

ONLINE SUPPLEMENTS FOR

**Heart Failure with Preserved Ejection Fraction  
is Associated with Increased Mortality and  
Heart Failure Readmissions Even When  
Natriuretic Peptide Levels are Normal**

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**Supplementary Table S1. Baseline characteristics of control subjects with normal versus high natriuretic peptide levels**

	<b>Control subjects with normal NP (n = 133)</b>	<b>Control subjects with high NP (n = 28)</b>	<b>P-value</b>
Age (years)	53 ± 14	60 ± 12	0.015
Female, n (%)	71 (54%)	18 (64%)	0.292
Body mass index (kg/m <sup>2</sup> )	27.9 ± 5.3	26.8 ± 4.7	0.332
Left ventricular ejection fraction (%)	65 ± 6	65 ± 5	0.837
Comorbidities, n (%)			
Hypertension	87 (65%)	15 (54%)	0.237
Diabetes	19 (14%)	2 (7%)	0.308
Obesity	43 (32%)	8 (29%)	0.698
Coronary artery disease	21 (16%)	8 (29%)	0.110
Sinus/paroxysmal/permanent AF	126 (95%)/7 (5%)/0 (0%)	26 (93%)/1 (4%)/1 (4%)	0.087
COPD	8 (6%)	1 (4%)	0.609
Laboratory results			
NT-proBNP (ng/L)†	52 (25-80)	219 (159-468)	N/A
Hemoglobin (g/dL)	13.7 ± 1.5	13.3 ± 1.5	0.241
eGFR (mL/min/1.73m <sup>2</sup> )	81 ± 20	73 ± 17	0.069
Medication use, n (%)			
Renin-angiotensin system blocker	35 (26%)	7 (25%)	0.885
Beta blocker	30 (23%)	8 (29%)	0.496
Diuretic	28 (21%)	8 (29%)	0.386
Continuous H <sub>2</sub> FPEF score probability (%)†,‡	34 (15-48)	36 (23-60)	0.304
HFA-PEFF score†,‡	1 (0-3)	3 (1-4)	0.011

†Reported as median (interquartile range)

‡Continuous H<sub>2</sub>FPEF score probability as determined from Reference [4] and HFA-PEFF score as determined from Reference [12]

AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate according to the Chronic Kidney Disease Epidemiology Collaboration formula; HFpEF, heart failure with preserved ejection fraction; NP, natriuretic peptides; NT-proBNP, N-terminal pro-hormone of B-type natriuretic peptide.

**Supplementary Table S2. Univariate and multivariate models for all-cause mortality**

	Univariate model		Multivariate model	
	HR (95% CI)	<i>P</i> -value	HR (95% CI)	<i>P</i> -value
Normal versus high NP HFpEF	0.38 (0.19–0.73)	0.004	0.50 (0.25–1.01)	0.052
Normal NP HFpEF versus control subjects	3.04 (0.97–9.57)	0.057	2.36 (0.70–7.90)	0.164
Age, per 1 year	1.07 (1.04–1.10)	<0.001	1.05 (1.02–1.08)	0.004
Female gender	0.64 (0.38–1.08)	0.094	0.58 (0.34–0.99)	0.044
Body mass index, per 1 kg/m <sup>2</sup>	1.00 (0.96–1.03)	0.883	1.00 (0.95–1.04)	0.822

HFpEF, heart failure with preserved ejection fraction; NP, natriuretic peptides.

**Supplementary Table S3. Univariate and multivariate models for heart failure readmissions**

	Univariate model		Multivariate model	
	HR (95% CI)	<i>P</i> -value	HR (95% CI)	<i>P</i> -value
Normal versus high NP HFpEF	0.36 (0.19–0.71)	<0.001	0.48 (0.24–0.96)	0.039
Normal NP HFpEF versus controls subjects	3.00 (0.95–9.43)	0.061	2.21 (0.66–7.41)	0.199
Age, per 1 year	1.07 (1.04–1.10)	<0.001	1.05 (1.02–1.08)	0.005
Female gender	0.69 (0.41–1.16)	0.160	0.62 (0.36–1.04)	0.071
Body mass index, per 1 kg/m <sup>2</sup>	1.00 (0.96–1.04)	0.982	1.00 (0.96–1.05)	0.857

HFpEF, heart failure with preserved ejection fraction; NP, natriuretic peptides.

**Supplementary Table S4. Baseline characteristics of the study population in sensitivity analysis matched for age, hypertension, diabetes and atrial fibrillation**

	<b>Control subjects without HFpEF (n = 86)</b>	<b>HFpEF with normal NP (n = 103)</b>	<b>HFpEF with high NP (n = 49)</b>	<b>P-value for HFpEF with normal NP versus controls</b>	<b>P-value for HFpEF with normal versus high NP</b>
Age (years)	57 ± 12	58 ± 10	57 ± 8	N/A	N/A
Men/women	55/45%	48/52%	31/69%	0.332	0.049
Body mass index (kg/m <sup>2</sup> )	29.0 ± 5.2	35.9 ± 7.6	35.3 ± 9.9	<0.001	0.877
Left ventricular ejection fraction (%)	66 ± 6	66 ± 5	64 ± 6	N/A	N/A
<b>Comorbidities</b>					
Hypertension	74 (86%)	90 (87%)	42 (86%)	N/A	N/A
Diabetes	21 (24%)	26 (25%)	12 (24%)	N/A	N/A
Obesity	36 (42%)	83 (81%)	33 (67%)	<0.001	0.073
Coronary artery disease*	22 (26%)	31 (30%)	9 (18%)	N/A	N/A
Atrial fibrillation	7 (8%)	8 (8%)	4 (8%)	N/A	N/A
COPD*	5 (6%)	16 (16%)	7 (14%)	N/A	N/A
<b>Laboratory results</b>					
NT-proBNP (ng/L)†	60 (25-99)	56 (30-79)	370 (194-816)	0.761	<0.001
Hemoglobin (g/dL)	14.0 ± 1.4	13.4 ± 1.3	12.8 ± 1.7	0.023	0.049
eGFR (mL/min/1.73m <sup>2</sup> )	77 ± 19	76 ± 17	69 ± 22	N/A	N/A

Medication use						
Renin-angiotensin system blocker*	30 (35%)	43 (42%)	16 (33%)	N/A	N/A	
Beta blocker	27 (31%)	36 (35%)	28 (57%)	0.606	0.010	
Diuretic	25 (29%)	52 (50%)	26 (53%)	0.003	0.767	
Continuous H <sub>2</sub> FPEF score	39 (22-59)	63 (47-83)	70 (47-87)	<0.001	0.701	
probability (%)†,‡						
HFA-PEFF score†,‡	2 (1-3)	2 (1-3)	3 (2-5)	0.454	<0.001	

All 3-group comparisons were first tested using ANOVA (or Kruskal Walls H test for nonparametric distributions), if the results of this test were not significant (indicated by an asterisk), no further between group testing was performed and individual group comparison p values are indicated as N/A.

†Reported as median (interquartile range)

‡Continuous H<sub>2</sub>FPEF score probability as determined from Reference [4] and HFA-PEFF score as determined from Reference [12]

AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate according to the Chronic Kidney Disease Epidemiology Collaboration formula; HFpEF, heart failure with preserved ejection fraction; NP, natriuretic peptides; NT-proBNP, N-terminal pro-hormone of B-type natriuretic peptide.



**Supplementary Table S5. Cardiac structure and function in sensitivity analysis matched for age, hypertension, diabetes and atrial fibrillation**

	<b>Control subjects without HFpEF (n = 86)</b>	<b>HFpEF with normal NP (n = 103)</b>	<b>HFpEF with high NP (n = 49)</b>	<b>P-value for HFpEF with normal NP versus controls</b>	<b>P-value for HFpEF with normal versus high NP</b>
<b>Dimensions</b>					
Interventricular septal thickness (mm)	10.0 ± 1.4	10.7 ± 1.9	10.7 ± 2.0	0.012	0.983
Posterior wall thickness (mm)*	9.7 ± 1.5	10.2 ± 1.4	10.2 ± 1.6	N/A	N/A
Left ventricular end-diastolic diameter (mm)*	48 ± 5	49 ± 5	50 ± 4	N/A	N/A
Left ventricular end-systolic diameter (mm)*	31 ± 4	31 ± 4	32 ± 4	N/A	N/A
Left atrial volume (mL)	54 (43-68)	55 (46-66)	66 (52-81)	0.613	0.040
Left atrial volume index (mL/m <sup>2</sup> )	27 (21-32)	25 (22-32)	31 (25-38)	0.623	0.004
<b>Left ventricular hypertrophy indices</b>					
Relative wall thickness (mm)*	0.41 ± 0.07	0.41 ± 0.06	0.41 ± 0.06	N/A	N/A
Concentric remodelling†, n (%)	33 (38%)	41 (40%)	21 (43%)	N/A	N/A
Left ventricular mass (g)	171 ± 50	194 ± 58	196 ± 64	0.021	0.973
Left ventricular mass index (g/m <sup>2</sup> )*	84 ± 19	86 ± 19	91 ± 24	N/A	N/A
Left ventricular hypertrophy‡, n (%)	37 (43%)	55 (53%)	27 (55%)	N/A	N/A
<b>Diastolic function</b>					
E-wave velocity (m/s)	0.6 (0.6-0.8)	0.8 (0.6-0.9)	0.9 (0.7-1.0)	0.004	0.350
A-wave velocity (m/s)*	0.6 (0.5-0.8)	0.7 (0.6-0.9)	0.7 (0.5-0.9)	N/A	N/A
E/A ratio	1.0 (0.8-1.3)	1.0 (0.8-1.2)	1.1 (0.9-1.5)	N/A	N/A
Septal e' velocity (cm/s)*	7.7 ± 2.0	7.7 ± 2.1	7.2 ± 2.4	N/A	N/A

Septal E/e'	8.8 (7.1-11.4)	10.0 (7.8-12.5)	11.7 (8.3-15.0)	0.110	0.128
Lateral e' velocity (cm/s)	10.2 ± 2.8	9.7 ± 2.7	8.6 ± 2.8	0.497	0.145
Lateral E/e'	6.4 (5.0-8.8)	8.0 (6.5-10.0)	10.0 (7.0-15.0)	0.001	0.068
<b>Right ventricle</b>					
Dilatation >mild, n (%)*	2 (2%)	7 (7%)	1 (2%)	N/A	N/A
Dilatation > moderate	0 (0%)	1 (1%)	0 (0%)	N/A	N/A
TAPSE (mm)*	22 ± 5	22 ± 5	22 ± 5	N/A	N/A
Tricuspid annular s' (cm/s)	12.8 ± 2.5	13.7 ± 2.0	13.4 ± 2.6	0.032	0.761
<b>Mitral valve regurgitation</b>					
Moderate or greater*	6 (7%)	4 (4%)	2 (4%)	N/A	N/A
More than moderate*	0 (0%)	0 (0%)	0 (0%)	N/A	N/A
<b>Tricuspid valve regurgitation</b>					
Moderate or greater	8 (9%)	5 (5%)	8 (16%)	0.229	0.018
More than moderate*	2 (2%)	0 (0%)	1 (2%)	N/A	N/A

All 3-group comparisons were first tested using ANOVA (or Kruskal Walls H test for nonparametric distributions), if the results of this test were not significant (indicated by an asterisk), no further between group testing was performed and individual group comparison p values are indicated as N/A.

†Concentric remodelling defined as relative wall thickness >0.42

‡Left ventricular hypertrophy defined as left ventricular mass index ≥115 g/m<sup>2</sup> in men or ≥95 g/m<sup>2</sup> in women

HFpEF, heart failure with preserved ejection fraction; NT-proBNP, N-terminal pro-hormone of B-type natriuretic peptide; TAPSE, tricuspid annular plane systolic excursion.

**Supplementary Table S6. Invasive hemodynamic assessment at rest and during exercise in sensitivity analysis matched for age, hypertension, diabetes and atrial fibrillation**

	Control subjects without HFpEF (n = 86)	HFpEF with normal NP (n = 103)	HFpEF with high NP (n = 49)	P-value for HFpEF with normal NP versus controls	P-value for HFpEF with normal versus high NP
<b>Rest</b>					
Heart rate (bpm)*	73 ± 13	71 ± 11	71 ± 11	N/A	N/A
Systolic blood pressure (mmHg)*	141 ± 23	145 ± 23	145 ± 27	N/A	N/A
Right atrial pressure (mmHg)	5 ± 2	10 ± 4	10 ± 5	<0.001	0.769
Systolic pulmonary arterial pressure (mmHg)	26 ± 5	36 ± 8	42 ± 16	<0.001	0.003
Mean pulmonary arterial pressure (mmHg)	16 ± 3	25 ± 6	28 ± 10	<0.001	0.018
Pulmonary arterial wedge pressure (mmHg)	9 ± 3	16 ± 5	18 ± 6	<0.001	0.004
Left ventricular transmural pressure (mmHg)	4 ± 2	5 ± 4	8 ± 4	0.018	<0.001
Cardiac output (L/min)*	5.73 ± 1.78	5.82 ± 1.68	5.40 ± 1.66	N/A	N/A
Cardiac index (L/min/m <sup>2</sup> )	2.84 ± 0.81	2.62 ± 0.66	2.51 ± 0.59	0.080	0.659
Stroke volume index (mL/m <sup>2</sup> )	39.7 ± 10.4	36.9 ± 8.5	35.9 ± 9.2	0.106	0.808
Systemic vascular resistance (dynes.s.cm <sup>-5</sup> )*	1,376 ± 395	1,348 ± 395	1,430 ± 445	N/A	N/A
Total arterial compliance (mL/mmHg)*	1.20 (0.92-1.50)	1.22 (0.93-1.49)	1.02 (0.81-1.43)	N/A	N/A
Effective arterial elastance (mmHg/mL)*	1.70 ± 0.57	1.70 ± 0.49	1.85 ± 0.66	N/A	N/A
Pulmonary vascular resistance (WU)	1.3 (0.9-1.7)	1.6 (1.0-2.2)	1.7 (1.0-2.6)	0.031	0.783
Pulmonary arterial compliance (mL/mmHg)	5.20 ± 1.86	4.54 ± 2.02	3.88 ± 1.93	0.056	0.127

<b>Peak exercise</b>						
Heart rate (bpm)	115 ± 23	109 ± 18	102 ± 22	0.098	0.212	
Systolic blood pressure (mmHg)*	175 ± 32	185 ± 29	184 ± 37	N/A	N/A	
Right atrial pressure (mmHg)	7 ± 3	18 ± 7	20 ± 7	<0.001	0.050	
Systolic pulmonary arterial pressure (mmHg)	39 ± 9	59 ± 13	66 ± 16	<0.001	0.007	
Mean pulmonary arterial pressure (mmHg)	25 ± 6	42 ± 10	47 ± 11	<0.001	0.003	
Pulmonary arterial wedge pressure (mmHg)	14 ± 5	31 ± 6	34 ± 6	<0.001	0.013	
Left ventricular transmural pressure (mmHg)	7 ± 3	14 ± 5	14 ± 5	<0.001	0.903	
Arterial oxygen saturation (%)	97 (96-98)	96 (94-97)	95 (92-97)	<0.001	0.170	
Cardiac output (L/min)	11.3 ± 3.13	11.4 ± 3.23	8.67 ± 2.53	0.974	<0.001	
Cardiac index (L/min/m <sup>2</sup> )	5.59 ± 1.47	5.16 ± 1.41	4.11 ± 1.10	0.108	<0.001	
Stroke volume index (mL/m <sup>2</sup> )	48.0 ± 11.3	47.6 ± 12.4	40.6 ± 10.4	0.972	0.003	
Systemic vascular resistance (dynes.s.cm <sup>-5</sup> )	786 ± 271	784 ± 294	972 ± 358	0.999	0.012	
Pulmonary vascular resistance (WU)	1.0 (0.8-1.3)	1.0 (0.5-1.4)	1.5 (0.8-2.1)	1.0	0.002	

All 3-group comparisons were first tested using ANOVA (or Kruskal Walls H test for nonparametric distributions), if the results of this test were not significant (indicated by an asterisk), no further between group testing was performed and individual group comparison p values are indicated as N/A.

HFpEF, heart failure with preserved ejection fraction; NT-proBNP, N-terminal pro-hormone of B-type natriuretic peptide.

**Supplementary Table S7. Baseline characteristics of the study population in sensitivity analysis with elevated NT-proBNP cut-off >220 ng/L in sinus rhythm and >660 ng/L in atrial fibrillation**

	<b>Control subjects without HFpEF (n = 161)</b>	<b>HFpEF with normal NP (n = 253)</b>	<b>HFpEF with high NP (n = 167)</b>	<b>P-value for HFpEF with normal NP versus controls</b>	<b>P-value for HFpEF with normal versus high NP</b>
Age (years)	54 ± 13	65 ± 11	73 ± 9	<0.001	<0.001
Men/women*	45/55%	42/58%	39/61%	N/A	N/A
Body mass index (kg/m <sup>2</sup> )	27.7 ± 5.2	34.7 ± 8.0	31.2 ± 6.4	<0.001	<0.001
Left ventricular ejection fraction (%)*	65 ± 5	65 ± 6	64 ± 6	N/A	N/A
<b>Comorbidities</b>					
Hypertension	63%	92%	96%	<0.001	0.156
Diabetes	13%	26%	30%	0.002	0.372
Obesity	32%	72%	54%	<0.001	<0.001
Coronary artery disease	18%	30%	38%	0.008	0.072
Paroxysmal AF	5%	8%	32%	<0.001	<0.001
Persistent/permanent AF	1%	9%	46%	<0.001	<0.001
COPD	6%	16%	12%	0.002	0.319
<b>Laboratory results</b>					
NT-proBNP (ng/L)†	73 (30-144)	125 (57-278)	1,279 (825-2,156)	<0.001	N/A
Hemoglobin (g/dL)	13.6 ± 1.5	13.2 ± 1.5	12.7 ± 1.7	0.012	0.003
eGFR (mL/min/1.73m <sup>2</sup> )	79 ± 20	69 ± 18	53 ± 19	<0.001	<0.001

Medication use					
Renin-angiotensin system blocker	26%	44%	52%	<0.001	0.135
Beta blocker	24%	47%	69%	<0.001	<0.001
Diuretic	22%	55%	77%	<0.001	<0.001
Continuous H <sub>2</sub> FPEF score	34 (16-48)	77 (57-92)	96 (89-99)	<0.001	<0.001
probability (%)†,‡					
HFA-PEFF score†,‡	2 (1-3)	3 (2-3)	6 (5-6)	<0.001	<0.001

All 3-group comparisons were first tested using ANOVA (or Kruskal Walls H test for nonparametric distributions), if the results of this test were not significant (indicated by an asterisk), no further between group testing was performed and individual group comparison p values are indicated as N/A.

†Reported as median (interquartile range)

‡Continuous H<sub>2</sub>FPEF score probability as determined from Reference [4] and HFA-PEFF score as determined from Reference [12]

AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate according to the Chronic Kidney Disease Epidemiology Collaboration formula; HFpEF, heart failure with preserved ejection fraction; NP, natriuretic peptides; NT-proBNP, N-terminal pro-hormone of B-type natriuretic peptide.

**Supplementary Table S8. Cardiac structure and function in sensitivity analysis with elevated NT-proBNP cut-off >220 ng/L in sinus rhythm and >660 ng/L in atrial fibrillation**

	<b>Control subjects without HFpEF (n = 161)</b>	<b>HFpEF with normal NP (n = 253)</b>	<b>HFpEF with high NP (n = 167)</b>	<b>P-value for HFpEF with normal NP versus controls</b>	<b>P-value for HFpEF with normal versus high NP</b>
<b>Dimensions</b>					
Interventricular septal thickness (mm)	9.7 ± 1.5	10.8 ± 1.8	11.0 ± 2.1	<0.001	0.352
Posterior wall thickness (mm)	9.5 ± 1.4	10.2 ± 1.6	10.3 ± 1.6	<0.001	0.558
Left ventricular end-diastolic diameter (mm)*	48 ± 5	49 ± 5	49 ± 5	N/A	N/A
Left ventricular end-systolic diameter (mm)*	31 ± 4	32 ± 5	32 ± 4	N/A	N/A
Left atrial volume (mL)	52 (42-67)	62 (50-78)	89 (68-108)	<0.001	<0.001
Left atrial volume index (mL/m <sup>2</sup> )	27 (22-32)	29 (24-37)	43 (35-56)	0.010	<0.001
<b>Left ventricular hypertrophy indices</b>					
Relative wall thickness	0.40 ± 0.06	0.42 ± 0.07	0.43 ± 0.08	0.014	0.187
Concentric remodelling†	30%	43%	48%	0.005	0.373
Left ventricular mass (g)	166 ± 47	193 ± 58	193 ± 56	<0.001	0.998
Left ventricular mass index (g/m <sup>2</sup> )	84 ± 18	89 ± 22	96 ± 24	0.042	0.010
Left ventricular hypertrophy‡	38%	57%	62%	<0.001	0.311
<b>Diastolic function</b>					
E-wave velocity (m/s) (n=579)	0.7 (0.6-0.8)	0.8 (0.7-0.9)	1.0 (0.8-1.2)	<0.001	<0.001
A-wave velocity (m/s) (n=579)	0.6 (0.5-0.8)	0.7 (0.6-0.9)	0.3 (0-0.8)	<0.001	<0.001
E/A ratio (n=486)	1.17 (0.83-1.43)	1.00 (0.75-1.20)	1.33 (0.88-2.00)	0.003	<0.001
Septal e' velocity (cm/s) (n=571)	8.5 ± 2.5	7.2 ± 2.0	6.5 ± 2.0	<0.001	0.006

Septal E/e' (n=571)	8.3 (6.7-10.0)	10.0 (8.6-14.0)	15.0 (11.3-22.0)	<0.001	<0.001
Lateral e' velocity (cm/s) (n=515)	11.2 ± 3.4	8.8 ± 2.7	8.5 ± 2.6	<0.001	0.671
Lateral E/e' (n=515)	6.0 (5.0-7.8)	8.9 (7.0-11.7)	11.2 (8.7-16.4)	<0.001	<0.001
<b>Right ventricle</b>					
Dilatation >mild	3.1%	6.7%	24.0%	0.122	<0.001
Dilatation > moderate	0.6%	0.8%	7.2%	1.000	<0.001
TAPSE (mm) (n=334)	22 ± 5	22 ± 5	19 ± 5	0.932	<0.001
Tricuspid annular s' (cm/s) (n=481)	13.1 ± 2.6	13.1 ± 2.6	11.3 ± 3.0	0.994	<0.001
<b>Mitral valve regurgitation</b>					
Mild or greater	6.2%	8.3%	30.5%	0.566	<0.001
More than moderate	0.6%	0.4%	3.0%	1.000	0.039
<b>Tricuspid valve regurgitation</b>					
Mild or greater	6.8%	14.2%	49.7%	0.025	<0.001
More than moderate	1.9%	2.4%	21.6%	1.000	<0.001

All 3-group comparisons were first tested using ANOVA (or Kruskal Walls H test for nonparametric distributions), if the results of this test were not significant (indicated by an asterisk), no further between group testing was performed and individual group comparison p values are indicated as N/A.

†Concentric remodelling defined as relative wall thickness >0.42

‡Left ventricular hypertrophy defined as left ventricular mass index ≥115 g/m<sup>2</sup> in men or ≥95 g/m<sup>2</sup> in women

HFpEF, heart failure with preserved ejection fraction; NT-proBNP, N-terminal pro-hormone of B-type natriuretic peptide; TAPSE, tricuspid annular plane systolic excursion.



**Supplementary Table S9. Invasive hemodynamic assessment at rest and during exercise in sensitivity analysis with elevated NT-proBNP cut-off >220 ng/L in sinus rhythm and >660 ng/L in atrial fibrillation**

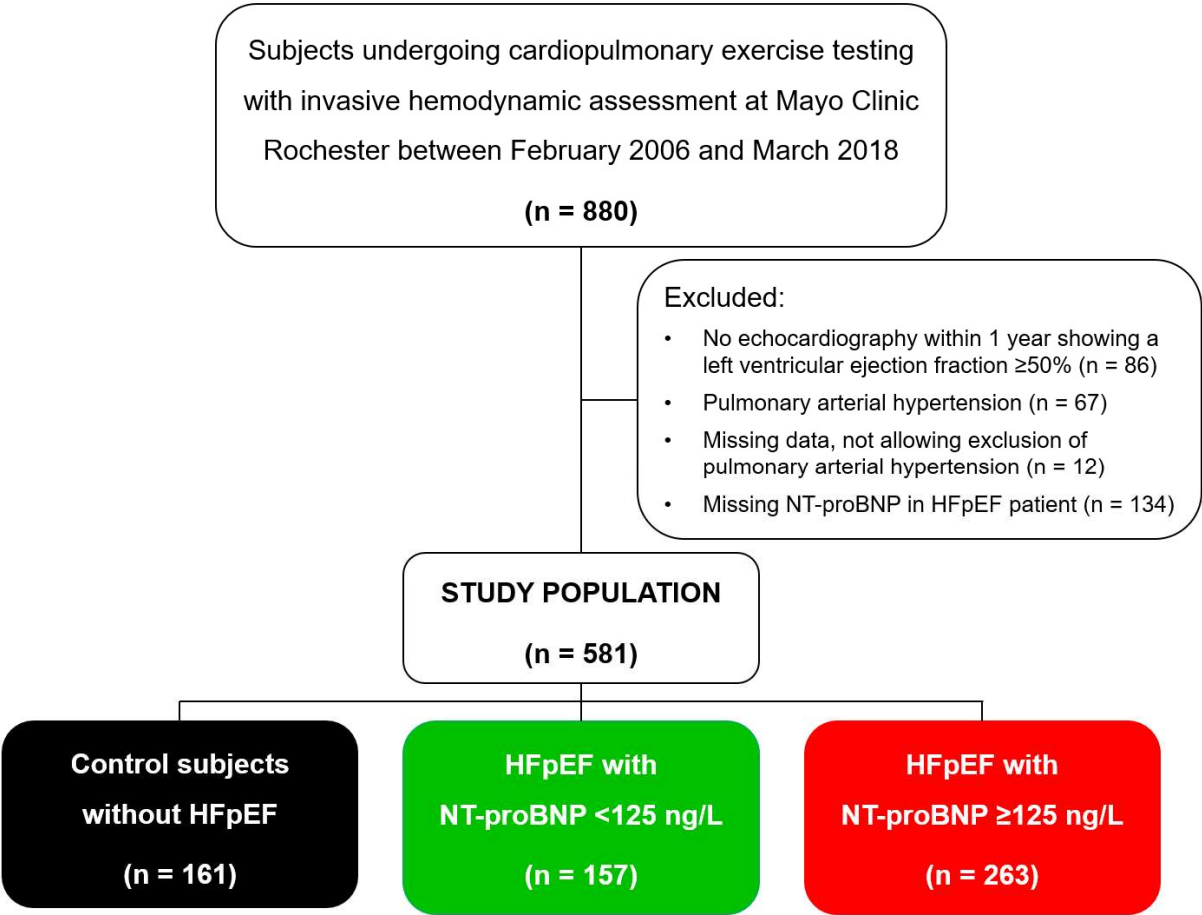
	Control subjects without HFpEF (n = 161)	HFpEF with normal NP (n = 253)	HFpEF with high NP (n = 167)	P-value for HFpEF with normal NP versus controls	P-value for HFpEF with normal versus high NP
<b>Rest</b>					
Heart rate (bpm)	74 ± 13	70 ± 12	70 ± 13	0.016	0.997
Systolic blood pressure (mmHg)	135 ± 23	147 ± 23	147 ± 26	<0.001	0.940
Right atrial pressure (mmHg)	5 ± 2	10 ± 4	12 ± 5	<0.001	<0.001
Systolic pulmonary arterial pressure (mmHg)	26 ± 6	38 ± 11	50 ± 16	<0.001	<0.001
Mean pulmonary arterial pressure (mmHg)	16 ± 3	26 ± 7	33 ± 10	<0.001	<0.001
Pulmonary arterial wedge pressure (mmHg)	9 ± 3	16 ± 5	19 ± 6	<0.001	<0.001
Left ventricular transmural pressure (mmHg)	4 ± 2	6 ± 4	7 ± 5	<0.001	0.003
Cardiac output (L/min)	5.70 ± 1.65	5.44 ± 1.66	4.54 ± 1.37	0.245	<0.001
Cardiac index (L/min/m <sup>2</sup> )	2.93 ± 0.80	2.54 ± 0.66	2.26 ± 0.63	<0.001	<0.001
Stroke volume index (mL/m <sup>2</sup> )	40.4 ± 10.4	36.7 ± 9.6	33.0 ± 10.2	<0.001	<0.001
Systemic vascular resistance (dynes.s.cm <sup>-5</sup> )	1,318 ± 379	1,443 ± 465	1,648 ± 613	0.033	<0.001
Total arterial compliance (mL/mmHg)	1.26 (0.97-1.60)	1.07 (0.81-1.40)	0.87 (0.60-1.12)	<0.001	<0.001
Effective arterial elastance (mmHg/mL)	1.66 ± 0.56	1.83 ± 0.61	2.25 ± 0.93	0.057	<0.001
Pulmonary vascular resistance (WU)	1.3 (0.9-1.7)	1.7 (1.1-2.5)	2.9 (1.7-4.1)	<0.001	<0.001
Pulmonary arterial compliance (mL/mmHg)	5.18 ± 2.04	4.07 ± 1.87	2.61 ± 1.22	<0.001	<0.001

<b>Peak exercise</b>						
Heart rate (bpm)	119 ± 23	105 ± 20	95 ± 22	<0.001	<0.001	
Systolic blood pressure (mmHg)	170 ± 33	185 ± 32	168 ± 33	<0.001	<0.001	
Right atrial pressure (mmHg)	7 ± 4	19 ± 7	23 ± 8	<0.001	<0.001	
Systolic pulmonary arterial pressure (mmHg)	39 ± 9	64 ± 15	72 ± 17	<0.001	<0.001	
Mean pulmonary arterial pressure (mmHg)	25 ± 6	45 ± 10	49 ± 10	<0.001	<0.001	
Pulmonary arterial wedge pressure (mmHg)	15 ± 5	32 ± 6	32 ± 6	<0.001	0.836	
Left ventricular transmural pressure (mmHg)	7 ± 4	13 ± 6	9 ± 9	<0.001	<0.001	
Arterial oxygen saturation (%)	97 (95-98)	95 (93-97)	95 (92-97)	<0.001	0.116	
Cardiac output (L/min)	11.48 ± 3.29	9.86 ± 3.15	6.80 ± 2.26	<0.001	<0.001	
Cardiac index (L/min/m <sup>2</sup> )	5.87 ± 1.59	4.61 ± 1.35	3.38 ± 1.05	<0.001	<0.001	
Stroke volume index (mL/m <sup>2</sup> )	49.6 ± 12.7	44.4 ± 13.4	36.7 ± 11.4	<0.001	<0.001	
Systemic vascular resistance (dynes.s.cm <sup>-5</sup> )	759 ± 263	906 ± 364	1,075 ± 392	0.002	<0.001	
Pulmonary vascular resistance (WU)	0.9 (0.7-1.2)	1.3 (0.8-2.0)	2.2 (1.4-3.8)	<0.001	<0.001	

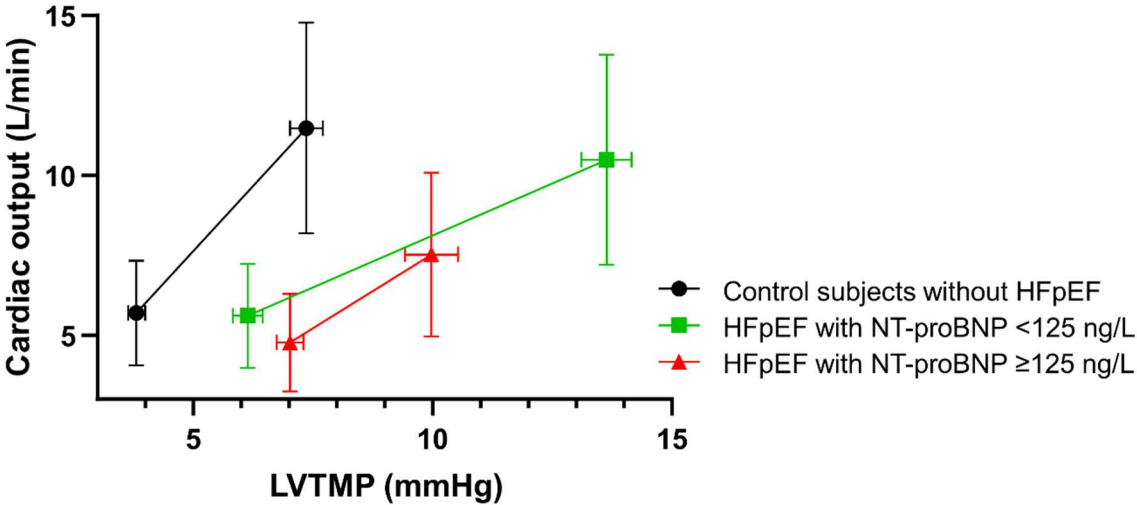
All 3-group comparisons were first tested using ANOVA (or Kruskal Walls H test for nonparametric distributions), if the results of this test were not significant (indicated by an asterisk), no further between group testing was performed and individual group comparison p values are indicated as N/A.

HFpEF, heart failure with preserved ejection fraction; NT-proBNP, N-terminal pro-hormone of B-type natriuretic peptide.

**Supplementary Figure S1. Study flowchart.**

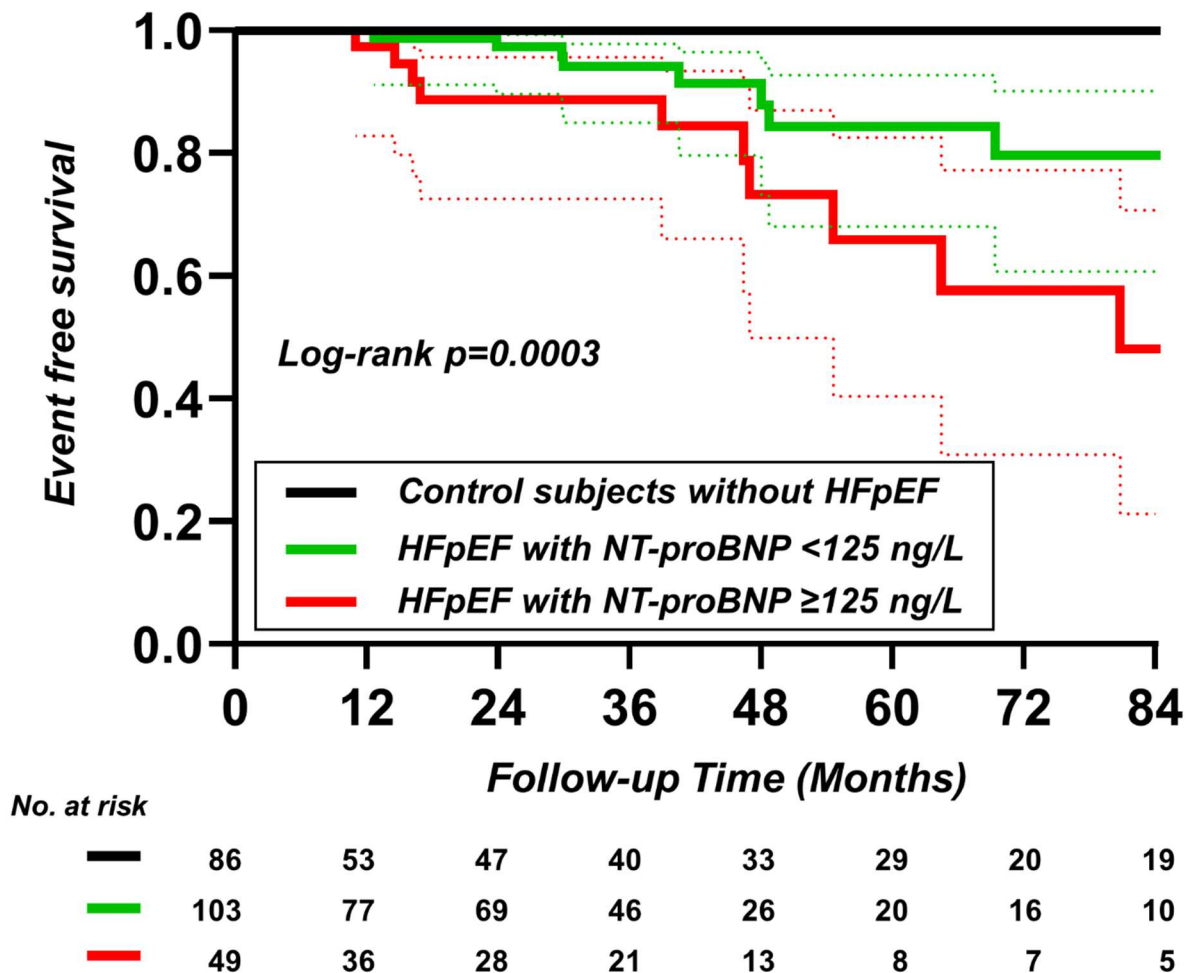


**Supplementary Figure S2. Cardiac output increase from rest to exercise as a function of left ventricular preload reflected by LVTMP.**



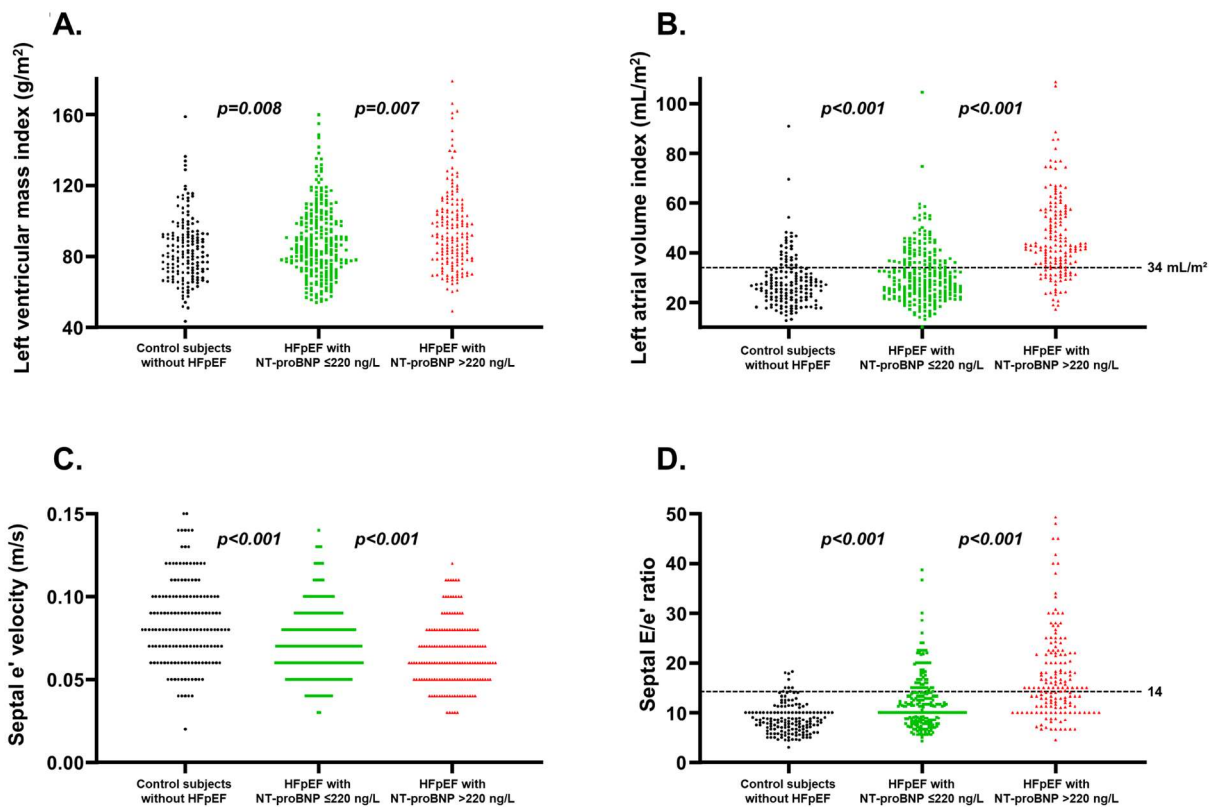
Bars indicating mean with standard deviations

Supplementary Figure S3: Freedom from all-cause mortality or heart failure readmissions in control subjects, patients with HFpEF and NT-proBNP <125 ng/L versus ≥125 ng/L in sensitivity analysis matched for age, hypertension, diabetes and atrial fibrillation.



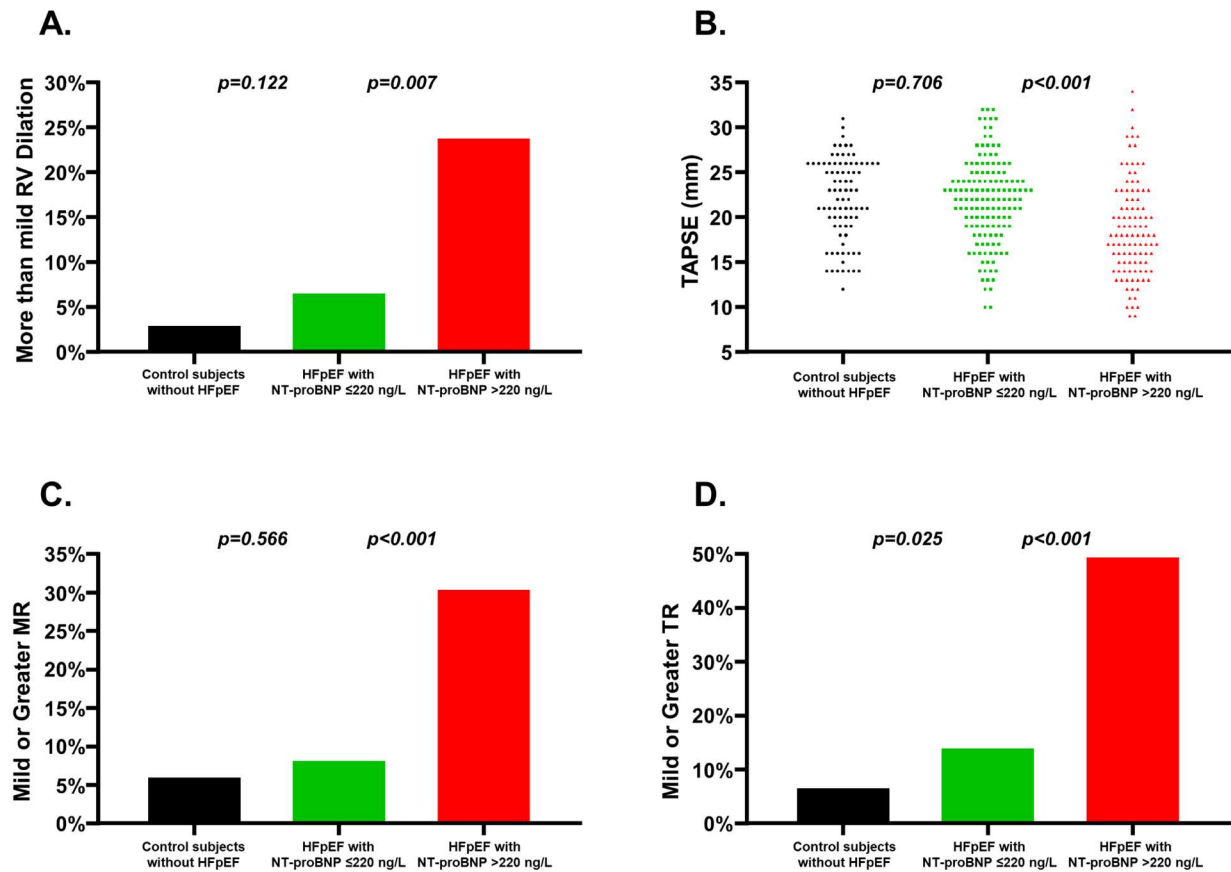
HFpEF, heart failure with preserved ejection fraction; NT proBNP, N terminal pro hormone of B type natriuretic peptide.

Supplementary Figure S4: (A.) Left ventricular mass index, (B.) left atrial volume index, (C.) septal  $e'$  velocity, and (D.) septal  $E/e'$  ratio in control subjects (black dots), patients with HFpEF and low NT proBNP (green squares), and patients with HFpEF and high NT proBNP (red triangles). Sensitivity analysis with elevated NT proBNP cut-off  $>220$  ng/L in sinus rhythm and  $>660$  ng/L in atrial fibrillation.



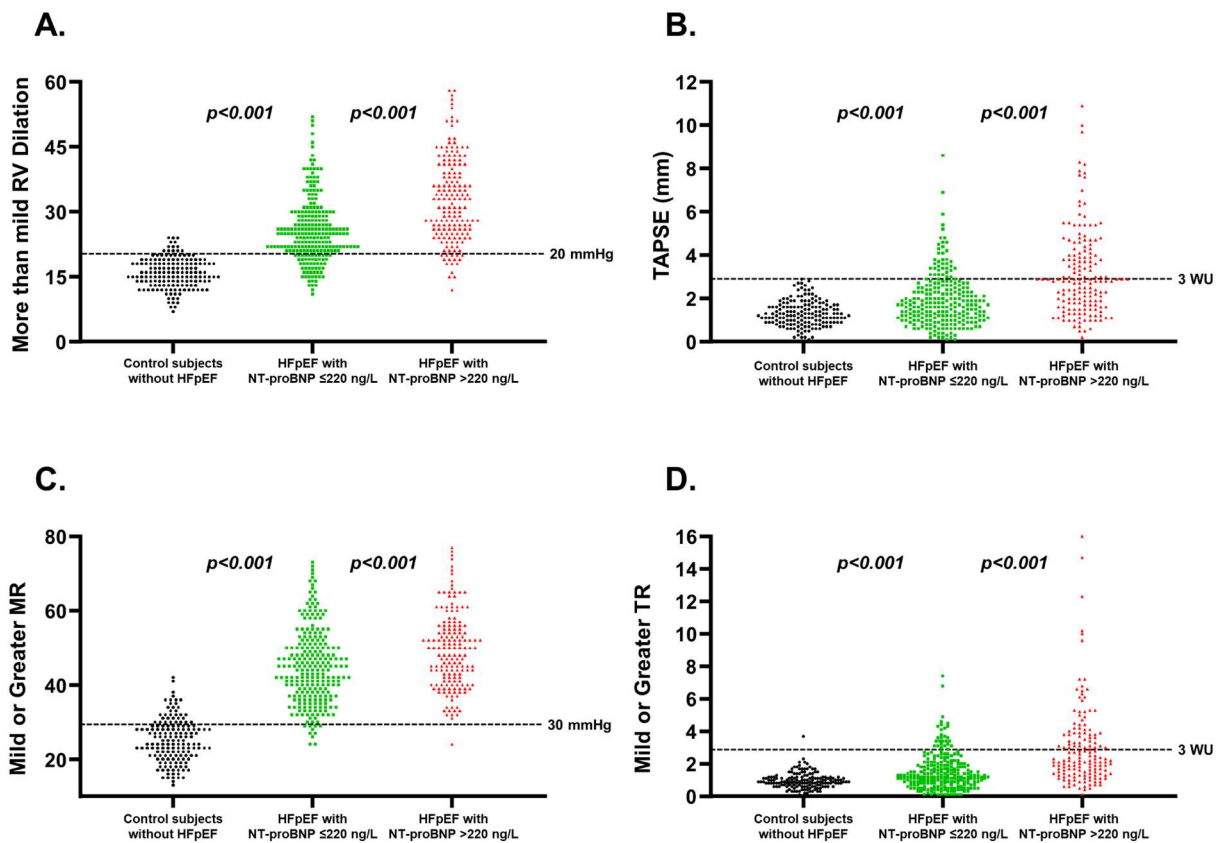
E, transmitral early velocity on pulsed-wave Doppler;  $e'$ , septal mitral annular early velocity on pulsed-wave tissue Doppler; HFpEF, heart failure with preserved ejection fraction; NT-proBNP, N-terminal pro-hormone of B-type natriuretic peptide.

Supplementary Figure S5: (A.) RV dilation, (B.) TAPSE, (C.) MR, and (D.) TR in control subjects (black dots), patients with HFpEF and low NT proBNP (green squares), and patients with HFpEF and high NT proBNP (red triangles). Sensitivity analysis with elevated NT proBNP cut-off >220 ng/L in sinus rhythm and >660 ng/L in atrial fibrillation.



HFpEF, heart failure with preserved ejection fraction; MR, mitral valve regurgitation; NT-proBNP, N-terminal pro-hormone of B-type natriuretic peptide; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid valve regurgitation.

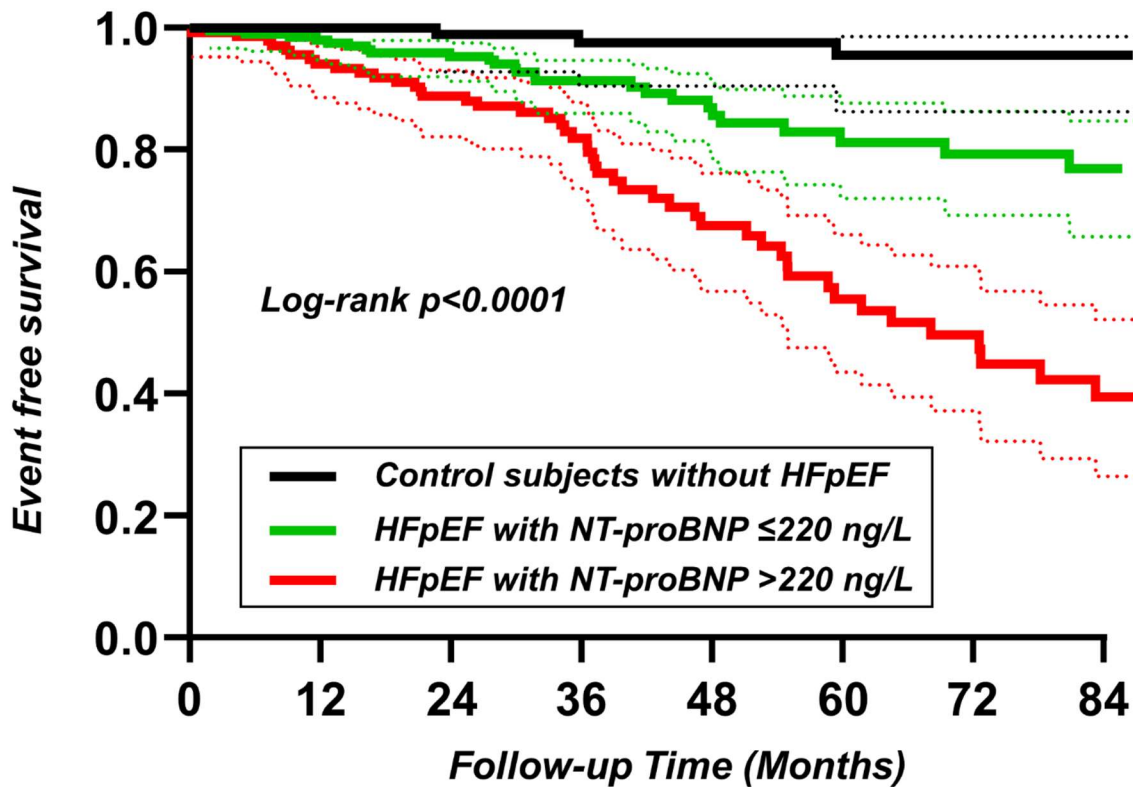
Supplementary Figure S6. (A.) mPAP at rest; (B.) PVR at rest; (C.) mPAP at peak exercise; and (D.) PVR at peak exercise in control subjects (black dots), patients with HFpEF and low NT proBNP (green squares), and patients with HFpEF and high NT proBNP (red triangles). Sensitivity analysis with elevated NT proBNP cut-off >220 ng/L in sinus rhythm and >660 ng/L in atrial fibrillation.



HFpEF, heart failure with preserved ejection fraction; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-terminal pro-hormone of B-type natriuretic peptide; PVR, pulmonary vascular resistance.



Supplementary Figure S7. Freedom from all-cause mortality or heart failure readmission in control subjects, patients with HFpEF and low NT proBNP, and patients with HFpEF and high NT proBNP. Sensitivity analysis with elevated NT proBNP cut-off >220 ng/L in sinus rhythm and >660 ng/L in atrial fibrillation.



No. at risk

—	161	105	94	71	57	47	35	29
—	253	194	167	111	70	48	40	29
—	167	126	112	73	44	30	21	14

HFpEF, heart failure with preserved ejection fraction; NT-proBNP, N-terminal pro-hormone of B-type natriuretic peptide.