# Trajectories in New York heart association functional class in heart failure across the ejection fraction spectrum: data from the Swedish Heart Failure registry

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**Table S1. Flowchart depicting patient selection.**

| **Criteria** | **Number** | **Percent** |
| --- | --- | --- |
| Unique patients in SwedeHF | 90,383 |  |
| . Excluded: NYHA missing | 25,283 | 28.0% |
| . Excluded: EF missing | 5,435 | 6.0% |
| Patients with no missing data | 59,665 |  |
| . Excluded: No second NYHA 12 (+/-9) months from baseline | 46,130 | 77.3% |
| Study population (unique patients) | 13,535 |  |

**Abbreviations:** EF, ejection fraction; NYHA, New York Heart Association; SwedeHF, Swedish Heart Failure Registry

Table S2. Patient characteristics in patients with HFrEF

| **Variable** | **NYHA stable** | **NYHA improved** | **NYHA worsened** | **P-value** | **Missing** |
| --- | --- | --- | --- | --- | --- |
| *n* | 5,424 | 1,707 | 1,036 |  |  |
| **Sociodemographics** | | | | | |
| Index 2012-2018 (vs. 2000-2011) | 2,923 (53.9%) | 1,022 (59.9%) | 491 (47.4%) | <0.001 | 0.0% |
| Female | 1,398 (25.8%) | 466 (27.3%) | 240 (23.2%) | 0.056 | 0.0% |
| Age, years | 71 (11) | 67 (12) | 72 (11) | <0.001 | 0.0% |
| . ≥75 years | 2,263 (41.7%) | 534 (31.3%) | 470 (45.4%) | <0.001 | 0.0% |
| Income level: Lowest tertile | 2,651 (49.0%) | 733 (43.1%) | 520 (50.3%) | <0.001 | 0.4% |
| Education: Secondary school or less | 4,455 (83.8%) | 1,352 (80.5%) | 869 (85.4%) | 0.001 | 1.9% |
| Single living | 2,362 (43.7%) | 735 (43.3%) | 430 (41.6%) | 0.469 | 0.4% |
| Children | 4,472 (82.4%) | 1,403 (82.2%) | 861 (83.1%) | 0.825 | 0.0% |
| **Clinical and laboratory variables** | | | | | |
| NYHA class at baseline |  |  |  | <0.001 | 0.0% |
| I | 413 (7.6%) | 0 (0.0%) | 263 (25.4%) |  |  |
| II | 2,713 (50.0%) | 459 (26.9%) | 647 (62.5%) |  |  |
| III | 2,199 (40.5%) | 1,129 (66.1%) | 126 (12.2%) |  |  |
| IV | 99 (1.8%) | 119 (7.0%) | 0 (0.0%) |  |  |
| NYHA class at follow-up |  |  |  | <0.001 | 0.0% |
| I | 413 (7.6%) | 620 (36.3%) | 0 (0.0%) |  |  |
| II | 2,713 (50.0%) | 1,015 (59.5%) | 206 (19.9%) |  |  |
| III | 2,199 (40.5%) | 72 (4.2%) | 664 (64.1%) |  |  |
| IV | 99 (1.8%) | 0 (0.0%) | 166 (16.0%) |  |  |
| NT-proBNP, ng/L | 2,248 [1019, 4868] | 2,646 [1329, 5338] | 2,546 [1248, 5141] | <0.001 | 42.5% |
| . NT-proBNP≥median (by EF phenotype) | 1,304 (42.2%) | 526 (47.2%) | 226 (45.7%) | 0.010 | 42.5% |
| HF duration ≥6 months | 2,714 (51.1%) | 572 (34.3%) | 562 (54.7%) | <0.001 | 1.9% |
| Mean arterial pressure, mmHg | 90 (13) | 91 (14) | 88 (13) | <0.001 | 1.0% |
| . <90 mmHg | 2,640 (49.1%) | 788 (46.8%) | 558 (54.3%) | 0.001 | 1.0% |
| Heart rate, b.p.m. | 73 (15) | 76 (16) | 73 (14) | <0.001 | 3.7% |
| . ≥70 b.p.m. | 3,051 (58.3%) | 1,070 (65.2%) | 585 (59.3%) | <0.001 | 3.7% |
| Body mass index, kg/m² | 27 (5) | 27 (5) | 27 (5) | 0.130 | 38.6% |
| . ≥30 kg/m² (Obese) | 832 (24.9%) | 270 (26.1%) | 155 (24.3%) | 0.634 | 38.6% |
| eGFR, mL/min/1.73m² | 65 [48, 82] | 70 [53, 85] | 60 [45, 79] | <0.001 | 1.0% |
| . <60 mL/min/1.73m² | 2,268 (42.2%) | 575 (34.0%) | 509 (49.7%) | <0.001 | 1.0% |
| Hemoglobin, g/dL | 13.6 (1.7) | 13.8 (1.7) | 13.4 (1.7) | <0.001 | 3.5% |
| Potassium, mmol/L | 4 (0) | 4 (0) | 4 (0) | 0.494 | 20.1% |
| **Comorbidities** | | | | | |
| Peripheral arterial disease | 415 (7.7%) | 95 (5.6%) | 98 (9.5%) | 0.001 | 0.0% |
| Stroke/transitory ischaemic attack | 799 (14.7%) | 204 (12.0%) | 181 (17.5%) | <0.001 | 0.0% |
| Anaemia | 1,463 (27.9%) | 387 (23.6%) | 334 (33.3%) | <0.001 | 3.5% |
| Cancer past 3 years | 687 (12.7%) | 163 (9.5%) | 135 (13.0%) | 0.002 | 0.0% |
| Liver disease | 96 (1.8%) | 44 (2.6%) | 20 (1.9%) | 0.110 | 0.0% |
| Major bleeding | 757 (14.0%) | 198 (11.6%) | 149 (14.4%) | 0.031 | 0.0% |
| Diabetes mellitus | 1,262 (23.3%) | 339 (19.9%) | 264 (25.5%) | 0.001 | 0.0% |
| Atrial fibrillation | 2,202 (40.6%) | 653 (38.3%) | 430 (41.5%) | 0.151 | 0.0% |
| Hypertension | 2,031 (37.4%) | 648 (38.0%) | 418 (40.3%) | 0.211 | 0.0% |
| Chronic obstructive pulmonary disease | 674 (12.4%) | 165 (9.7%) | 138 (13.3%) | 0.003 | 0.0% |
| Ischaemic heart disease | 766 (14.1%) | 173 (10.1%) | 163 (15.7%) | <0.001 | 0.0% |
| Valvular disease | 846 (15.6%) | 225 (13.2%) | 169 (16.3%) | 0.029 | 0.0% |
| **Organisation** | | | | | |
| Caregiver: In-patient | 1,441 (26.6%) | 492 (28.8%) | 441 (42.6%) | <0.001 | 0.0% |
| Planned follow-up: Specialty care (vs. Primary care/Other) | 4,262 (81.0%) | 1,464 (88.8%) | 782 (78.0%) | <0.001 | 3.1% |
| Referral to follow-up in a nurse-led HF unit | 4,105 (78.3%) | 1,389 (84.6%) | 688 (69.0%) | <0.001 | 3.5% |
| **Treatments** | | | | | |
| Beta-blockers | 4,917 (90.8%) | 1,589 (93.4%) | 937 (90.5%) | 0.003 | 0.2% |
| RASi/ARNi | 5,049 (93.9%) | 1,598 (94.9%) | 951 (92.9%) | 0.091 | 1.0% |
| Mineralocorticoid receptor antagonists | 2,063 (38.2%) | 705 (41.5%) | 396 (38.4%) | 0.047 | 0.3% |
| Diuretics | 4,180 (77.3%) | 1,307 (76.8%) | 811 (78.5%) | 0.579 | 0.3% |
| Digoxin | 737 (13.6%) | 252 (14.8%) | 141 (13.6%) | 0.459 | 0.2% |
| Nitrates | 676 (12.5%) | 118 (6.9%) | 146 (14.2%) | <0.001 | 0.3% |
| Anticoagulants | 2,496 (46.1%) | 783 (46.0%) | 491 (47.6%) | 0.668 | 0.3% |
| Antiplatelets | 2,381 (44.0%) | 690 (40.6%) | 486 (47.1%) | 0.003 | 0.3% |
| Statins | 2,907 (53.7%) | 815 (47.9%) | 590 (57.1%) | <0.001 | 0.2% |
| Cardiac resynchronisation therapy | 330 (6.2%) | 79 (4.7%) | 95 (9.3%) | <0.001 | 1.8% |
| Implantable cardioverter-defibrillator | 471 (8.9%) | 101 (6.0%) | 122 (11.9%) | <0.001 | 1.8% |
| Summary statistics based on unimputed data. Data is presented as absolute (relative) frequencies, mean (±standard deviations), and median [interquartile range], and compared by Chi-squared-test, ANOVA, and Kruskal-Wallis test, respectively.  **Abbreviations:** ARNi, angiotensin-receptor-neprilysin inhibitor; b.p.m, beats per minutes; EF, ejection fraction; eGFR, estimated glomerular filtration rate (calculated by Chronic Kidney Disease Epidemiology Collaboration formula); HF, heart failure; HFrEF, heart failure with reduced ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association functional class; RASi, renin-angiotensin-system inhibitor. | | | | | |

Table S3. Patient characteristics in patients with HFmrEF

| **Variable** | **NYHA stable** | **NYHA improved** | **NYHA worsened** | **P-value** | **Missing** |
| --- | --- | --- | --- | --- | --- |
| *n* | *2,270* | *355* | *444* |  |  |
| **Sociodemographics** | | | | | |
| Index 2012-2018 (vs. 2000-2011) | 1,442 (63.5%) | 229 (64.5%) | 236 (53.2%) | <0.001 | 0.0% |
| Female | 818 (36.0%) | 133 (37.5%) | 170 (38.3%) | 0.617 | 0.0% |
| Age, years | 74 (11) | 71 (12) | 75 (11) | <0.001 | 0.0% |
| . ≥75 years | 1,232 (54.3%) | 159 (44.8%) | 277 (62.4%) | <0.001 | 0.0% |
| Income level: Lowest tertile | 1,231 (54.2%) | 172 (48.5%) | 251 (56.7%) | 0.058 | 0.0% |
| Education: Secondary school or less | 1,844 (83.1%) | 284 (81.1%) | 365 (83.7%) | 0.594 | 2.1% |
| Single living | 1,014 (44.7%) | 160 (45.1%) | 234 (52.8%) | 0.007 | 0.0% |
| Children | 1,933 (85.2%) | 304 (85.6%) | 379 (85.4%) | 0.969 | 0.0% |
| **Clinical and laboratory variables** | | | | | |
| NYHA class at baseline |  |  |  | <0.001 | 0.0% |
| I | 283 (12.5%) | 0 (0.0%) | 125 (28.2%) |  |  |
| II | 1,324 (58.3%) | 122 (34.4%) | 288 (64.9%) |  |  |
| III | 641 (28.2%) | 211 (59.4%) | 31 (7.0%) |  |  |
| IV | 22 (1.0%) | 22 (6.2%) | 0 (0.0%) |  |  |
| NYHA class at follow-up |  |  |  | <0.001 | 0.0% |
| I | 283 (12.5%) | 155 (43.7%) | 0 (0.0%) |  |  |
| II | 1,324 (58.3%) | 187 (52.7%) | 98 (22.1%) |  |  |
| III | 641 (28.2%) | 13 (3.7%) | 290 (65.3%) |  |  |
| IV | 22 (1.0%) | 0 (0.0%) | 56 (12.6%) |  |  |
| NT-proBNP, ng/L | 1,528 [664, 3106] | 1,378 [661, 3254] | 1,798 [788, 3778] | 0.181 | 40.6% |
| . NT-proBNP≥median (by EF phenotype) | 632 (46.0%) | 94 (43.9%) | 120 (51.3%) | 0.238 | 40.6% |
| HF duration ≥6 months | 1,203 (54.9%) | 157 (45.1%) | 283 (65.4%) | <0.001 | 3.2% |
| Mean arterial pressure, mmHg | 93 (12) | 94 (13) | 92 (13) | 0.144 | 0.5% |
| . <90 mmHg | 829 (36.7%) | 129 (36.4%) | 181 (41.0%) | 0.214 | 0.5% |
| Heart rate, b.p.m. | 72 (15) | 73 (16) | 73 (13) | 0.470 | 3.2% |
| . ≥70 b.p.m. | 1,199 (54.4%) | 187 (54.4%) | 260 (61.3%) | 0.030 | 3.2% |
| Body mass index, kg/m² | 28 (5) | 29 (6) | 28 (6) | 0.008 | 34.5% |
| . ≥30 kg/m² (Obese) | 435 (29.6%) | 91 (36.7%) | 87 (30.1%) | 0.077 | 34.5% |
| eGFR, mL/min/1.73m² | 63 [47, 80] | 69 [52, 84] | 58 [42, 75] | <0.001 | 1.3% |
| . <60 mL/min/1.73m² | 1,007 (45.0%) | 122 (34.9%) | 232 (53.0%) | <0.001 | 1.3% |
| Hemoglobin, g/dL | 13.4 (1.6) | 13.3 (1.7) | 13.2 (1.7) | 0.065 | 4.6% |
| Potassium, mmol/L | 4 (0) | 4 (0) | 4 (0) | 0.187 | 16.1% |
| **Comorbidities** | | | | | |
| Peripheral arterial disease | 180 (7.9%) | 16 (4.5%) | 31 (7.0%) | 0.068 | 0.0% |
| Stroke/transitory ischaemic attack | 380 (16.7%) | 48 (13.5%) | 72 (16.2%) | 0.311 | 0.0% |
| Anaemia | 636 (29.4%) | 101 (30.1%) | 153 (35.9%) | 0.027 | 4.6% |
| Cancer past 3 years | 305 (13.4%) | 49 (13.8%) | 84 (18.9%) | 0.010 | 0.0% |
| Liver disease | 38 (1.7%) | 7 (2.0%) | 17 (3.8%) | 0.013 | 0.0% |
| Major bleeding | 352 (15.5%) | 54 (15.2%) | 90 (20.3%) | 0.039 | 0.0% |
| Diabetes mellitus | 479 (21.1%) | 77 (21.7%) | 102 (23.0%) | 0.675 | 0.0% |
| Atrial fibrillation | 1,077 (47.4%) | 158 (44.5%) | 240 (54.1%) | 0.014 | 0.0% |
| Hypertension | 983 (43.3%) | 163 (45.9%) | 214 (48.2%) | 0.134 | 0.0% |
| Chronic obstructive pulmonary disease | 273 (12.0%) | 47 (13.2%) | 66 (14.9%) | 0.237 | 0.0% |
| Ischaemic heart disease | 300 (13.2%) | 46 (13.0%) | 61 (13.7%) | 0.942 | 0.0% |
| Valvular disease | 438 (19.3%) | 74 (20.8%) | 102 (23.0%) | 0.191 | 0.0% |
| **Organisation** | | | | | |
| Caregiver: In-patient | 437 (19.3%) | 71 (20.0%) | 157 (35.4%) | <0.001 | 0.0% |
| Planned follow-up: Specialty care (vs. Primary care/Other) | 1,235 (56.0%) | 255 (73.1%) | 238 (55.1%) | <0.001 | 2.7% |
| Referral to follow-up in a nurse-led HF unit | 1,739 (79.0%) | 283 (81.1%) | 285 (66.4%) | <0.001 | 3.0% |
| **Treatments** | | | | | |
| Beta-blockers | 1,959 (86.4%) | 311 (87.9%) | 376 (85.1%) | 0.523 | 0.2% |
| RASi/ARNi | 1,975 (87.3%) | 320 (91.2%) | 356 (81.3%) | <0.001 | 0.6% |
| Mineralocorticoid receptor antagonists | 568 (25.1%) | 99 (28.0%) | 128 (29.0%) | 0.152 | 0.5% |
| Diuretics | 1,566 (69.1%) | 237 (66.9%) | 341 (77.5%) | 0.001 | 0.3% |
| Digoxin | 282 (12.4%) | 47 (13.3%) | 59 (13.3%) | 0.814 | 0.2% |
| Nitrates | 300 (13.2%) | 33 (9.3%) | 75 (17.0%) | 0.006 | 0.2% |
| Anticoagulants | 1,109 (49.0%) | 173 (48.7%) | 215 (48.8%) | 0.994 | 0.3% |
| Antiplatelets | 930 (41.1%) | 147 (41.4%) | 185 (42.0%) | 0.939 | 0.3% |
| Statins | 1,205 (53.2%) | 180 (50.8%) | 206 (46.6%) | 0.036 | 0.3% |
| Cardiac resynchronisation therapy | 42 (2.0%) | 10 (2.9%) | 6 (1.4%) | 0.327 | 5.9% |
| Implantable cardioverter-defibrillator | 56 (2.6%) | 13 (3.8%) | 9 (2.1%) | 0.339 | 5.9% |
| Summary statistics based on unimputed data. Data is presented as absolute (relative) frequencies, mean (±standard deviations), and median [interquartile range], and compared by Chi-squared-test, ANOVA, and Kruskal-Wallis test, respectively.  **Abbreviations:** ARNi, angiotensin-receptor-neprilysin inhibitor; b.p.m, beats per minutes; EF, ejection fraction; eGFR, estimated glomerular filtration rate (calculated by Chronic Kidney Disease Epidemiology Collaboration formula); HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association functional class; RASi, renin-angiotensin-system inhibitor. | | | | | |

Table S4. Patient characteristics in patients with HFpEF

| **Variable** | **NYHA stable** | **NYHA improved** | **NYHA worsened** | **P-value** | **Missing** |
| --- | --- | --- | --- | --- | --- |
| *n* | *1,684* | *272* | *343* |  |  |
| **Sociodemographics** | | | | | |
| Index 2012-2018 (vs. 2000-2011) | 1,024 (60.8%) | 168 (61.8%) | 176 (51.3%) | 0.003 | 0.0% |
| Female | 858 (51.0%) | 145 (53.3%) | 165 (48.1%) | 0.428 | 0.0% |
| Age, years | 77 (11) | 75 (11) | 78 (10) | 0.015 | 0.0% |
| . ≥75 years | 1,130 (67.1%) | 158 (58.1%) | 238 (69.4%) | 0.006 | 0.0% |
| Income level: Lowest tertile | 1,052 (62.5%) | 155 (57.0%) | 215 (62.7%) | 0.212 | 0.0% |
| Education: Secondary school or less | 1,385 (84.7%) | 223 (83.2%) | 295 (89.7%) | 0.041 | 2.9% |
| Single living | 894 (53.1%) | 130 (47.8%) | 185 (53.9%) | 0.232 | 0.0% |
| Children | 1,413 (83.9%) | 226 (83.1%) | 292 (85.1%) | 0.777 | 0.0% |
| **Clinical and laboratory variables** | | | | | |
| NYHA class at baseline |  |  |  | <0.001 | 0.0% |
| I | 191 (11.3%) | 0 (0.0%) | 106 (30.9%) |  |  |
| II | 848 (50.4%) | 77 (28.3%) | 207 (60.3%) |  |  |
| III | 622 (36.9%) | 183 (67.3%) | 30 (8.7%) |  |  |
| IV | 23 (1.4%) | 12 (4.4%) | 0 (0.0%) |  |  |
| NYHA class at follow-up |  |  |  | <0.001 | 0.0% |
| I | 191 (11.3%) | 95 (34.9%) | 0 (0.0%) |  |  |
| II | 848 (50.4%) | 166 (61.0%) | 75 (21.9%) |  |  |
| III | 622 (36.9%) | 11 (4.0%) | 224 (65.3%) |  |  |
| IV | 23 (1.4%) | 0 (0.0%) | 44 (12.8%) |  |  |
| NT-proBNP, ng/L | 1,558 [762, 2886] | 1,910 [939, 3328] | 1,594 [913, 3480] | 0.107 | 40.8% |
| . NT-proBNP≥median (by EF phenotype) | 441 (43.3%) | 96 (53.9%) | 75 (45.5%) | 0.031 | 40.8% |
| HF duration ≥6 months | 1,047 (63.8%) | 146 (55.5%) | 200 (60.6%) | 0.027 | 2.9% |
| Mean arterial pressure, mmHg | 93 (12) | 93 (13) | 92 (13) | 0.302 | 0.8% |
| . <90 mmHg | 619 (37.0%) | 106 (39.6%) | 136 (39.9%) | 0.495 | 0.8% |
| Heart rate, b.p.m. | 73 (14) | 72 (14) | 73 (15) | 0.408 | 2.9% |
| . ≥70 b.p.m. | 930 (56.7%) | 141 (53.6%) | 192 (58.2%) | 0.521 | 2.9% |
| Body mass index, kg/m² | 29 (6) | 29 (6) | 29 (6) | 0.587 | 36.1% |
| . ≥30 kg/m² (Obese) | 384 (36.1%) | 54 (29.5%) | 87 (39.5%) | 0.104 | 36.1% |
| eGFR, mL/min/1.73m² | 58 [43, 73] | 59 [44, 77] | 55 [39, 72] | 0.049 | 2.0% |
| . <60 mL/min/1.73m² | 899 (54.6%) | 144 (53.3%) | 202 (59.9%) | 0.158 | 2.0% |
| Haemoglobin, g/dL | 13.1 (1.7) | 13.2 (1.7) | 12.8 (1.5) | 0.001 | 4.2% |
| Potassium, mmol/L | 4 (0) | 4 (0) | 4 (0) | 0.031 | 20.2% |
| **Comorbidities** | | | | | |
| Peripheral arterial disease | 143 (8.5%) | 22 (8.1%) | 26 (7.6%) | 0.848 | 0.0% |
| Stroke/transitory ischaemic attack | 293 (17.4%) | 43 (15.8%) | 60 (17.5%) | 0.804 | 0.0% |
| Anaemia | 541 (33.6%) | 70 (27.0%) | 132 (39.6%) | 0.005 | 4.2% |
| Cancer past 3 years | 283 (16.8%) | 44 (16.2%) | 52 (15.2%) | 0.748 | 0.0% |
| Liver disease | 31 (1.8%) | 5 (1.8%) | 11 (3.2%) | 0.257 | 0.0% |
| Major bleeding | 360 (21.4%) | 48 (17.6%) | 67 (19.5%) | 0.316 | 0.0% |
| Diabetes mellitus | 402 (23.9%) | 58 (21.3%) | 89 (25.9%) | 0.410 | 0.0% |
| Atrial fibrillation | 918 (54.5%) | 152 (55.9%) | 194 (56.6%) | 0.747 | 0.0% |
| Hypertension | 937 (55.6%) | 150 (55.1%) | 189 (55.1%) | 0.976 | 0.0% |
| Chronic obstructive pulmonary disease | 235 (14.0%) | 40 (14.7%) | 39 (11.4%) | 0.386 | 0.0% |
| Ischaemic heart disease | 126 (7.5%) | 25 (9.2%) | 26 (7.6%) | 0.616 | 0.0% |
| Valvular disease | 425 (25.2%) | 62 (22.8%) | 98 (28.6%) | 0.245 | 0.0% |
| **Organisation** | | | | | |
| Caregiver: In-patient | 456 (27.1%) | 69 (25.4%) | 157 (45.8%) | <0.001 | 0.0% |
| Planned follow-up: Specialty care (vs. Primary care/Other) | 705 (43.7%) | 144 (54.8%) | 150 (45.6%) | 0.004 | 4.0% |
| Referral to follow-up in a nurse-led HF unit | 1,181 (73.5%) | 196 (75.4%) | 202 (62.0%) | <0.001 | 4.7% |
| **Treatments** | | | | | |
| Beta-blockers | 1,407 (83.9%) | 225 (82.7%) | 278 (82.0%) | 0.633 | 0.5% |
| RASi/ARNi | 1,350 (81.0%) | 218 (80.7%) | 256 (76.4%) | 0.150 | 1.2% |
| Mineralocorticoid receptor antagonists | 483 (28.8%) | 96 (35.4%) | 106 (31.0%) | 0.079 | 0.4% |
| Diuretics | 1,364 (81.2%) | 224 (82.4%) | 290 (84.5%) | 0.341 | 0.2% |
| Digoxin | 255 (15.2%) | 49 (18.1%) | 54 (15.7%) | 0.475 | 0.3% |
| Nitrates | 248 (14.8%) | 32 (11.8%) | 62 (18.1%) | 0.091 | 0.2% |
| Anticoagulants | 901 (53.6%) | 150 (55.1%) | 173 (50.4%) | 0.455 | 0.2% |
| Antiplatelets | 529 (31.5%) | 88 (32.4%) | 136 (39.9%) | 0.011 | 0.3% |
| Statins | 775 (46.2%) | 121 (44.6%) | 163 (47.5%) | 0.778 | 0.3% |
| Cardiac resynchronisation therapy | 18 (1.2%) | 1 (0.4%) | 2 (0.6%) | 0.388 | 9.7% |
| Implantable cardioverter-defibrillator | 21 (1.4%) | 2 (0.8%) | 4 (1.3%) | 0.747 | 9.7% |
| |  | | --- | | Summary statistics based on unimputed data. Data is presented as absolute (relative) frequencies, mean (±standard deviations), and median [interquartile range], and compared by Chi-squared-test, ANOVA, and Kruskal-Wallis test, respectively.  **Abbreviations:** ARNi, angiotensin-receptor-neprilysin inhibitor; b.p.m, beats per minutes; EF, ejection fraction; eGFR, estimated glomerular filtration rate (calculated by Chronic Kidney Disease Epidemiology Collaboration formula); HF, heart failure; HFpEF, heart failure with preserved ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association functional class; RASi, renin-angiotensin-system inhibitor. | | | | | | |

Table S5. Predictors of improving NYHA class across the EF spectrum

|  | **OR (95%CI)** | | |  |
| --- | --- | --- | --- | --- |
| **Variable** | **HFrEF** | **HFmrEF** | **HFpEF** | **P-int** |
| Index year 2012-2018 vs. 2000-2011 | 1.55 (1.36 - 1.77)\*\*\* | 1.22 (0.94 - 1.58) | 1.43 (1.07 - 1.91)\* | 0.235 |
| Female | 1.04 (0.90 - 1.19) | 1.03 (0.80 - 1.33) | 1.02 (0.77 - 1.35) | 0.993 |
| Age≥75 years | 0.69 (0.60 - 0.79)\*\*\* | 0.66 (0.51 - 0.84)\*\*\* | 0.61 (0.46 - 0.81)\*\*\* | 0.744 |
| Income<median | 0.80 (0.71 - 0.91)\*\*\* | 0.74 (0.58 - 0.94)\* | 0.72 (0.54 - 0.96)\* | 0.701 |
| Secondary school or less | 0.86 (0.73 - 1.00) | 0.92 (0.67 - 1.26) | 1.05 (0.72 - 1.54) | 0.594 |
| Living alone | 0.98 (0.87 - 1.11) | 0.99 (0.78 - 1.27) | 0.82 (0.62 - 1.08) | 0.467 |
| Children | 1.06 (0.90 - 1.24) | 1.11 (0.79 - 1.56) | 0.90 (0.62 - 1.30) | 0.683 |
| NT-proBNP≥median | 0.98 (0.85 - 1.14) | 0.84 (0.63 - 1.12) | 0.93 (0.68 - 1.27) | 0.776 |
| HF duration≥6 months | 0.51 (0.45 - 0.59)\*\*\* | 0.69 (0.54 - 0.89)\*\* | 0.81 (0.61 - 1.08) | 0.004 |
| Median arterial pressure<90mmHg | 0.83 (0.73 - 0.94)\*\* | 0.86 (0.67 - 1.11) | 0.99 (0.74 - 1.31) | 0.541 |
| Heart rate≥70 b.p.m. | 1.07 (0.94 - 1.22) | 0.87 (0.68 - 1.11) | 0.77 (0.58 - 1.02) | 0.066 |
| Obesity | 0.88 (0.75 - 1.02) | 1.02 (0.75 - 1.37) | 0.74 (0.53 - 1.03) | 0.367 |
| Peripheral artery disease | 0.77 (0.60 - 0.99)\* | 0.53 (0.30 - 0.92)\* | 0.88 (0.53 - 1.45) | 0.367 |
| Stroke/transitory ischaemic attack | 0.83 (0.70 - 1.00)\* | 0.77 (0.55 - 1.09) | 1.02 (0.71 - 1.49) | 0.520 |
| Anaemia | 0.86 (0.75 - 1.00)\* | 1.05 (0.80 - 1.38) | 0.69 (0.50 - 0.94)\* | 0.129 |
| Cancer last 3 years | 0.69 (0.57 - 0.84)\*\*\* | 0.93 (0.66 - 1.32) | 1.01 (0.70 - 1.46) | 0.123 |
| Liver disease | 1.08 (0.73 - 1.61) | 0.84 (0.35 - 1.99) | 0.88 (0.32 - 2.41) | 0.833 |
| Major bleeding | 0.93 (0.77 - 1.12) | 1.05 (0.75 - 1.47) | 0.81 (0.57 - 1.15) | 0.570 |
| eGFR<60 mL/min/1.73m² | 0.82 (0.71 - 0.94)\*\* | 0.67 (0.52 - 0.86)\*\* | 0.92 (0.69 - 1.22) | 0.204 |
| Diabetes mellitus | 0.81 (0.70 - 0.94)\*\* | 0.93 (0.69 - 1.25) | 0.79 (0.57 - 1.11) | 0.691 |
| Atrial fibrillation | 0.84 (0.72 - 0.98)\* | 0.70 (0.54 - 0.92)\*\* | 0.86 (0.64 - 1.15) | 0.422 |
| Hypertension | 1.14 (1.01 - 1.30)\* | 0.98 (0.77 - 1.25) | 0.88 (0.67 - 1.16) | 0.169 |
| COPD | 0.66 (0.54 - 0.80)\*\*\* | 0.77 (0.54 - 1.11) | 0.87 (0.59 - 1.29) | 0.399 |
| Ischaemic heart disease | 0.80 (0.66 - 0.97)\* | 1.02 (0.71 - 1.46) | 1.39 (0.85 - 2.26) | 0.079 |
| Valvular disease | 0.88 (0.74 - 1.05) | 1.05 (0.78 - 1.42) | 0.73 (0.52 - 1.00) | 0.247 |
| In-patient vs. Out-patient | 0.98 (0.85 - 1.13) | 0.99 (0.73 - 1.35) | 0.79 (0.57 - 1.09) | 0.447 |
| Follow-up nurse-led HF unit | 1.21 (1.02 - 1.44)\* | 0.96 (0.70 - 1.32) | 0.92 (0.66 - 1.28) | 0.200 |
| Follow-up specialty care | 1.54 (1.27 - 1.86)\*\*\* | 1.68 (1.28 - 2.21)\*\*\* | 1.06 (0.80 - 1.41) | 0.038 |
| Beta-blockers | 1.36 (1.08 - 1.71)\*\* | 0.92 (0.64 - 1.33) | 0.85 (0.59 - 1.23) | 0.052 |
| RASi/ARNi | 1.10 (0.85 - 1.44) | 1.43 (0.95 - 2.16) | 1.11 (0.78 - 1.59) | 0.554 |
| MRA | 1.02 (0.90 - 1.16) | 0.98 (0.75 - 1.28) | 1.07 (0.80 - 1.43) | 0.905 |
| Diuretics | 0.75 (0.65 - 0.87)\*\*\* | 0.68 (0.52 - 0.88)\*\* | 0.66 (0.46 - 0.96)\* | 0.703 |
| Digoxin | 1.18 (0.99 - 1.42) | 0.99 (0.69 - 1.42) | 1.25 (0.87 - 1.80) | 0.612 |
| Nitrates | 0.59 (0.47 - 0.74)\*\*\* | 0.66 (0.44 - 0.98)\* | 0.77 (0.51 - 1.17) | 0.520 |
| Anticoagulants | 1.05 (0.90 - 1.24) | 0.97 (0.74 - 1.26) | 1.10 (0.82 - 1.48) | 0.749 |
| Antiplatelets | 0.99 (0.86 - 1.15) | 1.12 (0.86 - 1.45) | 1.13 (0.83 - 1.53) | 0.578 |
| Statins | 0.89 (0.78 - 1.02) | 1.01 (0.79 - 1.29) | 1.02 (0.77 - 1.35) | 0.519 |
| CRT | 0.87 (0.64 - 1.19) | 1.28 (0.60 - 2.72) | 1.79 (0.76 - 4.20) | 0.251 |
| ICD | 0.56 (0.42 - 0.73)\*\*\* | 1.44 (0.72 - 2.90) | 1.27 (0.61 - 2.68) | 0.011 |
| \*, p-value<0.05; \*\*, p-value<0.01; \*\*\*, p-value<0.001. HR with 95% CI and p-values for the interaction between each predictor and ejection fraction were calculated by multivariable logistic regression models with NYHA class improvement (with stable/worsening NYHA class as referent) as dependent variable. Variables labeled with a dagger (†) in Table 2 were included as covariates along with an interaction term between NYHA class and one covariate at a time.  **Abbreviations:** ARNi, angiotensin-receptor-neprilysin inhibitor; b.p.m, beats per minutes; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronisation therapy; EF, ejection fraction; eGFR, estimated glomerular filtration rate (calculated by Chronic Kidney Disease Epidemiology Collaboration formula); HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; MRA, mineralocorticoid receptor antagonists; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association functional class; P-int, p-value for interaction; RASi, renin-angiotensin-system inhibitor. | | | | |

Table S6. Predictors of worsening NYHA class across the EF spectrum

|  | **OR (95%CI)** | | |  |
| --- | --- | --- | --- | --- |
| **Variable** | **HFrEF** | **HFmrEF** | **HFpEF** | **P-int** |
| Index year 2012-2018 vs. 2000-2011 | 0.82 (0.70 - 0.96)\* | 0.88 (0.69 - 1.11) | 0.82 (0.62 - 1.08) | 0.881 |
| Female | 0.91 (0.77 - 1.09) | 1.07 (0.85 - 1.36) | 0.99 (0.76 - 1.29) | 0.526 |
| Age≥75 years | 1.27 (1.08 - 1.49)\*\* | 1.43 (1.13 - 1.81)\*\* | 1.34 (1.01 - 1.78)\* | 0.692 |
| Income<median | 1.11 (0.96 - 1.29) | 1.15 (0.92 - 1.45) | 1.11 (0.85 - 1.45) | 0.964 |
| Secondary school or less | 1.12 (0.91 - 1.37) | 0.97 (0.72 - 1.32) | 1.43 (0.95 - 2.14) | 0.335 |
| Living alone | 0.89 (0.77 - 1.03) | 1.33 (1.06 - 1.67)\* | 1.04 (0.81 - 1.35) | 0.012 |
| Children | 1.00 (0.82 - 1.22) | 0.99 (0.72 - 1.36) | 1.23 (0.86 - 1.77) | 0.574 |
| NT-proBNP≥median | 1.14 (0.95 - 1.36) | 1.24 (0.95 - 1.63) | 1.26 (0.93 - 1.71) | 0.724 |
| HF duration≥6 months | 1.39 (1.19 - 1.62)\*\*\* | 1.63 (1.28 - 2.07)\*\*\* | 0.96 (0.73 - 1.25) | 0.011 |
| Median arterial pressure<90mmHg | 1.41 (1.22 - 1.64)\*\*\* | 1.24 (0.99 - 1.56) | 1.26 (0.97 - 1.64) | 0.580 |
| Heart rate≥70 b.p.m. | 1.10 (0.94 - 1.28) | 1.36 (1.08 - 1.72)\*\* | 1.19 (0.91 - 1.55) | 0.311 |
| Obesity | 1.10 (0.89 - 1.37) | 1.32 (0.99 - 1.75) | 1.19 (0.87 - 1.62) | 0.548 |
| Peripheral artery disease | 1.37 (1.06 - 1.77)\* | 0.71 (0.46 - 1.11) | 1.00 (0.62 - 1.62) | 0.034 |
| Stroke/transitory ischaemic attack | 1.25 (1.03 - 1.52)\* | 0.98 (0.73 - 1.33) | 0.85 (0.60 - 1.19) | 0.105 |
| Anaemia | 1.22 (1.04 - 1.43)\* | 1.14 (0.90 - 1.46) | 1.26 (0.96 - 1.66) | 0.853 |
| Cancer last 3 years | 1.11 (0.89 - 1.38) | 1.63 (1.22 - 2.18)\*\* | 0.90 (0.64 - 1.28) | 0.027 |
| Liver disease | 1.11 (0.65 - 1.90) | 2.29 (1.17 - 4.48)\* | 1.37 (0.62 - 3.02) | 0.251 |
| Major bleeding | 0.98 (0.79 - 1.21) | 1.23 (0.93 - 1.64) | 0.88 (0.63 - 1.21) | 0.253 |
| eGFR<60 mL/min/1.73m² | 1.37 (1.17 - 1.61)\*\*\* | 1.33 (1.06 - 1.67)\* | 1.32 (1.01 - 1.72)\* | 0.954 |
| Diabetes mellitus | 1.11 (0.94 - 1.33) | 1.08 (0.82 - 1.42) | 1.11 (0.82 - 1.50) | 0.983 |
| Atrial fibrillation | 1.10 (0.93 - 1.31) | 1.33 (1.04 - 1.70)\* | 1.08 (0.82 - 1.41) | 0.332 |
| Hypertension | 1.11 (0.96 - 1.30) | 1.25 (1.00 - 1.57)\* | 1.07 (0.83 - 1.39) | 0.603 |
| COPD | 1.18 (0.95 - 1.47) | 1.48 (1.07 - 2.05)\* | 0.91 (0.61 - 1.35) | 0.169 |
| Ischaemic heart disease | 1.16 (0.94 - 1.42) | 1.06 (0.76 - 1.48) | 1.05 (0.65 - 1.70) | 0.874 |
| Valvular disease | 1.04 (0.85 - 1.27) | 1.17 (0.89 - 1.54) | 1.26 (0.94 - 1.69) | 0.515 |
| In-patient vs. Out-patient | 2.28 (1.94 - 2.68)\*\*\* | 1.96 (1.52 - 2.54)\*\*\* | 2.35 (1.78 - 3.11)\*\*\* | 0.521 |
| Follow-up nurse-led HF unit | 0.78 (0.65 - 0.93)\*\* | 0.90 (0.70 - 1.17) | 0.91 (0.68 - 1.20) | 0.511 |
| Follow-up specialty care | 0.87 (0.72 - 1.05) | 1.06 (0.84 - 1.33) | 1.28 (0.98 - 1.67) | 0.059 |
| Beta-blockers | 0.89 (0.69 - 1.14) | 0.96 (0.70 - 1.32) | 0.88 (0.63 - 1.23) | 0.906 |
| RASi/ARNi | 0.90 (0.67 - 1.20) | 0.76 (0.56 - 1.03) | 0.83 (0.61 - 1.14) | 0.753 |
| MRA | 1.11 (0.95 - 1.29) | 1.09 (0.85 - 1.41) | 1.24 (0.94 - 1.65) | 0.739 |
| Diuretics | 1.16 (0.97 - 1.38) | 1.35 (1.03 - 1.76)\* | 1.45 (1.03 - 2.05)\* | 0.390 |
| Digoxin | 0.89 (0.71 - 1.11) | 1.04 (0.74 - 1.45) | 0.98 (0.69 - 1.40) | 0.716 |
| Nitrates | 1.14 (0.91 - 1.42) | 1.27 (0.93 - 1.74) | 1.20 (0.85 - 1.70) | 0.847 |
| Anticoagulants | 1.13 (0.94 - 1.36) | 1.14 (0.88 - 1.47) | 0.91 (0.69 - 1.21) | 0.327 |
| Antiplatelets | 1.09 (0.92 - 1.31) | 0.99 (0.77 - 1.27) | 1.45 (1.09 - 1.93)\* | 0.084 |
| Statins | 1.07 (0.91 - 1.26) | 0.74 (0.59 - 0.93)\*\* | 1.06 (0.82 - 1.38) | 0.016 |
| CRT | 1.79 (1.31 - 2.44)\*\*\* | 0.65 (0.26 - 1.63) | 0.40 (0.16 - 1.00) | <0.001 |
| ICD | 1.59 (1.21 - 2.10)\*\* | 0.67 (0.31 - 1.44) | 0.51 (0.24 - 1.09) | 0.002 |
| \*, p-value<0.05; \*\*, p-value<0.01; \*\*\*, p-value<0.001. HR with 95% CI and p-values for the interaction between each predictor and ejection fraction were calculated by multivariable logistic regression models with NYHA class worsening (with stable/improving NYHA class as referent) as dependent variable. Variables labeled with a dagger (†) in Table 2 were included as covariates along with an interaction term between NYHA class and one covariate at a time.  **Abbreviations:** ARNi, angiotensin-receptor-neprilysin inhibitor; b.p.m, beats per minutes; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronisation therapy; EF, ejection fraction; eGFR, estimated glomerular filtration rate (calculated by Chronic Kidney Disease Epidemiology Collaboration formula); HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; MRA, mineralocorticoid receptor antagonists; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association functional class; P-int, p-value for interaction; RASi, renin-angiotensin-system inhibitor. | | | | |

**Table** **S7. Outcomes by NYHA change trajectory across the EF spectrum**

| **Subgroup** | **NYHA class** | **Patients** | **Events** | **Events (%)** | **Patient-years** | **Median follow-up time (IQR)** | **Events / 100 patient-years (95% CI)** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **All-cause mortality** | | | | | | | |
| Overall cohort | NYHA stable | 9,378 | 4,569 | 48.7% | 36,295 | 3.0 (1.5 - 5.6) | 12.6 (12.2-13.0) |
|  | NYHA improved | 2,334 | 826 | 35.4% | 9,812 | 3.0 (1.7 - 6.1) | 8.4 (7.9-9.0) |
|  | NYHA worsened | 1,823 | 1,075 | 59.0% | 5,809 | 2.1 (1.0 - 4.5) | 18.5 (17.4-19.6) |
| HFrEF | NYHA stable | 5,424 | 2,623 | 48.4% | 21,887 | 3.1 (1.5 - 5.9) | 12.0 (11.5-12.5) |
|  | NYHA improved | 1,707 | 578 | 33.9% | 7,502 | 3.1 (1.7 - 6.6) | 7.7 (7.1-8.4) |
|  | NYHA worsened | 1,036 | 588 | 56.8% | 3,471 | 2.2 (1.0 - 4.9) | 16.9 (15.6-18.4) |
| HFmrEF | NYHA stable | 2,270 | 1,030 | 45.4% | 8,679 | 3.1 (1.6 - 5.2) | 11.9 (11.2-12.6) |
|  | NYHA improved | 355 | 131 | 36.9% | 1,308 | 2.7 (1.6 - 4.8) | 10.0 (8.4-11.9) |
|  | NYHA worsened | 444 | 271 | 61.0% | 1,368 | 2.1 (1.0 - 4.1) | 19.8 (17.5-22.3) |
| HFpEF | NYHA stable | 1,684 | 916 | 54.4% | 5,729 | 2.7 (1.3 - 4.5) | 16.0 (15.0-17.1) |
|  | NYHA improved | 272 | 117 | 43.0% | 1,002 | 2.8 (1.5 - 5.2) | 11.7 (9.7-14.0) |
|  | NYHA worsened | 343 | 216 | 63.0% | 971 | 2.0 (0.8 - 3.8) | 22.2 (19.4-25.4) |
| **Cardiovascular mortality** | | | | | | | |
| Overall cohort | NYHA stable | 9,378 | 2,823 | 30.1% | 36,295 | 3.0 (1.5 - 5.6) | 7.8 (7.5-8.1) |
|  | NYHA improved | 2,334 | 495 | 21.2% | 9,812 | 3.0 (1.7 - 6.1) | 5.0 (4.6-5.5) |
|  | NYHA worsened | 1,823 | 718 | 39.4% | 5,809 | 2.1 (1.0 - 4.5) | 12.4 (11.5-13.3) |
| HFrEF | NYHA stable | 5,424 | 1,683 | 31.0% | 21,887 | 3.1 (1.5 - 5.9) | 7.7 (7.3-8.1) |
|  | NYHA improved | 1,707 | 354 | 20.7% | 7,502 | 3.1 (1.7 - 6.6) | 4.7 (4.2-5.2) |
|  | NYHA worsened | 1,036 | 404 | 39.0% | 3,471 | 2.2 (1.0 - 4.9) | 11.6 (10.5-12.8) |
| HFmrEF | NYHA stable | 2,270 | 608 | 26.8% | 8,679 | 3.1 (1.6 - 5.2) | 7.0 (6.5-7.6) |
|  | NYHA improved | 355 | 79 | 22.3% | 1,308 | 2.7 (1.6 - 4.8) | 6.0 (4.8-7.5) |
|  | NYHA worsened | 444 | 180 | 40.5% | 1,368 | 2.1 (1.0 - 4.1) | 13.2 (11.3-15.2) |
| HFpEF | NYHA stable | 1,684 | 532 | 31.6% | 5,729 | 2.7 (1.3 - 4.5) | 9.3 (8.5-10.1) |
|  | NYHA improved | 272 | 62 | 22.8% | 1,002 | 2.8 (1.5 - 5.2) | 6.2 (4.7-7.9) |
|  | NYHA worsened | 343 | 134 | 39.1% | 971 | 2.0 (0.8 - 3.8) | 13.8 (11.6-16.3) |
| **First HF hospitalization** | | | | | | | |
| Overall cohort | NYHA stable | 9,378 | 3,550 | 37.9% | 28,119 | 2.1 (0.9 - 4.2) | 12.6 (12.2-13.0) |
|  | NYHA improved | 2,334 | 681 | 29.2% | 8,032 | 2.4 (1.3 - 4.9) | 8.5 (7.9-9.1) |
|  | NYHA worsened | 1,823 | 883 | 48.4% | 3,871 | 1.2 (0.3 - 2.9) | 22.8 (21.3-24.4) |
| HFrEF | NYHA stable | 5,424 | 2,255 | 41.6% | 16,299 | 2.1 (0.8 - 4.3) | 13.8 (13.3-14.4) |
|  | NYHA improved | 1,707 | 522 | 30.6% | 6,093 | 2.4 (1.3 - 5.2) | 8.6 (7.8-9.3) |
|  | NYHA worsened | 1,036 | 521 | 50.3% | 2,229 | 1.2 (0.2 - 2.9) | 23.4 (21.4-25.5) |
| HFmrEF | NYHA stable | 2,270 | 701 | 30.9% | 7,234 | 2.4 (1.1 - 4.4) | 9.7 (9.0-10.4) |
|  | NYHA improved | 355 | 91 | 25.6% | 1,097 | 2.3 (1.3 - 4.2) | 8.3 (6.7-10.2) |
|  | NYHA worsened | 444 | 196 | 44.1% | 957 | 1.4 (0.4 - 2.9) | 20.5 (17.7-23.6) |
| HFpEF | NYHA stable | 1,684 | 594 | 35.3% | 4,586 | 2.0 (0.8 - 3.8) | 13.0 (11.9-14.0) |
|  | NYHA improved | 272 | 68 | 25.0% | 842 | 2.2 (1.1 - 4.2) | 8.1 (6.3-10.2) |
|  | NYHA worsened | 343 | 166 | 48.4% | 685 | 1.2 (0.3 - 2.8) | 24.2 (20.7-28.2) |
| Event rate confidence intervals calculated by exact Poisson test.  **Abbreviations:** CI, confidence interval; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; IQR, inter-quartile range; NYHA, New York Heart Association functional class. | | | | | | | |

Table S8. Association NYHA change trajectory and outcomes across the EF spectrum

|  | | **Crude** | | **Adjusted** | |
| --- | --- | --- | --- | --- | --- |
| **Subgroup** | **NYHA change trajectory** | **HR (95% CI)** | **P-int** | **HR (95% CI)** | **P-int** |
| **All-cause mortality** |  |  |  |  |  |
| Ejection fraction |  |  | 0.037 |  | 0.092 |
| . HFrEF | NYHA improved | 0.65 (0.59 - 0.71)\*\*\* |  | 1.04 (0.95 - 1.15) |  |
|  | NYHA worsened | 1.40 (1.28 - 1.53)\*\*\* |  | 0.94 (0.85 - 1.03) |  |
| . HFmrEF | NYHA improved | 0.84 (0.70 - 1.01) |  | 1.22 (1.01 - 1.47)\* |  |
|  | NYHA worsened | 1.65 (1.44 - 1.88)\*\*\* |  | 0.89 (0.77 - 1.02) |  |
| . HFpEF | NYHA improved | 0.73 (0.61 - 0.89)\*\* |  | 1.02 (0.84 - 1.25) |  |
|  | NYHA worsened | 1.38 (1.19 - 1.60)\*\*\* |  | 0.95 (0.81 - 1.11) |  |
| **Cardiovascular mortality** |  |  |  |  |  |
| Ejection fraction |  |  | 0.052 |  | 0.358 |
| . HFrEF | NYHA improved | 0.62 (0.55 - 0.69)\*\*\* |  | 1.08 (0.95 - 1.22) |  |
|  | NYHA worsened | 1.49 (1.34 - 1.67)\*\*\* |  | 0.93 (0.83 - 1.04) |  |
| . HFmrEF | NYHA improved | 0.85 (0.68 - 1.08) |  | 1.30 (1.02 - 1.66)\* |  |
|  | NYHA worsened | 1.84 (1.56 - 2.18)\*\*\* |  | 0.91 (0.76 - 1.08) |  |
| . HFpEF | NYHA improved | 0.67 (0.52 - 0.87)\*\* |  | 1.00 (0.77 - 1.31) |  |
|  | NYHA worsened | 1.46 (1.21 - 1.77)\*\*\* |  | 0.93 (0.77 - 1.14) |  |
| **First HF hospitalization** |  |  |  |  |  |
| Ejection fraction |  |  | 0.126 |  | 0.090 |
| . HFrEF | NYHA improved | 0.64 (0.59 - 0.71)\*\*\* |  | 0.96 (0.86 - 1.06) |  |
|  | NYHA worsened | 1.57 (1.43 - 1.73)\*\*\* |  | 1.03 (0.93 - 1.13) |  |
| . HFmrEF | NYHA improved | 0.82 (0.66 - 1.02) |  | 1.14 (0.91 - 1.42) |  |
|  | NYHA worsened | 1.90 (1.62 - 2.22)\*\*\* |  | 1.04 (0.88 - 1.23) |  |
| . HFpEF | NYHA improved | 0.65 (0.51 - 0.83)\*\*\* |  | 0.82 (0.63 - 1.05) |  |
|  | NYHA worsened | 1.72 (1.45 - 2.04)\*\*\* |  | 1.15 (0.96 - 1.37) |  |
| \*, p-value<0.05; \*\*, p-value<0.01; \*\*\*, p-value<0.001. HR with 95% CI for the association between NYHA class and outcomes per EF phenotype were calculated by multivariable Cox regression including longitudinal NYHA class change trajectory, EF phenotype, and an interaction term between longitudinal NYHA class change trajectory and EF phenotype. The adjusted models included variables labeled with a dagger (†) in Table 1, the time between the NYHA class assessments, and NYHA class at follow-up as covariates.  **Abbreviations:** CI, confidence interval; EF, ejection fraction; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; NYHA, New York Heart Association functional class; P-int, p-value for interaction. | | | | | |

Table S9. Consistency analysis: NYHA change trajectory and outcomes in patients where both assessments were made in an out-patient setting

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Crude model** | **Baseline modela** | **Follow-up modelb** |
| **NYHA change** | **HR (95% CI)** | **HR (95% CI)** | **HR (95% CI)** |
| **All-cause mortality** |  |  |  |
| NYHA stable | ref | ref | ref |
| NYHA improved | 0.68 (0.62 - 0.75)\*\*\* | 0.67 (0.61 - 0.75)\*\*\* | 1.03 (0.93 - 1.14) |
| NYHA worsened | 1.40 (1.27 - 1.55)\*\*\* | 1.41 (1.26 - 1.56)\*\*\* | 0.92 (0.83 - 1.02) |
| NYHA I |  | ref | ref |
| NYHA II |  | 1.46 (1.28 - 1.67)\*\*\* | 1.33 (1.17 - 1.51)\*\*\* |
| NYHA III |  | 2.14 (1.85 - 2.47)\*\*\* | 2.03 (1.77 - 2.33)\*\*\* |
| NYHA IV |  | 3.44 (2.60 - 4.54)\*\*\* | 3.61 (2.78 - 4.69)\*\*\* |
| **Cardiovascular mortality** |  |  |  |
| NYHA stable | ref | ref | ref |
| NYHA improved | 0.65 (0.57 - 0.74)\*\*\* | 0.63 (0.55 - 0.72)\*\*\* | 1.04 (0.90 - 1.19) |
| NYHA worsened | 1.53 (1.36 - 1.73)\*\*\* | 1.56 (1.37 - 1.79)\*\*\* | 0.94 (0.82 - 1.07) |
| NYHA I |  | ref | ref |
| NYHA II |  | 1.61 (1.34 - 1.94)\*\*\* | 1.39 (1.17 - 1.65)\*\*\* |
| NYHA III |  | 2.52 (2.07 - 3.07)\*\*\* | 2.29 (1.89 - 2.76)\*\*\* |
| NYHA IV |  | 4.49 (3.16 - 6.37)\*\*\* | 4.41 (3.20 - 6.10)\*\*\* |
| **First HF hospitalization** |  |  |  |
| NYHA stable | ref | ref | ref |
| NYHA improved | 0.72 (0.65 - 0.80)\*\*\* | 0.63 (0.57 - 0.71)\*\*\* | 0.98 (0.87 - 1.10) |
| NYHA worsened | 1.62 (1.46 - 1.80)\*\*\* | 1.72 (1.53 - 1.93)\*\*\* | 1.11 (1.00 - 1.24) |
| NYHA I |  | ref | ref |
| NYHA II |  | 1.39 (1.21 - 1.61)\*\*\* | 1.32 (1.15 - 1.52)\*\*\* |
| NYHA III |  | 2.11 (1.81 - 2.47)\*\*\* | 2.11 (1.81 - 2.46)\*\*\* |
| NYHA IV |  | 2.90 (2.04 - 4.11)\*\*\* | 3.04 (2.20 - 4.20)\*\*\* |
| \*, p-value<0.05; \*\*, p-value<0.01; \*\*\*, p-value<0.001. Crude and adjusted HR with 95% CI for the association between longitudinal change in NYHA class and outcomes were calculated by multivariable Cox regression. | | | |
| aAdjusted for variables labeled with a dagger (†) in Table 2 (at the time of the follow-up NYHA class assessment), the time between the NYHA class assessments, and NYHA class at baseline. | | | |
| bAdjusted for variables labeled with a dagger (†) in Table 2 (at the time of the follow-up NYHA class assessment), the time between the NYHA class assessments, and NYHA class at 2nd assessment.  **Abbreviations:** CI, confidence interval; HF, heart failure; HR, hazard ratio; NYHA, New York Heart Association functional class. | | | |

Table S10. Consistency analysis: NYHA change trajectory and outcomes in subset of patients with <1 year between NYHA class assessments

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Crude model** | **Baseline modela** | **Follow-up modelb** |
| **NYHA change** | **HR (95% CI)** | **HR (95% CI)** | **HR (95% CI)** |
| **All-cause mortality** |  |  |  |
| NYHA stable | ref | ref | ref |
| NYHA improved | 0.66 (0.61 - 0.73)\*\*\* | 0.69 (0.63 - 0.76)\*\*\* | 0.99 (0.90 - 1.10) |
| NYHA worsened | 1.54 (1.42 - 1.68)\*\*\* | 1.42 (1.29 - 1.56)\*\*\* | 0.95 (0.87 - 1.05) |
| NYHA I |  | ref | ref |
| NYHA II |  | 1.36 (1.18 - 1.55)\*\*\* | 1.23 (1.08 - 1.40)\*\* |
| NYHA III |  | 1.95 (1.68 - 2.25)\*\*\* | 1.74 (1.51 - 2.00)\*\*\* |
| NYHA IV |  | 2.46 (1.97 - 3.08)\*\*\* | 3.14 (2.58 - 3.83)\*\*\* |
| **Cardiovascular mortality** |  |  |  |
| NYHA stable | ref | ref | ref |
| NYHA improved | 0.64 (0.57 - 0.72)\*\*\* | 0.66 (0.59 - 0.75)\*\*\* | 1.01 (0.89 - 1.15) |
| NYHA worsened | 1.69 (1.52 - 1.87)\*\*\* | 1.53 (1.36 - 1.72)\*\*\* | 0.95 (0.85 - 1.06) |
| NYHA I |  | ref | ref |
| NYHA II |  | 1.51 (1.26 - 1.81)\*\*\* | 1.24 (1.04 - 1.47)\* |
| NYHA III |  | 2.29 (1.89 - 2.79)\*\*\* | 1.85 (1.53 - 2.22)\*\*\* |
| NYHA IV |  | 2.92 (2.20 - 3.87)\*\*\* | 3.77 (2.95 - 4.81)\*\*\* |
| **First HF hospitalization** |  |  |  |
| NYHA stable | ref | ref | ref |
| NYHA improved | 0.70 (0.63 - 0.77)\*\*\* | 0.65 (0.58 - 0.72)\*\*\* | 0.92 (0.83 - 1.03) |
| NYHA worsened | 1.66 (1.51 - 1.83)\*\*\* | 1.45 (1.30 - 1.61)\*\*\* | 1.03 (0.93 - 1.14) |
| NYHA I |  | ref | ref |
| NYHA II |  | 1.36 (1.17 - 1.58)\*\*\* | 1.29 (1.12 - 1.49)\*\*\* |
| NYHA III |  | 1.89 (1.61 - 2.22)\*\*\* | 1.85 (1.58 - 2.17)\*\*\* |
| NYHA IV |  | 2.20 (1.70 - 2.85)\*\*\* | 2.23 (1.76 - 2.83)\*\*\* |
| \*, p-value<0.05; \*\*, p-value<0.01; \*\*\*, p-value<0.001. Crude and adjusted HR with 95% CI for the association between longitudinal change in NYHA class and outcomes were calculated by multivariable Cox regression. | | | |
| aAdjusted for variables labeled with a dagger (†) in Table 2 (at the time of the follow-up NYHA class assessment), the time between the NYHA class assessments, and NYHA class at baseline. | | | |
| bAdjusted for variables labeled with a dagger (†) in Table 2 (at the time of the follow-up NYHA class assessment), the time between the NYHA class assessments, and NYHA class at 2nd assessment.  **Abbreviations:** CI, confidence interval; HF, heart failure; HR, hazard ratio; NYHA, New York Heart Association functional class. | | | |

Table S11. Consistency analysis: NYHA change trajectory and outcomes in subset of patients with NYHA class II-III at baseline

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Crude model** | **Baseline modela** | **Follow-up modelb** |
| **NYHA change** | **HR (95% CI)** | **HR (95% CI)** | **HR (95% CI)** |
| **All-cause mortality** |  |  |  |
| NYHA stable | ref | ref | ref |
| NYHA improved | 0.58 (0.54 - 0.63)\*\*\* | 0.67 (0.62 - 0.73)\*\*\* | 0.98 (0.89 - 1.08) |
| NYHA worsened | 1.71 (1.59 - 1.84)\*\*\* | 1.51 (1.39 - 1.63)\*\*\* | 0.92 (0.84 - 1.00) |
| NYHA I |  |  | ref |
| NYHA II |  | ref | 1.24 (1.06 - 1.46)\*\* |
| NYHA III |  | 1.50 (1.41 - 1.59)\*\*\* | 1.83 (1.53 - 2.18)\*\*\* |
| NYHA IV |  |  | 4.01 (3.16 - 5.10)\*\*\* |
| **Cardiovascular mortality** |  |  |  |
| NYHA stable | ref | ref | ref |
| NYHA improved | 0.56 (0.50 - 0.62)\*\*\* | 0.65 (0.59 - 0.72)\*\*\* | 1.01 (0.89 - 1.15) |
| NYHA worsened | 1.87 (1.71 - 2.04)\*\*\* | 1.64 (1.48 - 1.80)\*\*\* | 0.90 (0.81 - 1.01) |
| NYHA I |  |  | ref |
| NYHA II |  | ref | 1.26 (1.01 - 1.56)\* |
| NYHA III |  | 1.62 (1.50 - 1.74)\*\*\* | 1.98 (1.57 - 2.50)\*\*\* |
| NYHA IV |  |  | 4.87 (3.62 - 6.57)\*\*\* |
| **First HF hospitalization** |  |  |  |
| NYHA stable | ref | ref | ref |
| NYHA improved | 0.60 (0.55 - 0.65)\*\*\* | 0.62 (0.57 - 0.68)\*\*\* | 0.92 (0.83 - 1.02) |
| NYHA worsened | 1.93 (1.78 - 2.09)\*\*\* | 1.55 (1.42 - 1.69)\*\*\* | 1.04 (0.95 - 1.15) |
| NYHA I |  |  | ref |
| NYHA II |  | ref | 1.38 (1.15 - 1.65)\*\*\* |
| NYHA III |  | 1.43 (1.34 - 1.53)\*\*\* | 2.02 (1.65 - 2.46)\*\*\* |
| NYHA IV |  |  | 3.05 (2.32 - 4.01)\*\*\* |
| \*, p-value<0.05; \*\*, p-value<0.01; \*\*\*, p-value<0.001. Crude and adjusted HR with 95% CI for the association between longitudinal change in NYHA class and outcomes were calculated by multivariable Cox regression. | | | |
| aAdjusted for variables labeled with a dagger (†) in Table 2 (at the time of the follow-up NYHA class assessment), the time between the NYHA class assessments, and NYHA class at baseline. | | | |
| bAdjusted for variables labeled with a dagger (†) in Table 2 (at the time of the follow-up NYHA class assessment), the time between the NYHA class assessments, and NYHA class at 2nd assessment.  **Abbreviations:** CI, confidence interval; HF, heart failure; HR, hazard ratio; NYHA, New York Heart Association functional class. | | | |

Graphical user interface, diagram, application

Description automatically generated

Figure S1. 1-Kaplan-Meier curves for A) all-cause mortality, B) CV mortality, and C) first HF hospitalisation by NYHA change trajectory across the EF spectrum

**Abbreviations:** EF, ejection fraction; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NYHA, New York Heart Association functional class.