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RESEARCH ARTICLE

# 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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**Aims** To investigate incidence, predictors and prognostic implications of longitudinal New York Heart Association (NYHA) class changes (i.e. improving or worsening vs. stable NYHA class) in heart failure (HF) across the ejection fraction (EF) spectrum.

**Methods and results** From the Swedish HF Registry, 13 535 patients with EF and ≥2 NYHA class assessments were considered. Multivariable multinomial regressions were fitted to identify the independent predictors of NYHA change. Over a 1-year follow-up, 69% of patients had stable, 17% improved, and 14% worsened NYHA class. Follow-up in specialty care predicted improving NYHA class, whereas an in-hospital patient registration, lower EF, renal disease, lower mean arterial pressure, older age, and longer HF duration predicted worsening. The association between NYHA change and subsequent outcomes was assessed with multivariable Cox models. When adjusting for the NYHA class at baseline, improving NYHA class was independently associated with lower while worsening with higher risk of all-cause and cardiovascular mortality, and first HF hospitalization. After adjustment for the NYHA class at follow-up, NYHA class change did not predict morbidity/mortality. NYHA class assessment at baseline and follow-up predicted morbidity/mortality on top of the changes. Results were consistent across the EF spectrum.

**Conclusion** In a large real-world HF population, NYHA class trajectories predicted morbidity/mortality after extensive adjustments. However, the prognostic role was entirely explained by the resulting NYHA class, i.e. the follow-up value. Our results highlight that considering one-time NYHA class assessment, rather than trajectories, might be the preferable approach in clinical practice and for clinical trial design.

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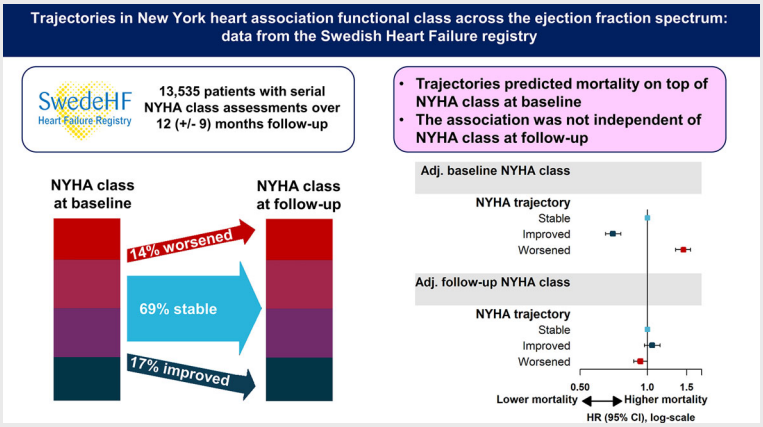
## Graphical Abstract




Stable NYHA class over time was much more frequent than an improvement or a worsening. Follow-up NYHA class assessment, but not change in NYHA class over time, was independently associated with better prognosis.

**Keywords** Heart failure • NYHA functional class • Symptoms • Prognosis • Ejection fraction

# Introduction

The New York Heart Association (NYHA) functional classification has been a widely used clinical tool to assess dyspnoea and symptom severity in patients with heart failure (HF) for almost a century.[1] Among patients with chronic HF, around a quarter experience symptoms at modest exertion/at rest (NYHA class III–IV),[2] and poor NYHA functional class is associated with adverse outcomes in HF.[2,3] The use of NYHA class as a single-point assessment ranges from prognostication purposes and eligibility for HF treatments in clinical practice to enrolment criteria for trials.[4] However, HF is a progressive syndrome, and symptom severity may change dynamically over its clinical course.

Few studies have comprehensively evaluated longitudinal changes in NYHA class over time and their associated factors, and they were often affected by several limitations, e.g. small sample sizes,[5,6] inclusion of only patients with HF with reduced ejection fraction (HFrEF),[7] or the setting of a specific intervention.[8] Whether the trajectories of NYHA class over time (i.e. whether symptoms are stable, improving, or worsening) independently predict mortality/morbidity on top of a single-point assessment across the ejection fraction (EF) spectrum might have implications for clinical trial design and prognostic assessment in clinical practice.

Therefore, in a large, contemporary, and nationwide HF registry enrolling patients across the EF spectrum, we aimed to comprehensively focus on longitudinal changes in NYHA class by investigating (i) their incidence, (ii) their independent predictors, and (iii) their independent associations with mortality/morbidity on top of one-time NYHA class assessment.

# Methods

## Material

The Swedish HF (SwedeHF) Registry has previously been described in detail.[9] Briefly, this is an ongoing registry enrolling patients at discharge from HF hospitalization and outpatient clinics in Sweden since 11 May 2000. A diagnosis of HF is the only inclusion criterion, which before 2017 was defined as clinical diagnosis and since 2017 according to the International Classification of Diseases, Tenth Revision (ICD-10) codes I50.0, I50.1, I50.9, I42.0, I42.6, I42.7, I25.5, I11.0, I13.0, and I13.2. Approximately 80 variables on demographics, clinical characteristics, comorbidities, laboratory data, treatments, and use of care are recorded into the registry database. In SwedeHF, the coverage of prevalent HF in Sweden is approximately 32%.[10]

For the present analysis, SwedeHF was linked to other national registries: (1) Statistics Sweden to obtain socioeconomic data, (2) the National Patient Registry to extract additional comorbidities and the outcome HF hospitalization according to ICD-10 codes, and (3) the Cause of Death Registry to obtain data on all-cause and cardiovascular (CV) mortality. The current analysis approved by the Swedish Ethical Review Authority. While individual consent was not required to be enrolled in SwedeHF, patients were informed of entry and able to opt out.

## Patients

Patients with EF, a baseline NYHA class assessment, and a follow-up NYHA class assessment within 1 year (±9 months) from baseline recorded in SwedeHF were included. For patients with >2 follow-up NYHA class assessments, the one closest to 1-year follow-up was selected as follow-up value. A flowchart depicting the patient selection

is reported in online supplementary *Table S1*. Based on the two NYHA class assessments, the trajectory was defined as stable if NYHA class was unchanged, improved if NYHA class decreased, and worsened if NYHA class increased between baseline and follow-up. EF was classified as EF <40%, 40% to 49%, and ≥50%, i.e. HFrEF, HF with mildly reduced EF (HFmrEF), and HF with preserved EF (HFpEF), respectively. The HFrEF cut-off was EF <40%, and not ≤40% as according to the 2021 European Society of Cardiology guidelines on HF,[4] due to the fact that EF was recorded as a categorized variable in the registry. Patients were censored at death/emigration or at the end of the study follow-up, i.e. 31 December 2019, with a median follow-up of 2.9 (interquartile range [IQR] 1.4–5.5) years from the second NYHA class assessment.

## Statistical analysis

### Patient characteristics

Baseline patient characteristics were compared across patients with stable, improved, and worsened NYHA class over time. Continuous variables were compared by Kruskal–Wallis test or analysis of variance, and categorical by $\chi^2$ test. Missing data in multivariable models were handled by multiple imputation while stratifying by EF phenotype (10 imputed sets, 10 iterations, R-package: *mice*).[11] The imputation model included all the variables marked with an asterisk (*) in *Table 1* (at baseline, i.e. at the time of the baseline NYHA class assessment, as well as at follow-up, i.e. at the time of the follow-up NYHA class assessment, using wide format),[12] the time between the baseline and follow-up NYHA class assessments, and all-cause mortality as Nelson–Aalen estimate. The incidence and direction of NYHA class transitions were calculated in the full cohort and stratified by EF and inpatient/outpatient status.

### Predictors of NYHA class change trajectories

The independent predictors of NYHA class trajectories were identified by a multivariable multinomial regression model with NYHA class change trajectory as dependent variable, and the variables labelled with an asterisk (*) in *Table 1* as covariates (values collected at baseline, i.e. at the time of the baseline NYHA class assessment). The time between the NYHA class assessments and NYHA class at baseline were included in the models as well. To assess differences in predictors of NYHA improvement and worsening across the EF spectrum, logistic regression models were constructed with the same adjustments as the overall multinomial model, but including also an interaction term between each predictor and EF. Results were reported as odds ratio (OR) with 95% confidence intervals (CI).

### Outcome analyses

The primary outcome of the current analysis was all-cause mortality. Secondary outcomes were CV mortality and first HF hospitalization, with censoring at competing deaths. The outcomes data have full coverage in Sweden but censoring was performed in the event of emigration. The index date for the outcome analysis was defined as the date of the follow-up NYHA class assessment. Event rates per 100 patient-years with 95% CI were calculated and compared across patients with stable versus improved versus worsened NYHA class by the exact Poisson test. To assess the associations between NYHA class trajectory and outcomes, survival functions were illustrated by Kaplan–Meier curves. Multivariable Cox proportional hazards models included the variables labelled with an asterisk (*) in *Table 1* as covariates (with values taken at the index date for the outcome analyses, i.e. the time of the follow-up NYHA class assessment), and the time between NYHA class assessments. Separate models were performed adjusting for NYHA class at either baseline ('baseline model') or follow-up ('follow-up model'). In a third multivariable model ('stratified model'), NYHA class at baseline and follow-up was dichotomized as NYHA class I–II (low) or III–IV (high), and trajectories were analysed as low–low, low–high, high–low, and high–high. Results were reported as hazard ratio (HR) with 95% CI. The differences in the associations between NYHA class change trajectory and outcomes across the EF phenotypes were assessed by including an interaction term between NYHA class trajectory and EF phenotype in the models. Three sensitivity analyses were performed where we considered (1) only patients who were encountered as outpatients both at the baseline and follow-up NYHA class assessments; (2) only patients whose time between NYHA class assessments was <1 year; and (3) only patients with NYHA class II–III at baseline to minimize floor and ceiling effects.

All analyses were performed using the statistical software R version 4.0.4. A two-sided *p*-value <0.05 was considered statistically significant.

# Results

Of 13 535 patients considered for the current analysis, 60.3% had HFrEF, 22.7% had HFmrEF and 17.0% had HFpEF. The median age was 74 (IQR 65–81) years and 32.5% were female.

## NYHA class change trajectories

In the overall population, 9378 (69%) patients experienced no change, 2334 (17%) improved, and 1823 (14%) worsened in NYHA class over 1-year follow-up. Corresponding estimates were 66%, 21%, and 13% in HFrEF; 74%, 12%, and 14% in HFmrEF; and 73%, 12%, and 15% in HFpEF, respectively. The incidence of NYHA class changes in the overall cohort and stratified by EF and inpatient versus outpatient status, as well as changes to and from each NYHA class are depicted in *Figure 1*.

## Patient characteristics by NYHA class trajectories (*Table 1*)

Patients who reported an improvement in NYHA class were younger, had higher income, and more likely had HFrEF at baseline. They were also more often referred to follow-up in specialty care and/or nurse-led HF clinics, and more often prescribed with beta-blockers, renin–angiotensin system inhibitors/angiotensin receptor–neprilysin inhibitors (RASi/ARNi) and mineralocorticoid receptor antagonists (MRA), but less often with diuretics.

Patients with worsened NYHA class had longer HF duration, were more often registered as inpatients, and had a higher comorbidity burden, i.e. anaemia, cancer, diabetes mellitus, ischaemic heart disease, and valvular disease.

For most patient characteristics, patients with stable NYHA class resembled more those with worsened than with improved NYHA class. Similar patterns in patient characteristics were observed across the EF spectrum (online supplementary *Tables S2–S4*), except that in HFpEF the use of RASi/ARNi, beta-blockers, and MRA did not differ by NYHA trajectory.

**Table 1 Patient characteristics at baseline**

| Variable | NYHA worsened | NYHA stable | NYHA improved | *p*-value | Missing |
|---|---|---|---|---|---|
| *n* | 1823 (13.5%) | 9378 (69.3%) | 2334 (17.2%) | | |
| **Sociodemographics** | | | | | |
| Index 2012–2018 (vs. 2000–2011)*† | 903 (49.5%) | 5389 (57.5%) | 1419 (60.8%) | <0.001 | 0.00% |
| Female sex*† | 575 (31.5%) | 3074 (32.8%) | 744 (31.9%) | 0.473 | 0.00% |
| Age, years | 74 (11) | 73 (12) | 69 (12) | <0.001 | 0.00% |
| ≥75 years*† | 985 (54.0%) | 4625 (49.3%) | 851 (36.5%) | <0.001 | 0.00% |
| Income level: lowest tertile*† | 986 (54.2%) | 4934 (52.7%) | 1060 (45.6%) | <0.001 | 0.20% |
| Education: secondary school or less*† | 1529 (85.8%) | 7684 (83.8%) | 1859 (80.9%) | <0.001 | 2.10% |
| Single living*† | 849 (46.7%) | 4270 (45.6%) | 1025 (44.1%) | 0.224 | 0.20% |
| Children*† | 1532 (84.0%) | 7818 (83.4%) | 1933 (82.8%) | 0.578 | 0.00% |
| **Clinical and laboratory variables** | | | | | |
| EF phenotype† | | | | <0.001 | 0.00% |
| HFrEF | 1036 (56.8%) | 5424 (57.8%) | 1707 (73.1%) | | |
| HFmrEF | 444 (24.4%) | 2270 (24.2%) | 355 (15.2%) | | |
| HFpEF | 343 (18.8%) | 1684 (18.0%) | 272 (11.7%) | | |
| Baseline NYHA* | | | | <0.001 | 0.00% |
| I | 494 (27.1%) | 887 (9.5%) | 0 (0.0%) | | |
| II | 1142 (62.6%) | 4885 (52.1%) | 658 (28.2%) | | |
| III | 187 (10.3%) | 3462 (36.9%) | 1523 (65.3%) | | |
| IV | 0 (0.0%) | 144 (1.5%) | 153 (6.6%) | | |
| Follow-up NYHA | | | | <0.001 | 0.00% |
| I | 0 (0.0%) | 887 (9.5%) | 870 (37.3%) | | |
| II | 379 (20.8%) | 4885 (52.1%) | 1368 (58.6%) | | |
| III | 1178 (64.6%) | 3462 (36.9%) | 96 (4.1%) | | |
| IV | 266 (14.6%) | 144 (1.5%) | 0 (0.0%) | | |
| NT-proBNP, pg/L | 2160 [1023–4530] | 1912 [860–4010] | 2346 [1165–4596] | <0.001 | 41.80% |
| NT-proBNP ≥ median (by EF phenotype)*† | 421 (47.1%) | 2377 (43.3%) | 716 (47.5%) | 0.004 | 41.80% |
| HF duration ≥6 months*† | 1045 (58.4%) | 4964 (54.3%) | 875 (38.4%) | <0.001 | 2.40% |
| Mean arterial pressure, mmHg | 90 (13) | 92 (13) | 92 (14) | <0.001 | 0.80% |
| <90 mmHg*† | 875 (48.4%) | 4088 (43.9%) | 1023 (44.3%) | 0.002 | 0.80% |
| Heart rate, bpm | 73 (14) | 73 (15) | 75 (16) | <0.001 | 3.50% |
| ≥70 bpm*† | 1037 (59.6%) | 5180 (57.1%) | 1398 (62.2%) | <0.001 | 3.50% |
| Body mass index, kg/m$^2$ | 28 (5) | 28 (5) | 28 (6) | 0.356 | 37.30% |
| ≥30 kg/m$^2$ (obese)*† | 329 (28.7%) | 1651 (28.1%) | 415 (28.3%) | 0.915 | 37.30% |
| eGFR, ml/min/1.73 m$^2$ | 59 [44–77] | 63 [47–80] | 68 [51–84] | <0.001 | 1.20% |
| <60 ml/min/1.73 m$^2$*† | 943 (52.4%) | 4174 (45.1%) | 841 (36.4%) | <0.001 | 1.20% |
| Haemoglobin, g/dl | 13.3 (1.7) | 13.4 (1.7) | 13.7 (1.7) | <0.001 | 3.80% |
| Potassium, mmol/L | 4 (0) | 4 (0) | 4 (0) | 0.093 | 19.20% |
| Comorbidities | | | | | |
| Peripheral arterial disease*† | 155 (8.5%) | 738 (7.9%) | 133 (5.7%) | 0.001 | 0.00% |
| Stroke/transient ischaemic attack*† | 313 (17.2%) | 1472 (15.7%) | 295 (12.6%) | <0.001 | 0.00% |
| Anaemia*† | 619 (35.1%) | 2640 (29.3%) | 558 (25.0%) | <0.001 | 3.80% |
| Cancer in past 3 years*† | 271 (14.9%) | 1275 (13.6%) | 256 (11.0%) | <0.001 | 0.00% |
| Liver disease*† | 48 (2.6%) | 165 (1.8%) | 56 (2.4%) | 0.015 | 0.00% |
| Major bleeding*† | 306 (16.8%) | 1469 (15.7%) | 300 (12.9%) | 0.001 | 0.00% |
| Diabetes mellitus*† | 455 (25.0%) | 2143 (22.9%) | 474 (20.3%) | 0.001 | 0.00% |
| Atrial fibrillation*† | 864 (47.4%) | 4197 (44.8%) | 963 (41.3%) | <0.001 | 0.00% |
| Hypertension*† | 821 (45.0%) | 3951 (42.1%) | 961 (41.2%) | 0.032 | 0.00% |
| Chronic obstructive pulmonary disease*† | 243 (13.3%) | 1182 (12.6%) | 252 (10.8%) | 0.026 | 0.00% |
| Ischaemic heart disease*† | 250 (13.7%) | 1192 (12.7%) | 244 (10.5%) | 0.003 | 0.00% |
| Valvular disease*† | 369 (20.2%) | 1709 (18.2%) | 361 (15.5%) | <0.001 | 0.00% |

**Table 1 (Continued)**

| Variable | NYHA worsened | NYHA stable | NYHA improved | *p*-value | Missing |
|---|---|---|---|---|---|
| **Organization** | | | | | |
| Caregiver: inpatient*† | 755 (41.4%) | 2334 (24.9%) | 632 (27.1%) | <0.001 | 0.00% |
| Planned follow-up: specialty care (vs. primary care/other)*† | 1170 (66.3%) | 6202 (68.3%) | 1863 (82.4%) | <0.001 | 3.20% |
| Referral to follow-up in a nurse-led HF unit*† | 1175 (67.1%) | 7025 (77.7%) | 1868 (83.0%) | <0.001 | 3.60% |
| **Treatments** | | | | | |
| Beta-blockers*† | 1591 (87.6%) | 8283 (88.5%) | 2125 (91.3%) | <0.001 | 0.20% |
| RASi/ARNi*† | 1563 (87.0%) | 8374 (90.0%) | 2136 (92.7%) | <0.001 | 0.90% |
| Mineralocorticoid receptor antagonists*† | 630 (34.7%) | 3114 (33.3%) | 900 (38.7%) | <0.001 | 0.40% |
| Diuretics*† | 1442 (79.4%) | 7110 (76.0%) | 1768 (75.9%) | 0.007 | 0.30% |
| Digoxin*† | 254 (14.0%) | 1274 (13.6%) | 348 (14.9%) | 0.248 | 0.20% |
| Nitrates*† | 283 (15.6%) | 1224 (13.1%) | 183 (7.9%) | <0.001 | 0.30% |
| Anticoagulants*† | 879 (48.4%) | 4506 (48.2%) | 1106 (47.5%) | 0.797 | 0.30% |
| Antiplatelets*† | 807 (44.5%) | 3840 (41.0%) | 925 (39.7%) | 0.006 | 0.30% |
| Statins*† | 959 (52.7%) | 4887 (52.2%) | 1116 (48.0%) | 0.001 | 0.30% |
| Cardiac resynchronization therapy*† | 103 (5.8%) | 390 (4.4%) | 90 (4.0%) | 0.01 | 4.00% |
| Implantable cardioverter-defibrillator*† | 135 (7.6%) | 548 (6.1%) | 116 (5.1%) | 0.004 | 4.00% |

Summary statistics based on unimputed data. Data are presented as absolute (relative) frequencies, mean (± standard deviations), and median [interquartile range], and compared by Chi-squared-test, ANOVA, and Kruskal–Wallis test, respectively.
ARNi, angiotensin receptor–neprilysin inhibitor; EF, ejection fraction; eGFR, estimated glomerular filtration rate (calculated by the 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; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RASi, renin–angiotensin system inhibitor.
*Multiple imputation models included labelled variables (with values taken both at baseline, i.e. the time of the baseline NYHA class assessment, and at follow-up, i.e. the time of the follow-up NYHA class assessment), time between NYHA class measurements, all-cause mortality as Nelson–Aalen estimator, and were stratified by EF phenotype.
†Labelled variables were included in the multinomial regression model assessing independent predictors of NYHA class change (with values taken at baseline, i.e. the time of the baseline NYHA class assessment) and the adjusted Cox proportional hazards models (with values taken at follow-up, i.e. the time of the follow-up NYHA class assessment).

## Independent predictors of NYHA class trajectory

Independent predictors of NYHA class improvement were a more recent registration in SwedeHF and referral to follow-up in specialty care, whereas longer HF duration, older age, having HFmrEF versus HFrEF, and the presence of several comorbidities such as chronic obstructive pulmonary disease, atrial fibrillation, and diabetes mellitus were associated with lower likelihood of an improvement (*Figure 2*). Independent predictors of worsening NYHA class included a registration as inpatient, renal disease, lower blood pressure, older age, use of diuretics, and longer HF duration, whereas HFpEF and HFmrEF versus HFrEF, follow-up in a nurse-led HF clinic, and a more recent registration in SwedeHF were independently associated with lower likelihood of worsening in NYHA class (*Figure 3*).

Predictors were mostly consistent across the EF spectrum, with some exceptions (online supplementary *Tables S5* and *S6*). The association between HF duration and lower likelihood of improving NYHA class, as well as with greater likelihood of worsening NYHA class, was stronger in HFrEF versus HFmrEF versus HFpEF ($p$-interaction = 0.004 and 0.011 for improving and worsening, respectively). Follow-up in specialty care was associated with improving NYHA class in HFrEF and HFmrEF, but not HFpEF ($p$-interaction = 0.038). Implantable cardioverter-defibrillator (CD) use was associated with lower likelihood of improving NYHA class in HFrEF, but not in HFmrEF or HFpEF ($p$-interaction = 0.011). Moreover, both ICD and cardiac resynchronization therapy (CRT) use were associated with worsening NYHA class in HFrEF, but not HFmrEF or HFpEF ($p$-interaction = 0.002 and < 0.001 for ICD and CRT use, respectively).

## Association between NYHA class trajectories and morbidity/mortality

Kaplan–Meier curves and crude association with outcomes by NYHA class trajectory in the overall population are depicted in *Figure 4*. Median follow-up for the outcome analysis, with the second NYHA class assessment as index date, was 2.9 (IQR 1.4–5.5) years. Among patients with unchanged, improved, and worsened NYHA class, respectively, event rates for all-cause mortality were 12.6 (95% CI 12.2–13.0), 8.4 (95% CI 7.9–9.0), and 18.5 (95% CI 17.4–19.6) per 100 patient-years, respectively (online supplementary *Table S7*). As compared to stable NYHA class, an improvement in NYHA class was associated with lower crude risk, and a worsening in NYHA class with higher crude risk of all outcomes.

*Figure 5* presents the independent association between NYHA class change trajectory and outcomes, as assessed by the baseline model (adjusted for patient characteristics, the time between NYHA class assessments, and NYHA class at baseline), follow-up

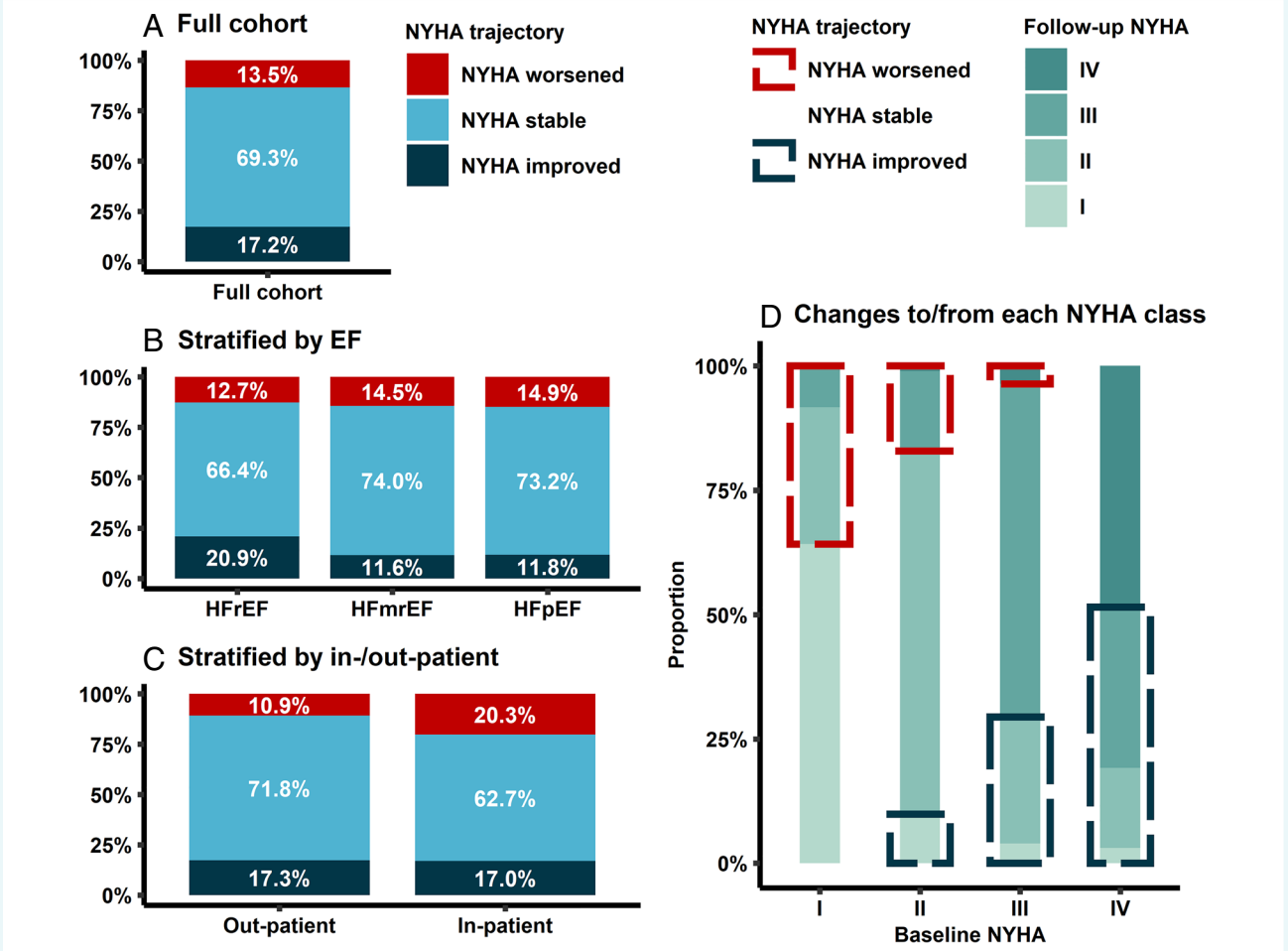



**Figure 1** Changes in New York Heart Association (NYHA) class in the full cohort (*A*), stratified by ejection fraction (EF) (*B*) and by inpatient/outpatient status (*C*), and to and from each NYHA class (*D*).

model (adjusting for NYHA class at follow-up instead of at baseline), and stratified model (same adjustments as in the follow-up model).

In the baseline model, as compared with stable NYHA class over time, an improvement in NYHA class was associated with lower all-cause mortality, CV mortality, and risk of first HF hospitalization (adjusted HR [95% CI]: 0.70 [0.65–0.76], 0.68 [0.61–0.75] and 0.66 [0.60–0.72], respectively), whereas a worsening in NYHA class was associated with higher risk of all these outcomes (1.45 [1.34–1.56], 1.57 [1.43–1.72] and 1.51 [1.39–1.64], respectively). As a one-time assessment, NYHA class at baseline independently predicted risk on top of NYHA class trajectories for all-cause mortality (adjusted HR [95% CI] vs. NYHA class I: class II, 1.37 [1.23–1.53]; class III, 2.06 [1.84–2.31]; class IV, 2.69 [2.26–3.22]), CV mortality (class II, 1.45 [1.26–1.67]; class III, 2.35 [2.03–2.73]; class IV, 3.22 [2.58–4.01]), and first HF hospitalization (class II, 1.35 [1.20–1.52]; class III, 1.90 [1.67–2.16]; class IV, 2.28 [1.86–2.80]).

In the follow-up model there was no significant association between NYHA class change and outcomes. NYHA class at follow-up independently predicted risk on top of NYHA class trajectories for all-cause mortality (adjusted HR [95% CI] vs. NYHA class I: class II, 1.27 [1.14–1.41]; class III, 1.89 [1.68–2.12]; class IV, 3.22 [2.74–3.79]), CV mortality (class II, 1.30 [1.12–1.50]; class III, 2.07 [1.78–2.41]; class IV, 3.87 [3.17–4.73]), and first HF hospitalization (class II, 1.35 [1.20–1.52]; class III, 1.97 [1.73–2.24]; class IV, 2.44 [2.02–2.96]).

In the stratified model, with low–low (i.e. having NYHA class I–II both at baseline and follow-up) as reference, high–low (i.e. transitioning from NYHA class III–IV at baseline to I–II at follow-up) was not associated with any outcome. Low–high and high–high were both associated with highest risk of all-cause mortality (adjusted HR [95% CI] vs. low–low: low–high, 2.80 [2.37–3.30]; high–high, 3.10 [2.66–3.61]), CV mortality (low–high, 3.26 [2.65–4.00]; high–high, 3.67 [3.04–4.43]), and HF hospitalization (low–high, 2.62 [2.16–3.17]; high–high, 2.52 [2.11–3.02]).

Survival curves by EF category are presented in online supplementary *Figure S1*. There was no interaction between NYHA class change and EF after adjusting for patient characteristics and NYHA class at follow-up (online supplementary *Table S8*). The sensitivity

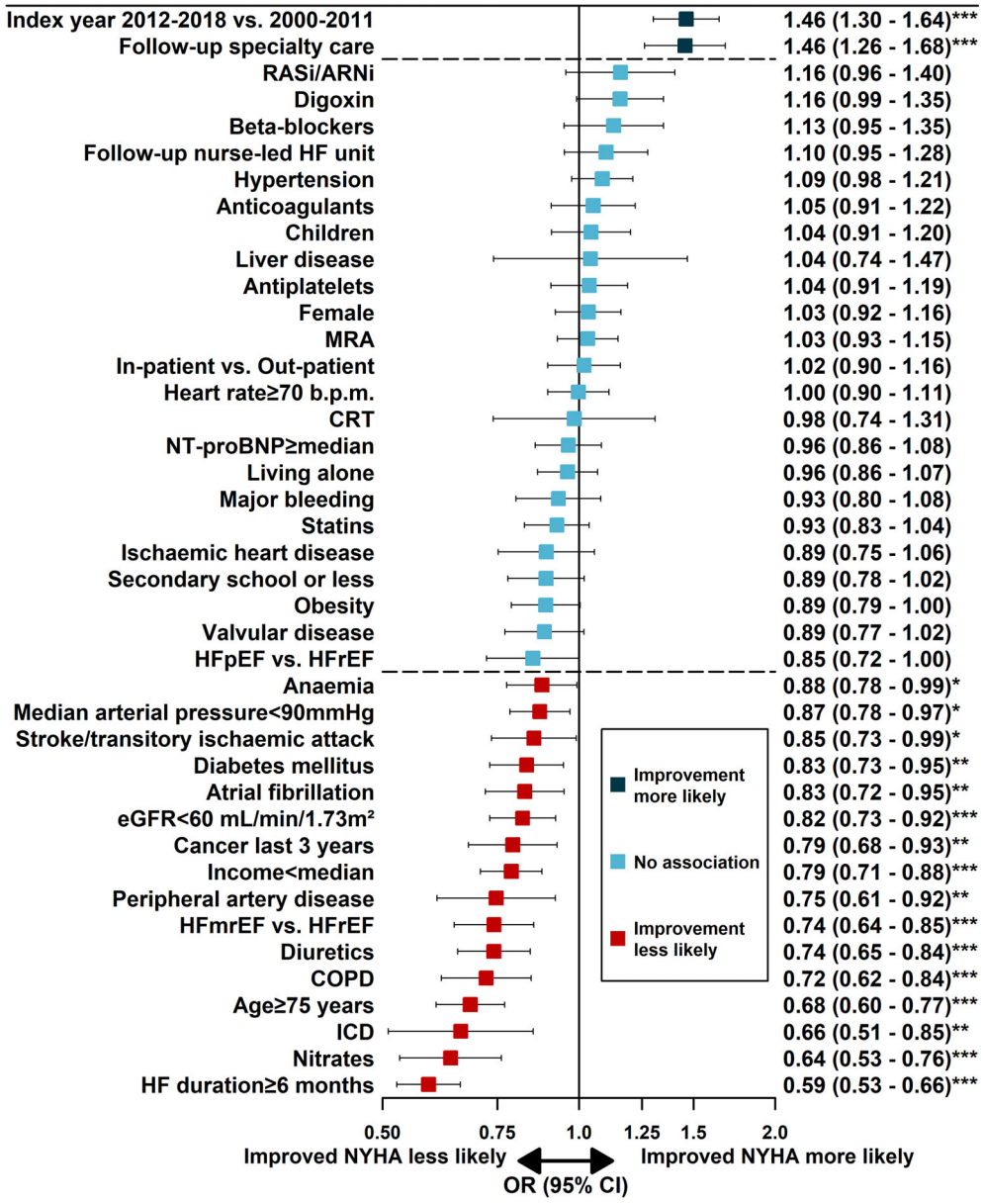



**Figure 2** Predictors of New York Heart Association (NYHA) class improvement. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$. Multivariable multinomial model included the variables labelled with a dagger (†) in *Table 1*, the time between NYHA class assessments, and NYHA class at baseline as covariates. The full model, including non-significant predictors, is shown in online supplementary *Table S5*. ARNi, angiotensin receptor–neprilysin inhibitor; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate (calculated by the 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 antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OR, odds ratio; RASi, renin–angiotensin system inhibitor.

analyses considering (1) only those patients whose NYHA class baseline and follow-up assessment was performed in an outpatient setting (online supplementary *Table S9*), (2) patients with <1 year between NYHA class assessments (online supplementary *Table S10*), and (3) patients with NYHA class II–III at baseline (online supplementary *Table S11*) showed consistent results.

## Discussion

In this nationwide real-world HF population, we observed that: (i) the majority of patients in all the EF categories reported no change in NYHA class, whereas 17% improved and 14% worsened over a median follow-up time of approximately 1 year; (ii) a follow-up

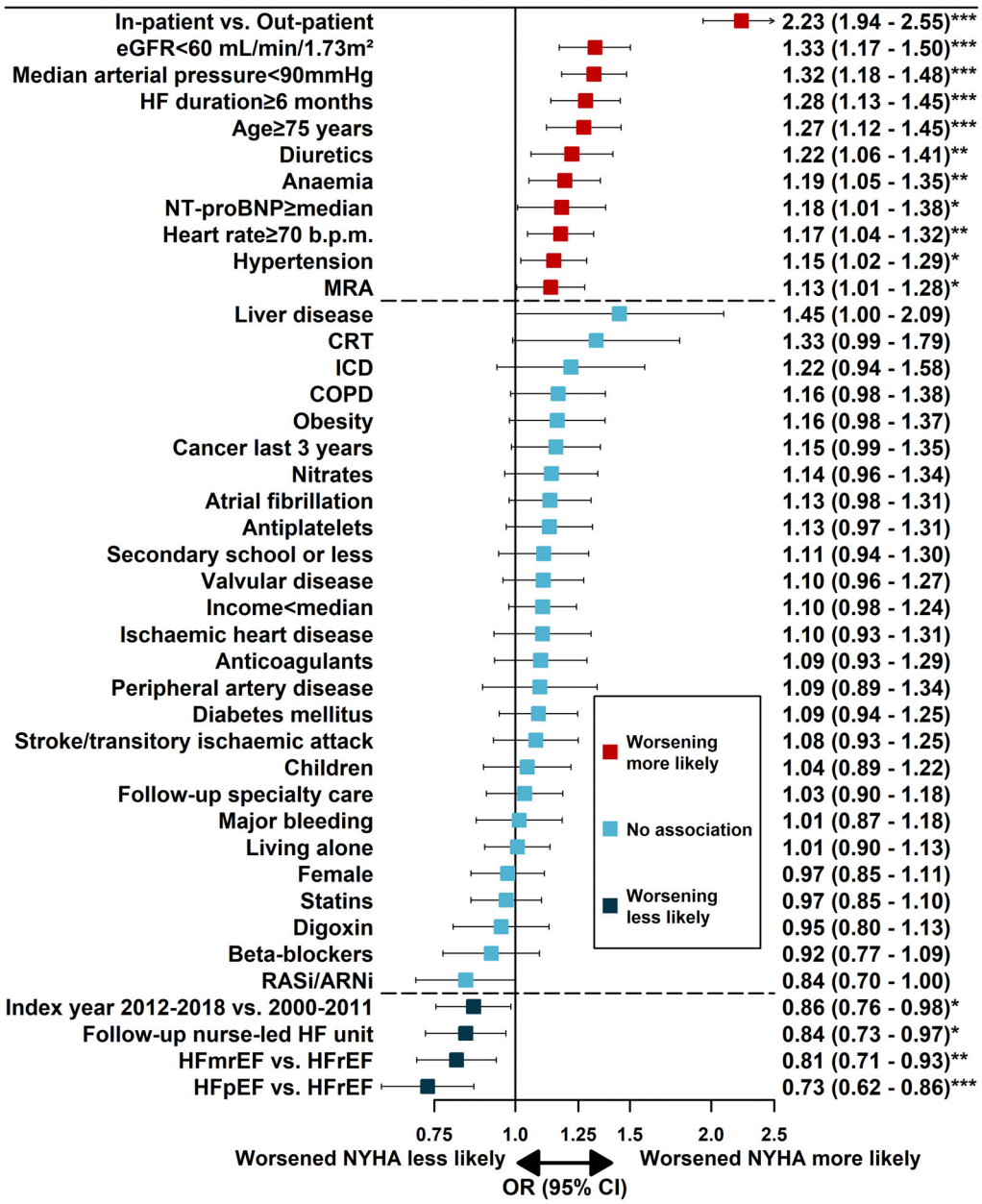



**Figure 3** Predictors of New York Heart Association (NYHA) class worsening. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$. Multivariable multinomial model included the variables labelled with a dagger (†) in *Table 1*, the time between NYHA class assessments, and NYHA class at baseline as covariates. The full model, including non-significant predictors, is shown in online supplementary *Table S6*. ARNi, angiotensin receptor–neprilysin inhibitor; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate (calculated by the 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 antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OR, odds ratio; RASi, renin–angiotensin system inhibitor.

in specialty care predicted improvement in NYHA class, whereas inpatient status, renal disease, lower blood pressure, older age, and longer HF duration, predicted a worsening in NYHA class; (iii) NYHA class improvement was associated with lower and NYHA class worsening with higher crude mortality and HF hospitalization risk; (iv) the prognostic role of NYHA trajectories was independent of baseline NYHA class value, but explained by the resulting NYHA class at follow-up; and (v) follow-up NYHA assessment predicted mortality/risk of HF hospitalization independently of NYHA trajectories (*Graphical Abstract*).

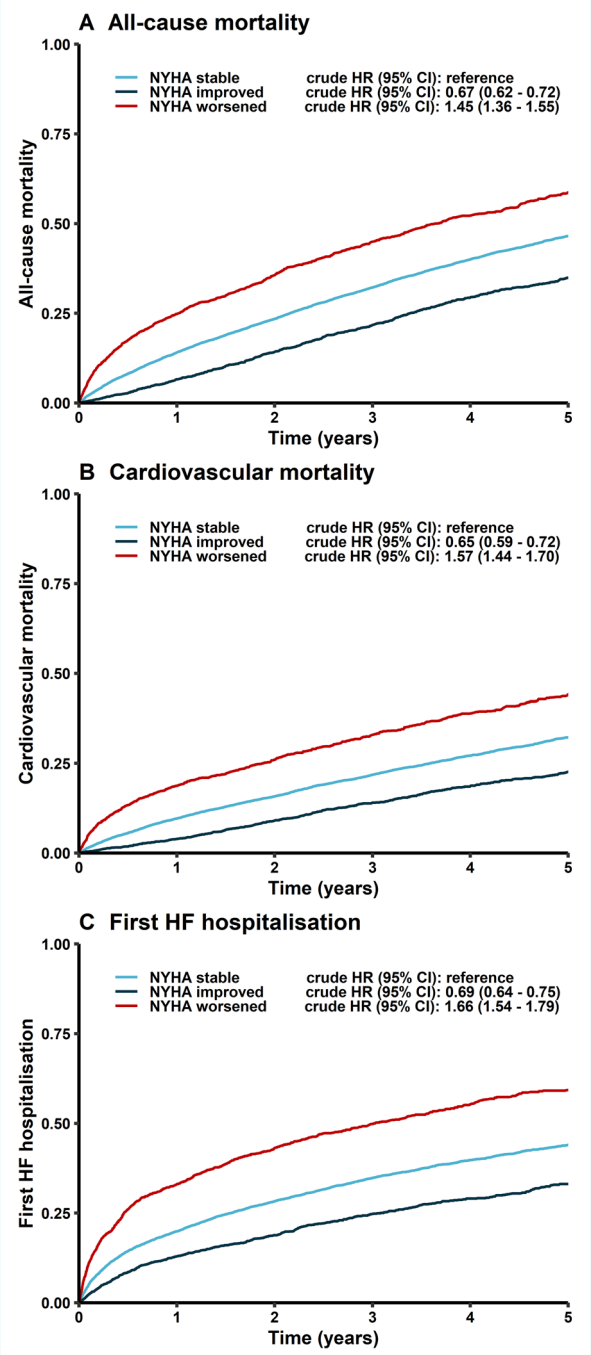



**Figure 4** Kaplan–Meier curves for (*A*) all-cause mortality, (*B*) cardiovascular mortality, and (*C*) first heart failure (HF) hospitalization by New York Heart Association (NYHA) class change trajectory. CI, confidence interval; HR, hazard ratio.

## Predictors of NYHA class trajectories

Evidence on NYHA class trajectories over time in a real-world setting is limited, and to the best of our knowledge, no study has been performed considering the different EF phenotypes. In the overall cohort of the present study, 17% improved and 14% worsened in NYHA class, whereas the majority remained stable. Our findings in patients with HFrEF, where 21% showed an improved and 13% a worsened NYHA class at the follow-up assessment, were consistent with the CHAMP-HF registry including 2872 outpatients with HFrEF from the US.[7] Across the EF spectrum, the NYHA class trajectories in HFrEF stood out as the most favourable, with a crude nearly two-fold higher proportion of patients experiencing an improvement compared with HFmrEF and HFpEF, and more patients experiencing a worsening in NYHA class (15%) in HFpEF and HFmrEF compared with HFrEF. These findings might be explained by (i) the benefit linked with use of evidence-based treatments in HFrEF,[13] and lack of life-saving treatments for HFpEF and not implemented use of RASi/beta-blockers/MRA for HFmrEF during the time period considered by the current analysis[4]; (ii) differences in patient characteristics, such as older age and greater comorbidity burden associated with higher EF. Consistently, after multivariable analyses, both HFmrEF and HFpEF versus HFrEF were associated with lower likelihood of worsening NYHA class. However, it is also possible that our findings might underestimate the proportion of improved/worsened versus stable functional status over time. In HFrEF, clinician-assessed changes in NYHA class occur rarely, despite significant variations in patient-reported outcomes as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ),[7] highlighting that the NYHA classification may be less sensitive in detecting changes in clinical status than the KCCQ. However, an alternative explanation is that clinical inertia might contribute to a lag in NYHA re-classification but play a lesser role in patient-reported outcomes. Conversely, in HFpEF, where comorbidities are more common,[14] a change in functional status might be attributed to non-HF causes rather than to HF. The finding that patients with HFmrEF were also less likely to improve in NYHA class might seem counterintuitive at first glance, but might possibly reflect that some of these patients have partially recovered EF following successful HFrEF treatment or an EF reduction due to reversible causes, e.g. atrial fibrillation or ischaemic heart disease, and thus they may have limited room left for further improvement.

Patients who were referred to follow-up in specialty care, a nurse-led HF unit, and enrolled in the registry at a later date were more likely to experience overall more favourable NYHA class trajectories. These findings are consistent with previous reports of better outcomes and care associated with specialty care,[15,16] nurse-led HF units,[17] and temporal improvements in outcomes over the past decades also linked with the availability of further HF treatments.[18] Patients who were older and burdened by multi-comorbidity experienced less favourable NYHA class trajectories. This might reflect an adverse impact of age and comorbidities on HF progression, but possibly also a patient profile where the continuation of evidence-based HF treatments is hard to achieve or clinical inertia is more frequent.[19]

Previous reports showed that several markers of HF severity, e.g. inpatient care, hypotension, and longer HF duration, predicted EF decrease and/or lower likelihood of EF recovery.[20] Consistently, we found that these characteristics, along with lower EF, also predicted poor NYHA class trajectories. Overall, these findings indicate that HF severity and duration also entail continued worsening, highlighting the importance of an early initiation of HF treatments.[4]

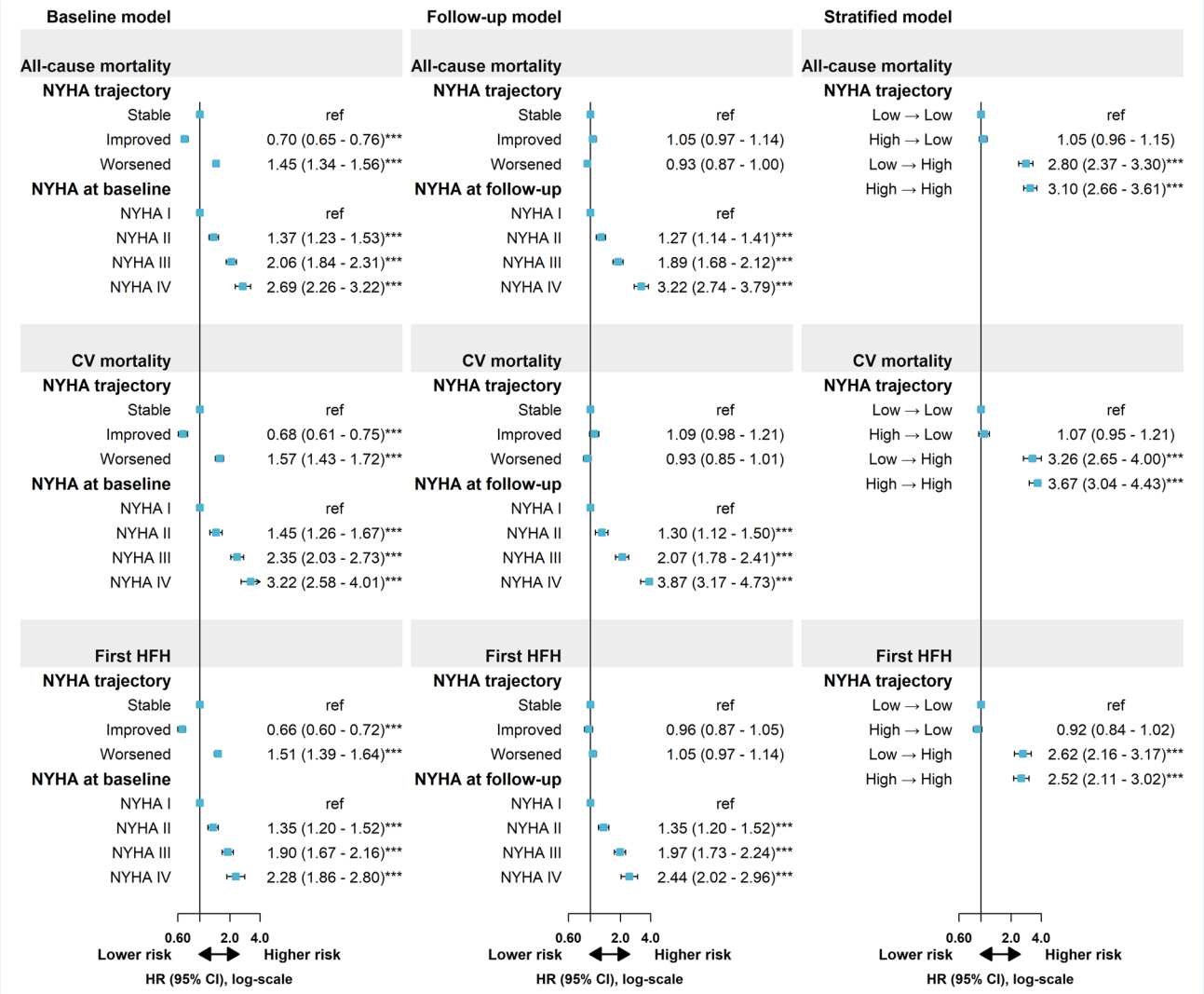



**Figure 5** Association between New York Heart Association (NYHA) class change and outcomes. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$. Adjusted hazard ratios (HR) with 95% confidence intervals (CI) for the association between longitudinal change in NYHA class and outcomes were calculated by multivariable Cox regression. Baseline model: adjusted for variables labelled with a dagger (†) in *Table 1*, the time between the NYHA class assessments, and NYHA class at baseline. Follow-up model: adjusted for variables labelled with a dagger (†) in *Table 1*, the time between the NYHA class assessments, and NYHA class at follow-up. Stratified model: low = NYHA class I–II; high = NYHA class III–IV; adjusted for variables labelled with a dagger (†) in *Table 1*, the time between the NYHA class assessments, and NYHA class at follow-up. CV, cardiovascular; HFH, heart failure hospitalization.

We identified few predictors that were influenced by EF in their association with NYHA class trajectories. However, one pattern that stood out was that CRT use was strongly associated with unfavourable trajectories in HFrEF, but not in HFmrEF or HFpEF. In a real-world setting, potential confounding by indication and reverse causation must be considered when approaching the interpretation of results. Since the evidence and indication for CRT use is limited to patients with HFrEF,[4,21] the presence of such devices in patients with HFmrEF/HFpEF suggests successful reverse remodelling following implantation, whereas their presence in patients with HFrEF might suggest no or later response.

## NYHA class trajectories and outcomes

Across the EF spectrum, our data showed that the prognostic role of NYHA class changes in terms of mortality and risk of HF hospitalization was independent of several patient characteristics including also the baseline NYHA class assessment, but not of follow-up NYHA class. Thus, the association with prognosis was mostly explained by the resulting state of the patient, rather than the trajectory of change. For the clinician who aims to assess patients' prognosis based on reported symptoms, the implication of our results is that repeating NYHA assessment is useful to obtain the most updated view of the patient's status, but that

the assessment of change across encounters adds little prognostic information.

A meaningful trial surrogate endpoint should be able to gauge the risk of hard outcomes, such as hospitalizations or death, or evaluate changes in clinical status.[22] In HF trials, the approach to NYHA class as surrogate endpoint has varied from comparing the follow-up value across study arms,[23,24] to comparing trajectories (i.e. improvement or worsening) from each patient's baseline value.[25,26] Although it is known that higher NYHA class predicts hard outcomes,[2,3] our findings highlight that changes in NYHA trajectories are less prognostically relevant compared with the last known value as a surrogate for long-term risk outcome.

It has been previously reported that an improvement in NYHA class would not predict lower mortality in patients with HFrEF, but that improvements in the KCCQ would.[7] Also, patient-reported outcomes might correlate to changes in clinical status with greater sensitivity than NYHA class.[27] Greater discordance between NYHA class and patient-derived scores might be observed in HFpEF.[28] The complementing use of patient-centred measures with NYHA class assessment might be a relevant approach for optimizing prognostic assessment. Consistently, in a recent analysis from the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) study reported that worsening of a clinical composite endpoint, combining NYHA class changes with a patient global assessment, was highly predictive of subsequent mortality.[29]

## Strengths and limitations

One major strength of the present study was the large sample size and the use of a well-characterized real-world cohort of HF patients across the entire EF spectrum, enabling analyses across the EF spectrum, extensive adjustments for potential confounders and a detailed analysis of predictors of NYHA class trajectories. However, some limitations warrant discussion. First, as in any observational study, residual confounding cannot be ruled out. Second, the assessment of NYHA class was done at the clinician's discretion, and not at pre-specified time points, potentially resulting in a higher likelihood of NYHA class change in patients with a longer time between NYHA class assessments, and patients with repeated NYHA class evaluations in the short term being sicker. We aimed to mitigate this by limiting the allowed time interval and adjusting for the time between NYHA class assessments, and by performing a sensitivity analysis separately in those patients with a shorter follow-up time. Third, the NYHA classification is subject to floor and ceiling effects, since those with class I cannot improve, and those with class IV cannot worsen. This was addressed by a separate sensitivity analysis where patients with NYHA classes I and IV were excluded. Lastly, the assessment of NYHA class itself is subject to significant inter-clinician variation and subjective in nature.[30]

# Conclusion

In a large real-world population, 17% of patients improved and 14% worsened in NYHA class over 1-year follow-up. Across the EF spectrum, NYHA class changes predicted mortality/morbidity independently of patient characteristics including baseline NYHA class, but not of last known NYHA class, whereas one-time NYHA class assessment predicted mortality/morbidity independently of NYHA trajectories. These findings suggest that one-time NYHA assessment might outweigh NYHA class trajectories as a prognostic marker in clinical practice and as a clinical trial endpoint.

# Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Conflict of interest**: L.H.L. reports research grants from AstraZeneca, Novartis, Boerhinger Ingelheim, Vifor-Fresenius, and Boston Scientific, and consulting or speaker's honoraria from AstraZeneca, Novartis, Boehringer Ingelheim, Vifor-Fresenius, Bayer, Sanofi, Merck, Myokardia, Orion Pharma, MedScape, Radcliffe Cardiology, Lexicon, and Respicardia, and stock ownership in AnaCardio, outside the submitted work. U.D. reports research grants from AstraZeneca, Pfizer, Vifor, Boehringer Ingelheim, Boston Scientific, Roche Diagnostics and consultancies/honoraria from Amgen, Pfizer and AstraZeneca, all ouside the submitted work. P.K. reports personal fees from AstraZeneca. C.L. reports consulting fees from AstraZeneca, Roche Diagnostics, Bayer and speaker honoraria from Novartis, Astra, Bayer, Medtronic, Impulse Dynamics, Boehringer Ingelheim and Vifor. G.S. reports grants and personal fees from Vifor, AstraZeneca, grants and non-financial support from Boehringer Ingelheim, personal fees from Società Prodotti Antibiotici, Roche, Servier, GENESIS, Cytokinetics, Medtronic, grants from Novartis, Boston Scientific, PHARMACOSMOS, Merck, Bayer, outside the submitted work. All other authors have nothing to disclose.

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