**SUPPLEMENTARY APPENDIX**

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

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Overall****(n=2389)** | **Moderate or Severe MR****(n=1121)** | **No or Mild MR****(n=1268)** | ***p*-value** |
| 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/m2) | 27.8 ± 5.5 | 27.4 ± 5.2 | 28.2 ± 5.7 | **<0.001** |
| HF hospitalization in last year | 752 (31.5) | 379 (33.8) | 373 (29.4) | **0.021** |
| Smoking |  |  |  | **0.012** |
|  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) | **0.011** |
|  CABG | 407 (17.0) | 188 (16.8) | 219 (17.3) | 0.745 |
|  Prior valvular surgery | 167 (7.0) | 65 (5.8) | 102 (8.0) | **0.032** |
|  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) | **0.007** |
| 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 |  |  |  | **0.002** |
|  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) | **<0.001** |
|  SBP (mmHg)  | 125 ± 22 | 123 ± 21 | 126 ± 22 | **<0.001** |
|  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) | **<0.001** |
|  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) | **<0.001** |
|  |  |  |  |  |

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****(n=1634)** | **Moderate or Severe MR****(n=532)** | **No or Mild MR****(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) | **<0.001** |
| BMI (kg/m2) | 29.0 ± 6.4 | 27.5 ± 6.1 | 29.7 ± 6.4 | **<0.001** |
| 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) | **0.024** |
|  Atrial fibrillation | 723 (44.6) | 273 (51.7) | 450 (41.2) | **<0.001** |
|  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) | **0.044** |
|  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) | **<0.001** |
| Device therapy |  |  |  | **<0.001** |
|  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 | **0.002** |
|  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) | **0.020** |
|  MRA use | 528 (32.5) | 195 (36.9) | 333 (30.3) | **0.009** |
|  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) | **0.038** |
|  |  |  |  |  |

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.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Overall****(n=2389)** | **Moderate or Severe MR****(n=1121)** | **No or Mild MR****(n=1268)** | ***p*-value** |
| ***Echocardiographic data*** |  |  |  |  |
| LVEF (%) | 30 (25-36) | 30 (24-35) | 30 (25-38) | **<0.001** |
| LVEF categories |  |  |  | **0.001** |
|  HFrEF (LVEF <40%) | 1799 (81.2) | 900 (84.4) | 899 (78.2) |  |
|  HFmrEF (LVEF 40-49%) | 279 (12.6) | 112 (10.5) | 167 (14.5) |  |
|  HFpEF (LVEF ≥50%) | 138 (6.2) | 55 (5.2) | 83 (7.2) |  |
| LV remodeling |  |  |  | **<0.001** |
|  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) | **<0.001** |
| LVESD (mm) | 50 (43-57) | 52 (46-59) | 48 (41-55) | **<0.001** |
| Left atrium diameter (mm) | 47 (43-52) | 49 (44-54) | 46 (41-50) | **<0.001** |
| ***Laboratory data*** |  |  |  |  |
| 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 m2) | 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) | **<0.001** |
| 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) | **<0.001** |
| ***QoL measures*** |  |  |  |  |
| KCCQ clinical summary score | 48 (29-67) | 44 (26-64) | 50 (31-69) | **<0.001** |
| KCCQ overall summary score | 48 (31-67) | 45 (29-64) | 51 (34-69) | **<0.001** |
| EQ-5D index value | 0.72 (0.57-0.81) | 0.69 (0.57-0.81) | 0.72 (0.57-0.84) | **0.047** |
| EQ-5D VAS | 50 (40-70) | 50 (40-70) | 55 (40-70) | **0.012** |
|  |  |  |  |  |

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; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = 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.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Overall****(n=1634)** | **Moderate or Severe MR****(n=532)** | **No or Mild MR****(n=1102)** | ***p*-value** |
| ***Echocardiographic data*** |  |  |  |  |
| LVEF (%) | 40 (35-50) | 35 (28-45) | 43 (35-52) | **<0.001** |
| LVEF categories |  |  |  | **<0.001** |
|  HFrEF (LVEF <40%) | 715 (46.0) | 315 (63.0) | 400 (38.0) |  |
|  HFmrEF (LVEF 40-49%) | 400 (25.7) | 108 (21.6) | 292 (27.7) |  |
|  HFpEF (LVEF ≥50%) | 439 (28.3) | 77 (15.4) | 362 (34.4) |  |
| LV remodeling |  |  |  | **<0.001** |
|  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) | **<0.001** |
| LVESD (mm) |  44 (36-54) | 49 (40-56) | 41 (33-49) | **<0.001** |
| Left atrium diameter (mm) | 45 (41-50) | 47 (44-52) | 44 (40-48) | **<0.001** |
| ***Laboratory data*** |  |  |  |  |
| Haemoglobin (g/dL) | 13.2 (11.8-14.5) | 13.0 (11.8-14.3) | 13.3 (11.8-14.7) | **0.039** |
| Creatinine (µmol/L) | 97 (80-125) | 102 (82-133) | 95 (79-123) | **0.001** |
| eGFR CKD-EPI (mL/min/1.73 m2) | 60 (43-78) | 56 (39-74) | 62 (45-80) | **<0.001** |
| Urea (mmol/L) | 8.6 (6.5-12.0) | 9.1 (6.9-13.4) | 8.4 (6.4-11.3) | **<0.001** |
| 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) | **<0.001** |
| ***QoL measures*** |  |  |  |  |
| 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; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = 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.**

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.

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

**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.