Clinical correlates and outcome associated with changes in 6-Minute Walking Distance in Patients with Heart Failure: findings from the BIOSTAT-CHF study

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Disclosures

The authors have nothing to disclose with regards to the present manuscript.

Abstract

Background: The 6-minute walking test (6MWT) is a simple and inexpensive test to establish exercise capacity in patients with heart failure. A lower 6MWT distance has been identified as an independent predictor of morbidity and mortality in heart failure (HF). However, data on clinical correlates, association with treatment up-titration and predictive value of the changes in 6MWT in larger cohorts of HF patients are scarce.

Methods: In BIOSTAT-CHF, a 6MWT was performed both at baseline (n=1,714) and at the 9-month visit (n=1,520). Cox-proportional hazards models were used to assess the associations between 6MWT distance and the primary outcome of death or HF hospitalization and the secondary outcome of death.

Results: The mean±SD 6MWT distance at baseline was 294±130m. Strong and independent predictors of a lower 6MWT distance were higher age, female sex, higher heart rate, NYHA III/IV, orthopnea, ischemic etiology of HF, a previous stroke, a current malignancy, and higher NT-proBNP (all $p<0.05$). Patients in the lower baseline 6MWT tertile (≤240m) were less frequently treated with disease-modifying therapies and were less frequently up-titrated to optimal therapeutic doses ($p<0.05$ for both). Compared to patients in the higher baseline 6MWT tertile (>360m), those in the lower and intermediate tertiles had worse prognosis: primary outcome adjusted HR (95%CI)=1.73 (1.38-2.18) and =1.44 (1.14-1.80), for the lower and intermediate tertiles, respectively. Patients that decreased their walking distance from baseline to 9 months had worse prognosis: primary outcome adjusted HR (95%CI) per each 50m decrease=1.09 (1.06-1.12).

Conclusions: 6MWT distance at baseline and a decrease in walking distance were independently associated with worse prognosis in HF. These results support the use of the 6MWT to assess patients` exercise capacity, prognosis, and as a clinically meaningful end-point in phase II clinical trials.

Key-words: 6-minute walking test; heart failure; prognosis

Introduction

The 6-minute walk test (6MWT) is a simple, reproducible and inexpensive method to assess patients` physical capacity[1, 2]. The 6MWT is sensitive to changes in quality of life and showed a good correlation with objective measures of exercise tolerance, such as exercise duration and oxygen uptake at the peak of exercise[3, 4]. Furthermore, some studies showed that the distance walked in the 6MWT is strongly associated with prognosis in heart failure (HF)[5-7]. However, only one of these reports is derived from an international trial, incorporating a random sample of 898 patients from the Studies of Left Ventricular Dysfunction (SOLVD) registry performed two decades ago[5]. Moreover, the prognostic implication of the changes in the 6MWT distance was only assessed in one single centre study[6].

The systems BIOlogy Study to TAilored Treatment in Chronic Heart Failure (BIOSTAT-CHF) is a multicentric international European project designed to determine profiles of patients with HF that do or do not respond to recommended therapies, regardless of (anticipated) up-titration[8]. In BIOSTAT-CHF 1,714 HF patients underwent 6MWT both at baseline and 1,520 patients at the 9 months visit, making the present study the largest to date in studying the association between (change in) 6MWT with clinical variables and outcomes in HF. Moreover, the uniqueness of the study design also allows to study the association of the 6MWT with the up-titration of guideline-recommended therapies.

The aims of the present study are: 1) to assess the clinical correlates of 6MWT; 2) to ascertain the prognostic implications of the 6MWT (both at baseline and change); 3) to study the association between the 6MWT distance with the up-titration of ACE-inhibitors/ARBs and beta-blockers.

Methods

Patient population

BIOSTAT-CHF is a European project that enrolled 2,516 HF patients from 69 centres in 11 European countries to determine profiles of patients with HF who not respond to recommended therapies, despite anticipated up-titration. The design and first results of the study and patients have been described elsewhere[8]. Briefly, patients were aged ≥18 years with signs and symptoms of worsening HF, confirmed either by a left ventricular ejection fraction (LVEF) of ≤40% or a BNP and/or NT-proBNP plasma levels >400 pg/mL and/or >2000 pg/mL, respectively. Patients needed to be treated with either oral or intravenous furosemide ≥40 mg/day or equivalent at the time of inclusion. Patients should not have been previously treated with evidence-based therapies (ACEi/ARBs and beta-blockers) or were receiving <50% of the target doses of at least one of these

drugs at the time of inclusion[9, 10]. The first three months of treatment were considered to be the optimization phase after which a stabilization phase of 6 months was defined. During the optimization phase, initiation or up-titration of ACEi/ARB and/or β-blocker was performed according to the routine clinical practice of the treating physicians, who were encouraged to follow the ESC guidelines at the time of treatment[9, 10]. Patients reaching at least 50% of the recommended dose of ACEi/ARB and/or β-blocker were considered successfully up-titrated.

The recruitment period was 24 months, starting from December 2010. The last patient was included on December 15, 2012. Median follow-up was 21 months. Ethics Board approval was obtained and all participants signed written informed consent before entering the study.

The BIOSTAT-CHF risk models used for adjustment throughout these analyses have been previously developed and validated[11].

6-Minute Walking Test

The 6MWT was performed in a long, straight hospital corridor, over a 30-m distance. Each participant was asked to walk (not run) back and forth along the corridor as briskly as possible, so that the longest possible distance was covered in six minutes. The participant was allowed to slow down or stop and rest if necessary, particularly in the case of symptoms such as severe dyspnoea or fatigue. During any rest period, the participant was informed of the elapsed time and encouraged to recommence walking when the symptoms attenuated enough to allow walking. However, the test was discontinued if the symptoms persisted. The participant was also allowed to discontinue the test at will at any time. Moreover, the test was interrupted by the investigator immediately one of the following symptoms appeared: chest pain that did not resolve at rest, dyspnoea precluding continuation of walking, cramps of the lower limb muscles, balance difficulty, severe sweating, pallor, or cyanosis. Otherwise, every two minutes during the test, an investigator informed the participant of the amount of time left and encouraged him to continue the test. At six minutes, the participant was advised to stop and be seated. The distance walked was measured to the nearest whole metre. The procedure was standardized across centres *i.e.*, consistent 6MW test methodology was specified in the BIOSTAT-CHF manual of operations, including standardized phrasing (e.g., “cover as much ground as possible… keep going… don’t worry if you have to sit down or stop to rest…”) and consistent timing of encouragement (1-minute intervals). 802 patients did not perform the 6MWT – the characteristics of these patients and the reasons for not performing the test are described in the **Supplemental Table 1**.

Statistical analysis

Population description and comparison of outpatients vs. inpatients was performed using t-test, Mann-Whitney or chi-square test, as appropriate.

Cox proportional hazard regression models were used to model long-term event rate of the variables included in the previously published BIOSTAT-CHF risk models[11]. Proportional hazard assumption was verified graphically using "log-log" plots. Log-linearity was checked by testing the functional forms of the covariable by the Kolmogorov-type supremum test and by visual inspection

by plotting the beta estimates versus the mean across quintiles. No multiple imputation was performed. The covariates used for adjustment when assessing the hazard ratio associated with the 6MWT distance were chosen from demographic (age and sex), clinical (previous HF hospitalization, use of beta-blockers and systolic blood pressure), and laboratory (NT-proBNP, blood urea nitrogen, hemoglobin, HDL-cholesterol, estimated glomerular filtration rate [eGFR] by the CKD-EPI formula[12, 13], and sodium). All these variables were previously found to be independently associated with the outcomes in the BIOSTAT-CHF cohort and were the variables used to build the risk models depicted herein (URL: https://biostat-chf.shinyapps.io/calc/)[11]. For visualization purposes, the relationship between 6MWT and the log-hazard of outcome was also assessed using restricted cubic splines with 3 knots located to the 10th, 50th and 90th percentiles according to the Harrell rule[14]. The adjusted changes (delta) in the walking distance were calculated by the 6MWT distance at month 9 minus the 6MWT distance at baseline adjusted on the baseline 6MWT distance. For the study of 6MWT distance changes between baseline and 9 months, the time-to-event was set at the 9-month visit and non-fatal outcomes before the 9-month visit were censored ("landmark analysis").

The primary outcome was a composite of HF hospitalization and all-cause death. All-cause death was also assessed separately as exploratory outcome. The adjudication of events (heart failure hospitalizations) were done by the treating physician.

All the analyses were performed using STATA (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). A p-value <0.05 was considered as statistically significant.

Results

Characteristics of the study population

Of a total of 2,516 patients, the 6MWT was performed at baseline in 1,714 and at the 9-month visit in 1,520 patients. The comparison of those who performed vs. those who did not perform the 6MWT is depicted in the **Supplemental Table 1.** The 802 patients who did not perform 6MWT were older, more often female, inpatients, had higher BMI, heart rate, congestive signs and symptoms, had lower blood pressure, had been more often hospitalized in the previous year, had higher proportion of stroke, peripheral vascular disease history and cancer, had lower hemoglobin, eGFR, sodium and potassium levels, had higher NT-proBNP and troponin levels, and were less often treated with beta-blockers and ACEi/ARBs. Most of these patients had no specific reason for not performing 6MWT written in the CRF but they were clearly in poorer "health status" and more often hospitalized compared to those who did perform the test. **Supplemental Table 1** (legend).

Compared to the intermediate (241-360m) and the higher (>360m) 6MWT distance tertiles, patients in the lower tertile (≤240m) were older, more often female, more often observed as inpatients, had higher heart rate, more congestive signs and symptoms, more often HF of ischemic etiology, previous HF hospitalization, atrial fibrillation, peripheral artery disease, and COPD, had lower

hemoglobin levels, worse renal function, higher NT-proBNP and troponin levels and were less often up-titrated with regards to ACEi/ARBs and beta-blockers (all $p<0.05$ for trend). **Table 1** for baseline and **Supplemental Table 2** for the 9-month visit.

6MWT and its clinical correlates

Older age, higher heart rate, in-hospital treatment, congestive symptoms, HF of ischemic etiology, previous stroke, cancer, and higher values of NT-proBNP and troponin I were all independent and negatively associated with 6MWT distance, whereas male sex and higher sodium levels were positively associated. **Table 2** for baseline and **Supplemental Table 3** for the 9-month visit.

Prognostic associations

The 6MWT distance was linearly associated with the study outcomes: for each 50m less in the 6MWT distance, patients had an adjusted 8% increment in the risk for HF hospitalization or death and 14% increased risk for death. **Table 3** & **Figure 1**. Compared to patients walking more than 360m, those walking between 241 and 360m and those walking 240m or less had increased rates of all outcome events: adjusted HR (95%CI) for the primary outcome of HF hospitalization or death =1.44 (1.14-1.80) and 1.73 (1.38-2.18), respectively. **Table 3**. Similar results were found for the 9-month visit. **Supplemental Table 4.** The 6MWT did not improve the discrimination (c-index) of the BIOSTAT prognostic models (c-index =0.71 for the primary outcome and 0.73 for death).

Patients who decreased their walking distance from baseline to the 9-month visit also had worse prognosis in a linear fashion: HR (95%CI) =1.09 (1.06-1.12) per each 50m decrease for the primary outcome. **Table 6** & **Figure 2**. Older patients, those with diabetes and higher NT-proBNP values were less likely to improve their walking distance. **Supplemental Tables 5** & **6**. The distribution of the baseline and the changes in the walked distance is represented in the **Supplemental Figure 1** & **2.**

Comparison with other common risk factors

Patients walking 240m or less had worse prognosis than those aged above 75, those with diabetes, atrial fibrillation, severe renal impairment, COPD or previous stroke. **Figure 3**.

Association with treatment up-titration

Patients walking shorter distances in the 6MWT were less likely to be up-titrated above 50% of the recommended doses of ACEi/ARBs and beta-blockers. **Table 4**. However, up-titration of ACEi/ARBs and/or beta-blockers was not associated with changes in the walking distance. **Table 5**.

Discussion

Our study shows that patients who walked shorter distances in the 6MWT were older, had more co-morbid conditions, were more often treated as inpatients and had higher natriuretic peptide levels. In particular, older age, hospitalization, higher heart rate, congestive signs and symptoms, HF of ischemic etiology, previous stroke, cancer, and higher values of NT-proBNP and troponin I were all negatively associated with 6MWT distance, whereas male sex and higher sodium levels were positively associated. The 6MWT distance had a linear association with the studied outcomes *i.e*. the less patients walked the worse their prognosis (19% event-rate increase per each 50m less for the baseline 6MWT distance) and a decrease the walked distance from baseline visit to the 9-month visit was also associated with worse subsequent outcomes (9% event-rate increase per each 50m decrease between visits). Patients who walked shorter distances were also less likely to be up-titrated on ACE-inhibitors/ARBs and beta-blockers. The present study is relevant in several aspects: 1) it is contemporary, multicentric, and international; 2) assesses the clinical correlates of 6MWT; 3) identifies the prognostic associations of 6MWT at baseline and also the changes between two time-points and subsequent outcomes; 4) compares the prognostic associations of the 6MWT with those of common clinical conditions such as diabetes and atrial fibrillation; 5) it is also the first to study the association between 6MWT and HF treatment up-titration. From a clinical standpoint, the present study provides insight on the use of this simple and inexpensive text. In routine practice, performing a 6MWT provides relevant prognostic information and an objective assessment of patients` exercise capacity, allowing close monitorization of the clinical course of the disease.

The 6MWT is performed by asking the patient to walk the longest distance possible in a 6-minute interval through a walking corridor (preferably 30m long). The patient can stop or slow down at any time and then resume walking, depending on the degree of fatigue[1]. Even though other variables can be monitored during the test (*e.g*. blood pressure, oxygen saturation and/or heart rate), the distance walked is the parameter that has proven to be most useful in nearly all clinical studies[1]. The association of the 6MWT distance with morbidity and mortality is not surprising since the 6MWT is itself a reflection of exercise tolerance, limited by several non-cardiovascular factors such as conditioning, osteoarticular pathology, patient effort and willingness/motivation to perform the test. In addition, the 6MWT (and other exercise parameters) also rely on the ability of skeletal muscle to extract oxygen from blood, pulmonary and endothelial function, and cardiac output[15]. Moreover, the 6MWT is likely to perform better (as prognostic tool) in patients with severe and symptomatic HF (like those enrolled in the BIOSTAT-CHF) whose 6MWT is most severely limited and an improvement could be clinically meaningful[16].

In the SOLVD trial[5], a stratified random sample of 898 patients with symptomatic HF and an ejection fraction ≤45% or less underwent a 6MWT. During a mean follow-up of 8 months 52 (6%) patients died and 252 (30%) were hospitalized. Compared with those walking at least 450m, patients walking less than 300m had higher event rates. Smaller observational studies with assessment of baseline 6MWT also demonstrated an independent association between the walked distance and

mortality in patients with systolic dysfunction[5, 7, 16]. An analysis from the HF-ACTION trial including 2,054 HF patients also showed that a shorter walked distance in the baseline 6MWT was associated with worse outcomes[17]. The association between the changes in the walked distance between two visits and subsequent outcome was analysed in a single centre study with 600 HF patients followed for 8 years[6]. In this study, a decrease in the 6MWT distance from the baseline visit to the 1-year visit was independently associated with increased death rates[6]. To the best of our knowledge our study is the first contemporary multicentric and international study to study the association between the changes in the 6MWT distance between two time-point and subsequent outcomes. The demonstration that older patients, diabetics and those with higher natriuretic peptide values were less likely to improve the distance walked and that a decrease in the 6MWT distance is associated with worse subsequent outcomes in a linear fashion suggests that we may identify the patients more prone to decrease the distance walked and that any deterioration in the 6MWT distance may be of clinical significance.

In the present study a lower 6MWT distance was also associated with lower proportion of treatment up-titration. However, treatment up-titration was not associated with changes in the 6MWT distance. In should be noted that the 6MWT distance improved in the majority of trials of cardiac resynchronization therapy but showed inconsistent results in pharmacologic (such as ACE-inhibitors and beta-blockers) and device (such as vagus nerve stimulation) trials[18].

6MWT as a clinically meaningful endpoint

The 6MWT is an inexpensive and reproducible method to assess exercise tolerance that can be performed in the majority of HF patients (even when exercise capacity in limited by severity of disease or multiple co-morbidities). The 6MWT can be applied in the setting of a RCT and is itself a clinically meaningful endpoint *i.e*. it is associated with clinical status, quality of life, and capacity to perform activities of daily living. Therefore, the 6MWT can be used in phase II trials and is also a good surrogate for "hard" clinical endpoints in phase III trials (as supported by the present study). Cardiopulmonary exercise testing (CPX) is an evidence-based relevant tool for risk stratification and prognosis in HF[19]. However, CPX requires specific equipment and personnel adequately trained in the performance and interpretation of the test[20], making CPX a complex procedure to be widely applied in the setting of a RCT. Moreover, results of the 6MWT show good correlation with exercise capacity measured by formal treadmill and CPX[5, 21]. In general, a 30-50m increase in 6MWT distance is considered a clinically significant improvement, is associated with a significant improvement in NYHA class and health related quality of life and has been used in the "device" trials as relevant to pre-market approval[22-25].

In resume, the 6MWT can be used as end-point *per se*, and if aligned with other measures (such as natriuretic peptides and imaging) it is associated with morbidity and mortality in HF[18].

Limitations

Several limitations should be acknowledged in this analysis. First, this is a post-hoc analysis of a prospective non-randomized observational study, therefore all limitations inherent to such analysis are applied herein, including the inability to infer causality. Second, the data from the BIOSTAT-CHF come from European centres only and may not be representative of HF patients in other world regions. Third, all patients enrolled in the BIOSTAT-CHF had severe symptoms and high natriuretic peptide levels, hence these findings cannot be generalized to less symptomatic HF patients.

Conclusion

The 6MWT distance at baseline and a decrease in the walked distance in a 9-month period were independently associated with worse prognosis in HF in a linear fashion. Patients with lower walked distance were also less likely to have their HF treatments up-titrated, but treatment up-titration did not improve the distance walked. These results support the use of the 6MWT to assess patients` exercise capacity, prognosis, and could be used as a clinically meaningful end-point in phase II clinical trials.

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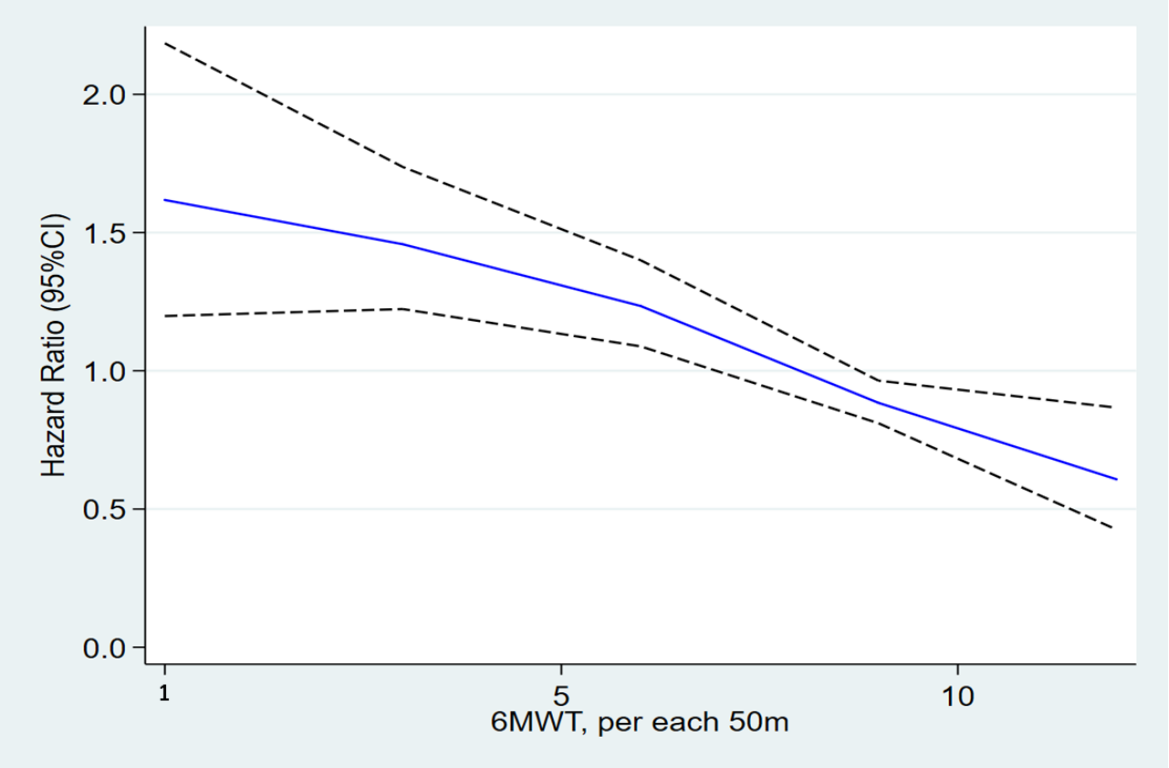
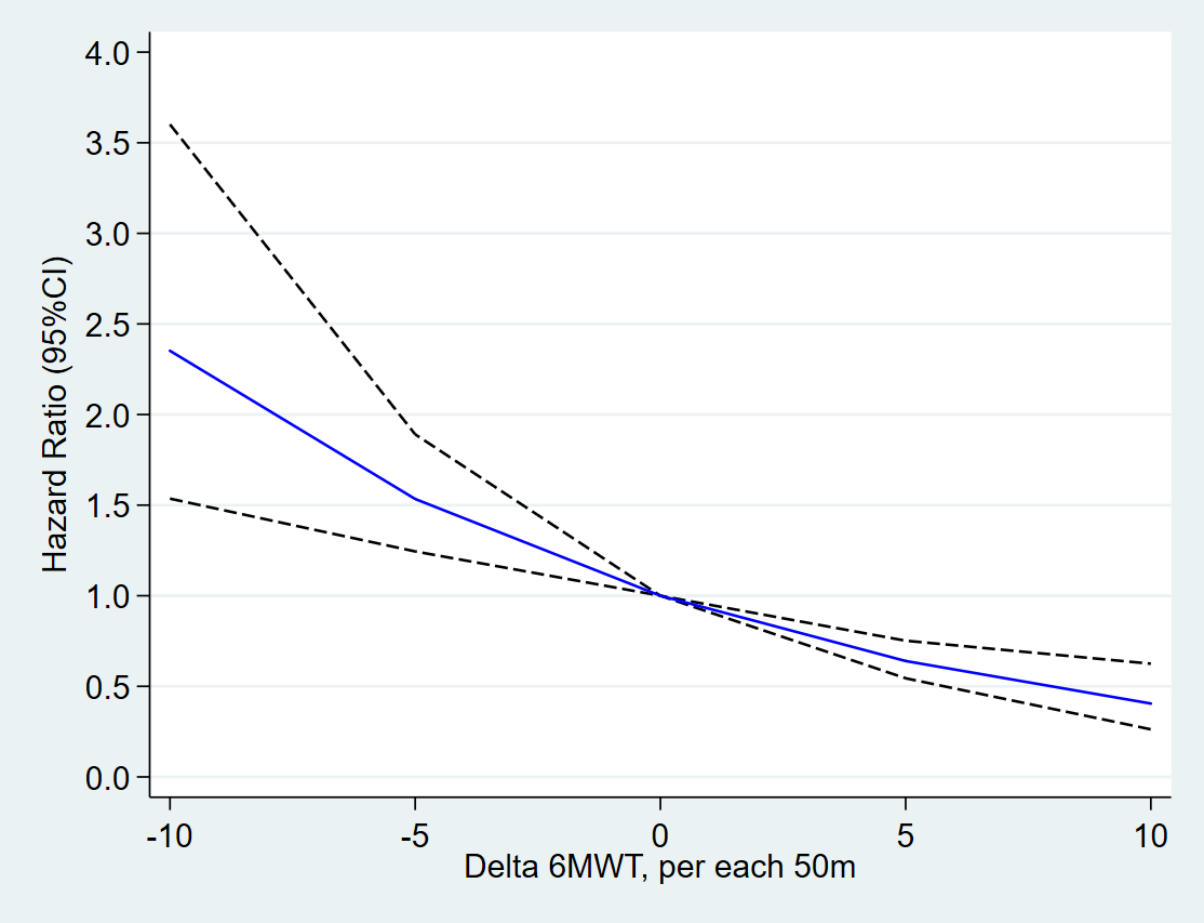
Figure 1. Spline for the association of baseline 6MWT with regards to the primary outcome



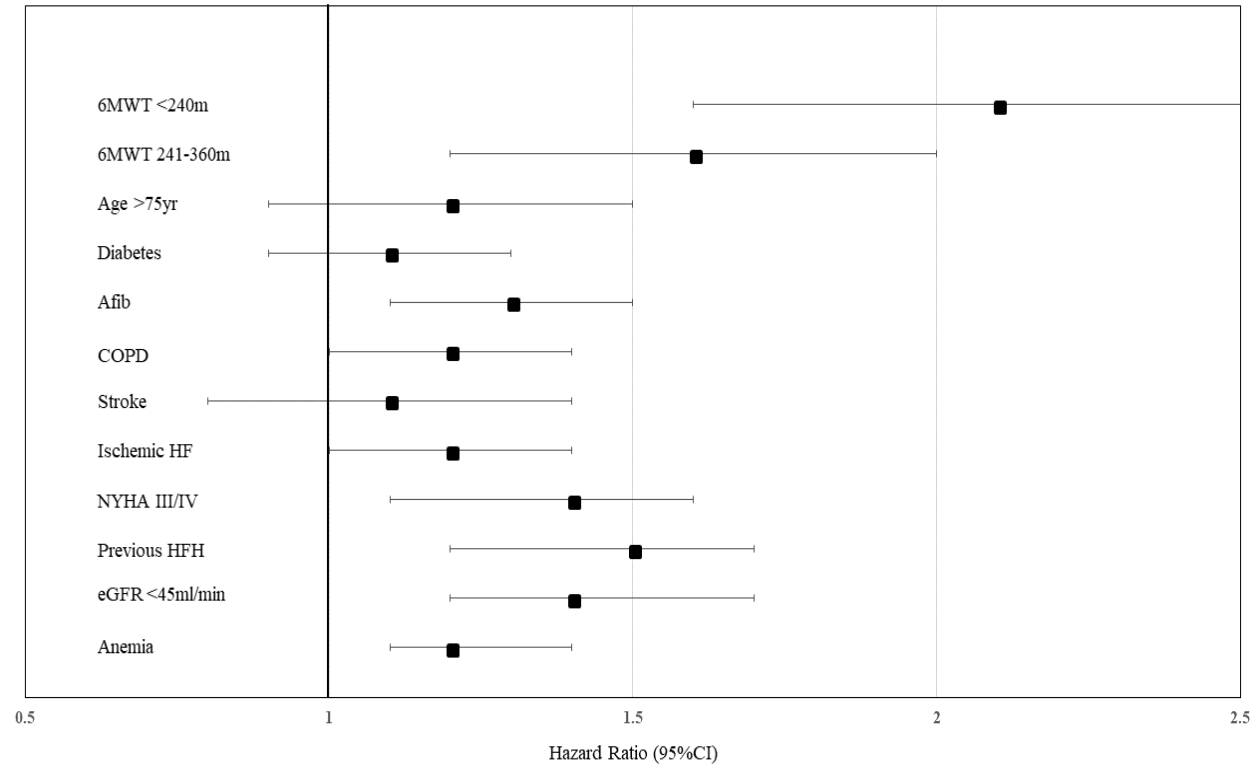
Legend: 6MWT, 6-minute walking test distance; X-axis, distance in meters x 50 (1 =50m; 5 =250m;10 =500m).

Figure 2. Spline for the association of the delta 6MWT with regards to the primary outcome



Legend: 6MWT, 6-minute walking test distance; X-axis, distance in meters x 50 (5 =250m;10 =500m).

Figure 3. Forest plot comparing the primary outcome event rates associated with 6MWT with those of common risk factors in HF



Legend: 6MWT, 6-minute walking test; Afib, atrial fibrillation; COPD, chronic obstructive pulmonary disease; HF, heart failure; eGFR, estimated glomerular filtration rate.

Table 1. Characteristics of the study population by baseline 6MWT tertiles

6MWT (tertiles)	≤240 m	241-360 m	>360 m	p-value
N.	591	586	537	
Age (years)	73.2 ± 10.1	67.0 ± 11.5	62.3 ± 11.2	<0.001
Male sex	374 (63.3%)	453 (77.3%)	465 (86.6%)	<0.001
Inpatient visit	391 (66.2%)	329 (56.1%)	252 (46.9%)	<0.001
BMI (Kg/m^2)	27.8 ± 5.4	27.5 ± 4.9	27.7 ± 4.8	0.68
Heart rate (bpm)	82.2 ± 19.4	78.5 ± 18.7	78.9 ± 20.9	0.002
SBP (mmHg)	125.4 ± 21.2	125.1 ± 20.1	125.6 ± 20.3	0.92
Pulmonary rales	345 (59.2%)	278 (48.5%)	157 (30.3%)	<0.001
Peripheral edema	343 (68.2%)	271 (55.2%)	167 (39.2%)	<0.001
Elevated JVP	127 (32.6%)	95 (23.2%)	72 (18.6%)	<0.001
NYHA class III/IV	421 (72.3%)	312 (54.4%)	203 (38.1%)	<0.001
Orthopnea	196 (33.3%)	150 (25.6%)	105 (19.6%)	<0.001
LVEF (%)	32.3 ± 11.1	30.0 ± 10.1	29.9 ± 8.5	<0.001
Ischemic HF	295 (49.9%)	256 (43.7%)	195 (36.3%)	<0.001
PCI or CABG	223 (37.7%)	192 (32.8%)	151 (28.1%)	0.003
HFH in the last 12 months	228 (38.6%)	193 (32.9%)	162 (30.2%)	0.009
Atrial fibrillation	299 (50.6%)	246 (42.0%)	217 (40.4%)	<0.001
Previous stroke	61 (10.3%)	40 (6.8%)	33 (6.1%)	0.018
Peripheral arterial disease	73 (12.4%)	42 (7.2%)	45 (8.4%)	0.006
Hypertension	404 (68.4%)	380 (64.8%)	307 (57.2%)	<0.001
Device therapy	151 (25.5%)	133 (22.7%)	113 (21.0%)	0.19
Current smoking	73 (12.4%)	78 (13.3%)	80 (14.9%)	0.005
Diabetes	238 (40.3%)	173 (29.5%)	132 (24.6%)	<0.001
COPD	138 (23.4%)	90 (15.4%)	64 (11.9%)	<0.001
Malignancy	25 (4.2%)	15 (2.6%)	9 (1.7%)	0.032
Hemoglobin (g/dL)	12.7 ± 1.8	13.3 ± 1.8	13.9 ± 1.6	<0.001
eGFR (ml/min/1.73m2)	56.9 ± 21.5	64.8 ± 23.6	72.3 ± 21.1	<0.001
Urea (mmol/L)	15.8 ± 10.3	13.3 ± 10.8	12.2 ± 8.8	<0.001
Sodium (mmol/L)	139.1 ± 4.1	139.4 ± 3.5	140.0 ± 3.1	<0.001
Potassium (mmol/L)	4.2 ± 0.6	4.2 ± 0.5	4.3 ± 0.5	0.66
Glucose (mmol/L)	7.2 ± 3.1	6.9 ± 2.9	6.7 ± 2.4	0.047
Total cholesterol (mmol/L)	4.1 ± 1.37	4.4 ± 1.3	4.5 ± 1.2	<0.001
HDL cholesterol (mmol/L)	1.1 ± 0.4	1.1 ± 0.4	1.1 ± 0.3	0.52
NT-pro BNP (NPX)	3.3 ± 1.3	2.7 ± 1.3	2.4 ± 1.1	<0.001
Log_{10} TnI (pg/mL)	1.2 ± 0.5	1.1 ± 0.5	0.9 ± 0.5	<0.001
MRA	289 (48.9%)	327 (55.8%)	302 (56.2%)	0.019
Loop diuretics	590 (99.8%)	582 (99.3%)	534 (99.4%)	0.40
Digoxin	110 (18.6%)	108 (18.4%)	102 (19.0%)	0.97
Beta-blocker	475 (80.4%)	513 (87.5%)	465 (86.6%)	0.001
Beta-blocker >=50% at 3 mo.	196 (33.2%)	222 (37.9%)	223 (41.5%)	0.014
ACEi/ARB	408 (69.0%)	449 (76.6%)	418 (77.8%)	0.001
ACEi/ARB >=50% at 3 mo.	282 (47.7%)	324 (55.3%)	342 (63.7%)	<0.001
6MWT (meters)	147.8 ± 62.8	307.0 ± 34.7	439.4 ± 61.9	-

Legend: BMI, body mass index; JVP, jugular venous pressure; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; HFH, heart failure hospitalization; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonist; ACEi/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker.

Table 2. Multivariable linear regression for baseline 6MWT (m) as dependent variable

Continuous 6MWT (baseline)	Std. beta-coefficient	Std. Err.	P-value
Age (per 10 yr)	-33.0 (-39.2 to -26.7)	3.2	<0.001
Male sex	59.2 (43.1 to 75.3)	8.2	<0.001
Inpatient	-68.4 (-85.6 to -51.2)	8.8	<0.001
Heart rate (per 10 bpm)	-6.1 (-9.5 to -2.7)	1.7	<0.001
NYHA III/IV	-58.9 (-75.2 to -42.6)	8.3	<0.001
Orthopnea	-31.5 (-47.6 to -15.4)	8.2	<0.001
Ischemic heart failure	-32.8 (-47.3 to -18.3)	7.4	<0.001
Previous stroke	-37.2 (-60.6 to -13.7)	11.9	0.002
Current malignancy	-46.2 (-83.9 to -8.6)	19.2	0.016
Sodium (per 1 mmol/L)	4.0 (2.3 to 5.7)	0.9	<0.001
NT-proBNP (per NPX doubling)	-12.4 (-18.0 to -6.9)	2.8	<0.001
LogTnI (per each Log10)	-28.8 (-42.2 to -15.5)	6.8	<0.001

Model adjusted R^2 =0.35

Constant = 147.6

The standardized (std.) beta-coefficient compares the strength of the effect of each individual independent variable to the dependent variable (6MWT). The higher the absolute value of the beta coefficient, the stronger the effect.

Table 3. Cox-proportional hazards models for baseline 6MWT

HFH or Death	N. (%) of events	Crude HR (95%CI)	P-value	Adjusted HR (95%CI)*	P-value
Continuous 6MWT (m)					
Per each 50m less	641 (37.4%)	1.19 (1.15-1.22)	<0.001	1.08 (1.04-1.11)	<0.001
Tertile 6MWT (m)					
>360 m	118 (22.0%)	Reference	-	Reference	-
241-360 m	210 (35.8%)	1.85 (1.47-2.31)	<0.001	1.44 (1.14-1.80)	0.002
≤240 m	313 (53.0%)	3.07 (2.48-3.79)	<0.001	1.73 (1.38-2.18)	<0.001
Death	N. (%) of events	Crude HR (95%CI)	P-value	Adjusted HR (95%CI)*	P-value
Continuous 6MWT (m)					
Per each 50m less	385 (22.5%)	1.25 (1.19-1.30)	<0.001	1.14 (1.09-1.18)	<0.001
Tertile 6MWT (m)					
>360 m	57 (10.6%)	Reference	-	Reference	-
241-360 m	109 (18.6%)	1.88 (1.37-2.60)	<0.001	1.49 (1.08-2.06)	0.016
≤240 m	219 (37.1%)	4.11 (3.08-5.50)	<0.001	2.41 (1.76-3.29)	<0.001

*Adjusted on the BIOSTAT-CHF risk model including: age, heart failure hospitalizations in previous year, systolic blood pressure, presence of peripheral edema, NT-proBNP, hemoglobin, sodium, HDL cholesterol, and the use of beta-blockers (https://biostat-chf.shinyapps.io/calc/).

Total n. =1,714; Tertile n. ≤240m =591; 241-360m =586; >360m =537.

Table 4. Logistic regression for 6MWT as treatment up-titration determinant

Treatment up-titration	OR (95%CI)*	p-value
ACEi/ARB or β-blocker ≥50%		
Continuous 6MWT (m)		
6MWT per each 50m less	0.91 (0.85-0.97)	0.002
Tertile 6MWT (m)		
>360 m	Reference	-
241-360 m	0.66 (0.47-0.92)	0.014
≤240 m	0.63 (0.43-0.92)	0.016
ACEi/ARB ≥50%		
Continuous 6MWT (m)		
6MWT per each 50m less	0.95 (0.90-1.01)	0.052
Tertile 6MWT (m)		
>360 m	Reference	-
241-360 m	0.76 (0.56-1.02)	0.075
≤240 m	0.75 (0.54-1.04)	0.088
β-blocker ≥50%		
Continuous 6MWT (m)		
6MWT per each 50m less	0.91 (0.85-0.96)	0.001
Tertile 6MWT (m)		
>360 m	Reference	-
241-360 m	0.85 (0.63-1.16)	0.31
≤240 m	0.66 (0.46-0.94)	0.022

*Adjusted on the "best" up-titration prediction model including: age, sex, race, heart failure duration, heart failure hospitalization in the previous year, heart failure of ischemic etiology, diabetes mellitus, hypertension, body mass index, systolic blood pressure, heart rate, left ventricular ejection fraction, NT-pro BNP, estimated glomerular filtration rate,

Table 5. Logistic and linear regression for the association of medication up-titration with 6MWT change in meters (from baseline to 9-months)

Logistic regression for 6MWT change as categorical variable				
Up-titration	6MWT decrease	6MWT increase	OR (95%CI)	P-value
ACEi/ARB or BB ≥50%	339 (71.8%)	889 (71.3%)	0.97 (0.77-1.23)	0.83
ACEi/ARB ≥50%	266 (56.4%)	705 (56.5%)	1.01 (0.81-1.25)	0.95
Beta-blocker ≥50%	200 (42.4%)	497 (39.9)	0.90 (0.73-1.12)	0.34
Linear regression for 6MWT change as continuous variable				
Up-titration	6MWT change : beta coefficient (95%CI)		Std. error	P-value
ACEi/ARB or beta-blocker ≥50%	4.42 (-13.78 to 22.63)		9.28	0.63
ACEi/ARB ≥50%	2.78 (-13.80 to 19.37)		8.46	0.74
Beta-blocker ≥50%	-7.21 (-23.95 to 9.53)		8.54	0.40

Legend: 6MWT, 6-minute walking test distance in meters; ACEi/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker.

The standardized beta-coefficient compares the strength of the effect of each individual independent variable to the dependent variable (6MWT). The higher the absolute value of the beta coefficient, the stronger the effect.

Table 6. Cox-proportional hazards models 6MWT distance increase from baseline to 9 months

HFH or Death	Crude HR (95%CI)	P-value	Adjusted HR (95%CI)*	P-value
Per each 50m decrease (continuous)	1.09 (1.06-1.12)	<0.001	1.09 (1.06-1.12)	<0.001
6MWT (decrease vs. increase)	1.56 (1.30-1.85)	<0.001	1.54 (1.30-1.85)	<0.001
Death	Crude HR (95%CI)	P-value	Adjusted HR (95%CI)*	P-value
Per each 50m decrease (continuous)	1.09 (1.04-1.14)	<0.001	1.09 (1.04-1.14)	<0.001
6MWT (decrease vs. increase)	1.59 (1.20-2.08)	<0.001	1.64 (1.25-2.13)	<0.001

*Adjusted on the BIOSTAT-CHF risk model including: age, heart failure hospitalizations in previous year, systolic blood pressure, presence of peripheral edema, NT-proBNP, hemoglobin, sodium, HDL cholesterol, and the use of beta-blockers (https://biostat-chf.shinyapps.io/calc/).

Supplemental Table 1. comparing those who did 6MWT with those who did not

6MWT	Missing	Non-missing	p-value
N.	802	1,714	
Age (years)	69.9 ± 12.1	67.6 ± 11.8	<0.001
Male sex	554 (69.1%)	1292 (75.4%)	<0.001
Inpatients	722 (90.0%)	80 (10%)	<0.001
BMI (Kg/m^2)	28.4 ± 6.3	27.7 ± 5.1	0.004
Heart rate (bpm)	87.3 ± 23.8	79.9 ± 19.7	<0.001
SBP (mmHg)	123.3 ± 24.5	125.4 ± 20.6	0.026
Pulmonary rales	511 (66.3%)	780 (46.6%)	<0.001
Peripheral edema	475 (70.0%)	781 (55.0%)	<0.001
Elevated JVP	260 (45.9%)	294 (24.8%)	<0.001
NYHA class III/IV	586 (77.4%)	936 (55.4%)	<0.001
Orthopnea	428 (53.5%)	451 (26.4%)	<0.001
LVEF (%)	31.7 ± 11.9	30.7 ± 10.0	0.056
Ischemic HF	357 (44.5%)	746 (43.5%)	0.24
PCI or CABG	276 (34.4%)	566 (33.0%)	0.49
HFH in the last 12 months	211 (26.3%)	583 (34.0%)	<0.001
Atrial fibrillation	381 (47.5%)	762 (44.5%)	0.15
Previous stroke	99 (12.3%)	134 (7.8%)	<0.001
Peripheral arterial disease	113 (14.1%)	160 (9.3%)	<0.001
Hypertension	478 (59.6%)	1091 (63.7%)	0.051
Device therapy	221 (27.6%)	397 (23.2%)	0.017
Current smoking	122 (15.3%)	231 (13.5%)	0.49
Diabetes	276 (34.4%)	543 (31.7%)	0.17
COPD	144 (18.0%)	292 (17.0%)	0.57
Malignancy	48 (6.0%)	49 (2.9%)	<0.001
Hemoglobin (g/dL)	12.9 ± 1.9	13.3 ± 1.8	<0.001
eGFR (ml/min/1.73m2)	58.1 ± 23.2	64.4 ± 22.9	<0.001
Urea (mmol/L)	16.8 ± 14.0	13.8 ± 10.1	<0.001
Sodium (mmol/L)	138.4 ± 4.4	139.5 ± 3.7	<0.001
Potassium (mmol/L)	4.2 ± 0.5	4.3 ± 0.6	<0.001
Glucose (mmol/L)	7.5 ± 3.3	6.9 ± 2.9	<0.001
Total Cholesterol (mmol/L)	4.0 ± 1.3	4.3 ± 1.3	<0.001
HDL (mmol/L)	1.1 ± 0.4	1.1 ± 0.4	0.14
NT-pro BNP (NPX)	3.4 ± 1.4	2.8 ± 1.3	<0.001
Log_{10} TnI (pg/mL)	1.3 ± 0.5	1.1 ± 0.6	0.002
MRA	421 (52.5%)	918 (53.6%)	0.62
Loop diuretics	798 (99.5%)	1706 (99.5%)	0.91
Digoxin	171 (21.3%)	320 (18.7%)	0.12
Beta-blocker	640 (79.8%)	1453 (84.8%)	0.002
Beta-blocker >=50% at 3 mo.	261 (32.5%)	641 (37.4%)	0.018
ACE/ARB	545 (68.0%)	1275 (74.4%)	<0.001
ACE/ARB >=50% at 3 mo.	364 (45.4%)	948 (55.3%)	<0.001
6MWT (meters)	-	293.6 ± 130.5	-

Legend: BMI, body mass index; JVP, jugular venous pressure; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; HFH, heart failure hospitalization; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonist; ACEi/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker.

Of the 802 patients who did not perform the 6MWT, 710 (89%) had no specific reason written in the CRF, the following reasons were “not a routine” (n=7; 0.9%) and “no time” (n=6; 0.8%).

Supplemental Table 2. Characteristics of the study population by 9-month 6MWT tertiles

6MWT (tertiles)	≤240 m	241-396 m	>396 m	p-value
N.	510	505	505	
Age (years)	73.3 ± 10.4	69.0 ± 10.5	61.5 ± 11.5	<0.001
Male sex	392 (63.8%)	433 (76.8%)	495 (84.0%)	<0.001
BMI (Kg/m^2)	28.1 ± 6.1	28.1 ± 5.5	27.8 ± 4.9	0.44
Heart rate (bpm)	73.8 ± 14.3	72.3 ± 15.4	69.8 ± 13.2	<0.001
SBP (mmHg)	124.4 ± 22.3	124.1 ± 19.4	125.9 ± 19.9	0.25
Pulmonary rales	84 (16.2%)	52 (10.0%)	17 (3.2%)	<0.001
Peripheral edema	195 (36.9%)	104 (21.6%)	45 (9.3%)	<0.001
Elevated JVP	60 (15.0%)	27 (6.6%)	12 (2.8%)	<0.001
NYHA class III/IV	303 (50.8%)	106 (18.9%)	33 (5.6%)	<0.001
Orthopnea	120 (19.7%)	39 (7.0%)	15 (2.6%)	<0.001
LVEF (%)	34.9 ± 11.7	33.8 ± 10.5	36.8 ± 10.5	0.002
Ischemic HF	299 (48.7%)	247 (43.8%)	203 (34.5%)	<0.001
Atrial fibrillation	310 (50.5%)	227 (40.2%)	224 (38.0%)	<0.001
Previous stroke	74 (12.1%)	47 (8.3%)	36 (6.1%)	0.001
Peripheral arterial disease	87 (14.2%)	49 (8.7%)	30 (5.1%)	<0.001
Hypertension	426 (69.4%)	365 (64.7%)	309 (52.5%)	<0.001
Device therapy	166 (27.0%)	134 (23.8%)	113 (19.2%)	0.005
Current smoking	82 (13.4%)	72 (12.8%)	96 (16.3%)	0.14
Diabetes	240 (39.1%)	193 (34.2%)	114 (19.4%)	<0.001
COPD	118 (19.2%)	102 (18.1%)	67 (11.4%)	<0.001
Malignancy	32 (5.2%)	15 (2.7%)	12 (2.0%)	0.005
Hemoglobin (g/dL)	12.6 ± 1.7	13.2 ± 1.6	13.8 ± 1.5	<0.001
eGFR (ml/min/1.73m2)	59.3 ± 24.7	67.0 ± 23.4	77.5 ± 22.4	<0.001
Urea (mmol/L)	15.4 ± 10.7	12.6 ± 9.7	11.3 ± 7.4	<0.001
Sodium (mmol/L)	138.9 ± 3.8	139.3 ± 3.2	139.7 ± 2.9	0.003
Potassium (mmol/L)	4.4 ± 0.5	4.4 ± 0.5	4.3 ± 0.4	0.054
Glucose (mmol/L)	7.1 ± 3.4	6.5 ± 2.4	6.3 ± 2.1	0.003
NT-pro BNP (NPX)	3.1 ± 1.3	2.7 ± 1.2	2.5 ± 1.2	<0.001
Log_{10} TnI (pg/mL)	1.2 ± 0.5	1.1 ± 0.5	1.0 ± 0.5	<0.001
MRA	335 (54.7%)	355 (63.1%)	358 (60.8%)	0.011
Loop diuretics	448 (73.0%)	424 (75.2%)	429 (72.8%)	0.60
Digoxin	131 (21.3%)	104 (18.4%)	88 (14.9%)	0.016
Beta-blocker >=50%	224 (36.5%)	213 (37.8%)	246 (41.8%)	0.15
ACE/ARB >=50%	302 (49.2%)	317 (56.2%)	382 (64.9%)	<0.001
6MWT (m)	93.8 ± 91.5	325.9 ± 42.2	486.4 ± 75.6	-

Legend: BMI, body mass index; JVP, jugular venous pressure; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; HFH, heart failure hospitalization; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonist; ACEi/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker.

Supplemental Table 3. Multivariable linear regression for 9-month 6MWT as dependent variable

6MWT (9 months)	Std. beta-coefficient	Std. Err.	P-value
Age (per 10 yr)	-47.5 (-55.9 to -39.2)	4.2	<0.001
Male sex	56.5 (35.4 to 77.7)	10.7	<0.001
Peripheral edema	-60.9 (-83.6 to -38.1)	11.6	<0.001
NYHA III/IV	-107.1 (-130.4 to -83.9)	11.8	<0.001
Orthopnea	-39.7 (-71.9 to -7.5)	16.4	0.016
Peripheral artery disease	-59.7 (-90.3 to -29.1)	15.5	<0.001
Diabetes	-36.7 (-56.9 to -16.4)	10.3	<0.001
Sodium (per 1 mmol/L)	3.0 (0.3 to 5.7)	1.4	0.027
NT-proBNP (per NPX doubling)	-13.5 (-20.6 to -6.3)	3.6	<0.001

Model adjusted R^2 =0.38

Constant =253.4

The standardized beta-coefficient compares the strength of the effect of each individual independent variable to the dependent variable (6MWT). The higher the absolute value of the beta coefficient, the stronger the effect.

Supplemental Table 4. Cox-proportional hazards models for 9-month 6MWT

HFH or Death	N. (%) events	Crude HR (95%CI)	P-value	Adjusted HR (95%CI)*	P-value
Per each 50m less	411 (27.0%)	1.17 (1.15-1.20)	<0.001	1.12 (1.09-1.15)	<0.001
>396 m	74 (14.7%)	Reference	-	Reference	-
241-396 m	108 (21.4%)	1.83 (1.41-2.37)	<0.001	1.42 (1.08-1.84)	0.010
≤240 m	229 (44.9%)	3.86 (3.05-4.87)	<0.001	2.53 (1.98-3.23)	<0.001
Death	N. (%) events	Crude HR (95%CI)	P-value	Adjusted HR (95%CI)*	P-value
Per each 50m less	164 (10.8%)	1.21 (1.17-1.26)	<0.001	1.16 (1.12-1.20)	<0.001
>396 m	22 (4.4%)	Reference	-	Reference	-
241-396 m	45 (8.9%)	2.63 (1.66-4.15)	<0.001	2.08 (1.31-3.31)	0.002
≤240 m	97 (19.0%)	5.87 (3.87-8.91)	<0.001	3.87 (2.51-5.98)	<0.001

*Adjusted on the BIOSTAT-CHF risk model including: age, heart failure hospitalizations in previous year, systolic blood pressure, presence of peripheral edema, NT-proBNP, hemoglobin, sodium, HDL cholesterol, and the use of beta-blockers (https://biostat-chf.shinyapps.io/calc/).

Total n. =1,520; Tertiles n. ≤240m =510; 241-396m =505; >396m =505.

Supplemental Table 5. Characteristics of the study population by 6MWT changes between baseline and 9 months

6MWT (m)	Decrease (≤0 m)	Increase (>0 m)	p-value
N.	472	1247	
Age (years)	68.7 ± 11.2	66.8 ± 12.1	0.003
Male sex	364 (77.1%)	919 (73.7%)	0.15
BMI (Kg/m^2)	27.8 ± 5.1	28.1 ± 5.5	0.37
Heart rate (bpm)	77.0 ± 18.8	83.2 ± 21.7	<0.001
SBP (mmHg)	126.0 ± 20.2	125.2 ± 21.8	0.46
Pulmonary rales	196 (43.0%)	639 (52.6%)	<0.001
Peripheral edema	208 (52.5%)	585 (56.0%)	0.23
Elevated JVP	78 (23.4%)	274 (30.5%)	0.014
NYHA class III/IV	254 (54.6%)	738 (60.5%)	0.027
Orthopnea	118 (25.1%)	430 (34.5%)	<0.001
LVEF (%)	31.5 ± 9.9	30.3 ± 10.1	0.043
Ischemic HF	220 (46.6%)	512 (41.1%)	0.038
HFH in the last 12 months	185 (39.2%)	333 (26.7%)	<0.001
Atrial fibrillation	229 (48.5%)	508 (40.7%)	0.004
Previous stroke	40 (8.5%)	114 (9.1%)	0.67
Peripheral arterial disease	45 (9.5%)	116 (9.3%)	0.88
Hypertension	331 (70.1%)	746 (59.8%)	<0.001
Device therapy	129 (27.3%)	275 (22.1%)	0.021
Current smoking	59 (12.5%)	186 (14.9%)	0.40
Diabetes	166 (35.2%)	368 (29.5%)	0.024
COPD	76 (16.1%)	209 (16.8%)	0.74
Current malignancy	13 (2.8%)	45 (3.6%)	0.38
Hemoglobin (g/dL)	13.2 ± 1.7	13.4 ± 1.8	0.026
eGFR (ml/min/1.73m2)	63.5 ± 22.6	65.4 ± 22.9	0.14
Urea (mmol/L)	14.4 ± 9.3	13.4 ± 11.0	0.13
Sodium (mmol/L)	139.5 ± 3.6	139.3 ± 3.6	0.40
Potassium (mmol/L)	4.2 ± 0.5	4.2 ± 0.5	0.16
Glucose (mmol/L)	7.1 ± 3.2	7.0 ± 2.8	0.76
Total Cholesterol (mmol/L)	4.3 ± 1.2	4.4 ± 1.3	0.27
HDL cholesterol (mmol/L)	1.1 ± 0.3	1.1 ± 0.3	0.83
NT-pro BNP (NPX)	2.8 ± 1.2	2.8 ± 1.3	0.56
logTnI, mean ± SD	1.0 ± 0.5	1.1 ± 0.5	0.005
MRA	267 (56.6%)	663 (53.2%)	0.21
Loop Diuretics	472 (100.0%)	1241 (99.5%)	0.13
Digoxin	93 (19.7%)	244 (19.6%)	0.95
Beta-blocker	400 (84.7%)	1069 (85.7%)	0.61
Beta-blocker >=50% at 3 mo.	199 (42.2%)	462 (37.0%)	0.052
ACE/ARB	357 (75.6%)	935 (75.0%)	0.78
ACE/ARB >=50% at 3 mo.	266 (56.4%)	705 (56.5%)	0.95
Delta 6MWT (m)	-104.7 ± 108.6	130.0 ± 148.4	<0.001

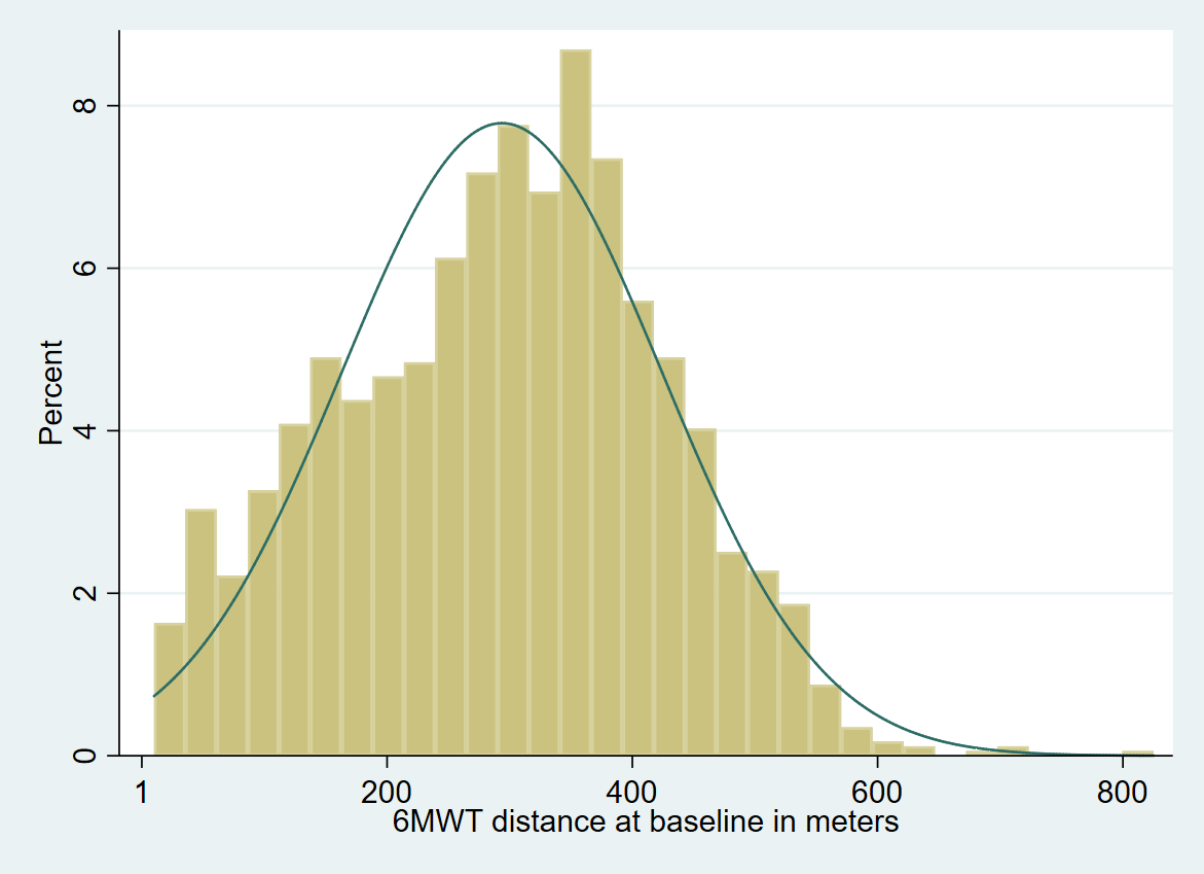
Legend: BMI, body mass index; JVP, jugular venous pressure; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; HFH, heart failure hospitalization; COPD, chronic

obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonist; ACEi/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker.

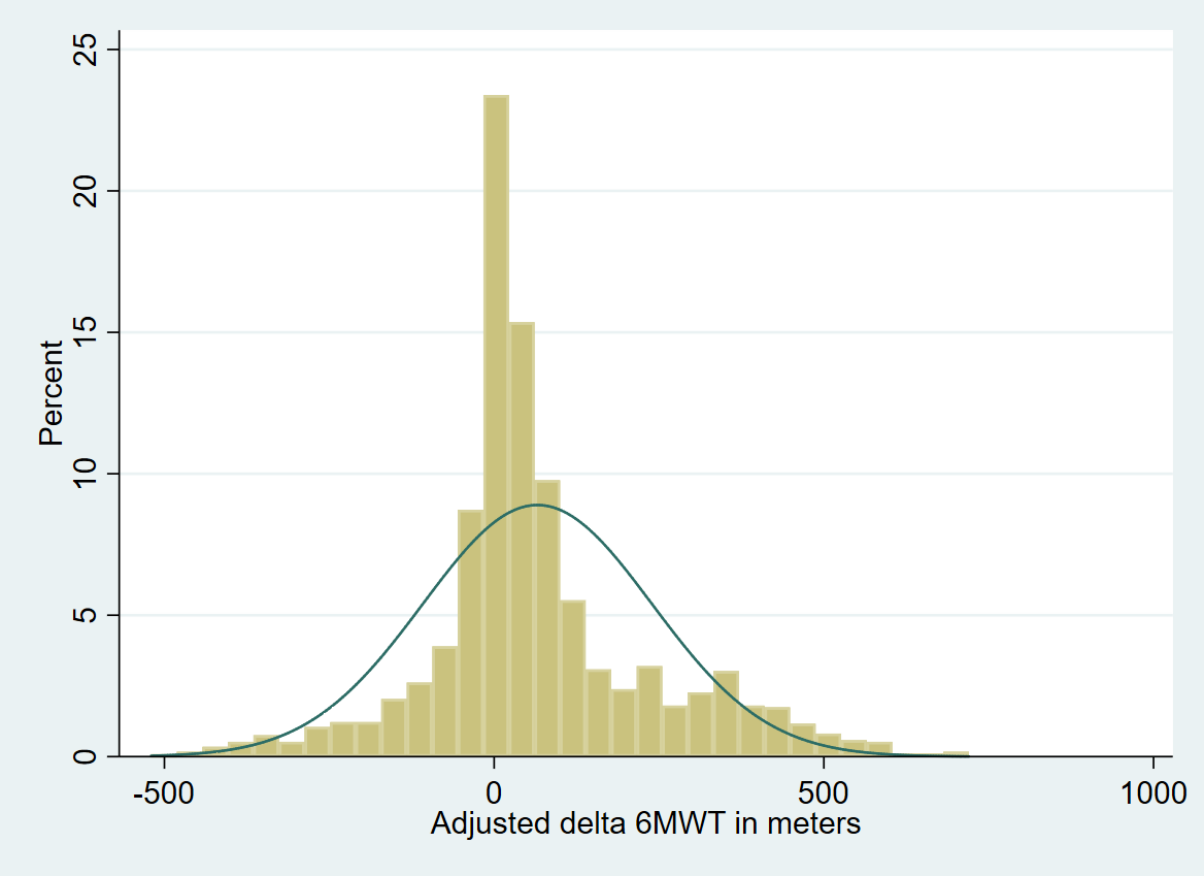
Supplemental Table 6. Logistic regression for 6MWT increase from baseline to 9 months

Variable	OR (95%CI) for 6MWT increase	p-value
Age (per 10 yr)	0.68 (0.60-0.77)	<0.001
Diabetes	0.58 (0.44-0.76)	<0.001
NT-proBNP (per NPX doubling)	0.89 (0.81-0.99)	0.03

Supplemental Figure 1. Baseline 6MWT distribution



Supplemental Figure 2. Delta 6MWT distribution



Adjusted delta = 6MWT distance at month 9 minus 6MWT distance at baseline adjusted on the baseline 6MWT distance value.