

**SUPPLEMENTARY APPENDIX**

**Supplementary Table 1 – Baseline clinical characteristics in the index cohort.**

|                                 | <b>Overall<br/>(n=2389)</b> | <b>Moderate or Severe MR<br/>(n=1121)</b> | <b>No or Mild MR<br/>(n=1268)</b> | <b>p-value</b>   |
|---------------------------------|-----------------------------|---|-----------------------------------|------------------|
| Age (years)                     | 68.9 ± 12.0                 | 68.8 ± 11.9                               | 68.9 ± 12.1                       | 0.869            |
| Men                             | 1760 (73.7)                 | 820 (73.2)                                | 940 (74.1)                        | 0.586            |
| BMI (kg/m <sup>2</sup> )        | 27.8 ± 5.5                  | 27.4 ± 5.2                                | 28.2 ± 5.7                        | <b>&lt;0.001</b> |
| HF hospitalization in last year | 752 (31.5)                  | 379 (33.8)                                | 373 (29.4)                        | <b>0.021</b>     |
| Smoking                         |                             |   |                                   | <b>0.012</b>     |
| Past                            | 1139 (47.7)                 | 526 (47.1)                                | 613 (48.3)                        |                  |
| Current                         | 341 (14.3)                  | 139 (12.4)                                | 202 (15.9)                        |                  |
| Medical history                 |                             |   |                                   |                  |
| Hypertension                    | 1491 (62.4)                 | 684 (61.0)                                | 807 (63.6)                        | 0.186            |
| Diabetes mellitus               | 773 (32.4)                  | 349 (31.1)                                | 424 (33.4)                        | 0.229            |
| Atrial fibrillation             | 1087 (45.5)                 | 526 (46.9)                                | 561 (44.2)                        | 0.189            |
| Myocardial infarction           | 908 (38.0)                  | 404 (36.0)                                | 504 (39.8)                        | 0.062            |
| PCI                             | 506 (21.2)                  | 212 (18.9)                                | 294 (23.2)                        | <b>0.011</b>     |
| CABG                            | 407 (17.0)                  | 188 (16.8)                                | 219 (17.3)                        | 0.745            |
| Prior valvular surgery          | 167 (7.0)                   | 65 (5.8)                                  | 102 (8.0)                         | <b>0.032</b>     |
| Peripheral artery disease       | 251 (10.5)                  | 117 (10.4)                                | 134 (10.6)                        | 0.917            |
| COPD                            | 413 (17.3)                  | 181 (16.2)                                | 232 (18.3)                        | 0.165            |
| Stroke                          | 223 (9.3)                   | 100 (8.9)                                 | 123 (9.7)                         | 0.513            |
| Current malignancy              | 92 (3.9)                    | 40 (3.6)                                  | 52 (4.1)                          | 0.499            |
| CKD                             | 652 (27.3)                  | 335 (29.9)                                | 317 (25.0)                        | <b>0.007</b>     |
| Device therapy                  |                             |   |                                   | 0.343            |
| Pacemaker                       | 173 (7.2)                   | 80 (7.1)                                  | 93 (7.3)                          |                  |
| ICD                             | 183 (7.7)                   | 87 (7.8)                                  | 96 (7.6)                          |                  |
| CRT-P                           | 43 (1.8)                    | 25 (2.2)                                  | 18 (1.4)                          |                  |
| CRT-D                           | 152 (6.4)                   | 76 (6.8)                                  | 76 (6.0)                          |                  |
| NYHA functional class           |                             |   |                                   | <b>0.002</b>     |
| I                               | 53 (2.3)                    | 22 (2.0)                                  | 31 (2.5)                          |                  |
| II                              | 835 (35.9)                  | 357 (32.5)                                | 478 (38.9)                        |                  |
| III                             | 1158 (49.8)                 | 567 (51.6)                                | 591 (48.1)                        |                  |
| IV                              | 280 (12.0)                  | 152 (13.8)                                | 128 (10.4)                        |                  |
| Clinical profile                |                             |   |                                   |                  |
| Peripheral oedema               | 580 (29.2)                  | 286 (30.1)                                | 294 (28.3)                        | 0.368            |
| Hepatomegaly                    | 338 (14.2)                  | 190 (17.0)                                | 148 (11.7)                        | <b>&lt;0.001</b> |
| SBP (mmHg)                      | 125 ± 22                    | 123 ± 21                                  | 126 ± 22                          | <b>&lt;0.001</b> |
| DBP (mmHg)                      | 75 ± 13                     | 75 ± 13                                   | 75 ± 14                           | 0.515            |
| HR (bpm)                        | 80 ± 19                     | 81 ± 19                                   | 79 ± 19                           | 0.064            |
| Type of visit                   |                             |   |                                   | 0.159            |
| Inpatient hospitalization       | 1603 (67.1)                 | 764 (68.2)                                | 839 (66.2)                        |                  |
| Outpatient clinic               | 786 (32.9)                  | 357 (31.9)                                | 429 (33.8)                        |                  |
| HF therapy                      |                             |   |                                   |                  |
| ACEi/ARB use                    | 1736 (72.7)                 | 794 (70.8)                                | 942 (74.3)                        | 0.058            |
| β-blocker use                   | 1992 (83.4)                 | 926 (82.6)                                | 1066 (84.1)                       | 0.337            |
| MRA use                         | 1275 (53.4)                 | 643 (57.4)                                | 632 (49.8)                        | <b>&lt;0.001</b> |
| Loop diuretic use               | 2377 (99.5)                 | 1116 (99.6)                               | 1261 (99.5)                       | 0.715            |
| Digoxin use                     | 470 (19.7)                  | 264 (23.6)                                | 206 (16.3)                        | <b>&lt;0.001</b> |

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; DBP = diastolic blood pressure; HF = heart failure; HR = heart rate; ICD = implantable cardioverter-defibrillator; JVP = jugular venous pressure; MR = mitral regurgitation; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; SBP = systolic blood pressure.

**Supplementary Table 2 – Baseline clinical characteristics in the validation cohort.**

|                                 | Overall<br>(n=1634) | Moderate or Severe MR<br>(n=532) | No or Mild MR<br>(n=1102) | p-value          |
|---------------------------------|---------------------|----------------------------------|---------------------------|------------------|
| Age (years)                     | 73.7 ± 10.6         | 74.3 ± 10.9                      | 73.4 ± 10.4               | 0.100            |
| Men                             | 1083 (66.3)         | 319 (60.0)                       | 764 (69.3)                | <b>&lt;0.001</b> |
| BMI (kg/m <sup>2</sup> )        | 29.0 ± 6.4          | 27.5 ± 6.1                       | 29.7 ± 6.4                | <b>&lt;0.001</b> |
| HF hospitalization in last year | 432 (26.8)          | 149 (28.4)                       | 283 (26.1)                | 0.348            |
| Smoking                         |                     |                                  |                           | 0.062            |
| Past                            | 566 (34.9)          | 172 (32.6)                       | 394 (36.0)                |                  |
| Current                         | 220 (13.6)          | 86 (16.3)                        | 134 (12.2)                |                  |
| Medical history                 |                     |                                  |                           |                  |
| Hypertension                    | 947 (58.1)          | 290 (54.9)                       | 657 (59.7)                | 0.078            |
| Diabetes mellitus               | 528 (32.5)          | 152 (28.6)                       | 376 (34.3)                | <b>0.024</b>     |
| Atrial fibrillation             | 723 (44.6)          | 273 (51.7)                       | 450 (41.2)                | <b>&lt;0.001</b> |
| Myocardial infarction           | 803 (49.2)          | 247 (46.5)                       | 556 (50.5)                | 0.141            |
| PCI                             | 303 (18.7)          | 86 (16.3)                        | 217 (19.9)                | 0.088            |
| CABG                            | 297 (18.2)          | 90 (16.9)                        | 207 (18.8)                | 0.392            |
| Prior valvular surgery          | 105 (6.4)           | 27 (5.1)                         | 78 (7.1)                  | 0.149            |
| Peripheral artery disease       | 358 (22.5)          | 101 (19.4)                       | 257 (24.0)                | <b>0.044</b>     |
| COPD                            | 303 (18.7)          | 89 (16.9)                        | 214 (19.5)                | 0.230            |
| Stroke                          | 297 (18.4)          | 95 (18.1)                        | 202 (18.5)                | 0.885            |
| Current malignancy              | 71 (4.4)            | 20 (3.8)                         | 51 (4.6)                  | 0.501            |
| CKD                             | 738 (45.9)          | 275 (52.2)                       | 463 (42.8)                | <b>&lt;0.001</b> |
| Device therapy                  |                     |                                  |                           | <b>&lt;0.001</b> |
| Pacemaker                       | 107 (6.6)           | 32 (6.0)                         | 75 (6.8)                  |                  |
| ICD                             | 65 (4.0)            | 34 (6.4)                         | 31 (2.8)                  |                  |
| CRT-P                           | 23 (1.4)            | 8 (1.5)                          | 15 (1.4)                  |                  |
| CRT-D                           | 50 (3.1)            | 28 (5.3)                         | 22 (2.0)                  |                  |
| NYHA functional class           |                     |                                  |                           | 0.615            |
| I                               | 17 (1.0)            | 3 (0.6)                          | 14 (1.3)                  |                  |
| II                              | 676 (41.4)          | 221 (41.5)                       | 455 (41.3)                |                  |
| III                             | 722 (44.2)          | 238 (44.7)                       | 484 (44.0)                |                  |
| IV                              | 218 (13.3)          | 70 (13.2)                        | 148 (13.4)                |                  |
| Clinical profile                |                     |                                  |                           |                  |
| Peripheral oedema               | 442 (30.2)          | 152 (32.0)                       | 290 (29.3)                | 0.285            |
| Hepatomegaly                    | 59 (4.0)            | 20 (4.2)                         | 39 (3.9)                  | 0.898            |
| SBP (mmHg)                      | 126 ± 22            | 123 ± 22                         | 127 ± 23                  | <b>0.002</b>     |
| DBP (mmHg)                      | 69 ± 13             | 69 ± 12                          | 69 ± 13                   | 0.892            |
| HR (bpm)                        | 74 ± 16             | 75 ± 17                          | 74 ± 16                   | 0.330            |
| Type of visit                   |                     |                                  |                           | 0.387            |
| Inpatient hospitalization       | 859 (52.6)          | 271 (50.9)                       | 588 (53.4)                |                  |
| Outpatient clinic               | 775 (47.4)          | 261 (49.1)                       | 514 (46.6)                |                  |
| HF therapy                      |                     |                                  |                           |                  |
| ACEi/ARB use                    | 1148 (70.6)         | 377 (71.4)                       | 771 (70.2)                | 0.647            |
| β-blocker use                   | 1180 (72.5)         | 403 (76.3)                       | 777 (70.7)                | <b>0.020</b>     |
| MRA use                         | 528 (32.5)          | 195 (36.9)                       | 333 (30.3)                | <b>0.009</b>     |
| Loop diuretic use               | 1611 (99.0)         | 526 (99.6)                       | 1085 (98.7)               | 0.149            |
| Digoxin use                     | 294 (18.1)          | 111 (21.0)                       | 183 (16.7)                | <b>0.038</b>     |

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; DBP = diastolic blood pressure; HF = heart failure; HR = heart rate; ICD = implantable cardioverter-defibrillator; JVP = jugular venous pressure; MR = mitral regurgitation; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; SBP = systolic blood pressure.

**Supplementary Table 3 – Baseline echocardiographic data, laboratory characteristics, and quality of life measures in the index cohort.**

|  | <b>Overall<br/>(n=2389)</b> | <b>Moderate or Severe MR<br/>(n=1121)</b> | <b>No or Mild MR<br/>(n=1268)</b> | <b>p-value</b>   |
|--|-----------------------------|---|-----------------------------------|------------------|
| <b><i>Echocardiographic data</i></b>       |                             |   |                                   |                  |
| LVEF (%)                                   | 30 (25-36)                  | 30 (24-35)                                | 30 (25-38)                        | <b>&lt;0.001</b> |
| LVEF categories                            |                             |   |                                   | <b>0.001</b>     |
| HF <sub>r</sub> EF (LVEF <40%)             | 1799 (81.2)                 | 900 (84.4)                                | 899 (78.2)                        |                  |
| HF <sub>mr</sub> EF (LVEF 40-49%)          | 279 (12.6)                  | 112 (10.5)                                | 167 (14.5)                        |                  |
| HF <sub>p</sub> EF (LVEF ≥50%)             | 138 (6.2)                   | 55 (5.2)                                  | 83 (7.2)                          |                  |
| LV remodeling                              |                             |   |                                   | <b>&lt;0.001</b> |
| Normal geometry                            | 334 (20.1)                  | 142 (17.2)                                | 192 (23.1)                        |                  |
| Concentric remodeling                      | 55 (3.3)                    | 19 (2.3)                                  | 36 (4.3)                          |                  |
| Concentric hypertrophy                     | 262 (15.8)                  | 104 (12.6)                                | 158 (19.0)                        |                  |
| Eccentric hypertrophy                      | 1007 (60.7)                 | 563 (68.0)                                | 444 (53.5)                        |                  |
| LVEDD (mm)                                 | 61 (55-67)                  | 63 (57-69)                                | 59 (54-65)                        | <b>&lt;0.001</b> |
| LVESD (mm)                                 | 50 (43-57)                  | 52 (46-59)                                | 48 (41-55)                        | <b>&lt;0.001</b> |
| Left atrium diameter (mm)                  | 47 (43-52)                  | 49 (44-54)                                | 46 (41-50)                        | <b>&lt;0.001</b> |
| <b><i>Laboratory data</i></b>              |                             |   |                                   |                  |
| Haemoglobin (g/dL)                         | 13.3 (11.9-14.5)            | 13.3 (12.0-14.5)                          | 13.3 (11.9-14.5)                  | 0.981            |
| Creatinine (µmol/L)                        | 103 (84-130)                | 106 (84-133)                              | 100 (84-126)                      | 0.061            |
| eGFR CKD-EPI (mL/min/1.73 m <sup>2</sup> ) | 59 (44-77)                  | 58 (43-77)                                | 60 (45-78)                        | 0.063            |
| Urea (mmol/L)                              | 11.4 (7.6-18.2)             | 12.1 (7.8-19.6)                           | 10.7 (7.4-16.8)                   | <b>&lt;0.001</b> |
| Sodium (mmol/L)                            | 140 (137-142)               | 140 (137-142)                             | 140 (137-142)                     | 0.274            |
| NT-proBNP (ng/L)                           | 4322 (2373-8546)            | 4712 (2643-9111)                          | 3810 (2153-8000)                  | <b>&lt;0.001</b> |
| <b><i>QoL measures</i></b>                 |                             |   |                                   |                  |
| KCCQ clinical summary score                | 48 (29-67)                  | 44 (26-64)                                | 50 (31-69)                        | <b>&lt;0.001</b> |
| KCCQ overall summary score                 | 48 (31-67)                  | 45 (29-64)                                | 51 (34-69)                        | <b>&lt;0.001</b> |
| EQ-5D index value                          | 0.72 (0.57-0.81)            | 0.69 (0.57-0.81)                          | 0.72 (0.57-0.84)                  | <b>0.047</b>     |
| EQ-5D VAS                                  | 50 (40-70)                  | 50 (40-70)                                | 55 (40-70)                        | <b>0.012</b>     |

Data are presented as n (%), mean ± standard deviation, and median (Q25-Q75).

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 Analog Scale.

**Supplementary Table 4 – Baseline echocardiographic data, laboratory characteristics, and quality of life measures in the validation cohort.**

|  | <b>Overall<br/>(n=1634)</b> | <b>Moderate or Severe MR<br/>(n=532)</b> | <b>No or Mild MR<br/>(n=1102)</b> | <b>p-value</b>   |
|--|-----------------------------|--|-----------------------------------|------------------|
| <b><i>Echocardiographic data</i></b>       |                             |  |                                   |                  |
| LVEF (%)                                   | 40 (35-50)                  | 35 (28-45)                               | 43 (35-52)                        | <b>&lt;0.001</b> |
| LVEF categories                            |                             |  |                                   | <b>&lt;0.001</b> |
| HF <sub>r</sub> EF (LVEF <40%)             | 715 (46.0)                  | 315 (63.0)                               | 400 (38.0)                        |                  |
| HF <sub>mr</sub> EF (LVEF 40-49%)          | 400 (25.7)                  | 108 (21.6)                               | 292 (27.7)                        |                  |
| HF <sub>p</sub> EF (LVEF ≥50%)             | 439 (28.3)                  | 77 (15.4)                                | 362 (34.4)                        |                  |
| LV remodeling                              |                             |  |                                   | <b>&lt;0.001</b> |
| Normal geometry                            | 106 (14.6)                  | 33 (11.9)                                | 73 (16.3)                         |                  |
| Concentric remodeling                      | 88 (12.2)                   | 17 (6.1)                                 | 71 (15.9)                         |                  |
| Concentric hypertrophy                     | 247 (34.1)                  | 82 (29.6)                                | 165 (36.9)                        |                  |
| Eccentric hypertrophy                      | 283 (39.1)                  | 145 (52.4)                               | 138 (30.9)                        |                  |
| LVEDD (mm)                                 | 55 (48-61)                  | 58 (52-63)                               | 53 (47-59)                        | <b>&lt;0.001</b> |
| LVESD (mm)                                 | 44 (36-54)                  | 49 (40-56)                               | 41 (33-49)                        | <b>&lt;0.001</b> |
| Left atrium diameter (mm)                  | 45 (41-50)                  | 47 (44-52)                               | 44 (40-48)                        | <b>&lt;0.001</b> |
| <b><i>Laboratory data</i></b>              |                             |  |                                   |                  |
| Haemoglobin (g/dL)                         | 13.2 (11.8-14.5)            | 13.0 (11.8-14.3)                         | 13.3 (11.8-14.7)                  | <b>0.039</b>     |
| Creatinine (μmol/L)                        | 97 (80-125)                 | 102 (82-133)                             | 95 (79-123)                       | <b>0.001</b>     |
| eGFR CKD-EPI (mL/min/1.73 m <sup>2</sup> ) | 60 (43-78)                  | 56 (39-74)                               | 62 (45-80)                        | <b>&lt;0.001</b> |
| Urea (mmol/L)                              | 8.6 (6.5-12.0)              | 9.1 (6.9-13.4)                           | 8.4 (6.4-11.3)                    | <b>&lt;0.001</b> |
| Sodium (mmol/L)                            | 139 (137-141)               | 139 (137-141)                            | 139 (137-141)                     | 0.989            |
| NT-proBNP (ng/L)                           | 1360 (512-3494)             | 2263 (923-5307)                          | 1082 (400-2804)                   | <b>&lt;0.001</b> |
| <b><i>QoL measures</i></b>                 |                             |  |                                   |                  |
| KCCQ clinical summary score                | 47 (30-70)                  | 48 (30-68)                               | 46 (30-70)                        | 0.497            |
| KCCQ overall summary score                 | 48 (33-67)                  | 47 (32-66)                               | 48 (33-67)                        | 0.890            |
| EQ-5D index value                          | 0.74 (0.57-0.86)            | 0.78 (0.57-0.86)                         | 0.74 (0.57-0.86)                  | 0.397            |
| EQ-5D VAS                                  | 60 (50-75)                  | 60 (50-75)                               | 60 (50-75)                        | 0.768            |

Data are presented as n (%), mean ± standard deviation, and median (Q25-Q75).

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 Analog Scale.

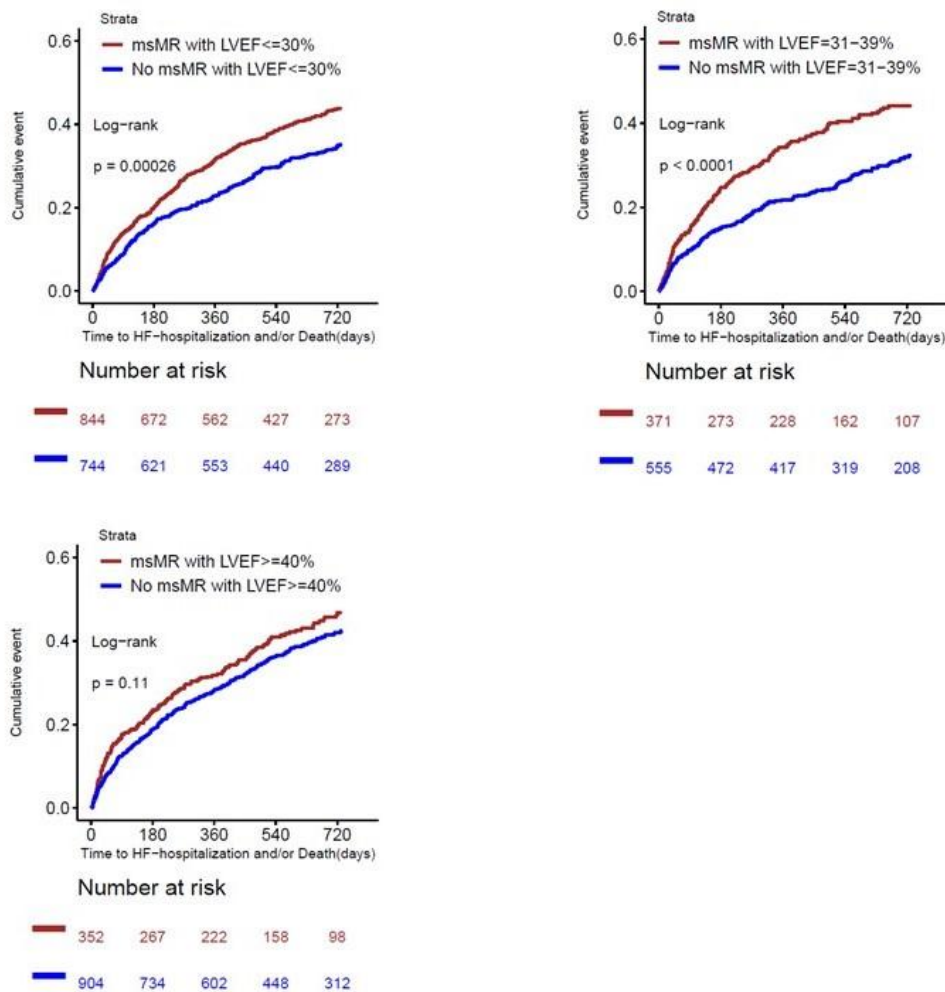
**Supplementary Table 5 – Impact of moderate-severe MR on 2-year primary endpoint (all-cause death or HF hospitalization) in NT-proBNP subgroups according to history of AF.**

|   | Patients | Unadjusted HR<br>(95% CI) | <i>p</i> -value | Adjusted HR<br>(95% CI)* | <i>p</i> -value |
|---|----------|---------------------------|-----------------|--------------------------|-----------------|
| Tertiles of NT-proBNP in patients with history of AF    |          |                           |                 |                          |                 |
| 1 <sup>st</sup> tertile ( $\leq 1513$ pg/mL)            | 565      | 1.00 (0.72-1.39)          | 0.992           | 1.00 (0.72-1.39)         | 0.991           |
| 2 <sup>nd</sup> tertile (1517-4012 pg/mL)               | 565      | 1.02 (0.79-1.30)          | 0.904           | 1.05 (0.82-1.34)         | 0.718           |
| 3 <sup>rd</sup> tertile ( $\geq 4022$ pg/mL)            | 564      | 1.38 (1.11-1.72)          | <b>0.004</b>    | 1.38 (1.11-1.72)         | <b>0.004</b>    |
| Tertiles of NT-proBNP in patients without history of AF |          |                           |                 |                          |                 |
| 1 <sup>st</sup> tertile ( $\leq 897$ pg/mL)             | 692      | 0.92 (0.61-1.40)          | 0.712           | 0.94 (0.62-1.43)         | 0.767           |
| 2 <sup>nd</sup> tertile (899-3194 pg/mL)                | 691      | 0.89 (0.68-1.16)          | 0.398           | 0.92 (0.70-1.20)         | 0.537           |
| 3 <sup>rd</sup> tertile ( $\geq 3205$ pg/mL)            | 691      | 1.01 (0.82-1.25)          | 0.909           | 1.06 (0.86-1.30)         | 0.601           |

Data are presented as HR and 95% CI. \*Adjusted for age and sex.

AF = atrial fibrillation; CI = confidence interval; HR = hazard ratio; MR = mitral regurgitation; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

**Supplementary Figure 1: Kaplan-Meier curves for the 2-year primary endpoint (all-cause mortality or HF hospitalization) in patients with versus without moderate-severe MR according to LVEF subgroups.**



The figure shows Kaplan-Meier curves for 2-year primary endpoint (all-cause mortality or HF hospitalization) in patients with vs. without moderate-severe MR according to LVEF subgroups: LVEF ≤ 30% (upper left panel), LVEF 31-39% (upper right panel), and LVEF ≥ 40% (lower left panel).

CV = cardiovascular; HF = heart failure; LVEF = left ventricular ejection fraction; MR = mitral regurgitation.