SUPPLEMENTAL MATERIAL

Supplemental Methods:

Echocardiographic assessment:

Echocardiography was performed according to American Society of Echocardiography guidelines and interpreted by Mayo staff cardiologists.[1] Left ventricular (LV) structure and geometry was assessed by LV end diastolic and systolic dimensions, LV septal and posterior wall thickness, and LV mass index. LV systolic function was assessed by ejection fraction. LV global longitudinal strain (a more sensitive measure of systolic function) was determined offline using commercial software as previously described (Syngo).[2] Early diastolic mitral inflow velocity (E), early diastolic mitral annular tissue velocity (e') and the E/e' ratio was used to assess LV diastolic function. Left atrial volume index was determined by the biplane method of disks. Right atrial pressure was estimated from the inferior vena caval diameter and its collapsibility with inspiration. Pulmonary artery systolic pressure was calculated as (4 x peak tricuspid regurgitation velocity) + estimated right atrial pressure.[3] Right ventricular (RV) dilation and dysfunction were reported based on qualitative visual estimation and graded nominally as present or absent.[4,5]

Supplemental Table 1: Invasive Hemodynamic Findings

		Rest			***Exercise***	
	Control (n=147)	**HFpEF (n=267)**	**p value**	**Control (n=147)**	**HFpEF (n=267)**	**p value**
Vital Signs						
Heart rate, bpm	67±14	63±12	0.005	110±25	97±21	<0.0001
Systolic BP, mm Hg	143±26	149±31	0.1	173±38	182±36	0.04
Mean BP, mm Hg	97±15	100±17	0.1	111±21	117±22	0.03
Central Hemodynamics						
Right atrial pressure mm Hg	5±2	10±4	<0.0001	7±4	19±8	<0.0001
PA mean pressure, mm Hg	17±4	26±8	<0.0001	27±8	45±10	<0.0001
PASP, mmHg	28±7	41±13	<0.0001	43±13	64±16	<0.0001
PA wedge pressure, mm Hg	9±3	16±6	<0.0001	14±5	31±6	<0.0001
Cardiac output, L/min	5.5±1.6	5.2±1.5	0.04	10.2±3.1	8.5±3.0	<0.0001
Cardiac index, L/min/m^2	2.9±0.8	2.6±0.6	<0.0001	5.3±1.5	4.2±1.3	<0.0001

Values are mean ± SD, %. bpm- beats per minute; BP-blood pressure; PA-Pulmonary artery; PASP-PA systolic pressure

Supplemental Table 2: All Univariate predictors of HFpEF

	OR [95% CI]	Beta estimate	AUC	Optimal Cut point	Sensitivity	Specificity	p value
Clinical							
Age per year	1.08 [1.06-1.10]	0.08	0.743	61	80	61	<0.0001
Female	1.11 [0.74-1.68]	0.11	0.513	-	61	42	0.6
Body Mass Index per kg/m2	1.13 [1.09-1.18]	0.12	0.703	30.5	64	68	<0.0001
Elevated NTproBNP >125pg/ml	3.74 [2.43-5.75]	3.74	0.649	-	77	53	<0.0001
NT proBNP per pg/ml	1.002 [1.001-1.003]	0.0002	0.730	272	60	77	<0.0001
Creatinine per mg/dl	7.09 [3.10-16.24]	1.96	0.628	1.2	36	85	<0.0001
eGFR per ml/min/1.73m^2	0.99 [0.98-0.99]	-0.01	0.611	75	46	74	0.0008
Number of HTN drugs	1.87 [1.58-2.22]	0.62	0.720	1	72	63	<0.0001
EKG							
1 degree AV block	1.92 [0.97-3.80]	0.65	0.532	-	15	92	0.006
QRS duration per ms	1.01 [1.0001-1.02]	0.01	0.499	134	14	95	0.05
PR interval per ms	1.02 [1.01-1.03]	0.02	0.644	160	69	56	<0.0001
Left axis	2.03 [1.15-3.60]	0.71	0.549	-	22	88	0.01
Q wave	3.52 [1.54-8.08]	1.26	0.557	-	17	95	0.0008
ST-T abnormality	3.05 [1.13-10.60]	1.12	0.526	-	8	93	0.03
QTc per ms	1.01 [1.005-1.02]	0.01	0.594	431	66	51	0.0008
Echocardiogram							
LV End diastolic dimension per mm	1.03 [0.99-1.08]	0.03	0.551	47	66	47	0.1
Ejection Fraction per %	0.99 [0.96-1.03]	-0.01	0.502	57	17	91	0.7
Left Atrial Volume Index per ml/m^2	1.09 [1.06-1.11]	0.08	0.735	30	75	64	<0.0001

LV Mass Index per g/m^2	1.02 [1.01-1.03]	0.02	0.621	77	75	41	<0.0001
E/e' per unit	1.22 [1.16-1.30]	0.20	0.744	9	79	57	<0.0001
Septal E' velocity per cm/s	0.78 [0.71-0.86]	-0.25	0.654	7	64	60	<0.0001
Estimated RA pressure per mmHg	1.31 [1.15-1.49]	0.27	0.631	5	53	66	<0.0001
Pulmonary Artery Systolic Pressure per mmHg	1.13 [1.09-1.11]	0.12	0.737	35	54	85	<0.0001
RV Fractional Area Change per %	0.95 [0.92-0.98]	-0.05	0.605	48	39	88	0.0002
Tricuspid Annular Plane Systolic Excursion per mm	0.87 [0.81-0.93]	-0.14	0.656	21	49	80	<0.0001
Global LV Longitudinal strain per %	0.87 [0.81-0.94]	-0.14	0.614	16	62	56	0.0001
Clinically relevant or current guideline based partition values							
Left Atrial Volume Index>34 ml/m^2	4.78 [2.92-7.81]	1.56	0.662	-	49	83	<0.0001
E/e'>9	5.23 [3.37-8.11]	1.65	0.687	-	78	59	<0.0001
E/e'>10	4.78 [3.07-7.44]	1.56	0.684	-	63	73	<0.0001
E/e'>13	5.20 [3.09-8.76]	1.65	0.661	-	46	86	<0.0001
E/e'>14	5.06 [2.85-8.99]	1.62	0.637	-	38	89	<0.0001
NT proBNP> 125 pg/ml	3.74 [2.44-5.78]	1.32	0.649	-	77	53	<0.0001
Global LV longitudinal strain<18%	1.48 [0.87-2.52]	0.39	0.528	-	86	20	0.2
Global LV longitudinal strain<16%	2.10 [1.39-3.16]	0.74	0.591	-	62	56	0.0004
Tricuspid Annular Plane Systolic Excursion<16 mm	7.16 [1.67-30.74]	1.97	0.538	-	9	99	0.0008

eGFR-estimated glomerular filtration rate; HTN-Hypertension; LV-Left Ventricle; RA-Right Atrial; RV-Right Ventricle; NT-proBNP –N terminal pro Brain Natriuretic Peptide

Supplemental Table 3: Incremental value of H_2FpEF score

	OR [95% CI]	AUC [95% CI]	AICc	AUC comparison	p value	Optimal cutpoint	Sensitivity	Specificity	LR+	LR-
Derivation cohort (n=414)										
ESC 2007 algorithm	5.00 [3.24-7.85]	0.690 [0.642-0.734]	486.5	-0.173 [-0.215 to -0.132]	<0.0001	NA	65.17	72.79	2.40	0.48
ESC 2016 algorithm	4.57 [2.92-7.29]	0.672 [0.626-0.716]	495.0	-0.169 [-0.120 to -0.217]	<0.0001	NA	56.93	77.55	2.54	0.56
CART model	--	0.886 [0.812-0.960]	--	+0.044 [0.017, 0.724]	0.002	NA	91.76	70.75	3.14	0.12
H_2FpEF score	**1.98 [1.73-2.30]**	**0.841 [0.798-0.876]**	**386.7**	**Reference**	**-**	**4**	**76.03**	**78.23**	**3.49**	**0.31**
HFpEF score (continual scale)	-	0.863 [0.824-0.894]	370.0	+0.022 [+0.002 to +0.042]	0.03	NA	-	-	-	-
Test (Validation) cohort (n=100)										
ESC 2007 algorithm	6.33 [2.07-22.44]	0.708 [0.585-0.807]	77.9	-0.224 [-0.343 to -0.106]	0.0002	NA	62.50	79.17	3.00	0.47
ESC 2016 algorithm	7.62 [2.29-34.94]	0.679 [0.584-0.762]	96.0	-0.207 [-0.103 to -0.310]	<0.0001	NA	45.83	90.00	4.58	0.60
CART Model	--	0.852 [0.749-0.917]	--	-0.034 [-0.065 to -0.003]	0.03	NA	83.93	72.73	3.08	0.22
H_2FpEF Score	**2.26 [1.69-3.26]**	**0.886 [0.789-0.941]**	**81.6**	**Reference**	**-**	**4**	**78.18**	**83.78**	**4.82**	**0.26**
HFpEF score (continual scale)	-	0.910 [0.819-0.957]	-	+0.024 [-0.006 to +0.053]	0.1	NA	-	-	-	-

ESC-European Society of Cardiology, CART-Classification and Regression Tree, LR-Likelihood Ratio, rest as above

Supplemental Table 4: Sensitivity Analysis Using Agnostic Logistic Model to Predict HFpEF

Agnostic Multivariable model including all significant univariate predictors (AICc=388.38) AUC-0.871, <0.0001	**OR [95% CI]**	**Beta estimate**	**p value**
Body Mass Index>30 kg/m^2	3.22 [1.80-5.76]	1.17	<0.0001
Left atrial volume index>30 ml/m^2	1.58 [0.86-2.90]	0.46	0.1
NT proBNP>275 pg/ml	1.00 [0.49-2.02]	-0.01	0.9
Global Longitudinal Strain<16%	0.88 [0.50-1.55]	-0.1	0.6
Age>60 years	2.08 [1.13-3.81]	0.73	0.02
Chronic kidney disease stage 3 or greater	1.68 [0.72-3.94]	0.52	0.2
Diabetes or prediabetes	1.64 [0.94-2.87]	0.50	0.08
Pacemaker	3.74 [0.40-34.92]	1.32	0.2
Treatment with 2 or more antihypertensives	1.84 [1.06-3.20]	0.61	0.03
Cardiomegaly on X ray	2.33 [0.84-6.50]	0.85	0.09
Pleural effusion on X ray	1.01 [0.15-6.69]	0.01	0.9
Left ventricular hypertrophy	0.88 [0.42-1.85]	-0.12	0.7
E/e' ratio>9	1.85 [1.04-3.29]	0.62	0.04
Pulmonary Artery Systolic Pressure>35 mmHg	1.33 [0.68-2.61]	0.29	0.4
RV Fractional Area Change<48%	3.36 [1.66-6.81]	1.21	0.0004
Tricuspid Annular Plane Systolic Excursion<21 mm	1.49 [0.75-2.99]	0.40	0.3
Atrial Fibrillation	2.97 [1.04-8.51]	1.09	0.03
Agnostic stepwise backward regression (AICc=380.91), AUC-0.857, <0.0001	**OR [95% CI]**	**Beta estimate**	**p value**
Body Mass Index>30 kg/m^2	3.29 [1.95-5.56]	1.19	<0.0001
Atrial Fibrillation	5.72 [2.25-14.56]	1.74	<0.0001
Age>60 years	2.91 [1.69-5.02]	1.07	0.0001

2 or more antihypertensives	2.13 [1.26-3.59]	0.75	0.005
E/e'>9	2.29 [1.34-3.93]	0.77	0.005
RV Fractional Area Change<48%	3.82 [1.98-7.39]	0.72	0.02

AICc- Akaike information criterion; AUC-Area Under the Curve; OR-Odds ratio; CI-Confidence Interval; NT-proBNP –N terminal pro Brain Natriuretic Peptide; RV-Right Ventricle

Supplemental Table 5: Baseline characteristics of test cohort:

	Non-Cardiac Dyspnea (n=39)	HFpEF (n=61)	p value
Age, years	53 ± 13	70 ± 10	<0.0001
Female, %	49	51	0.8
Body mass index, kg/m^2	27.9 ± 6.0	33.0 ± 8.9	0.002
Comorbidities			
Number of anti-hypertensive drugs, n	0.9 ± 1.1	2.4 ± 1.3	<0.0001
Impaired glucose tolerance any, %	33	56	0.04
Atrial Fibrillation any, %	8	39	0.0002
Paroxysmal Atrial Fibrillation, %	8	23	
Permanent Atrial Fibrillation, %	0	16	
NT-proBNP, pg/ml	61 [28.75-128.5]	237.5 [102.5-817]	0.02
Echocardiography			
LV end diastolic dimension, mm	47 ± 5	50 ± 6	0.1
LV mass index, g/m^2	82 ± 21	98 ± 30	0.02
LV hypertrophy, %	10	35	0.008
LA volume index, ml/m^2	26 ± 9	38 ± 16	<0.0001
E/e' ratio	8 ± 3	16 ± 9	<0.0001
Septal e', cm/s	8 ± 3	6 ± 2	<0.0001
Pulmonary artery systolic pressure, mmHg	26 ± 7	35 ± 12	0.0002

Supplemental References

1. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015;16:233-70.

2. Obokata M, Reddy YN, Pislaru SV, Melenovsky V, Borlaug BA. Evidence Supporting the Existence of a Distinct Obese Phenotype of Heart Failure with Preserved Ejection Fraction. Circulation. 2017;136:6-19.

3. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr. 2010;23:685-713; quiz 86-8.

4. Bleeker GB, Steendijk P, Holman ER, Yu CM, Breithardt OA, Kaandorp TA, Schalij MJ, van der Wall EE, Nihoyannopoulos P, Bax JJ. Assessing right ventricular function: the role of echocardiography and complementary technologies. Heart. 2006;92 Suppl 1:i19-26.

5. Mohammed SF, Hussain I, AbouEzzeddine OF, Takahama H, Kwon SH, Forfia P, Roger VL, Redfield MM. Right ventricular function in heart failure with preserved ejection fraction: a community-based study. Circulation. 2014;130:2310-20.

Supplemental Figure Legends:

Supplemental Figure 1A: 2016 European Society of Cardiology diagnostic criteria for Heart Failure with Preserved Ejection Fraction**.** HF-heart failure, NT-proBNP- N terminal pro Brain Natriuretic Peptide, BNP-Brain Natriuretic Peptide, LA-Left Atrium, LVMI - Left Ventricular Mass Index, E/e' –ratio of early diastolic mitral inflow velocity to septal mitral annulus tissue relaxation velocity

Supplemental Figure 1B: 2007 European Society of Cardiology modified non-invasive diagnostic criteria for Heart Failure with Preserved Ejection Fraction

Supplemental Figure 2: Nomogram for the prediction of the probability of HFpEF based on a logistic regression model with continuous variables as shown on the figure. The predicted probability for HFpEF can be obtained by drawing a vertical line up from each variable at the value for a patient to the "Points" line. The total points is the sum of the point values for the five variables including the model. The predicted probability is determined by drawing a vertical line down from the "Total Points" line to the probability line at the bottom of the figure. For example, a 60 year old person (34 points) with BMI of 35 (40 points), without AFib (0 points), E/e' of 5 (8 points) and pulmonary artery systolic pressure of 50 (40 points), has a total of 122 points. The predicted probability of HFpEF is then estimated to be between 0.70 and 0.90.

Supplemental Figure 3: Continuous HFPEF score calibration by deciles of predicted probability (X axis) indicating good calibration. The Hosmer-Lemeshow goodness of fit test results using deciles of predicted probabilities were p=0.12, 0.31, and 0.32 for the derivation, validation and pooled overall sample, respectively, indicating support for a properly calibrated model.

Supplemental Figure 4: Classification and Regression Tree (CART) Analysis to Diagnose HFpEF. AFib-Atrial Fibrillation , PASP-Pulmonary Artery Systolic Pressure, BMI-Body Mass Index, E/e'- ratio of early diastolic mitral inflow velocity to septal mitral annulus tissue relaxation velocity, NT-proBNP- N terminal pro Brain Natriuretic Peptide

The tree structure represents a non-parametric branching algorithm for whether or not a person would be predicted to have HFpEF based on the variables and thresholds presented in the tree. The shaded boxes (terminal nodes) along the bottom edge of the figure are shaded to represent the predicted probability that a person has HFpEF with darker shades indicating higher probability.

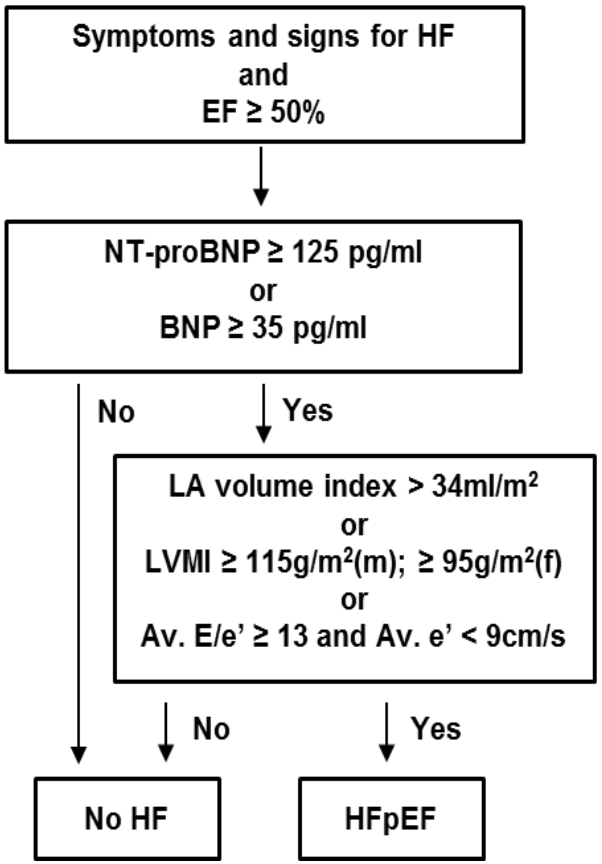
The top entry in each terminal node represents the predicted classification for that node. The second line reports the empirical probability of each classification level, not HFpEF and HFpEF, respectively. The final row in the cell gives the percentage of the development sample (n=414) that is classified into the node.

To illustrate the use of the tree more specifically, consider a person less than 60 years of age with a BMI of 25 kg/m^2. If that person has a NT-proBNP result under 130 pg/ml, he or she would be classified as not having HFpEF. In the 38/414 (9%) of the sample that were in this node, 97% (37/38) of them did not have HFpEF and were correctly classified accordingly. The false positive rate for this node was 3% (1/38). If this person

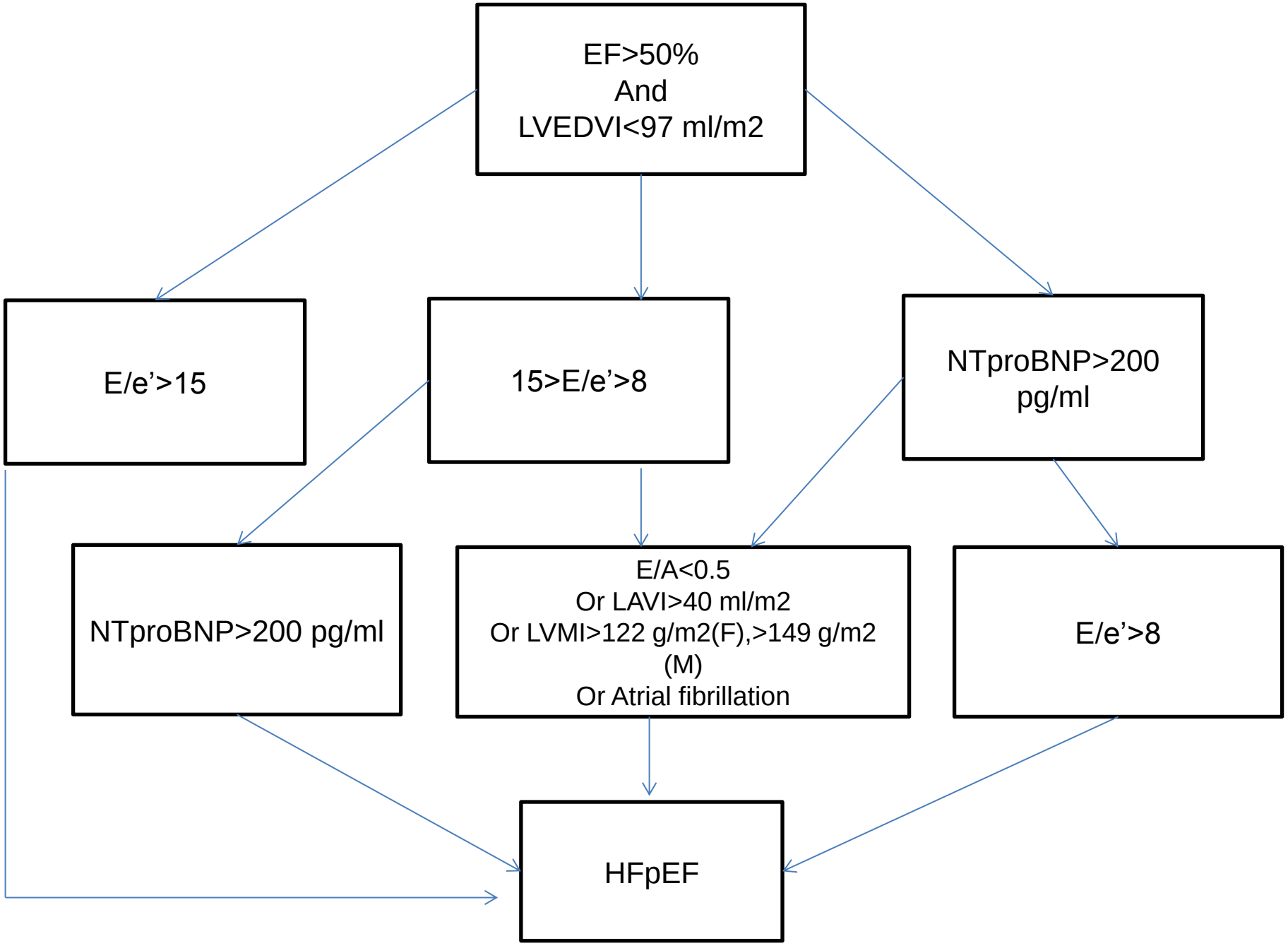
had an NT-proBNP result >= 130 pg/ml, the use of the PASP would be needed to further classify the individual as indicated in the tree.

Supplemental Figure 5: Calibration of H_2FpEF score in A) local patients not referred from tertiary academic medical centers, B) Early HFpEF (elevation in filling pressure during exercise only) and C) Advanced HFpEF (elevation in filling pressures at rest and during exercise).

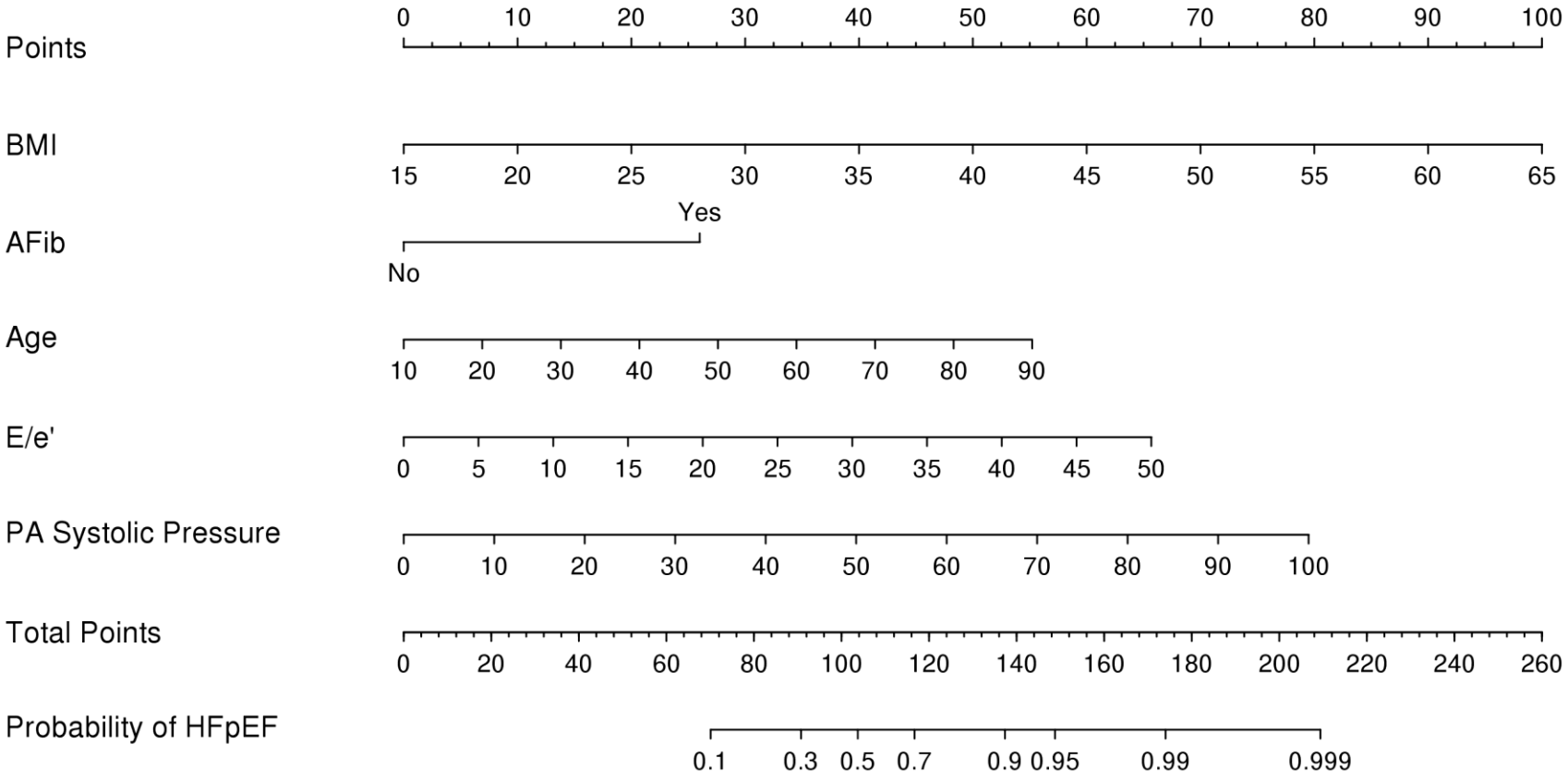
European Society of Cardiology HFpEF criteria



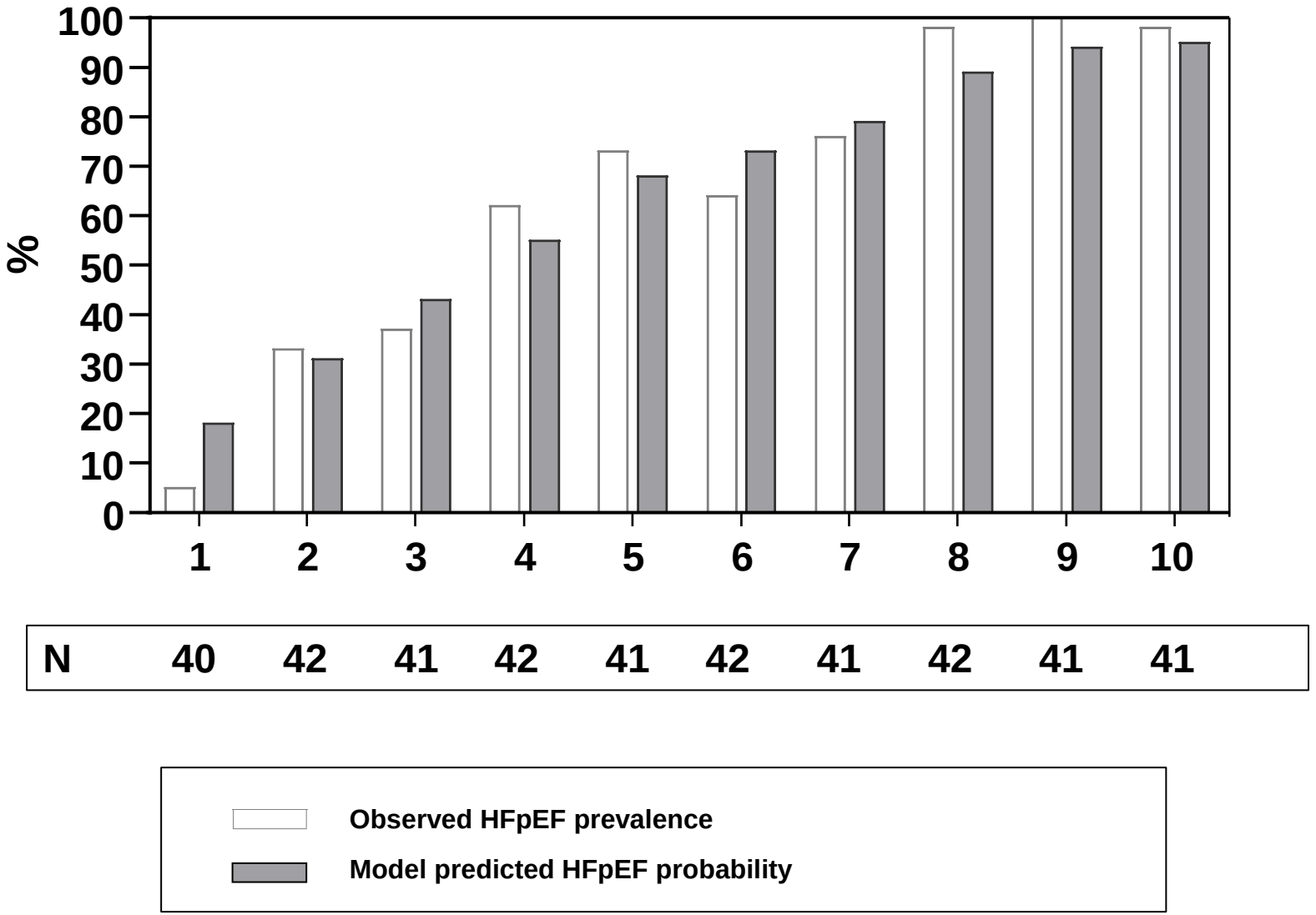
Supplemental Figure 1a: ESC 2016 algorithm for HFpEF diagnosis



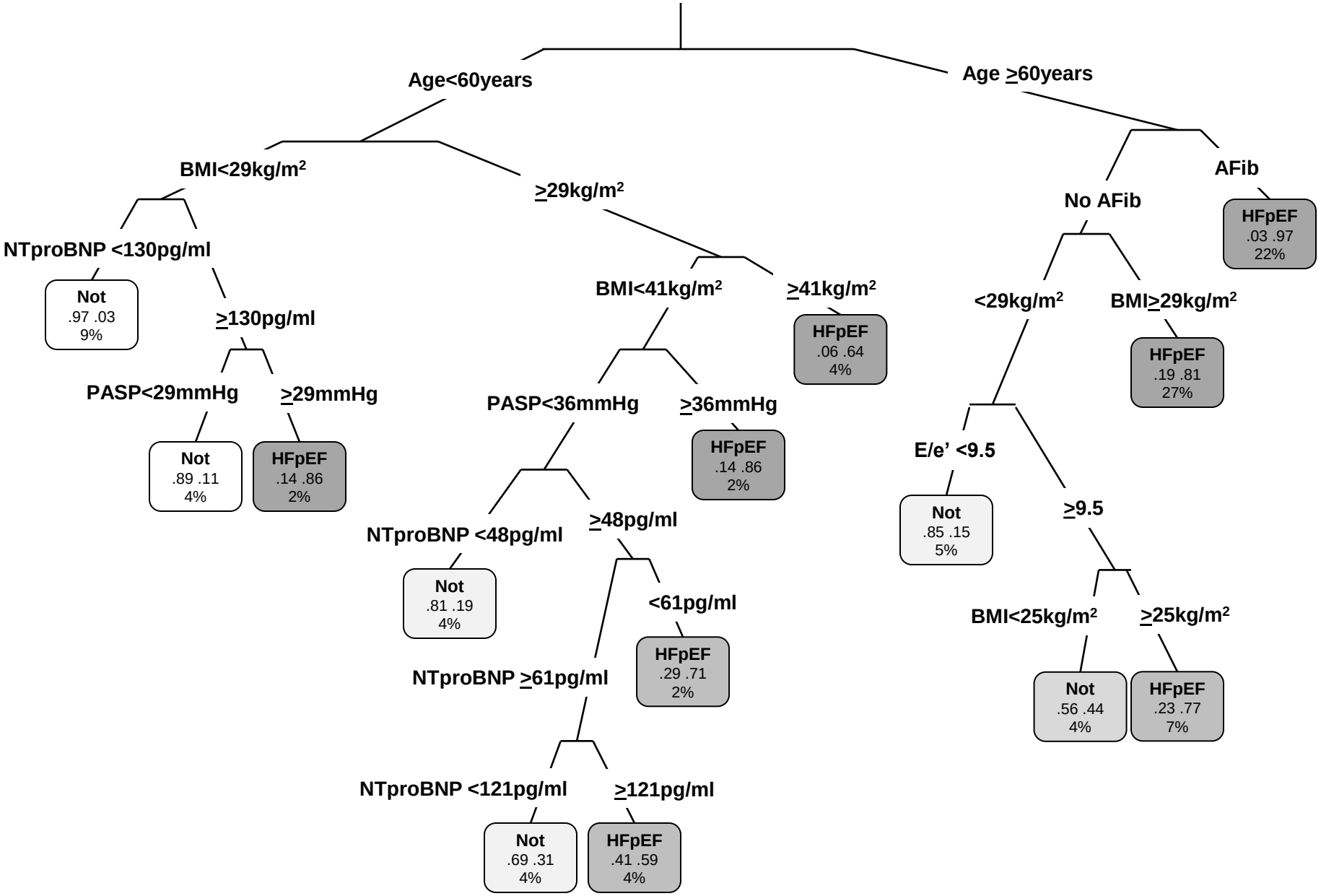
Supplemental Figure 1b: ESC 2007 algorithm for HFpEF diagnosis



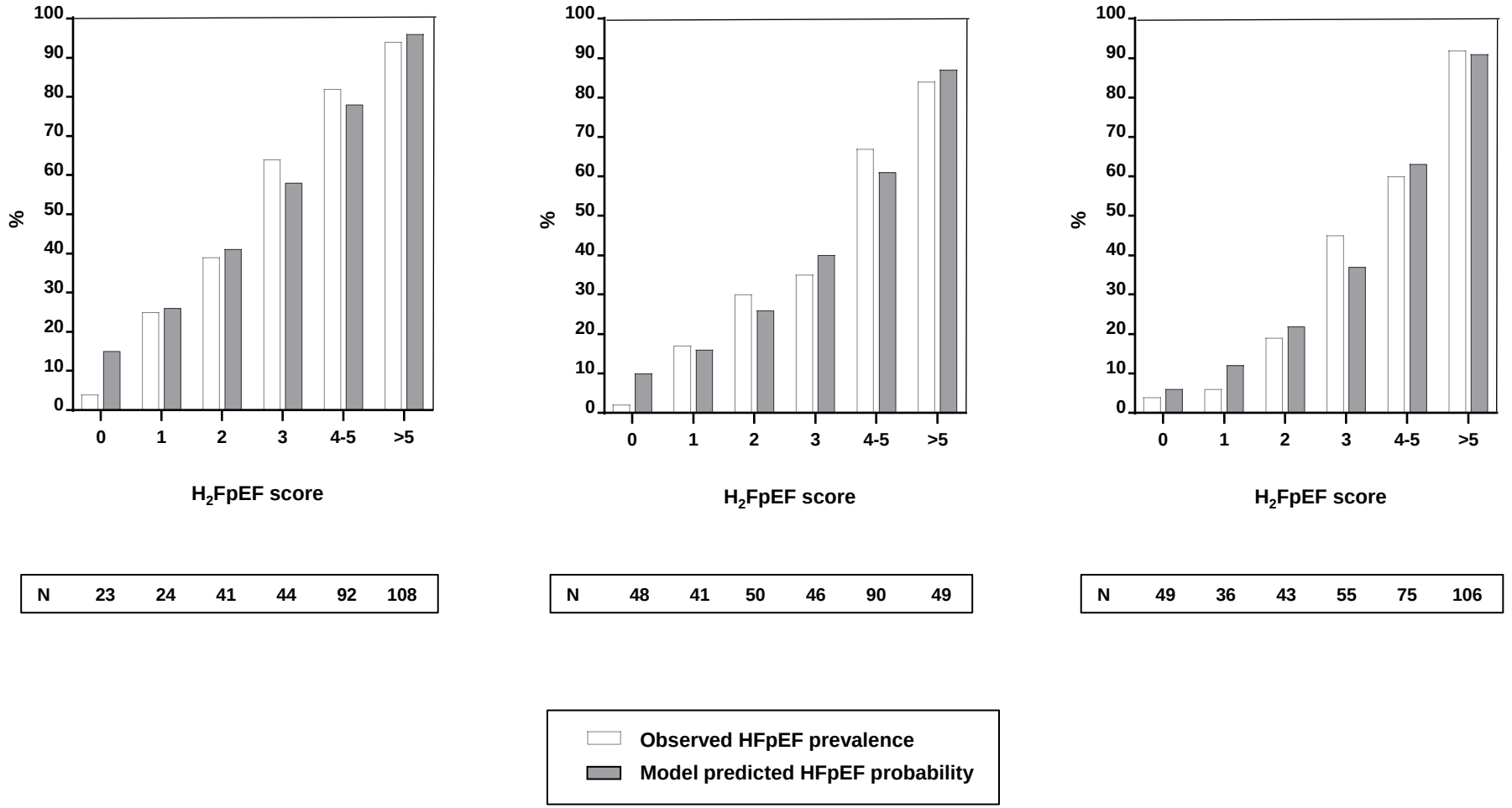
Supplemental Figure 2: Nomogram to diagnose HFpEF using continuous variables



Supplemental Figure 3: Calibration of the Continuous score by Deciles of predicted probability



Supplemental Figure 4: Results of CART Analysis



Supplemental Figure 5: Calibration of the points based H_2FpEF score in subgroups