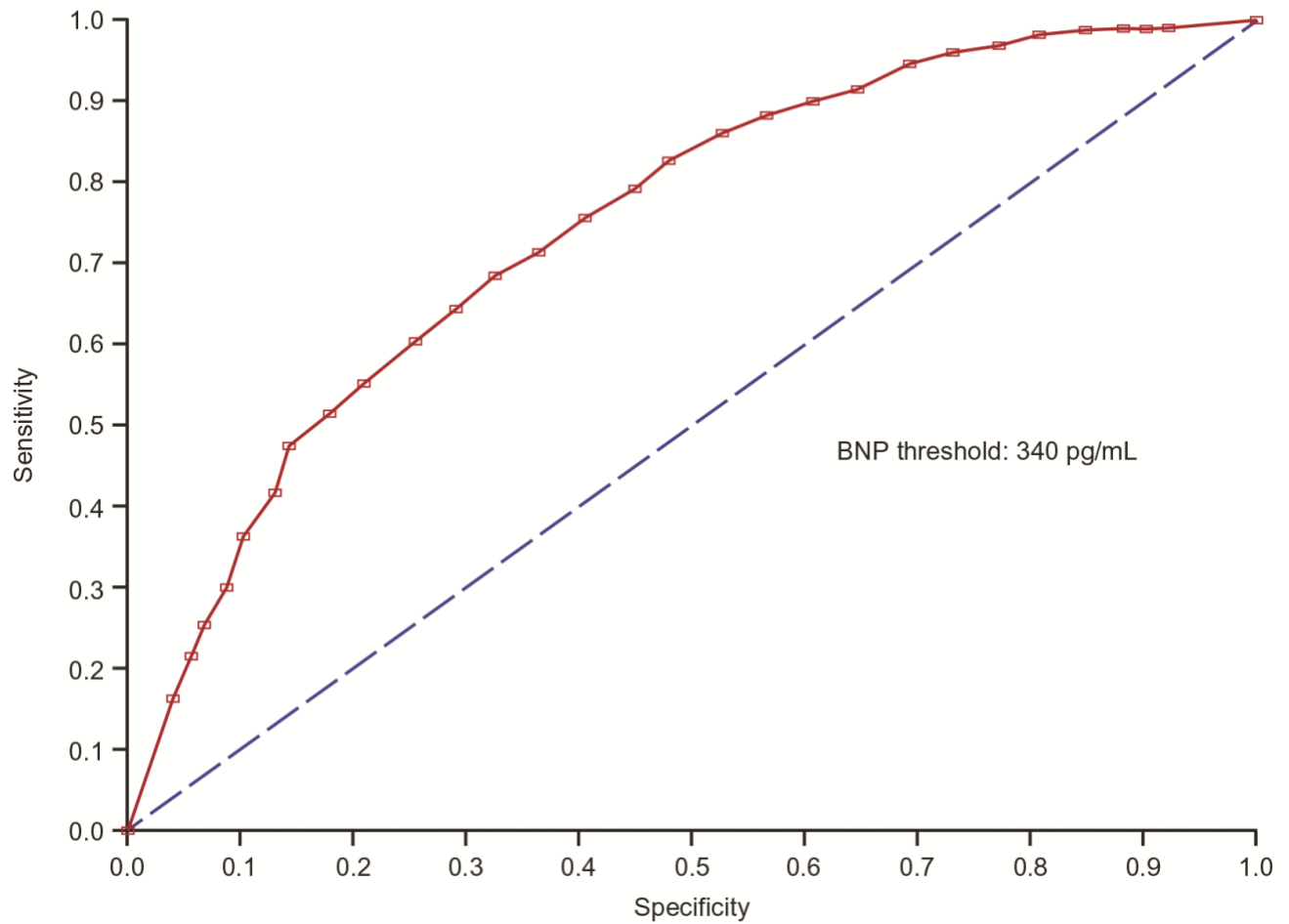
Change in BNP Score <sup>a</sup>	Between Baseline and Last Assessment Within 5 Years Post-enrollment (N = 1426)		Between Baseline and Last Assessment Within 1 Year Post-enrollment (N = 1426)	
	HR <sup>b</sup> (95% CI)	<i>P</i> value	HR <sup>b</sup> (95% CI)	<i>P</i> value
+1	1.7 (1.4-2.1)	< .001	1.5 (1.1-2.0)	.006
+2	4.1 (3.2-5.2)	< .001	3.7 (2.4-5.6)	< .001
+3 ≥	7.7 (5.6-10.8)	< .001	6.3 (3.5-11.6)	< .001
-1	0.7 (0.5-0.8)	< .001	0.7 (0.5-1.0)	.023
-2	0.4 (0.3-0.6)	< .001	0.4 (0.3-0.7)	.001
-3 ≥	0.3 (0.2-0.4)	< .001	0.3 (0.1-0.6)	< .001

BNP = brain natriuretic peptide; CI = confidence intervals; HR = hazard ratio.

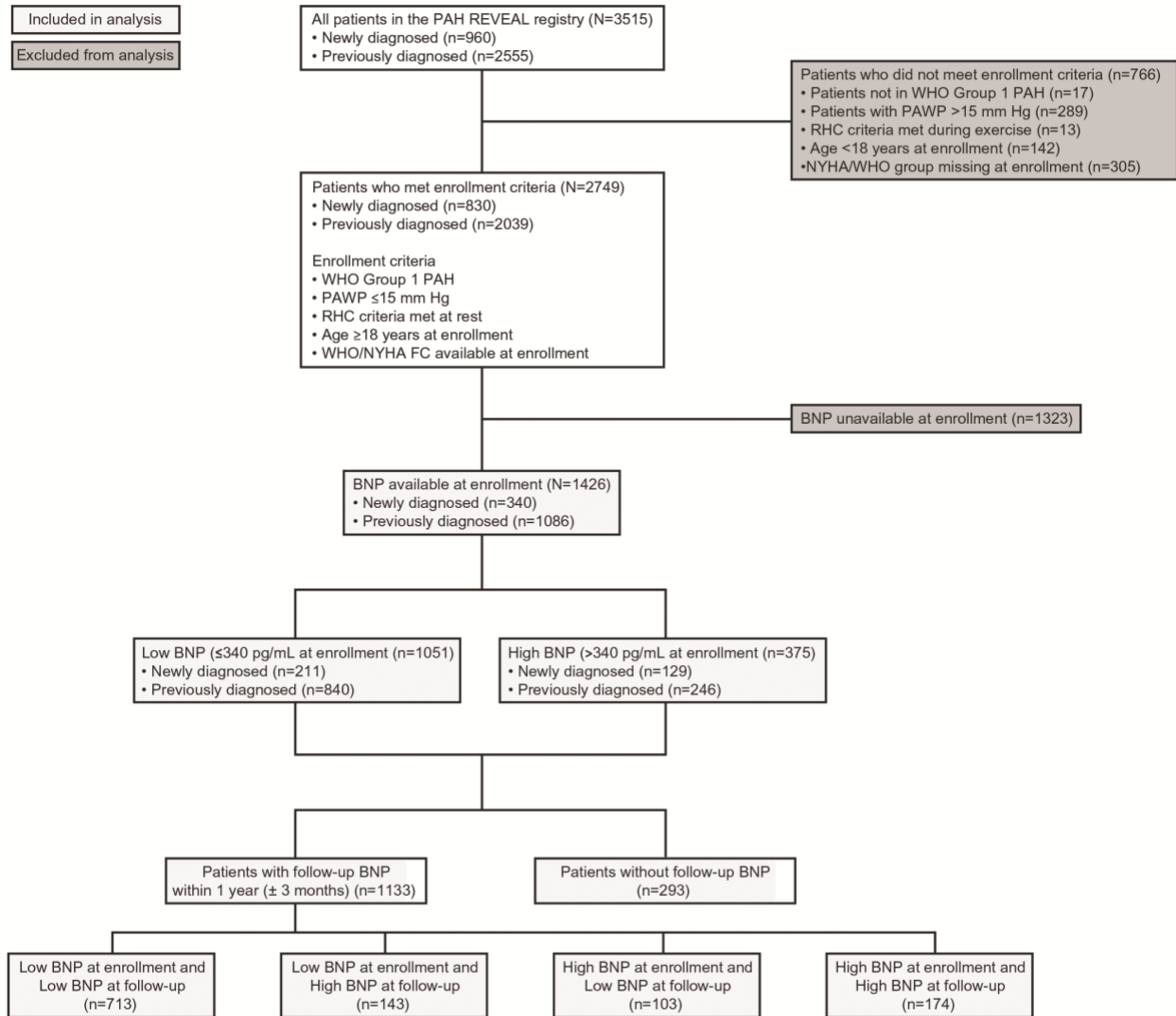
<sup>a</sup>BNP score change between baseline and post-assessment were: +1 (1 score increase), +2 (2 score increase), or +3 ≥ (3 or more score increase), no change, -1 (1 score decrease), -2 (2 score decrease), or -3 ≥ (3 or more score decrease).

<sup>b</sup>Compared with no change.

e-Figure 1 – Receiver operating characteristics (ROC) curve of optimal in brain natriuretic peptide (BNP) threshold. ROC curve was used to identify the optimal BNP threshold for predicting OS over 5 years.

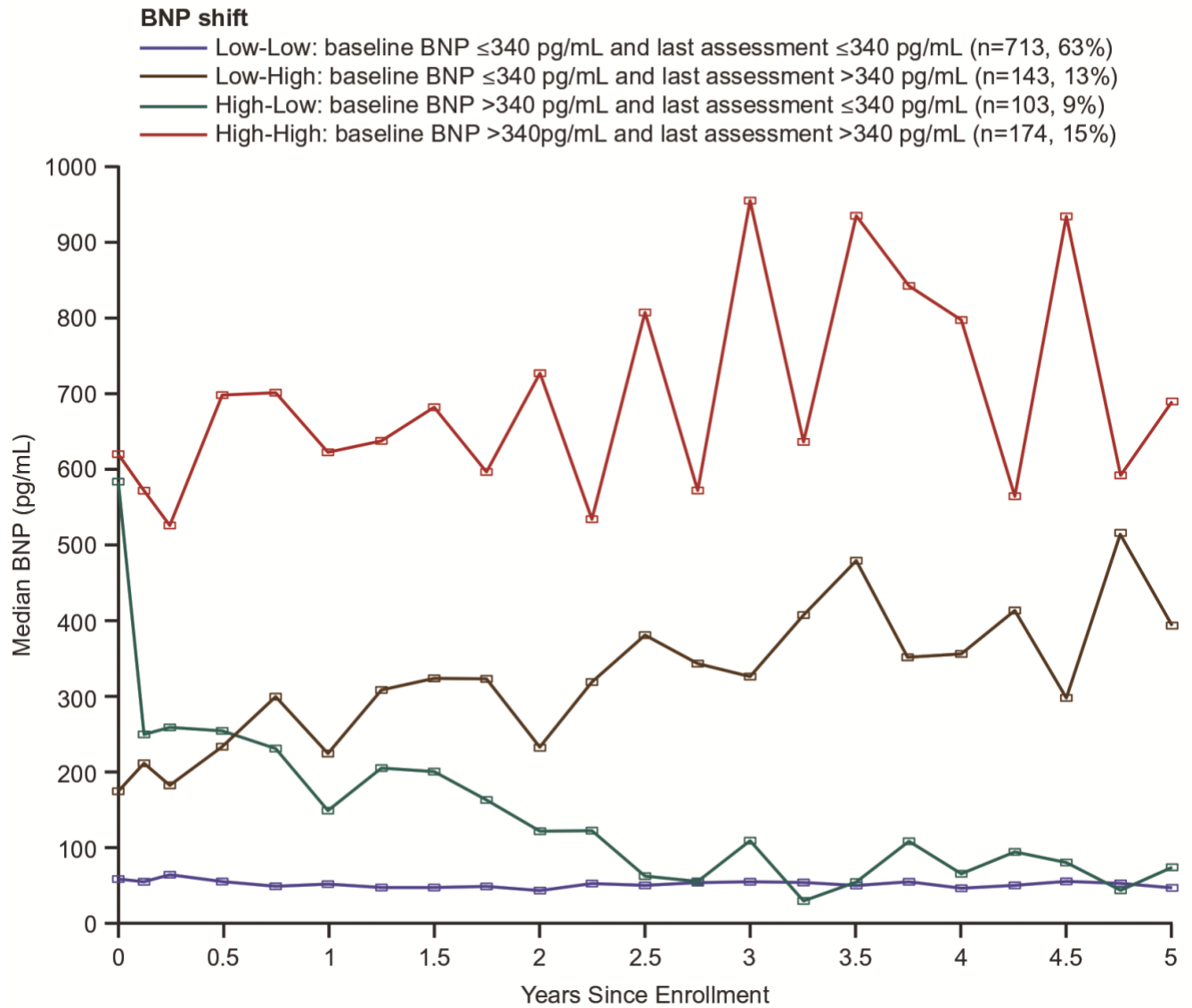


e-Figure 2 – CONSORT diagram.



BNP = brain natriuretic peptide; PAH = pulmonary arterial hypertension; NYHA = New York Heart Association; PAWP = pulmonary arterial wedge pressure; RHC = right heart catheterization; WHO = World Health Organization.

e-Figure 3 – Brain natriuretic peptide (BNP) measurement over time. Patients were stratified into 4 groups according to the value of BNP at baseline and within 60 months of enrollment.



e-Figure 4 – Scatter plots of changes in brain natriuretic peptide (BNP) over time using the baseline and the last assessment, by BNP value (low:  $\leq 340$  pg/mL or high:  $>340$  pg/mL) at baseline and at last assessment.

