

**SUPPLEMENTARY APPENDIX**

**Supplementary Table 1 – Clinical characteristics according to baseline and 9-month moderate-severe MR**

	No or Mild MR at Baseline and 9-month – Unchanged (n=470)	Moderate or Severe MR at Baseline, No or Mild MR at 9-month – Improved (n=192)	No or Mild MR at Baseline, Moderate or Severe MR at 9-month – Worsened (n=90)	Moderate or Severe MR at Baseline and 9-month – Unchanged (n=270)	<i>p</i> -value
Age (years)	66.1 ± 12.7	64.8 ± 12.1	71.4 ± 10.0	68.4 ± 11.4	<b>&lt;0.001</b>
Men	371 (78.9)	142 (74.0)	65 (72.2)	208 (77.0)	0.370
BMI (kg/m <sup>2</sup> )	28.7 ± 5.8	27.2 ± 5.4	26.3 ± 4.8	27.2 ± 4.6	<b>&lt;0.001</b>
HF hospitalization in last year	121 (25.7)	51 (26.6)	29 (32.2)	83 (30.7)	0.365
Primary ischemic HF etiology	207 (44.6)	67 (35.6)	47 (52.2)	121 (45.7)	<b>0.043</b>
Medical history (baseline)					
Hypertension	299 (63.6)	109 (56.8)	53 (58.9)	168 (62.2)	0.388
Diabetes mellitus	139 (29.6)	47 (24.5)	23 (25.6)	76 (28.2)	0.567
Atrial fibrillation	184 (39.2)	71 (37.0)	36 (40.0)	119 (44.1)	0.435
Myocardial infarction	170 (36.2)	60 (31.3)	43 (47.8)	96 (35.6)	0.063
PCI	108 (23.0)	38 (19.8)	23 (25.6)	38 (14.1)	<b>0.017</b>
CABG	71 (15.1)	19 (9.9)	19 (21.1)	40 (14.8)	0.086
Prior valve surgery	39 (8.3)	14 (7.3)	4 (4.4)	17 (6.3)	0.534
Peripheral artery disease	43 (9.2)	16 (8.3)	4 (4.4)	27 (10.0)	0.435
COPD	76 (16.2)	26 (13.5)	14 (15.6)	38 (14.1)	0.796
Stroke	44 (9.4)	16 (8.3)	6 (6.7)	27 (10.0)	0.781
Current malignancy	13 (2.8)	2 (1.0)	5 (5.6)	7 (2.6)	0.178
CKD	95 (20.2)	39 (20.3)	24 (26.7)	73 (27.0)	0.112
Device therapy					0.055
Pacemaker	31 (6.6)	6 (3.1)	6 (6.7)	24 (8.9)	
ICD	32 (6.8)	7 (3.7)	8 (8.9)	20 (7.4)	
CRT-P	6 (1.3)	5 (2.6)	1 (1.1)	7 (2.6)	
CRT-D	27 (5.7)	11 (5.7)	8 (8.9)	25 (9.3)	
Type of baseline visit					0.667
Inpatient hospitalization	284 (60.4)	123 (64.1)	51 (56.7)	159 (58.9)	
Outpatient clinic	186 (39.6)	69 (35.9)	39 (43.3)	111 (41.1)	
Reason for baseline visit					<b>&lt;0.001</b>
Worsening HF	190 (40.4)	69 (35.9)	44 (48.9)	141 (52.2)	
New-onset HF	160 (34.0)	75 (39.1)	19 (21.1)	57 (21.1)	
Other	120 (25.5)	48 (25.0)	27 (30.0)	72 (26.7)	
NYHA class					0.056
Baseline					
I	17 (3.7)	3 (1.6)	1 (1.1)	3 (1.1)	
II	219 (47.6)	79 (42.5)	37 (41.6)	119 (44.4)	
III	193 (42.0)	78 (41.9)	44 (49.4)	121 (45.2)	
IV	31 (6.7)	26 (14.0)	7 (7.9)	25 (9.3)	
9-month					<b>&lt;0.001</b>
I	95 (20.7)	57 (31.3)	10 (11.2)	28 (10.7)	
II	269 (58.6)	91 (50.0)	49 (55.1)	160 (61.1)	
III	89 (19.4)	33 (18.1)	28 (31.5)	69 (26.3)	
IV	6 (1.3)	1 (0.6)	2 (2.3)	5 (1.9)	
SBP					
Baseline	127 ± 22	125 ± 21	125 ± 25	122 ± 19	<b>0.028</b>
9-month	127 ± 22	127 ± 20	118 ± 20	121 ± 20	<b>&lt;0.001</b>
HF therapy					
ACEi/ARB					
Baseline use	380 (80.9)	144 (75.0)	64 (71.1)	214 (79.3)	0.115
3-month use	430 (91.5)	171 (89.1)	83 (92.2)	250 (92.6)	0.593
3-month target dose	139 (29.6)	60 (31.3)	17 (18.9)	54 (20.0)	<b>0.005</b>
3-month optimal dose fraction (%)	55 ± 41	57 ± 43	48 ± 39	48 ± 36	<b>0.024</b>
β-blockers					
Baseline use	400 (85.1)	157 (81.8)	78 (86.7)	232 (85.9)	0.591
3-month use	430 (91.5)	176 (91.7)	87 (96.7)	262 (97.0)	<b>0.011</b>
3-month target dose	63 (13.4)	29 (15.1)	14 (15.6)	35 (13.0)	0.866
3-month optimal dose fraction (%)	38 ± 31	38 ± 31	36 ± 30	38 ± 28	0.961
MRA baseline use	241 (51.3)	105 (54.7)	48 (53.3)	168 (62.2)	<b>0.038</b>
Loop diuretic baseline use	469 (99.8)	190 (99.0)	90 (100.0)	270 (100.0)	0.184
Digoxin baseline use	76 (16.2)	34 (17.7)	13 (14.4)	62 (23.0)	0.097

Data are presented as n (%) and mean ± standard deviation.

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; CABG = coronary artery bypass graft; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CRT-D = cardiac resynchronization therapy with defibrillator; CRT-P = cardiac resynchronization therapy with pacemaker; HF = heart failure; ICD = implantable cardioverter-defibrillator; MR = mitral regurgitation; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; PCI = percutaneous coronary intervention.

**Supplementary Table 2 – Echocardiographic data, laboratory characteristics, and QoL measures according to 9-month and baseline moderate-severe MR.**

	No or Mild MR at Baseline and 9-month – Unchanged (n=470)	Moderate or Severe MR at Baseline, No or Mild MR at 9-month – Improved (n=192)	No or Mild MR at Baseline, Moderate or Severe MR at 9-month – Worsened (n=90)	Moderate or Severe MR at Baseline and 9-month – Unchanged (n=270)	p-value
<b>Echocardiographic data</b>					
LVEF (%)					
Baseline	30 (25-35)	28 (23-35)	30 (25-36)	30 (23-35)	<b>0.003</b>
9-month	36 (30-45)	35 (30-45)	30 (25-38)	30 (25-38)	<b>&lt;0.001</b>
LVEF categories					
Baseline					0.062
HF <sub>r</sub> EF (LVEF <40%)	356 (84.0)	156 (84.3)	68 (81.0)	230 (88.8)	
HF <sub>mr</sub> EF (LVEF 40-49%)	52 (12.3)	16 (8.7)	14 (16.7)	20 (7.7)	
HF <sub>p</sub> EF (LVEF ≥50%)	16 (3.8)	13 (7.0)	2 (2.4)	9 (3.5)	
9-month					<b>&lt;0.001</b>
HF <sub>r</sub> EF (LVEF <40%)	236 (55.4)	106 (58.6)	67 (78.8)	202 (77.7)	
HF <sub>mr</sub> EF (LVEF 40-49%)	123 (28.9)	44 (24.3)	16 (18.8)	44 (16.9)	
HF <sub>p</sub> EF (LVEF ≥50%)	67 (15.7)	31 (17.1)	2 (2.4)	14 (5.4)	
LVEDD (mm)					
Baseline	61 (56-65)	63 (58-68)	61 (55-70)	65 (59-70)	<b>&lt;0.001</b>
9-month	59 (54-65)	61 (54-65)	64 (58-70)	64 (58-70)	<b>&lt;0.001</b>
LVESD (mm)					
Baseline	48 (43-54)	52 (46-58)	50 (42-56)	53 (47-60)	<b>&lt;0.001</b>
9-month	46 (39-52)	47 (41-53)	52 (44-61)	52 (45-60)	<b>&lt;0.001</b>
Left atrium diameter (mm)					
Baseline	45 (40-50)	47 (43-52)	45 (42-50)	49 (45-55)	<b>&lt;0.001</b>
9-month	44 (40-50)	44 (40-49)	47 (44-52)	49 (45-54)	<b>&lt;0.001</b>
<b>Laboratory data</b>					
Creatinine (μmol/L)					
Baseline	97 (81-123)	96 (79-123)	97 (80-120)	106 (84-129)	0.263
9-month	104 (81-129)	106 (88-133)	99 (81-122)	104 (88-137)	0.233
eGFR CKD-EPI (mL/min/1.73 m <sup>2</sup> )					
Baseline	65 (49-83)	64 (49-84)	64 (47-77)	60 (43-79)	0.095
9-month	60 (46-81)	60 (43-78)	61 (44-78)	59 (42-75)	0.280
Urea (mmol/L)					
Baseline	9.8 (7.1-15.7)	10.2 (7.0-15.4)	10.5 (7.4-15.7)	11.0 (7.4-18.2)	0.352
9-month	9.8 (6.7-15.5)	10.9 (7.9-15.0)	9.5 (7.0-18.1)	10.3 (7.3-17.9)	0.412
Sodium (mmol/L)					
Baseline	140 (137-142)	140 (138-142)	140 (138-142)	140 (137-142)	0.771
9-month	140 (138-142)	140 (138-142)	140 (138-142)	139 (137-142)	0.840
NT-proBNP (ng/L)					
Baseline	1718 (739-4333)	2374 (1087-4884)	2554 (1064-5671)	2778 (1276-5119)	<b>&lt;0.001</b>
9-month	811 (289-1882)	748 (247-1894)	1515 (619-2914)	1708 (807-3838)	<b>&lt;0.001</b>
<b>QoL measures</b>					
6MWT distance (m)					
Baseline	288 (33-390)	306 (67-400)	258 (43-381)	268 (120-360)	0.473
9-month	352 (218-465)	390 (286-460)	336 (206-434)	312 (200-410)	<b>&lt;0.001</b>
KCCQ clinical summary score					
Baseline	56 (36-75)	54 (32-71)	49 (36-70)	51 (32-70)	0.254
9-month	71 (51-87)	79 (57-92)	61 (45-87)	64 (46-81)	<b>&lt;0.001</b>
KCCQ overall summary score					
Baseline	56 (39-73)	53 (33-70)	52 (38-69)	52 (35-70)	0.204
9-month	71 (52-86)	77 (59-90)	63 (48-83)	64 (47-79)	<b>&lt;0.001</b>
EQ-5D index value					
Baseline	0.74 (0.62-0.84)	0.77 (0.65-0.84)	0.74 (0.57-0.86)	0.74 (0.57-0.81)	0.881
9-month	0.78 (0.66-0.90)	0.81 (0.69-1.00)	0.74 (0.57-0.90)	0.77 (0.65-0.86)	<b>0.002</b>
EQ-5D VAS					
Baseline	60 (45-70)	60 (45-70)	50 (40-70)	55 (40-70)	0.102
9-month	65 (50-80)	70 (55-80)	60 (40-75)	60 (50-77)	<b>&lt;0.001</b>

Data are presented as n (%) and median (Q25-Q75).

6MWT = 6-minute walking test; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; EQ-5D = EuroQol - 5 Dimension; HF<sub>mr</sub>EF = heart failure with mid-range ejection fraction; HF<sub>p</sub>EF = heart failure with preserved ejection fraction; HF<sub>r</sub>EF = heart failure with reduced ejection fraction; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic

diameter; MR = mitral regurgitation; NT-proBNP = N-terminal pro-B-type natriuretic peptide; QoL = quality-of-life; VAS = Visual Analogue Scale.

**Supplementary Table 3 – Clinical characteristics among patients included vs. not included in the study.**

	Included (n=1022)	Excluded (n=1494)	p-value
Age (years)	66.9 ± 12.2	70.2 ± 11.6	<0.001
Men	786 (76.9)	1060 (71.0)	0.001
BMI (kg/m <sup>2</sup> )	27.8 ± 5.4	27.9 ± 5.6	0.688
HF hospitalization in last year	284 (27.8)	510 (34.1)	0.001
Primary ischemic HF aetiology	442 (43.9)	684 (46.7)	0.175
Medical history			
Hypertension	629 (61.6)	940 (62.9)	0.485
Diabetes mellitus	285 (27.9)	534 (35.7)	0.001
Atrial fibrillation	410 (40.1)	733 (49.1)	<0.001
Myocardial infarction	369 (36.1)	594 (39.8)	0.064
PCI	207 (20.3)	337 (22.6)	0.168
CABG	149 (14.6)	284 (19.0)	0.004
Prior valve surgery	74 (7.2)	105 (7.0)	0.839
Peripheral artery disease	90 (8.8)	183 (12.3)	0.006
COPD	154 (15.1)	282 (18.9)	0.013
Stroke	93 (9.1)	140 (9.4)	0.818
Current malignancy	27 (2.6)	70 (4.7)	0.009
CKD	231 (22.6)	465 (31.1)	<0.001
Device therapy			0.151
Pacemaker	67 (6.6)	116 (7.8)	
ICD	67 (6.6)	138 (9.2)	
CRT-P	19 (1.9)	30 (2.0)	
CRT-D	71 (7.0)	102 (6.8)	
Type of baseline visit			<0.001
Inpatient hospitalization	617 (60.4)	1077 (72.1)	
Outpatient clinic	405 (39.6)	417 (27.9)	
Reason for baseline visit			<0.001
Worsening HF	444 (43.4)	928 (62.1)	
New-onset HF	311 (30.4)	391 (26.2)	
Other	267 (26.1)	175 (11.7)	
NYHA class			<0.001
Baseline			
I	24 (2.4)	32 (2.2)	
II	454 (45.3)	414 (28.7)	
III	436 (43.5)	792 (54.9)	
IV	89 (8.9)	205 (14.2)	
9-month			0.001
I	190 (19.2)	126 (13.6)	
II	569 (57.4)	538 (58.1)	
III	219 (22.1)	254 (27.4)	
IV	14 (1.4)	8 (0.9)	
SBP			
Baseline	125 ± 22	124 ± 22	0.528
9-month	124 ± 21	125 ± 20	0.704
HF therapy			
ACEi/ARB			
Baseline use	802 (78.5)	1018 (68.1)	<0.001
3-month use	934 (91.4)	1259 (84.3)	<0.001
3-month target dose	270 (26.4)	276 (18.5)	<0.001
3-month optimal dose fraction (%)	53 ± 40	44 ± 36	<0.001
β-blockers			
Baseline use	867 (84.8)	1226 (82.1)	0.068
3-month use	955 (93.4)	1342 (89.8)	0.002
3-month target dose	141 (13.8)	178 (11.9)	0.163
3-month optimal dose fraction (%)	38 ± 30	35 ± 31	0.015
MRA baseline use	562 (55.0)	777 (52.0)	0.141
Loop diuretic baseline use	1019 (99.7)	1485 (99.4)	0.269
Digoxin baseline use	185 (18.1)	306 (20.5)	0.139

Data are presented as n (%) and mean ± standard deviation.

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; CABG = coronary artery bypass graft; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CRT-D = cardiac resynchronization therapy with defibrillator; CRT-P = cardiac resynchronization therapy with pacemaker; HF = heart failure; ICD =

implantable cardioverter-defibrillator; MR = mitral regurgitation; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; SBP = systolic blood pressure.

**Supplementary Table 4 – Multivariable binary logistic regression analysis for the predictors of persistent moderate-severe MR (among patients with moderate-severe MR at baseline).**

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	<i>p</i> -value	OR (95% CI)	<i>p</i> -value
Age (years)	1.03 (1.01-1.04)	<b>0.001</b>	1.02 (1.00-1.05)	<b>0.029</b>
Sex (women)	0.85 (0.55-1.30)	0.447	0.95 (0.57-1.60)	0.857
Primary ischemic HF etiology	1.52 (1.03-2.23)	<b>0.033</b>	1.53 (0.98-2.38)	0.061
Previous HF hospitalization in last year	1.23 (0.81-1.85)	0.330	0.84 (0.54-1.29)	0.423
NYHA class III or IV	0.94 (0.65-1.37)	0.762	0.98 (0.62-1.57)	0.949
eGFR CKD-EPI (mL/min/1.73 m <sup>2</sup> )	0.99 (0.98-1.00)	0.070	1.00 (0.99-1.01)	0.733
Log-NT-proBNP (ng/L)	1.09 (0.92-1.29)	0.324	1.02 (0.83-1.26)	0.815
LVEF categories				
HF <sub>r</sub> EF (LVEF <40%) – reference	-	-	-	-
HF <sub>mr</sub> EF (LVEF 40-49%)	0.85 (0.43-1.69)	0.638	0.59 (0.27-1.27)	0.178
HF <sub>p</sub> EF (LVEF ≥50%)	0.47 (0.20-1.13)	0.090	0.37 (0.14-1.00)	<b>0.049</b>
ACEi/ARB optimal dose fraction at 3 months (%)	0.56 (0.35-0.90)	<b>0.017</b>	0.54 (0.31-0.94)	<b>0.030</b>
β-blocker optimal dose fraction at 3 months (%)	1.00 (0.53-1.90)	0.990	1.20 (0.58-2.49)	0.619

Data are presented as OR and 95% CI. The *C*-statistic for the multivariable model is 0.63, the Hosmer-Lemeshow goodness-of-fit test *p*-value is 0.32.

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CI = confidence interval; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; HF = heart failure; HF<sub>mr</sub>EF = heart failure with mid-range ejection fraction; HF<sub>p</sub>EF = heart failure with preserved ejection fraction; HF<sub>r</sub>EF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; NYHA = New York Heart Association; NT-proBNP = N-terminal pro-B-type natriuretic peptide; OR = odds ratio.

**Supplementary Table 5 – Multivariable binary logistic regression analysis for the predictors of worsening MR (among patients with no or mild MR at baseline).**

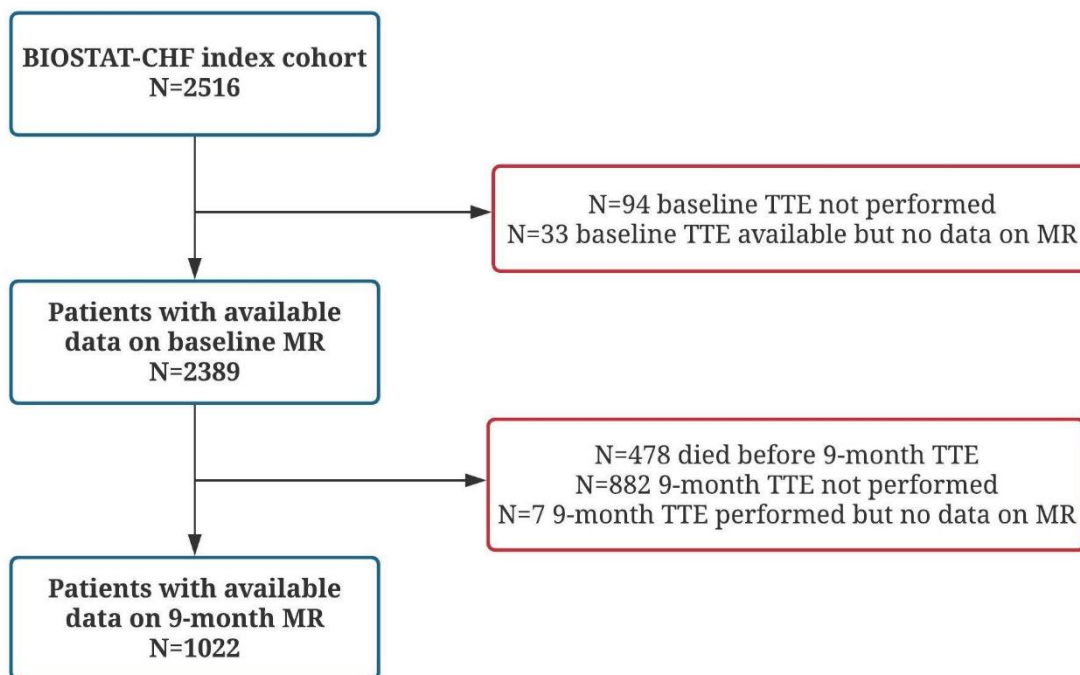
	Univariable analysis		Multivariable analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age (years)	1.04 (1.02-1.06)	< <b>0.001</b>	1.05 (1.02-1.08)	<b>0.001</b>
Sex (women)	1.44 (0.86-2.40)	0.162	1.28 (0.69-2.36)	0.433
Primary ischemic HF etiology	1.36 (0.86-2.13)	0.186	1.17 (0.69-2.00)	0.562
Previous HF hospitalization in last year	1.37 (0.84-2.23)	0.205	1.48 (0.84-2.59)	0.175
NYHA class III or IV	1.41 (0.89-2.24)	0.138	1.22 (0.71-2.11)	0.476
eGFR CKD-EPI (mL/min/1.73 m <sup>2</sup> )	1.00 (0.98-1.01)	0.350	1.01 (0.99-1.02)	0.255
Log-NT-proBNP (ng/L)	1.23 (1.02-1.49)	<b>0.030</b>	1.14 (0.91-1.44)	0.257
LVEF categories				
HF <sub>r</sub> EF (LVEF <40%) – reference	-	-	-	-
HF <sub>mr</sub> EF (LVEF 40-49%)	1.41 (0.74-2.69)	0.297	1.18 (0.56-2.48)	0.672
HF <sub>p</sub> EF (LVEF ≥50%)	0.65 (0.15-2.91)	0.578	0.42 (0.09-2.03)	0.283
ACEi/ARB optimal dose fraction at 3 months (%)	0.61 (0.33-1.10)	0.100	0.70 (0.34-1.43)	0.327
β-blocker optimal dose fraction at 3 months (%)	0.84 (0.40-1.77)	0.641	0.78 (0.33-1.87)	0.580

Data are presented as OR and 95% CI. The C-statistic for the multivariable model is 0.68, the Hosmer-Lemeshow goodness-of-fit test p-value is 0.52.

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CI = confidence interval; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; HF = heart failure; HF<sub>mr</sub>EF = heart failure with mid-range ejection fraction; HF<sub>p</sub>EF = heart failure with preserved ejection fraction; HF<sub>r</sub>EF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; NYHA = New York Heart Association; NT-proBNP = N-terminal pro-B-type natriuretic peptide; OR = odds ratio.



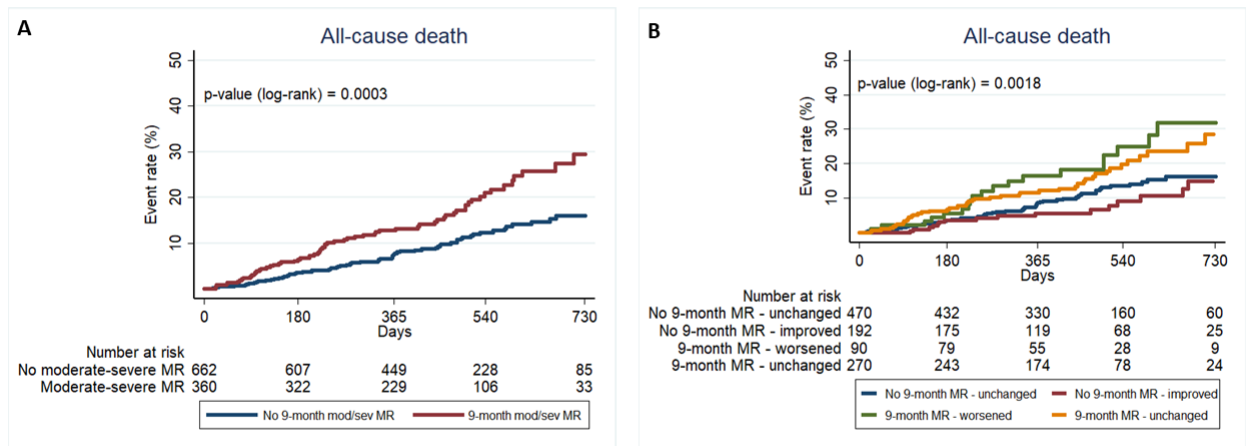
**Supplementary Figure 1 – Study flow-chart.**



The figure shows the flow-chart of included patients from BIOSAT-CHF index cohort.

MR = mitral regurgitation; TTE = transthoracic echocardiography.

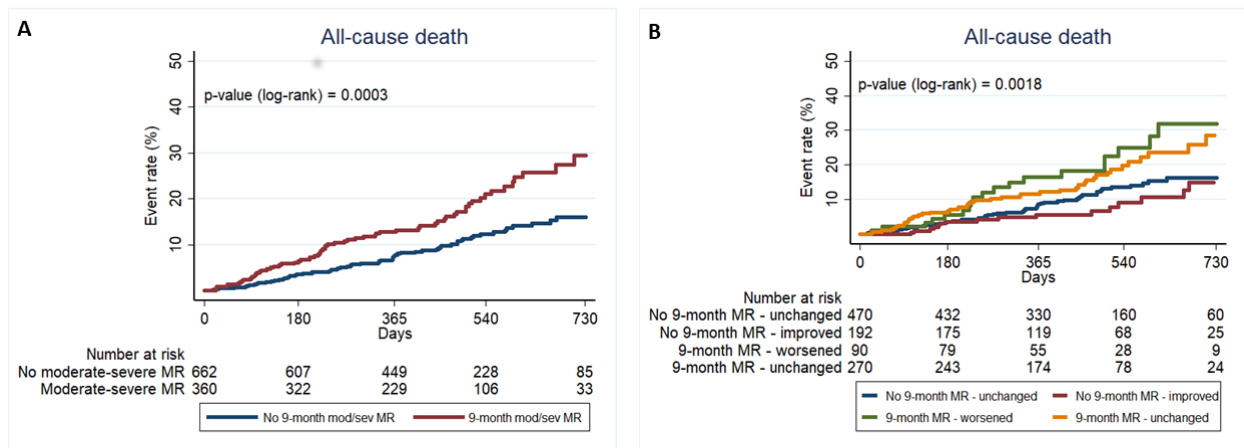
**Supplementary Figure 2 – All-cause mortality.**



The figure shows Kaplan-Meier curves for 2-year all-cause mortality in patients with vs. without 9-month moderate-severe MR (panel A) and in four patients' groups according to baseline and 9-month moderate-severe MR after GRMT optimization (panel B).

GRMT = guideline-directed medical therapy; MR = mitral regurgitation.

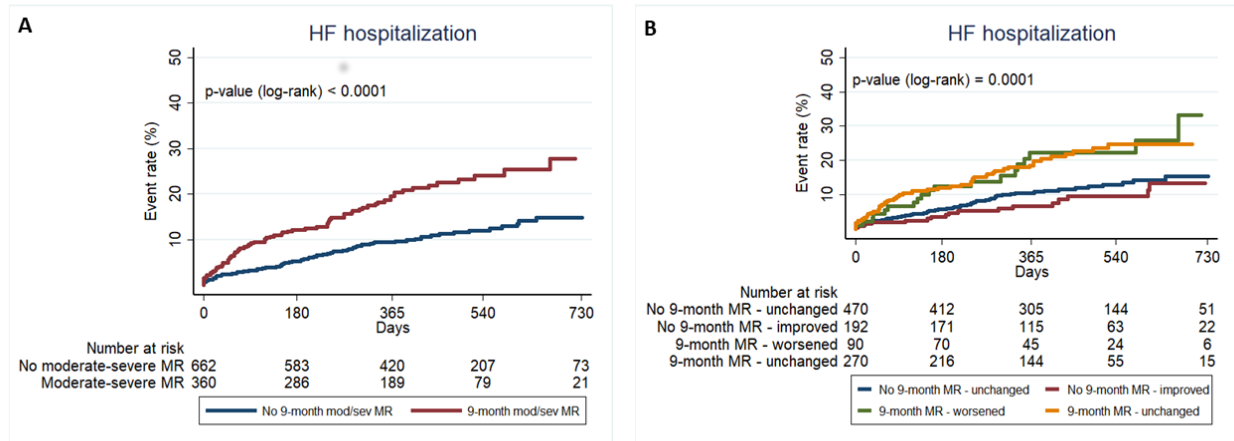
**Supplementary Figure 3 – Cardiovascular mortality.**



The figure shows Kaplan-Meier curves for 2-year cardiovascular mortality in patients with vs. without 9-month moderate-severe MR (panel A) and in four patients' groups according to baseline and 9-month moderate-severe MR after GRMT optimization (panel B).

GRMT = guideline-directed medical therapy; MR = mitral regurgitation.

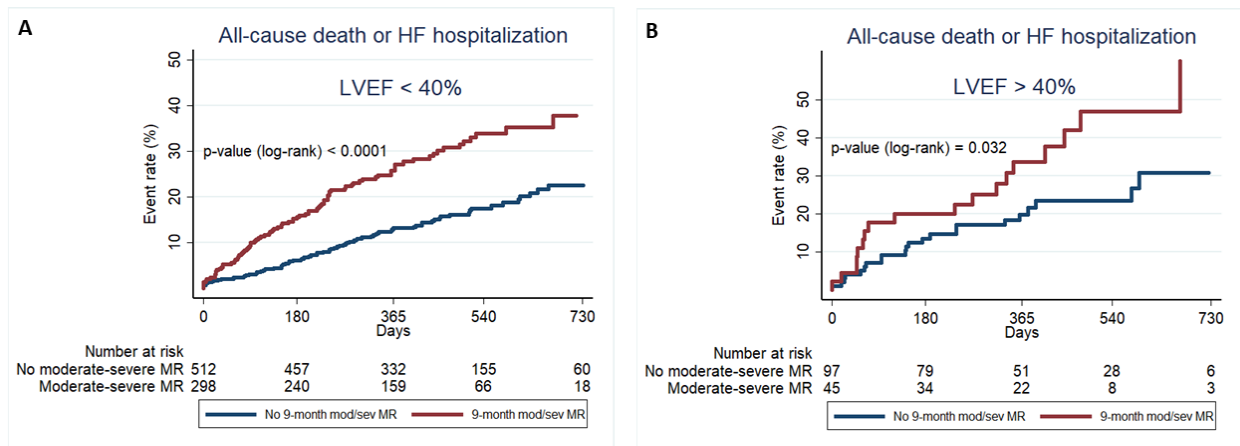
**Supplementary Figure 4 – HF hospitalization.**



The figure shows Kaplan-Meier curves for 2-year HF hospitalization in patients with vs. without 9-month moderate-severe MR (panel A) and in four patients' groups according to baseline and 9-month moderate-severe MR after GRMT optimization (panel B).

GRMT = guideline-directed medical therapy; HF = heart failure; MR = mitral regurgitation.

**Supplementary Figure 5 – Primary endpoint in LVEF subgroups.**



The figure shows Kaplan-Meier curves for 2-year primary endpoint (all-cause mortality or HF hospitalization) in patients with vs. without 9-month moderate-severe MR in the subgroup with LVEF <40% (panel A) and in the subgroup with LVEF  $\geq$ 40% (panel B).

GRMT = guideline-directed medical therapy; HF = heart failure; LVEF = left ventricular ejection fraction; MR = mitral regurgitation.