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RESEARCH ARTICLE

Changes in 6-min walk test is an independent predictor of death in chronic heart failure with reduced ejection fraction

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Aims Functional capacity provides important clinical information in patients with heart failure (HF) and reduced ejection fraction (HFrEF). The 6-min walk test (6MWT) is a simple and inexpensive tool for assessing functional capacity and risk. Although change in 6MWT is frequently used as a surrogate outcome in HF trials, the association with mortality is unclear. We aimed to assess the prognostic importance of changes in 6MWT.

Methods and results Patients with chronic HFrEF referred to HF outpatient clinics in Norway completed a 6MWT at the first visit (baseline) and at a stable follow-up visit after treatment optimization (follow-up). Absolute and relative changes in 6MWT were analysed in association with mortality risk using Cox regression models and flexible cubic splines. The study included 3636 HFrEF patients aged 67.3 ± 11.6 years, 23% women, with left ventricular ejection fraction 30 ± 7%. At baseline, mean 6MWT was 438 ± 125 m, median N-terminal pro-B-type natriuretic peptide (NT-proBNP) 1574 (732–3093) ng/L, and 27% had New York Heart Association (NYHA) class III/IV. After optimization of guideline-directed medical therapy (median 147 [86–240] days), 6MWT increased by mean 40 ± 74 m, NT-proBNP decreased by median 425 (14–1322) ng/L, and NYHA class improved in 38% of patients. Patients with greater improvements in 6MWT were younger, with greater improvements in NYHA class ($r = 0.27$, $p < 0.001$) and larger reductions in NT-proBNP concentrations ($r = 0.19$, $p < 0.001$). After mean 845 ± 595 days, 419 (11.5%) patients were dead. Both absolute and relative changes in 6MWT were non-linearly associated with survival, attenuating as 6MWT increased. A 50 m increase in 6MWT was associated with a 17% lower mortality risk (hazard ratio 0.84, 95% confidence interval 0.77–0.90, $p < 0.001$) in the fully adjusted model, including changes in NYHA class, NT-proBNP concentrations, and other established risk factors. The associations were more pronounced in patients with lower baseline 6MWT and higher age.

Conclusion Improvement in 6MWT in patients with HFrEF is associated with increased survival, independent of changes in NT-proBNP and NYHA class. These findings support 6MWT change as a surrogate outcome in HF trials.

Keywords Heart failure • 6-min walk test • Heart failure with reduced ejection fraction • Prognosis • Guideline-directed medical therapy

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Introduction

The 6-min walk test (6MWT) is a strong independent marker of risk and predictor of death in patients with heart failure (HF).[1–3] The prognostic impact of changes in 6MWT is less well studied.[4] Despite limited clinical documentation, changes in 6MWT are widely used as clinical endpoints in HF trials.[5–7] No study has compared the prognostic value of changes in 6MWT with changes in natriuretic peptides or alterations in functional class as survival predictors in HF patients. The minimal clinically important difference (MCID) in 6MWT change has been suggested to be between 15 and 35 m.[8–11] However, the MCID in 6MWT in chronic HF patients is still unclear. During cardiac rehabilitation or up-titration of guideline-directed medical therapy (GDMT) after an acute HF event, a 6MWT increase of more than 50–80 m has been proposed as a prognostic cutoff.[4,12,13] However, the MCID has not been validated in the up-titration of GDMT in stable chronic HF patients. Due to the limited data, there is a need for additional clinical studies to assess the prognostic importance of changes in 6MWT.

The primary aim of the present study was to determine the prognostic ability of changes in 6MWT to predict mortality in stable patients with HF and reduced ejection fraction (HFrEF) after adjusting for changes in N-terminal pro-B-type natriuretic peptide (NT-proBNP) and New York Heart Association (NYHA) functional class. The secondary aim was to identify predictors of changes in 6MWT.

Methods

Patient population

All chronic HF outpatients referred to HF clinics in Norwegian hospitals are included in the National Norwegian Heart Failure Registry (NNHFR). The registry includes data from 40 HF clinics (100% of all HF clinics in Norway), and data from 2013 through 2020 were retrospectively collected for the current analysis. The HF clinics are led by specially trained nurses collaborating closely with cardiologists. All patients had previously been diagnosed with chronic HF of any aetiology, according to current guidelines.[14] Patients were invited to serial visits focusing on titration of GDMT to maximally tolerated doses, i.e. beta-blockers, angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), angiotensin receptor–neprilysin inhibitors (ARNI) and mineralocorticoid receptor antagonists (MRA). Sodium–glucose cotransporter 2 inhibitors were not a standard treatment for HF during this study period. The number of visits and the time needed to reach the target doses varied depending on the clinical setting, and the end of the titration period was defined as when doses were up-titrated to the target dose as defined by the European Society of Cardiology HF guidelines,[14] or to maximally tolerated doses if that was not possible. Patients underwent a structured interview, a physical examination, blood sampling, and a 6MWT at the first and last up-titration visit. Estimated glomerular filtration rate (eGFR) was calculated by the Chronic Kidney Disease Epidemiology Collaboration equation using serum creatinine. The Roche immunoassay measured NT-proBNP in blood samples at each institution (Roche Diagnostics, Rotkreuz, Switzerland). The 6MWT was conducted following a standardized protocol where patients were instructed to walk at a self-selected pace in a suitable space (e.g. a corridor) of 20 to 50 m in length for 6 min. The total distance ambulated during 6 min of continuous walking, or until exhaustion, was measured to the nearest meter. To avoid performance bias from the HF nurse, all testers were instructed only to use neutral phrases like 'You are doing well' and 'Keep up the good work' to inspire performance. Medical history was collected by reviewing medical records and interviewing the patient. Mortality data were obtained continuously from the Norwegian national registry and automatically recorded in the NNHFR, and no patients were lost to follow-up concerning mortality. The National Institute of Public Health is responsible for correct information and ensuring that the data processed in the registry are correct, relevant, and necessary. The study complies with the Declaration of Helsinki. The study was approved as exempt from assessment by the Regional Committee for Health Research Ethics as the analyses were conducted on an anonymized data set.[1]

In the current study, we included all patients in the NNHFR who performed a 6MWT at the first visit (baseline) and at the visit when patients were stable on maximal tolerated doses of GDMT (follow-up). Patients with a left ventricular ejection fraction (LVEF) >40% ($n = 810$) were excluded. We also excluded patients with missing NT-proBNP measurements ($n = 431$) for the main analysis. These patients were from centres that used B-type natriuretic peptide (BNP) instead of NT-proBNP and were included in sensitivity analyses using conversion and imputation, as described below.

Statistical analysis

Values are reported as number (%), mean ± standard deviation for normally distributed variables, and median (quartile 1 to quartile 3) for skewed variables. The chi-square test was used to compare categorical variables, ANOVA was used for parametric continuous variables, and the Kruskal–Wallis test was used for non-parametric continuous variables. Absolute changes in 6MWT were calculated by subtracting the baseline visit value from the value at the last up-titration follow-up visit. Time at risk for the survival analysis was started on the day of the last up-titration follow-up visit when the last 6MWT was conducted. Changes in 6MWT were assessed both as a continuous variable (per 50 m increase) and as an ordinal variable (quartiles). Changes in NYHA class were stratified into three groups: 'stable' (no change in NYHA class), 'improved' (any improvement in NYHA class), or 'worsened' (any worsening of NYHA class). Using Cuzick's test, clinical characteristics were compared for trends across 6MWT quartiles. Spearman correlation was used to assess the associations between changes in 6MWT, NYHA class, and NT-proBNP. Unadjusted and adjusted Cox proportional hazard regression models were used to examine the associations between changes in 6MWT and time to all-cause death. Adjustment covariates were collected from the baseline visit, and multivariable model 1 was adjusted for age, sex, and baseline 6MWT. Multivariable model 2 was adjusted for the variables in model 1 in addition to baseline body mass index (BMI), smoking, HF aetiology, history of hypertension, diabetes, stroke, anaemia, chronic obstructive pulmonary disease or asthma, and cancer in addition to changes from the first visit to stable follow-up in blood pressure, eGFR, haemoglobin, potassium, doses of GDMT, NYHA class, and log-transformed NT-proBNP. A sensitivity analysis that included the duration of the titration period (log-transformed) as a covariate, in addition to model 2, was also conducted. Multiple regressions were performed as a complete case analysis, and 10 patients were excluded in the fully adjusted Cox regression model due to missing smoking status ($n = 2$), history of anaemia ($n = 4$), BMI ($n = 1$), eGFR ($n = 1$), and potassium

level ($n = 4$). The proportional hazards assumption was tested by Schoenfeld and scaled Schoenfeld residuals, and none of the models showed significant violations of proportionality. Linear regression and restricted cubic splines with 3–7 knots were used to assess and visualize the continuous association between changes in 6MWT (absolute and relative changes) and mortality. The best model fit was selected based on Akaike's information criterion and models were compared using the likelihood-ratio test. Interaction analyses were performed for five pre-specified variables: baseline 6MWT, sex, age, BMI, and eGFR. We performed two sensitivity analyses to assess the possible impact of excluding patients with BNP instead of NT-proBNP concentrations. First, we calculated NT-proBNP concentrations based on available BNP concentrations by multiplying BNP with 6.25 as this is the ratio found in large HFrEF cohorts.[15] Second, we imputed the missing NT-proBNP values using chained multiple imputations with predictive mean matching for the five closest neighbours with 20 imputations per missing variable. All statistical analyses were done using Stata Software (version 17, Stata Corp., College Station, TX, USA). A two-sided p-value of <0.05 was considered statistically significant.

Results

Baseline characteristics

Among 3636 patients with chronic HFrEF, the mean age was 67.3 ± 11.6 years, 23.0% were female, and the mean BMI was 27.2 ± 5.6 kg/m^2. The mean LVEF was 30 ± 7%, and 47.9% had an ischaemic HF aetiology (*Table 1*). At the first visit, the mean systolic blood pressure was 124 ± 20 mmHg, eGFR 69 ± 21 ml/min/1.73m^2, and potassium 4.4 ± 0.4 mmol/L. ACEi/ARB/ARNI were used by 93.1%, beta-blockers by 91.6%, and MRA by 23.6%. The median (Q1–Q3) NT-proBNP concentration was 1574 (732–3093) ng/L, and 26.6% of patients were in NYHA class III or IV. The mean baseline 6MWT was 438 ± 125 m.

Table 1 Baseline characteristics of patients with heart failure and reduced ejection fraction included in the study ($n = 3636$)

Age, years	67.3 ± 11.6
Female sex, *n* (%)	837 (23.0)
Body mass index, kg/m^2	27.2 ± 5.6
Current smoking, *n* (%)	573 (15.8)
Ischaemic heart failure aetiology, *n* (%)	1740 (47.9)
Months since heart failure diagnosis	22.6 ± 49.8
Left ventricular ejection fraction, %	30.0 ± 7.0
New York Heart Association functional class, *n* (%)	
I	483 (13.3)
II	2188 (60.2)
III	948 (26.1)
IV	17 (0.5)
Systolic blood pressure, mmHg	123.8 ± 20.1
N-terminal pro-B-type natriuretic peptide, ng/L	1574 [732–3093]
Estimated glomerular filtration rate, ml/min/1.73 m^2	70 [53–85]
Potassium, mmol/L	4.4 [4.2–4.7]
Haemoglobin, g/L	14.3 [13.1–15.3]
Low-density lipoprotein cholesterol, mmol/L	2.3 [1.8–3.2]
QRS duration, ms	117.2 ± 33.2
Medical history, *n* (%)	
Hypertension	1478 (40.6)
Diabetes	764 (21.0)
Stroke	338 (9.3)
Peripheral artery disease	263 (7.2)
Anaemia	625 (17.2)
Chronic obstructive pulmonary disease or asthma	644 (17.7)
Cancer	185 (5.1)
Baseline treatment, *n* (%)	
Beta-blocker	3329 (91.6)
Renin–angiotensin system inhibitor	3385 (93.1)
Mineralocorticoid receptor antagonist	774 (23.6)
Cardiac resynchronization therapy	292 (8.0)
Implantable cardioverter-defibrillator	483 (13.3)

Changes in 6-min walk test during optimization of guideline-directed medical therapy

The titration period consisted of median 4 (3–6) visits and lasted median 147 (86–240) days with a right-skewed distribution (online supplementary *Figure S1*). Compared to the lowest quartile of up-titration duration, patients in the highest quartile were younger, had higher BMI, lower LVEF, more often in NYHA class III/IV, lower systolic blood pressure, higher potassium, longer QRS duration, more diabetes, used less frequently MRA, and were more often treated with cardiac resynchronization therapy (online supplementary *Table S1*). During this period, there was a significant increase in the proportion of patients treated with ≥50% of the target dose of ACEi/ARB/ARNI (from 63% to 87%), beta-blockers (from 52% to 67%) and MRA (from 26% to 37%) (all $p < 0.001$). The mean 6MWT at the follow-up visit was 478 ± 127 m, corresponding to a mean absolute increase of 40 ± 74 m and a mean relative increase of 14 ± 41% (*Figure 1*) from the first visit ($p < 0.001$). An increase in 6MWT ≥50 m was present in 39.6% of patients, 53.6% of patients had relatively unchanged 6MWT (<50 m change), and 6.9% had a decrease in 6MWT of ≥50 m. Patients with a greater increase in 6MWT had lower 6MWT at baseline, were younger, had less frequent hypertension, ischaemic HF aetiology, and chronic obstructive pulmonary disease, and had less pronounced reductions in blood pressure, eGFR, and haemoglobin from the first visit to the follow-up visit (*Table 2*). Patients with a greater increase in 6MWT also reached higher doses of beta-blockers and MRA, while there was no significant difference for ACEi/ARB/ARNI.

At the follow-up visit, NYHA class had improved in 38.2% of patients, and NT-proBNP decreased by a median of 425 (14–1322) ng/L. Changes in 6MWT correlated weakly with changes in NT-proBNP ($r = 0.19$, $p < 0.001$) and changes in NYHA class ($r = 0.27$, $p < 0.001$).

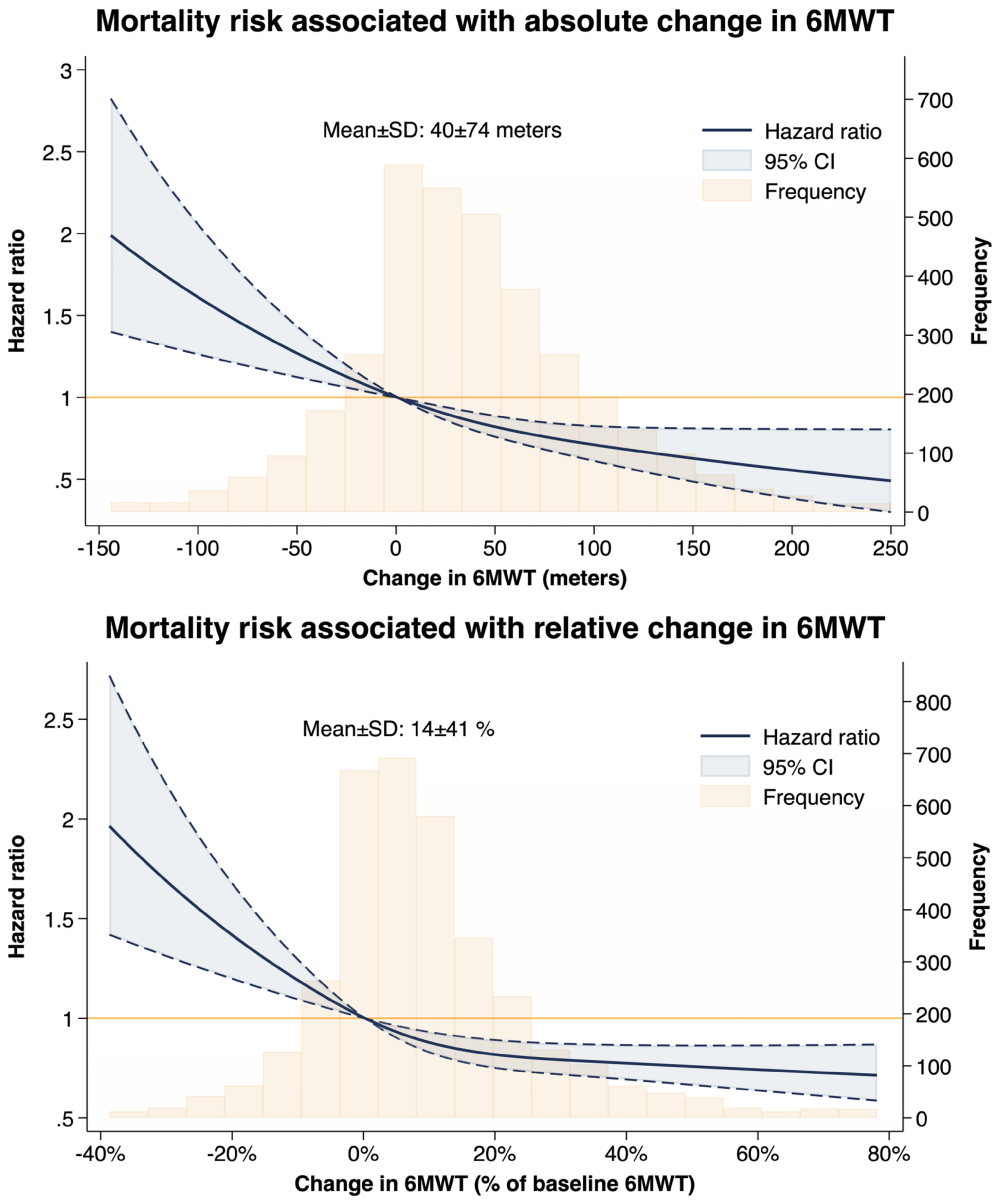

Figure 1 Association between all-cause mortality and absolute (*top*) and relative (*bottom*) change in 6-min walk test (6MWT) during optimization of guideline-directed medical therapy for patients with heart failure and reduced ejection fraction. CI, confidence interval; SD, standard deviation.

Changes in 6-min walk test and association with all-cause mortality

During the mean 2.3 ± 1.6 years of follow-up after the last up-titration visit, 419 (11.5%) patients died, with an incident rate of 4.9 (95% confidence interval [CI] 4.5–5.5) per 100 patient-years. Non-survivors were older and more frequently men with lower BMI, an ischaemic HF aetiology, hypertension, chronic obstructive pulmonary disease, and cancer. Patients with a greater increase in 6MWT from the first visit to the follow-up visit had a lower risk of mortality (unadjusted hazard ratio [HR] 0.88, 95% CI 0.82–0.95 per 50 m increase, $p < 0.001$). This association persisted in the fully adjusted models (HR 0.84, 95% CI 0.77–0.90, $p < 0.001$) (*Table 3*). None of the Cox models violated the Cox proportional hazard assumption. In a sensitivity analysis, we also adjusted for the duration of the titration period, which did not change the association between changes in 6MWT and survival (online supplementary *Table S2*). We also performed two sensitivity analyses in the complete dataset where missing NT-proBNP values were calculated based on available BNP concentration (online supplementary *Table S3*) and estimated using multiple imputations (online supplementary *Table S4*). None of these sensitivity analyses changed the association between changes in 6MWT and survival. The follow-up 6MWT was also associated with mortality in fully

Table 2 Predictors of greater increases in 6-min walk test (6MWT) from the first visit to the stable follow-up visit in patients with reduced ejection fraction, presented by quartiles of change (delta) in 6MWT

	Δ 6MWT				*p*-value
	Q1 (*n* = 1042)	Q2 (*n* = 777)	Q3 (*n* = 912)	Q4 (*n* = 905)	
Δ 6MWT, m	−34 ± 46	18 ± 8	51 ± 11	131 ± 67	
6MWT baseline, m	459 ± 121	457 ± 119	450 ± 113	387 ± 133	
6MWT follow-up, m	425 ± 130	475 ± 119	501 ± 114	518 ± 123	
Age, years	69.0 ± 11.4	68.3 ± 11.6	66.9 ± 11.2	64.9 ± 12.0	<0.001
Female sex, *n* (%)	248 (23.8)	170 (21.9)	197 (21.6)	222 (24.5)	0.83
Body mass index, kg/m^2	27.1 ± 5.3	27.0 ± 5.0	27.2 ± 5.2	27.4 ± 6.5	0.19
Current smoking, *n* (%)	179 (17.2)	112 (14.4)	128 (14.0)	154 (17.0)	0.74
Ischaemic HF aetiology, *n* (%)	531 (51.0)	376 (48.4)	411 (45.1)	422 (46.6)	0.021
Hypertension, *n* (%)	452 (43.4)	317 (40.8)	363 (39.8)	346 (38.2)	0.019
Diabetes, *n* (%)	232 (22.3)	164 (21.1)	179 (19.6)	189 (20.9)	0.32
Stroke, *n* (%)	102 (9.8)	77 (9.9)	78 (8.6)	81 (9.0)	0.37
Peripheral artery disease, *n* (%)	83 (8.0)	65 (8.4)	51 (5.6)	64 (7.1)	0.16
Anaemia, *n* (%)	187 (17.9)	112 (14.4)	145 (15.9)	181 (20.1)	0.22
COPD or asthma, *n* (%)	213 (20.4)	129 (16.6)	164 (18.0)	138 (15.2)	0.008
Cancer, *n* (%)	49 (4.7)	41 (5.3)	53 (5.8)	42 (4.6)	0.87
Changes in					
Body mass index, kg/m^2	0.3 ± 1.5	0.3 ± 1.2	0.3 ± 1.3	0.2 ± 1.6	0.48
Systolic BP, mmHg	−3.8 ± 18.3	−2.8 ± 16.7	−2.1 ± 17.1	0.6 ± 17.6	<0.001
eGFR, ml/min/1.73 m^2	−2.7 ± 11.1	−2.0 ± 10.2	−1.2 ± 11.0	−0.7 ± 11.9	<0.001
Haemoglobin, g/L	−0.3 ± 1.2	−0.2 ± 1.1	−0.1 ± 1.3	0.0 ± 1.4	<0.001
Potassium, mmol/L	0.1 ± 0.4	0.1 ± 0.4	0.1 ± 0.5	0.1 ± 0.4	0.57
NT-proBNP, ng/L	−277 [−978, 59]	−315 [−1036, 0]	−439 [−1292, 30]	−746 [−2102, −138]	<0.001
NYHA class	−0.2 ± 0.6	−0.3 ± 0.6	−0.4 ± 0.6	−0.6 ± 0.7	<0.001
Reached target dose					
BB dose, %	54 ± 33	54 ± 34	53 ± 34	59 ± 33	0.010
ACEi/ARB/ARNI dose, %	75 ± 32	78 ± 31	78 ± 31	77 ± 32	0.12
MRA dose, %	24 ± 31	24 ± 32	24 ± 31	28 ± 33	0.016

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; BP, blood pressure; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HF, heart failure; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; Q, quartile.

adjusted models (HR 0.84, 95% CI 0.77–0.90) which included the baseline 6MWT (online supplementary *Table S5*). The associations for absolute and relative changes in 6MWT with mortality risk were non-linear, and restricted cubic spline models with 3 knots (test for non-linearity $p = 0.009$ for absolute change and $p < 0.001$ for relative change; *Figure 1*) yielded the best model fit. The additional prognostic benefit gradually decreased with increasing walking distance for both absolute and relative change. However, for relative change in walking distance, there seemed to be an infliction point at around 20% increase, with little prognostic benefit beyond this point.

Changes in 6-min walk test and all-cause mortality according to baseline covariates

We assessed the effect modification for pre-defined covariates on the prognostic value of absolute and relative changes in 6MWT. Variables assessed included age, baseline 6MWT, sex, BMI, and eGFR. For absolute changes in 6MWT, there was a significant interaction with age (p for interaction = 0.020), but not for baseline 6MWT (p for interaction = 0.62), sex (p for interaction = 0.33), BMI (p for interaction = 0.84), or eGFR (p for interaction = 0.50). For relative changes in 6MWT, there was a significant interaction with age (p for interaction = 0.007) and baseline 6MWT (p for interaction <0.001), but not for sex (p for interaction = 0.42), BMI (p for interaction = 0.77), or eGFR (p for interaction = 0.56). Increasing walking distance had a larger positive prognostic value for older patients and patients with shorter baseline walking distances (*Figure 2*).

Discussion

This study demonstrates that changes in 6MWT in HFrEF patients strongly predict mortality, independent of changes in NT-proBNP, alterations in NYHA class, and other risk factors. These findings document the important contribution of alterations in 6MWT as an independent marker of mortality in chronic HFrEF patients.

The average improvement in 6MWT was 40 ± 74 m, corresponding to a 14% increase in walking distance. Patients with the largest

Table 3 Association between absolute change in distance (m) covered during the 6-min walk tests and all-cause mortality in unadjusted and adjusted Cox proportional hazard models in patients with heart failure and reduced ejection fraction

	Unadjusted		Adjusted model 1		Adjusted model 2	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Change in 6MWT, per 50 m	0.88 (0.82–0.95)	<0.001	0.82 (0.77–0.88)	<0.001	0.84 (0.77–0.90)	<0.001
Baseline 6MWT, per 50 m			0.77 (0.74–0.81)	<0.001	0.79 (0.75–0.83)	<0.001
Age, per year			1.05 (1.04–1.06)	<0.001	1.03 (1.01–1.04)	<0.001
Female sex			0.60 (0.47–0.76)	<0.001	0.55 (0.43–0.71)	<0.001
Body mass index, per kg/m^2					0.94 (0.92–0.96)	<0.001
Current smoking					1.09 (0.81–1.45)	0.57
Ischaemic HF aetiology					1.28 (1.04–1.57)	0.021
Hypertension					1.24 (1.01–1.52)	0.044
Diabetes					0.99 (0.78–1.27)	0.97
Stroke					0.83 (0.60–1.15)	0.26
Peripheral artery disease					1.09 (0.81–1.48)	0.56
Anaemia					1.03 (0.80–1.32)	0.83
COPD or asthma					1.34 (1.06–1.68)	0.013
Cancer					3.78 (2.90–4.93)	<0.001
Changes in						
Body mass index, per kg/m^2					0.90 (0.83–0.97)	0.007
Systolic BP, per mmHg					1.00 (1.00–1.01)	0.61
eGFR, per 10 ml/min/1.73 m^2					0.98 (0.89–1.09)	0.76
Haemoglobin, per g/L					1.00 (0.92–1.09)	0.93
Potassium, per mmol/L					0.79 (0.64–0.98)	0.032
NT-proBNP, per log(ng/L)					1.27 (1.11–1.44)	0.001
NYHA class						
Stable					Ref	
Improved					0.95 (0.62–1.47)	0.83
Worsened					1.06 (0.85–1.32)	0.59
Reached target dose						
BB dose, per 25%					0.99 (0.91–1.07)	0.73
ACEi/ARB/ARNI dose, per 25%					0.90 (0.84–0.97)	0.005
MRA dose, per 25%					1.02 (0.92–1.12)	0.75

6MWT, 6-min walk test; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; BP, blood pressure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

improvement in 6MWT were younger, had greater reductions in NT-proBNP, and had larger improvements in NYHA functional class. The improvements in 6MWT were associated with lower mortality risk, independent of changes in NYHA class, NT-proBNP, and other established risk factors, and the association between changes in 6MWT and survival was non-linear with a deflection point around a 20% increase.

Exercise intolerance is a cardinal feature of HF, and most patients have impaired functional capacity. Physiologically measured cardiorespiratory fitness by peak oxygen uptake is one of the strongest prognostic markers of morbidity and mortality in patients with chronic HF.[16,17] However, given the substantial resources required for cardiopulmonary exercise testing, this is usually reserved for HF patients considered for advanced therapy such as ventricular assist devices and heart transplantation.[14] Therefore, the most frequently used measure of functional capacity is the 6MWT, which requires no sophisticated equipment and has been shown to correlate strongly with peak oxygen uptake in HF ($r = 0.68–0.79$).[18] The 6MWT is a submaximal assessment of functional capacity, which closely approximates the capacity to perform activities of daily living, as demonstrated by the close correlation with quality of life measures.[19] The distance covered at a single 6MWT also carries important prognostic information for patients with chronic HF,[1–3] but whether HF clinics should perform a second 6MWT to assess prognosis after an intervention such as up-titration of GDMT has not been well documented. The prognostic value of changes in 6MWT in HFrEF was first reported in 2006 by Passantino *et al.*[20] in a study of 476 patients admitted with acute HF. During 15 ± 8 days of up-titration of GDMT and intravenous diuretic treatment, patients improved their walking distance from 326 ± 107 m to 408 ± 109 m, and this increase was associated with improved survival during 2 years of follow-up. However, as this study included patients during an acute HF event, and the time

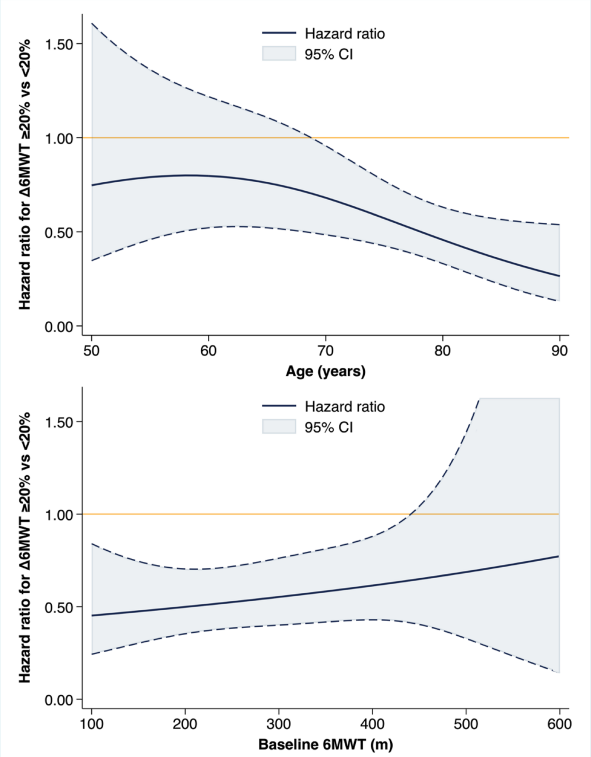

Figure 2 Subgroup comparison of patients achieving ≥20% improvement in 6-min walk test (6MWT) across the range of age and baseline 6MWT. CI, confidence interval.

between the two 6MWT was only 15 days, the change was most likely driven by decongestion and effects of diuretics and not the disease-modifying effect of GDMT. Changes in 6MWT have also been associated with long-term prognosis during short-term cardiac rehabilitation of HF patients, with a non-linear relationship and a suggested clinically meaningful endpoint of 50 m.[4,13] To our knowledge, a study from the BIOSTAT-CHF registry is the largest to assess the prognostic importance of changes in 6MWT during up-titration of GDMT.[12] The BIOSTAT-CHF study included HFrEF patients with new or worsening HF symptoms who were highly symptomatic (55% in NYHA class III/IV), received suboptimal (<50% of target dose) or no GDMT, and required diuretic treatment. Participants had a low mean baseline 6MWT of 300 m, and the study reported a 9% increase in mortality risk for each 50 m decrease in 6MWT from baseline to 9 months, which is less than what we found in our study. Notably, the baseline 6MWT in the BIOSTAT-CHF study was performed during an acute HF event requiring diuretic treatment, and improvements in walking distance might, in line with Passantino *et al.*, be attributed to decongestion. In contrast, patients in our study were clinically stable at inclusion and the changes in 6MWT observed during 147 (86–240) days of up-titration of treatment are more likely to reflect the disease-modifying effect of GDMT.

Risk prediction is essential to guide the initiation and intensity of HF treatment, including referral to device therapy, transplantation, and end-of-life care. Our study demonstrated the independent prognostic value of measuring changes in 6MWT during up-titration of GDMT in chronic HFrEF patients. The association was highly significant after adjusting for known risk factors, including baseline 6MWT and NT-proBNP. During the optimization of GDMT, we found a decrease in NT-proBNP (median −425 ng/L), which was inversely correlated with changes in 6MWT. Patients in the quartile with the greatest improvement in 6MWT (mean 131 m increase) experienced a much greater decrease in NT-proBNP during the up-titration period (median decrease of 746 ng/L), as compared to those in the quartile with the greatest deterioration in 6MWT (mean 34 m decrease in 6MWT and median decrease of 277 ng/L in NT-proBNP). Still, the correlation between changes in 6MWT and NT-proBNP was modest ($r = 0.19$), highlighting the distinct difference in prognosis and pathophysiology reflected by these measures. Notably, changes in NYHA class were not associated with mortality in our study, in contrast to changes in 6MWT. As both markers reflect symptoms of HF, this could indicate that changes in 6MWT can detect smaller changes that hold prognostic information. In line with the study by Passantino *et al.*,[20] we found that baseline walking distance and age interacted with the association between changes in 6MWT and prognosis. The prognostic value of an increase in 6MWT was largest for patients with short distances covered at the baseline test and for older patients. This finding might suggest that 6MWT change is of greater value in patients with more advanced HF. However, these findings warrant further investigations.

Changes in 6MWT as a surrogate endpoint have been widely adopted in HF trials to increase power and reduce sample size, given the continuous nature of this measure. However, evidence is scarce for defining a clinically meaningful change. Generally, a 50 m increase in 6MWT is considered a clinically significant improvement and has been used for pre-market approval of HF therapies. The results from our study add important knowledge to this field by demonstrating a non-linear association between changes in 6MWT and survival among patients with chronic HFrEF. The additional prognostic benefit gradually decreases with increasing change in distance covered, with no apparent deflection point for absolute change but a deflection point at approximately 20% relative increase. Our findings indicate that a 20% increase might be a benchmark for reducing mortality.

Limitations

Patients attending HF clinics in Norway are invited to optimize HF therapy; therefore, patients with limited life expectancy and advanced age may be underrepresented in the registry. We excluded patients with missing NT-proBNP measurements, which may introduce selection bias. However, only 8.8% of patients had missing values at either visit, and these patients had available BNP which was used in sensitivity analyses. Our study only included patients with LVEF ≤40% as these patients have documented effects and get reimbursement for HF medications. The results are, therefore, not necessarily applicable to HF patients with LVEF >40%. Another limitation of our analysis is the differences in the titration period, which corresponds to the time interval between the two 6MWTs. Although a short titration period might not be sufficient

time for changes in 6MWT to manifest, this did not impact our main findings which persisted when also adjusting for this in the regression models. This study was conducted before the introduction of sodium–glucose cotransporter 2 inhibitors for HF, which is a limitation as we know that this class of drugs improves 6MWT in HFrEF.[21]

Conclusion

Improvement in 6MWT in HFrEF patients is non-linearly associated with increased survival, independent of changes in NYHA class, NT-proBNP concentration, and other established risk factors. The additional prognostic benefit is limited beyond a 20% relative increase. These findings support the use of changes in 6MWT for monitoring HF patients and as a surrogate outcome in clinical trials.

Supplementary Information

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

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Conflict of interest: P.L.M. has served on advisory boards and/or received speaker fees from Amarin, AmGen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Novartis, Novo Nordisk, Pharmacosmos, Sanofi, US2.ai and Vifor. Ø.K. has received lecture fees from Boehringer Ingelheim, Bristol Myers Squibb, Novartis, and NovoNordisk. K.B. has received speaker fees from Boehringer Ingelheim and Novartis. M.G. has received lecture fees from Boehringer Ingelheim and AstraZeneca. L.G. received speaker fees from AstraZeneca, Bayer, Boehringer Ingelheim, Novartis, Novo Nordisk, and Pharmacosmos. S.Ø. has served on advisory boards and/or received speaker fees from AstraZeneca, Pfizer, Bayer, Boehringer Ingelheim, Novartis, Novo Nordisk, Sanofi, MSD, and Philips.

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