

SUPPLEMENTAL MATERIAL

Heart failure and mid-range ejection fraction: Implications of recovered ejection fraction for exercise tolerance and outcomes

Short title: *Nadruz et al; Mid-EF Heart Failure*

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Supplemental Table 1. Forward stepwise Cox regression analysis for death including all baseline clinical and treatment variables that showed significant differences among the studied groups in univariate analysis.

Variable	Hazard ratio [95% confidence interval]	p
Glomerular filtration rate	0.99 [0.99-0.99]	<0.001
Coronary artery disease	2.05 [1.44-2.94]	<0.001
Diabetes mellitus	1.84 [1.32-2.57]	<0.001
Pacemaker	1.71 [1.23-2.37]	0.001
Post-chemotherapy	2.18 [1.33-3.57]	0.001
Diuretics use	2.06 [1.29-3.29]	0.003
ACEI/ARB use	0.65 [0.45-0.93]	0.017
Hemoglobin	0.89 [0.81-0.97]	0.012
White race	1.79 [1.09-2.92]	0.021
Statins use	0.66 [0.46-2.92]	0.021

Legend. Only variables that showed significant association are shown.

ACEI/ARB – angiotensin converting enzyme inhibitor or angiotensin receptor blocker.

Supplemental Table 2. Forward stepwise Cox regression analysis for the composite endpoint including all baseline clinical and treatment variables that showed significant differences among the studied groups.

Variable	Hazard ratio [95% confidence interval]	p
Glomerular filtration rate	0.99 [0.98-0.99]	<0.001
Diuretics use	2.32 [1.56-3.45]	<0.001
Aldosterone antagonists use	1.61 [1.23-2.09]	<0.001
ACEI/ARB use	0.65 [1.56-3.45]	0.004
Coronary artery disease	1.46 [1.12-1.90]	0.005
Anticoagulation	1.46 [1.12-1.89]	0.005
Post-chemotherapy	1.59 [1.03-2.46]	0.037

Legend. Only variables that showed significant association are shown. The composite endpoint was defined as the composite outcome of left ventricular assistant device implantation, heart transplantation or all-cause mortality.

ACEI/ARB – angiotensin converting enzyme inhibitors or angiotensin receptor blockers.

Supplemental Table 3: Age-adjusted baseline cardiopulmonary exercise testing features of study participants.

Variables	HFrEF n=620 (66%)	HFm-recEF n=170 (18%)	HFmEF n=107 (11%)	HFpEF n=47 (5%)
<i>Ventilatory</i>				
Peak VO ₂ , mL/min/Kg	14.4 ± 0.2	17.5 ± 0.4*	17.1 ± 0.5*	15.9 ± 0.8
VE/VCO ₂ Slope	34.4 ± 0.3	29.3 ± 0.6*	30.7 ± 0.8*	30.5 ± 1.2*
<i>Hemodynamic</i>				
Resting HR, bpm	74.2 ± 0.6	68.7 ± 1.1*	69.4 ± 1.3*	71.2 ± 2.0
Peak HR, bpm	121.5 ± 1.0	129.2 ± 1.9*	123.8 ± 2.4	121.7 ± 3.7
Chronotropic index	0.52 ± 0.01	0.63 ± 0.02*	0.57 ± 0.03	0.53 ± 0.4†
Resting SBP, mmHg	114.0 ± 0.8	121.6 ± 1.4*	120.3 ± 1.8*	126.9 ± 2.8*‡
Peak SBP, mmHg	134.9 ± 1.1	151.8 ± 2.1*	151.6 ± 2.7*	156.2 ± 4.2*
Resting DBP, mmHg	73.5 ± 0.5	75.4 ± 0.9	73.8 ± 1.1	74.5 ± 1.7
Peak DBP, mmHg	74.4 ± 0.5	77.2 ± 0.9*	76.0 ± 1.2	76.1 ± 1.9
Peak RER	1.19 ± 0.01	1.20 ± 0.01	1.20 ± 0.01	1.15 ± 0.02†

Legend. *p<0.05 compared to HFrEF; † p<0.05 compared to HFm-recEF; ‡ p<0.05 compared to HFmEF. Data are presented as mean ± standard error of the mean.

HFrEF – HF with reduced LVEF; HFm-recEF – HF with mid-range and recovered LVEF; HFmEF – HF with mid-range and without recovered LVEF; HFpEF – heart failure with preserved LVEF; LVEF- left ventricular ejection fraction; DBP – diastolic blood pressure; HR – heart rate; RER - respiratory exchange ratio; SBP – systolic blood pressure; VE/VCO₂ - minute ventilation-carbon dioxide production relationship; VO₂ – oxygen consumption.

Supplemental Table 4. Features of heart failure with mid-range and recovered left ventricular ejection fraction (HFm-recEF) patients according to change in left ventricular ejection fraction

Variables	Δ LVEF	Δ LVEF	Δ LVEF	P for trend
	< -7%	-7 to +7%	> +7%	
	n=20 (16%)	n=78 (64%)	n=25 (20%)	
<i>LVEF, %</i>				
Baseline	50 [45, 55]	48 [44, 50]	40 [40, 47]	<0.001
Follow-up	34 [25, 40]	46 [43, 52]	57 [54, 60]	<0.001
<i>Baseline Clinical features</i>				
Age, years	57.1 \pm 15.1	51.5 \pm 12.3	44.6 \pm 11.6	0.001
Male gender, n(%)	14 (70)	47 (60)	12 (48)	0.13
White, n(%)	16 (80)	65 (83)	21 (84)	0.74
Body mass index, kg/m ²	29.9 \pm 5.5	28.66 \pm 6.62	28.93 \pm 6.97	0.67
Ischemic cardiomyopathy, n(%)	3 (15)	8 (10)	0 (0)	0.07
Post-Chemotherapy, n(%)	2 (10)	8 (10)	4 (16)	0.50
Symptomatic heart failure, n(%)	15 (75)	56 (72)	19 (76)	0.91
Hypertension, n(%)	16 (80)	39 (50)	10 (40)	0.009
Diabetes mellitus, n(%)	5 (25)	14 (18)	4 (16)	0.46
Coronary artery disease, n(%)	5 (25)	13 (17)	4 (16)	0.46
Atrial Fibrillation, n(%)	5 (25)	26 (33)	3 (12)	0.26
COPD, n(%)	3 (15)	8 (10)	0 (0)	0.07
Estimated GFR, mL/min	60.8 \pm 29.4	85.9 \pm 20.7	89.7 \pm 26.0	<0.001
Hemoglobin, g/dL	13.0 \pm 1.6	13.8 \pm 1.5	13.5 \pm 1.7	0.39
<i>Baseline treatment features</i>				
CRT/ICD, n(%)	3 (15)	21 (27)	5 (20)	0.77
Pacemaker, n(%)	3 (15)	23 (30)	5 (20)	0.80
Beta-blockers, n(%)	17 (85)	66 (85)	20 (80)	0.63
ACEI/ARB, n(%)	19 (95)	67 (86)	21 (84)	0.30
Aldosterone antagonists, n(%)	5 (25)	18 (23)	3 (12)	0.27
Diuretics, n(%)	13 (65)	37 (47)	12 (48)	0.30
Calcium channel blockers, n(%)	4 (20)	7 (9)	1 (4)	0.08
Anticoagulation, n(%)	5 (25)	21 (27)	3 (12)	0.27

Antiplatelets, n(%)	11 (55)	27 (35)	7 (28)	0.07
Antiarrhythmics, n(%)	3 (15)	22 (28)	3 (12)	0.69
Statins, n(%)	8 (40)	32 (41)	10 (40)	0.99
<i>Baseline CPET features</i>				
Peak VO ₂ , mL/min/Kg	16.7 ± 5.0	18.7 ± 7.1	18.0 ± 4.8	0.56
% Predicted Peak VO ₂	70.2 ± 18.0	72.0 ± 20.3	70.0 ± 18.7	0.93
VE/VCO ₂ Slope	28.9 ± 5.5	29.2 ± 6.5	27.0 ± 4.4	0.24
Resting HR, bpm	68.3 ± 12.9	68.5 ± 13.4	69.1 ± 11.4	0.83
Peak HR, bpm	125.8 ± 28.2	132.2 ± 23.9	138.0 ± 24.5	0.10
Chronotropic index	0.61 ± 0.26	0.64 ± 0.23	0.66 ± 0.24	0.50
Resting SBP, mmHg	124.4 ± 17.2	121.0 ± 20.9	118.1 ± 18.5	0.29
Peak SBP, mmHg	154.8 ± 19.6	151.7 ± 29.7	152.5 ± 25.7	0.80
Resting DBP, mmHg	74.9 ± 9.5	75.4 ± 11.5	72.7 ± 13.0	0.48
Peak DBP, mmHg	76.4 ± 8.8	78.2 ± 11.8	78.5 ± 13.7	0.58
Peak RER	1.19 ± 0.12	1.21 ± 0.11	1.24 ± 0.16	0.14

Legend. Data are presented as mean ± standard deviation for normally distributed continuous variables and median [25th,75th percentile] for non-normally distributed continuous variables.

ΔLVEF – change in follow-up LVEF compared to baseline LVEF; ACEI/ARB – angiotensin converting enzyme inhibitor or angiotensin receptor blocker; COPD – chronic obstructive pulmonary disease; CRT/ICD - cardiac resynchronization therapy and/or implantable cardioverter defibrillator; GFR – glomerular filtration rate; LVEF - left ventricular ejection fraction; DBP – diastolic blood pressure; HR – heart rate; RER - respiratory exchange ratio; SBP – systolic blood pressure; VE/VCO₂ - minute ventilation-carbon dioxide production relationship; VO₂ – oxygen consumption.

Supplemental Table 5. Features of heart failure with mid-range and without recovered left ventricular ejection fraction (HFmEF) patients according to change in left ventricular ejection fraction

Variables	Δ LVEF	Δ LVEF	Δ LVEF	P for trend
	< -7%	-7 to +7%	> +7%	
	n=9 (12%)	n=48 (61%)	n=21 (27%)	
<i>LVEF, %</i>				
Baseline	50 [45, 50]	50 [45, 55]	45 [40, 55]	0.09
Follow-up	33 [30, 35]	50 [45, 55]	55 [55, 65]	<0.001
<i>Baseline Clinical features</i>				
Age, years	49.4 ± 18.3	53.4 ± 14.8	51.5 ± 16.0	0.92
Male gender, n(%)	4 (44)	25 (52)	12 (57)	0.53
White, n(%)	7 (78)	46 (96)	19 (91)	0.52
Body mass index, kg/m ²	28.9 ± 9.7	28.8 ± 6.3	30.5 ± 6.6	0.41
Ischemic cardiomyopathy, n(%)	1 (11)	6 (13)	2 (10)	0.82
Post-Chemotherapy, n(%)	0 (0)	11 (23)	4 (19)	0.42
Symptomatic heart failure, n(%)	7 (78)	31 (65)	16 (76)	0.82
Hypertension, n(%)	4 (44)	26 (54)	12 (57)	0.57
Diabetes mellitus, n(%)	3 (33)	11 (23)	2 (10)	0.11
Coronary artery disease, n(%)	2 (22)	12 (25)	6 (29)	0.69
Atrial Fibrillation, n(%)	3 (33)	11 (23)	5 (24)	0.69
COPD, n (%)	1 (11)	5 (10)	1 (5)	0.48
Estimated GFR, mL/min	79.9 ± 28.0	75.7 ± 23.5	85.9 ± 22.7	0.30
Hemoglobin, g/dL	12.3 ± 2.1	13.4 ± 1.8	13.4 ± 2.3	0.28
<i>Baseline treatment features</i>				
CRT/ICD, n(%)	3 (33)	6 (13)	3 (14)	0.34
Pacemaker, n(%)	3 (33)	6 (13)	5 (24)	0.94
Beta-blockers, n(%)	8 (89)	30 (63)	16 (76)	0.90
ACEI/ARB, n(%)	7 (78)	27 (56)	11 (52)	0.27
Aldosterone antagonists, n(%)	1 (11)	6 (13)	2 (10)	0.82
Diuretics, n(%)	4 (44)	16 (33)	11 (52)	0.40
Calcium channel blockers, n(%)	2 (22)	11 (23)	3 (14)	0.50
Anticoagulation, n(%)	3 (33)	9 (19)	3 (14)	0.28

Antiplatelets, n(%)	4 (44.4)	20 (42)	6 (29)	0.32
Antiarrhythmics, n(%)	1 (11)	2 (4)	2 (10)	0.86
Statins, n(%)	2 (22)	16 (33)	7 (33)	0.65
<i>Baseline CPET features</i>				
Peak VO ₂ , mL/min/Kg	20.4 ± 13.0	18.6 ± 8.7	16.0 ± 8.9	0.19
% Predicted Peak VO ₂	76.0 ± 25.7	75.5 ± 24.1	62.3 ± 19.8	0.06
VE/VCO ₂ Slope	29.4 ± 4.9	30.3 ± 6.4	29.7 ± 4.2	0.94
Resting HR, bpm	65.4 ± 16.4	70.9 ± 14.8	68.8 ± 14.7	0.81
Peak HR, bpm	125.8 ± 34.4	132.0 ± 31.5	121.5 ± 29.2	0.47
Chronotropic index	0.56 ± 0.25	0.65 ± 0.31	0.51 ± 0.22	0.35
Resting SBP, mmHg	121.1 ± 25.4	115.5 ± 17.6	127.0 ± 20.3	0.17
Peak SBP, mmHg	148.9 ± 31.0	152.3 ± 32.3	147.3 ± 29.6	0.75
Resting DBP, mmHg	72.5 ± 9.1	72.2 ± 12.2	76.8 ± 9.5	0.19
Peak DBP, mmHg	71.7 ± 16.3	75.3 ± 13.0	76.7 ± 10.5	0.39
Peak RER	1.17 ± 0.10	1.21 ± 0.12	1.18 ± 0.13	0.14

Legend. Data are presented as mean ± standard deviation for normally distributed continuous variables and median [25th,75th percentile] for non-normally distributed continuous variables.

ΔLVEF – change in follow-up LVEF compared to baseline LVEF; ACEI/ARB – angiotensin converting enzyme inhibitor or angiotensin receptor blocker; COPD – chronic obstructive pulmonary disease; CRT/ICD - cardiac resynchronization therapy and/or implantable cardioverter defibrillator; GFR – glomerular filtration rate; LVEF- left ventricular ejection fraction; DBP – diastolic blood pressure; HR – heart rate; RER - respiratory exchange ratio; SBP – systolic blood pressure; VE/VCO₂ - minute ventilation-carbon dioxide production relationship; VO₂ – oxygen consumption.

Supplemental Table 6. Characteristics of heart failure patients from the Brigham and Women’s Hospital and from other studies that enrolled chronic heart failure patients.

Variables	Cardiovascular Health Study ¹			CHARM ²			He et al ³			Brigham and Women’s Hospital			
	HFrEF	HFmidEF	HFpEF	HFrEF ⁴	HFmidEF	HFpEF	HFrEF	HFmidEF	HFpEF	HFrEF	HFm-recEF	HFmEF	HFpEF
LVEF cut-off	<45%	45–54%	≥55%	≤40%	43–52%	>52%	<40%	40–55%	>55%	<40%	40–55%	40–55%	>55%
n	60	39	170	4576	1295	1500	98	38	128	620	170	107	47
Mean age, years	74	73	75	65	66	67	62	66	72	55	52	54	63
Men, %	63	49	44	74	68	51	75	79	65	73	61	55	49
Mean BMI, kg/m ²							24	25	25	28	29	29	32
Mean HR, bpm				74	71	71	77	69	71	74	69	70	70
Mean SBP, mmHg	127	136	138	127	135	138	126	141	139	114	121	120	129
Mean DBP, mmHg	66	68	68	76	78	77	76	79	76	74	75	74	75
Hypertension, %	57	72	59	49	60	70	54	77	88	59	51	58	77
CAD/MI, %	78	69	58	65-75	72	62	51	65	63	41	21	26	30
Diabetes, %	23	36	27	29	27	28	41	48	33	29	16	21	32
Atrial fibrillation, %							10	8	26	35	27	28	38
Hemoglobin, g/dL							13.4	14.5	13.5	13.6	13.5	13.0	12.8
ACE inhibitors, %	42	28	25	56	21	17	50	45	37	64	65	42	49

ARB, %							4	23	11	19	21	14	15
Beta-blockers, %	7	8	17	55	57	54	39	58	55	90	85	68	62
Aldosterone ant., %				20	11	12				36	22	14	4
Diuretics, %	78	74	59	88	64	63	67	56	37	76	47	45	72
CCB, %	30	46	31	13	26	37	26	39	57	4	8	25	23
Lipid lowering, %	2	3	5	41	43	40				52	43	38	45

Legend. HF_rEF – heart failure (HF) with reduced left ventricular ejection fraction (LVEF); HF_{mid}EF – HF with mid-range LVEF; HF_pEF – HF with preserved LVEF; HF_{m-rec}EF – HF with mid-range LVEF and recovered LVEF; HF_mEF – HF with mid-range LVEF without recovered LVEF. CHARM - Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity. BMI – body mass index; HR – heart rate; SBP – systolic blood pressure; DBP – diastolic blood pressure; CAD – coronary artery disease; MI – myocardial infarction; ACE – angiotensin-converting enzyme; ARB – angiotensin receptor blockers; Aldosterone ant. – aldosterone antagonists; CCB – calcium channel blockers.

¹Gottdiener JS, et al. Outcome of congestive heart failure in elderly persons: influence of left ventricular systolic function. The Cardiovascular Health Study. *Ann Intern Med* 2002;137:631–9. ²Solomon SD, et al. Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients. *Circulation*. 2005;112:3738-44. ³He KL, et al. Comparison of ventricular structure and function in Chinese patients with heart failure and ejection fractions >55% versus 40% to 55% versus <40%. *Am J Cardiol* 2009;103:845–51. ⁴Young JB, et al. Mortality and morbidity reduction with Candesartan in patients with chronic heart failure and left ventricular systolic dysfunction: results of the CHARM low-left ventricular ejection fraction trials. *Circulation*. 2004;110:2618-26.

Supplemental Table 7. Characteristics of heart failure patients from the Brigham and Women’s Hospital and from other studies that enrolled acutely-decompensated heart failure patients.

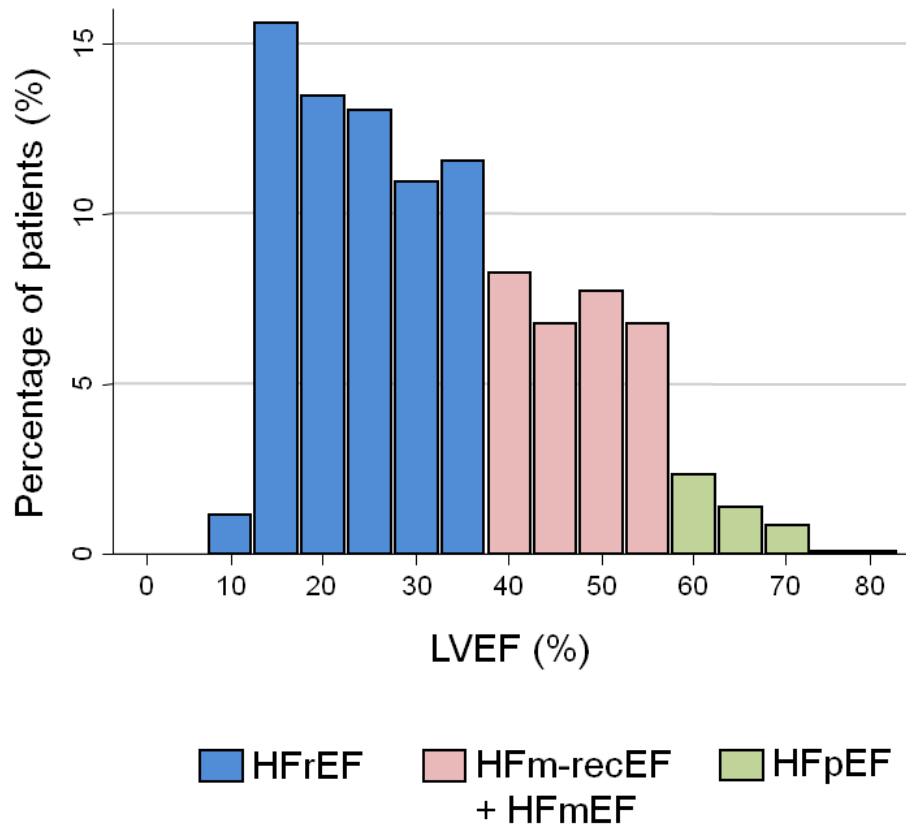
Variables	OPTIMIZE-HF ¹			ADHERE ²			ASCEND-HF ³			Brigham and Women’s Hospital			
	HFrEF	HFmidEF	HFpEF	HFrEF*	HFmidEF	HFpEF	HFrEF	HFmidEF	HFpEF	HFrEF	HFm-recEF	HFmEF	HFpEF
LVEF cut-off	<40%	40–50%	>50%	≤40%	40–55%	≥55%	<40%	40–50%	>50%	<40%	40–55%	40–55%	>55%
n	20118	7321	10070	40796	17045	17022	4474	674	539	620	170	107	47
Mean age, years	70	74	76	70	74	74	64	73	76	55	52	54	63
Men, %	62	48	32	61	46	31	71	59	42	73	61	55	49
Mean BMI, kg/m ²	39	44	41	28	30	31				28	29	29	32
Mean HR, bpm	89	86	84				83	78	74	74	69	70	70
Mean SBP, mmHg	135	147	150	136	150	152	120	130	132	114	121	120	129
Mean DBP, mmHg	77	77	75	78	79	77	75	72	70	74	75	74	75
Hypertension, %	66	74	77				68	82	89	59	51	58	77
CAD/MI, %	54	49	32	63	60	47	63	69	60	41	21	26	30
Diabetes, %	41	48	33	42	48	44	42	50	51	29	16	21	32
Atrial fibrillation, %				29	33	32	32	50	55	35	27	28	38
Hemoglobin, g/dL	12.5	11.9	11.8				12.8	12.3	11.6	13.6	13.5	13.0	12.8
eGFR, mL/min/1.73m ²							69	54	51	72	82	75	67

ACE inhibitors, %	45	38	34	66	57	51	63 [‡]	61 [‡]	60 [‡]	64	65	42	49
ARB, %	11	12	14	13	15	16				19	21	14	15
Beta-blockers, %	56	54	50	67	62	55	59	65	67	90	85	68	62
Aldosterone ant., %	10	6	4				33	21	13	36	22	14	4
Diuretics, %	63	59	57				95	97	96	76	47	45	72
CCB, %	5 [†]	9 [†]	11 [†]		31	39				4	8	25	23
Lipid lowering, %	40	41	37	36	36	31				52	43	38	45
Pacemaker, %							1	1	1	55	28	22	13
Defibrillator, %							11	4	2	54	26	14	2

Legend. HF_rEF – heart failure (HF) with reduced left ventricular ejection fraction (LVEF); HF_{mid}EF – HF with mid-range LVEF; HF_pEF – HF with preserved LVEF; HF_{m-rec}EF – HF with mid-range LVEF and recovered LVEF; HF_mEF – HF with mid-range LVEF without recovered LVEF. OPTIMIZE-HF - Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure; ADHERE - Acute Decompensated Heart Failure Registry; ASCEND-HF – Acute Studies of Nesiritide in Decompensated Heart Failure; BMI – body mass index; HR – heart rate; SBP – systolic blood pressure; DBP – diastolic blood pressure; CAD – coronary artery disease; MI – myocardial infarction; eGFR – estimated glomerular filtration rate; ACE – angiotensin-converting enzyme; ARB – angiotensin receptor blockers; Aldosterone ant. – aldosterone antagonists; CCB – calcium channel blockers. *values are weighted measures adapted from ref. 1. [†]amlodipine; [‡]ACE inhibitor or ARB; ¹Fonarow GC, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. J Am Coll Cardiol. 2007;50:768-77. ²Sweitzer NK, et al. Comparison of clinical features and outcomes of patients

hospitalized with heart failure and normal ejection fraction ($\geq 55\%$) versus those with mildly reduced (40% to 55%) and moderately to severely reduced ($<40\%$) fractions. Am J Cardiol. 2008;101:1151-6. ³Toma M, et al. The relationship between left ventricular ejection fraction and mortality in patients with acute heart failure: insights from the ASCEND-HF Trial. Eur J Heart Fail. 2014;16:334-41.

Supplemental Figure 1.



Legend: Left ventricular ejection fraction (LVEF) distribution of the studied sample. HFrEF – HF with reduced LVEF; HFm-recEF – HF with mid-range and recovered LVEF; HFmEF – HF with mid-range and without recovered LVEF; HFpEF – heart failure with preserved LVEF.