

# Short-Term Change in Distance Walked in 6 Min Is an Indicator of Outcome in Patients With Chronic Heart Failure in Clinical Practice

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<b>OBJECTIVES</b>	The purpose of this study was to investigate the prognostic value of change in distance walked in 6 min in chronic heart failure (CHF).
<b>BACKGROUND</b>	The strongest indication for the 6-min walking test (6MWT) is for measuring the response to therapeutic interventions in patients with CHF. Whether the increase in distance walked after a therapeutic intervention translates into improved clinical outcome is largely unknown.
<b>METHODS</b>	We studied 476 CHF patients with left ventricular systolic dysfunction who were referred to our institution for adjustment of heart failure therapy because of persisting or worsening symptoms. Adjustment of therapy involved four classes of drugs: angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, beta-blockers, loop diuretics, and aldosterone antagonists. A standardized 6MWT was performed at baseline and at discharge.
<b>RESULTS</b>	After $15.2 \pm 8$ days, the distance walked increased from $326 \pm 107$ m to $408 \pm 109$ m (+25%; $p = 0.001$ ). During a mean follow-up of 23.9 months, 94 patients died and 12 patients underwent cardiac transplantation. Among a set of variables, New York Heart Association functional class ( $p = 0.02$ ), serum creatinine concentration ( $p = 0.01$ ), left ventricular ejection fraction ( $p = 0.002$ ), distance walked at baseline ( $p = 0.0002$ ), and change in distance walked ( $p = 0.002$ ) were significant independent predictors of survival. When the patients were divided into two subgroups according to the median value of the distance walked at baseline, the increase in walking distance was significantly associated with survival only in the subgroup of patients who walked $<340$ m at baseline.
<b>CONCLUSIONS</b>	Our data indicate that repeating a 6MWT after drug intervention provides independent prognostic information in CHF patients with more compromised exercise capacity. (J Am Coll Cardiol 2006;48:99–105) © 2006 by the American College of Cardiology Foundation

The 6-min walking test (6MWT) is an easy to administer, safe, and inexpensive test reflective of daily life activities which can be performed by the majority of patients with chronic heart failure (CHF) (1,2). The 6MWT is widely used as a measure of functional status of patients with CHF (1). It has also been shown to provide prognostic information in several studies and has repeatedly been compared with cardiopulmonary exercise testing, although the information provided by the 6MWT and cardiopulmonary exercise testing should be considered complementary rather than duplicative (2–4). The strongest indication for the 6MWT is to measure the response to therapeutic interventions in patients with moderate to severe heart failure (4). Accordingly, it has also been used as a primary end point in clinical trials. In the clinical setting, a relevant question after pre- and post-treatment tests have been completed is whether the improvement in distance walked translates into fewer hospitalizations or improved survival. Data on such a relationship are still scarce. In the Cardiac Resynchronization in Chronic Heart Failure trial (5), the 6MWT was a primary end point. The patients assigned to cardiac resynchronization had a statistically significant improvement in the distance walked in 6 min, which was

apparent as early as after four weeks. Interestingly, such an improvement was followed by fewer deaths and a statistically significant lower risk of death or worsening heart failure requiring hospitalization during the follow-up.

The present study was undertaken to investigate the clinical significance of the change in the distance walked in 6 min after therapeutic intervention in a large population of patients with CHF due to left ventricular systolic dysfunction.

## METHODS

**Study population.** We studied 488 patients with CHF who were referred to our institution from other hospitals or by general practitioners for adjustment of heart failure therapy because of persisting or worsening symptoms and/or for clinical evaluation, even for their potential candidacy for heart transplantation. The following prospective selection criteria were used. Patients were included if they had symptoms of heart failure and a left ventricular ejection fraction (LVEF) of  $<40\%$ , as assessed by two-dimensional echocardiography. Patients with recent myocardial infarction ( $<3$  months), angina pectoris- or exercise-induced myocardial ischemia, surgically uncorrected valvular or congenital heart disease, suspected active myocarditis, obstructive, hypertrophic or restrictive cardiomyopathy, clinical manifestations of peripheral or cerebrovascular disease, or other noncardiac diseases limiting the ability to perform a 6MWT were excluded.

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#### Abbreviations and Acronyms

6MWT	= 6-min walking test
ACEI	= angiotensin-converting enzyme inhibitor
ARB	= angiotensin II receptor blockers
CHF	= chronic heart failure
LVEF	= left ventricular ejection fraction
VCO <sub>2</sub>	= exercise carbon dioxide output
VO <sub>2</sub>	= exercise oxygen consumption

Adjustment of therapy during hospitalization principally involved four classes of drugs: angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs), beta-blockers, loop diuretics (furosemide), and aldosterone antagonists. During hospitalization, treatment with ACEIs, ARBs, or both and beta-blockers was implemented or titrated to maximally tolerated dose by the in-hospital referring heart failure specialist. Furosemide was prescribed as needed, either orally or intravenously, and the dose personalized to obtain the maximal relief of symptoms and improvement of congestive state. At discharge, ACEIs and/or ARBs were prescribed to 441 patients (92.6%), beta-blockers to 338 (71%), furosemide to 403 (84.7%), and spironolactone to 218 (45.8%). A combination of ACEIs or ARBs and beta-blockers was prescribed to 310 patients (65%). Enalapril and ramipril were the most frequently prescribed ACEIs; their median daily dosage was 20 mg and 5 mg, respectively. The following beta-blockers (number of patients; percentage of the recommended dose) were prescribed: carvedilol ( $n = 315$ ; 32% of 50 mg daily), metoprolol ( $n = 15$ ; 55% of 200 mg daily), and bisoprolol, atenolol, or sotalol for the remaining 8 patients. The median daily dosages of furosemide and spironolactone were 50 mg and 25 mg, respectively. A rehabilitative intervention, principally aimed at preventing functional deterioration during hospitalization, was also offered to all patients. Each participant was given a low-intensity individual exercise program, supervised by a physiotherapist, consisting of respiratory, mobilization, musculoskeletal flexibility, movement coordination, and/or callisthenic exercises performed in 2 to 3 sessions daily, for 15 to 30 min at each session, 5 times per week. In more severely ill patients, such a program was started once symptoms at rest had subsided. During each session, heart rate and rhythm, symptoms, and perceived exertion were monitored.

The study was approved by the local institutional review board, and a standard informed consent to 6MWT and cardiopulmonary exercise test was obtained from all patients.

**Six-minute walking test.** The walking test was performed in an indoor unobstructed 60-m long corridor, according to the recommendations of Guyatt et al. (6) and the American Thoracic Society (4). All patients were informed in a standardized manner of the purpose and method of the test before the test was performed. They were instructed to walk the corridor from one end to the other at their own pace, as many times as possible, in the permitted time. The patients

were advised on the possibility of slowing down the pace and stopping or resting as needed to resume walking as soon as they felt they were able to do so. After 6 min had elapsed, patients were instructed to stop walking, and the total distance walked was measured. The test was supervised by a physical therapist who encouraged the patients in a standardized fashion at regular intervals. A baseline 6MWT was performed within 24 h of hospital admission or once symptoms at rest had subsided and fluid retention had resolved, and a second test was performed at discharge.

**Cardiopulmonary exercise testing.** Treadmill exercise testing with expiratory gas analysis was performed using the modified Bruce protocol (7). Patients were encouraged to continue exercising until dyspnea or fatigue forced them to stop. Those patients who were not familiar with exercise testing underwent a preliminary one. Oxygen uptake (VO<sub>2</sub>) and carbon dioxide output (VCO<sub>2</sub>) were measured breath-by-breath by an automated system (System 2900; Sensor Medics, Anaheim, California). Measurements were taken at rest and every 20 s throughout exercise and recovery. Anaerobic threshold was defined as the point at which the respiratory exchange ratio (VCO<sub>2</sub>/VO<sub>2</sub>) was 1.00 or by the V-slope method (8). Peak VO<sub>2</sub> was defined as the VO<sub>2</sub> measured at the end of exercise. A total of 199 patients (41.8%) did not undergo cardiopulmonary exercise testing during the index hospitalization because of the severity of worsening symptoms at entry, noncardiac reasons, or refusal.

**Statistical analysis.** The primary end point was all-cause mortality. The vital status was ascertained by interviewing patients, their relatives, and/or treating physician or by direct knowledge. In survival analysis, heart transplantation was considered a censored event. Continuous variables are expressed as mean  $\pm$  standard deviation. To identify the determinants of change in distance walked, a forward stepwise multivariable linear regression analysis was performed. The following variables were included in the analysis: age, gender, New York Heart Association (NYHA) functional class, LVEF, distance walked at baseline, time interval between baseline and the second 6MWT, and change in drug therapy. Survival curves were calculated by the Kaplan-Meier method. Univariate and multivariate survival analyses were performed using the Cox proportional hazards regression model. The following variables were considered in the univariate analysis: age, gender, NYHA functional class, LVEF, left bundle branch block, distance walked at baseline, change in distance walked, peak VO<sub>2</sub>, nonsustained ventricular tachycardia on Holter monitoring, hemoglobin, serum sodium concentration, serum creatinine concentration, total cholesterol level, and treatment with ACEIs or beta-blockers at discharge. Variables with a  $p$  value of  $<0.1$  at univariate analysis were entered into the multivariate Cox model. For survival analyses, continuous variables were dichotomized according to their median value. Analyses were performed using the SPSS version 8.0 statistical package (SPSS Inc., Chicago, Illinois).

**Table 1.** Baseline Characteristics

	Mean ± SD	Median Value	n (%)
<b>Demographic</b>			
Age	63.6 ± 11.9		
>70 yrs			164 (34.7)
Gender (male/female)			376/100
<b>Clinical history</b>			
Diabetes			75 (15.7)
Hypertension			193 (40.5)
Chronic obstructive pulmonary disease			47 (9)
Previous cerebrovascular disease			20 (4)
Previous myocardial infarction			209 (44)
Previous CABG			106 (22)
Implantable cardioverter-defibrillator			61 (13)
<b>Cardiovascular assessment</b>			
Cause of heart failure			
Ischemic			229 (48.1)
Idiopathic dilated cardiomyopathy			184 (38.7)
Hypertensive			35 (7.4)
Surgically corrected valvular disease			28 (5.7)
Body mass index	26.7 ± 5.2		
NYHA functional class	2.5 ± 4		
LVEF (%)	29.8 ± 9.7	25	
LVEF <30%			237 (49.8)
6-min walking test			
Distance walked at baseline (m)	326.8 ± 107	340	
<300 m at baseline			175 (36.8)
Peak VO <sub>2</sub> (ml/kg/min)	18.3 ± 4.5		
Atrial fibrillation			84 (17.6)
LBBB			122 (25.2)
NSVT at Holter monitoring			120 (25.2)
<b>Biochemical measurements</b>			
Hemoglobin (g/dl)	13.5 ± 1.8	13.6	
Serum sodium concentration (mmol/l)	137.6 ± 3.5	135	
Serum creatinine concentration (mg/dl)	1.14 ± 0.5	1.2	
Total cholesterol level (mg/dl)	179.4 ± 43	175	

CABG = coronary artery bypass graft; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; NSVT = nonsustained ventricular tachycardia; NYHA = New York Heart Association; VO<sub>2</sub> = exercise oxygen consumption.

## RESULTS

Twelve of the 488 patients were lost to follow-up. The baseline characteristics of the remaining 476 patients are reported in Table 1. Mean age was 63.6 ± 11.9 years; 34.7% of the patients were over 70 years old, and 79% were men. Ischemic heart disease was the most frequent cause of heart failure (48.1%), followed by idiopathic dilated cardiomyopathy (38.7%), hypertension (7.4%), and surgically corrected valvular disease (5.8%). Mean NYHA functional class and LVEF were 2.5 ± 4 and 29.8 ± 9.7%, respectively. Two hundred thirty-seven patients (49.7%) had severe left ventricular dysfunction (LVEF <30%). Eighty-four patients (17.6%) were in atrial fibrillation, and 61 (13%) had an implanted cardioverter defibrillator. At baseline, 175 patients (36.8%) walked <300 m. Medication use is reported in Table 2. Two hundred twenty-two patients (46.6%) were already on beta-blocker treatment at baseline, 372 (78.1%) on ACEIs and/or ARBs, and 388 (81.5%) on furosemide. During hospitalization, beta-blocker treatment was newly prescribed to 116 (24.3%), ACEIs or ARBs to 69 (14.5%), and furosemide to 16 (3.4%) patients. In addition, the daily dosage of beta-blockers was doubled and that of

ACEIs or furosemide increased in 25.7% (57 of 222), 19.9% (74 of 372), and 21.9% (85 of 388) of the patients who were already treated with these drugs at hospital entry, respectively. At baseline, only 199 patients (41.8%) were on

**Table 2.** Medication Use

	At Entry	At Discharge
ACEIs	306 (64.3)	375 (78.8)
Ramipril	166 (34.9)	203 (42.6)
Enalapril	131 (27.5)	147 (30.9)
Others	20 (4.2)	25 (5.3)
ARBs	62 (13)	73 (15.3)
ACEIs and/or ARBs	372 (78.1)	441 (92.6)
Beta-blockers	222 (46.6)	338 (71)
Carvedilol	199 (41.8)	315 (66.2)
Metoprolol	15 (3.2)	15 (3.2)
Others	8 (1.7)	8 (1.7)
ACEIs/ARBs or beta-blocker	308 (64.7)	465 (97.7)
ACEIs/ARBs and beta-blocker	199 (41.8)	310 (65.1)
Furosemide	388 (81.5)	403 (84.7)
Aldosterone antagonists	146 (30.7)	218 (45.8)
Statins	—	179 (37.8)

Values are n (%).

ACEI = angiotensin-converting enzyme inhibitor; ARBs = angiotensin II receptor blockers.

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**Table 3.** Results of Univariate Cox Proportional Hazards Survival Analysis

	Regression Coefficient	Standard Error	Hazard Ratio (95% CI)	p Value
Age >65 yrs	0.74	0.21	2.1 (1.37–3.21)	0.00006
Male gender	−0.07	0.25	0.92 (0.56–1.52)	0.76
NYHA functional class III/IV	0.95	0.21	2.59 (1.70–3.94)	0.00001
LVEF <25%	0.93	0.21	2.53 (1.65–3.87)	0.00001
LBBB	0.42	0.23	1.53 (0.95–2.45)	0.07
Distance walked at baseline <340 m	1.27	0.24	3.54 (2.19–5.72)	0.000001
Change in distance walked <70 m	0.62	0.22	1.87 (1.21–2.88)	0.0045
Peak VO <sub>2</sub> <14 ml/kg/min*	0.38	0.63	1.4 (0.41–5.15)	0.54
Nonsustained ventricular tachycardia	−0.04	0.23	0.95 (0.59–1.52)	0.84
Hemoglobin <13.6 g/dl	0.42	0.21	1.52 (1.00–2.29)	0.04
Serum sodium concentration <135 mmol/l	0.65	0.21	1.92 (1.26–2.92)	0.0023
Serum creatinine concentration >1.2 mg/dl	0.96	0.20	2.61 (1.73–3.94)	0.00001
Total cholesterol level <175 mg/dl	0.48	0.21	1.60 (1.06–2.43)	0.02
No beta-blockers at discharge	0.44	0.21	1.56 (1.03–2.36)	0.035
No ACEIs at discharge	0.18	0.24	1.2 (0.74–1.94)	0.44

\*Analysis performed on 201 patients.

CI = confidence interval; other abbreviations as in Tables 1 and 2.

treatment with the association of ACEIs/ARBs and beta-blockers compared with 310 (65.1%) at discharge.

During a mean follow-up of 23.9 months, 94 patients (19.7%) died and 12 (2.5%) underwent cardiac transplantation.

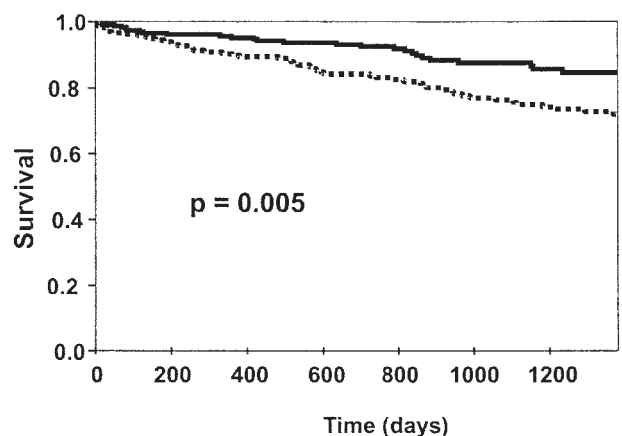
Two hundred seventy-seven patients underwent cardiopulmonary exercise testing at a mean of 14 ± 9 days after hospitalization. Seventy-six, in whom the anaerobic threshold could not be detected, were excluded from the analysis. In the remaining 201 patients, the attained peak VO<sub>2</sub> was 18.3 ± 4.5 ml/kg/min. During follow-up, 20 of them (10%) died and 7 (3.5%) underwent heart transplant.

**Six-minute walking test.** Baseline 6MWT was performed at a mean of 2.4 ± 3.8 days (median 1 day) after hospitalization. After a mean interval of 15.2 ± 8 days between the two 6MWTs, the distance walked in 6 min increased from 326.8 ± 107.1 m to 408.3 ± 109.2 m (p = 0.001), with a mean increase of 81.5 ± 56.3 m (+25%). The median value of the distance increase was 70 m. The rate of patients walking <300 m decreased from 36.8% at baseline (175 of 476) to 12.8% at discharge (61 of 476) (p < 0.001). Forward stepwise regression analysis identified age (p = 0.0001), male gender (p < 0.001), distance walked at baseline (p = 0.0001), and change in beta-blocker/ACEI therapy (i.e., new prescription or increase in daily dosage of beta-blockers and ACEIs) (p = 0.0001) as independent significant predictors of the increase in distance walked. Age and distance walked at baseline were inversely related to the increase in distance walked.

**Univariate survival analysis.** The results of univariate analysis are reported in Table 3. Age, NYHA functional class, LVEF, distance walked at baseline, change in distance walked, hemoglobin, serum sodium concentration, serum creatinine concentration, total cholesterol level, and treatment with beta-blockers were significant univariate predictors of prognosis. Survival was significantly better in patients who increased the distance walked in 6 min by more than 70 m (median value) compared with those who did not

(Fig. 1). The survival curves began to diverge as early as five months after and continued to diverge during the following months. When the patients were divided into two subgroups according to the median value of the distance walked at the baseline test, change in walking distance was significantly associated with survival only in the subgroup who walked <340 m at baseline (Fig. 2). Estimated survival probability at 1, 2, and 3 years as a function of change in distance walked is shown in Figure 3.

**Multivariate survival analysis.** Table 4 summarizes the results of the multivariate analysis. The NYHA functional class, serum creatinine concentration, LVEF, distance walked at baseline, and change in distance walked were significant independent prognostic predictors. According to the Cox model, each 50-m between-test increment in distance walked resulted in a 23% increased likelihood of survival. Change in distance walked remained an independent and incremental predictor of prognosis (p = 0.003), even after adjustment for continuous distance walked at

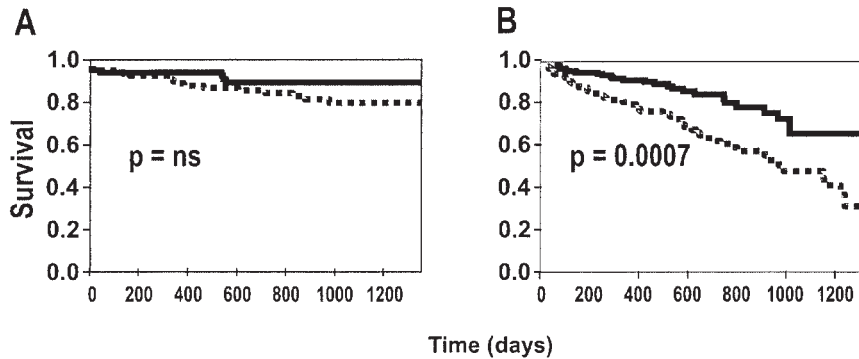


**Figure 1.** Survival according to the median value (70 m) of the increase in 6-min walking distance following drug intervention. **Solid line** = >70 m; **dotted line** = <70 m.

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T4



**Figure 2.** Survival according to the median value (70 m) of the increase in distance walked following drug intervention in the two subgroups of patients who walked >340 m (A) or <340 m (B) at baseline. Solid line = >70 m; dotted line = <70 m.

baseline and change in beta-blocker/ACEI therapy by Cox multivariate analysis.

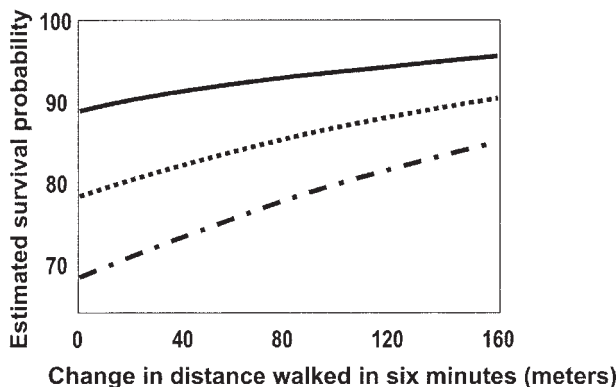
### DISCUSSION

The 6MWT is widely applied in clinical and research settings for assessing functional status, prognosis, and the response to therapeutic interventions in patients with CHF (1-4). A high concordance between change in distance walked following therapeutic interventions and the results of symptom assessment has been found in clinical trials (9). Zugck et al. (10) demonstrated that a change in 6MWT predicts change in peak  $\text{VO}_2$ . Moreover, Gualeni et al. (11) showed 6MWT distance, but not peak  $\text{VO}_2$ , to be sensitive to short-term changes in drug therapy. Little is known about the relationship between change in walking distance and subsequent clinical outcome.

To our knowledge, this is the first study to investigate the prognostic importance of the change in distance walked in 6 min in patients with CHF. Our data indicate that, in a clinical practice setting, short-term improvement in distance walked after drug intervention is independently associated with improved survival. The rehabilitative intervention, though of low intensity, may have contributed to improving submaximal exercise tolerance by preventing functional deterioration that may result from prolonged hospitalization

or bedrest. Survival of the patients who increased distance walked by more than 70 m (median value) was significantly better than that of patients who did not. At 1 and 2 years, a survival rate of 96% and 88% was observed in the former compared with 90% and 76% in the latter subgroup. Each 50-m between-test increment in distance walked resulted in a 23% increased likelihood of survival. These data parallel those by Pinto-Plata et al. (12) in patients with severe chronic obstructive pulmonary disease in whom a higher rate of decline in walking distance independently predicted a higher mortality. It is important to note that the association between change in walking distance and survival was definitely stronger among the more compromised patients, i.e., those who walked <340 m at baseline. Conversely, no prognostic impact of change in distance walked was seen for less compromised patients. The observed significant inverse relationship between distance walked at baseline and increase in walking distance confirms this figure. This is in line with a recent review showing that the 6MWT may be of greater value in patients with more advanced heart failure, where it may function as a maximal exercise test (9,13). Quite surprisingly, in the subgroup of patients who underwent cardiopulmonary exercise testing, peak  $\text{VO}_2$  dichotomized at 14 ml/kg/min was not statistically significant in terms of predicting survival. However, it should be considered that only 20 fatal events occurred in this subgroup and that 82% of the patients were being treated with beta-blocker therapy. Currently, the prognostic impact of peak  $\text{VO}_2$  and cut-off value of 14 ml/kg/min among patients treated with beta-blockers is under close reevaluation (14,15).

Some key points of the present study are worth noting. First, apart from the seminal multicenter study of Bittner et al. (16) including 833 patients, the present study is the largest to date to look at the relationship between 6MWT and survival in CHF. Second, this was a single-center study and all the tests were administered in a standardized manner by the same physical therapist to each patient, allowing for homogeneity in test administration. Third, we observed a mean increase in walking distance of 25%, which is far higher than the 10% threshold value required to confirm



**Figure 3.** Estimated 1-year (solid line), 2-year (dotted line), and 3-year (dashed line) survival probability as a function of change in distance walked in 6 min, according to univariate Cox model.

**Table 4.** Results of Multivariate Cox Proportional Hazards Survival Analysis

	Regression Coefficient	Standard Error	Hazard Ratio (95% CI)	p Value
NYHA functional class III/IV	0.51	0.22	1.67 (1.07–2.59)	0.02
Serum creatinine concentration >1.2 mg/dl	0.51	0.22	1.68 (1.09–2.59)	0.01
LVEF <25%	0.71	0.23	2.04 (1.29–3.21)	0.002
Distance walked at baseline <340 m	0.97	0.25	2.66 (1.6–4.42)	0.0002
Change in distance walked <70 m	0.70	0.22	2.03 (1.29–3.18)	0.002

CI = confidence intervals; other abbreviations as in Table 1.

with 99% confidence that a real change has occurred (17). Finally, at discharge, beta-blockers were prescribed to 71% of the patients and ACEIs and/or ARBs to 92.6%. Sixty-five percent of the patients received both beta-blockers and ACEIs and/or ARBs. These findings compare very favorably with ACEI and beta-blocker prescription rate in previous studies of heart failure in clinical practice (14,18–22). The daily doses of these drugs in the present study are in line with such studies (14,18–23).

From a general point of view, our findings may appear to be inconsistent with those of clinical trials that, as a whole, do not support a concordance between increased distance walked and improved survival (9). Treatment with ACEIs or beta-blockers, for example, is usually recognized as having a great impact on mortality and morbidity without improving exercise capacity (13), even though both ACEIs and beta-blockers were found to significantly improve submaximal exercise tolerance, as assessed by the distance walked in 6 min, in some studies (24–26). Perhaps a concordance between improved submaximal exercise capacity and improved survival may be better appreciated with cardiac resynchronization therapy (5,9). Some important differences between clinical trials and our study should, however, be recognized. Whereas the patients included in clinical trials are in stable clinical conditions, background therapy has been optimized, and the doses maintained stable before they are entered into the study, most of our patients had persisting or worsening symptoms at admission, requiring a therapeutic intervention which involved four classes of drugs. This implies a greater potential for improvement for patients included in our study. Actually, the magnitude of the effect of therapy on distance walked in most clinical trials (9), expressed either as absolute value or as percentage change, was substantially lower than what we measured (+81 m, +25%). Therefore, the magnitude of the change may not have been large enough to allow a possible concordance between 6MWT results and survival to be appreciated in clinical trials (9). Finally, the relationship between change in distance walked and subsequent clinical outcome is difficult to specifically address in clinical trials, because usually no serial tests are carried out and the timing of the on-treatment 6MWT coincides with the end of follow-up.

**Study limitations.** We failed to have two repeated 6MWT at baseline, and this may be a limitation of the study. However, the procedure of repeating the walking test may

be of discomfort for the patients, especially for those with more severely impaired functional capacity. In our study, 37% of patients walked less than 300 m at baseline, i.e., were at the worst functional and prognostic level (16). Moreover, the 6MWT has been found to be a reproducible measure in CHF in previous studies. A reproducibility of 0.96 was observed by Cahalin et al. (27) in patients with advanced heart failure. O’Keefe et al. (28) found a reproducibility of 0.91 in a population of very elderly and frail CHF patients, i.e., those very likely to present variability in distance walked. Opasich et al. (17) and Rostagno et al. (29) found that the difference between two walking test measurements performed on the same day or on two consecutive days does not exceed 5%, setting a 10% threshold value for the occurrence of a real change (17). In our study, a 25% increase in distance walked was observed. Finally, the validity of a single 6MWT has been confirmed in several studies (5,9,16,25,29), even in patients with advanced heart failure (27). Because individualized physical therapy could have contributed to the observed improvement in submaximal exercise capacity, some caution is required in extrapolating the prognostic utility of measuring change in distance walked to other patients who receive medications only. In addition, in our study, an in-hospital 6MWT was repeated after a mean of 15 days; whether repeating 6MWT very early during a hospitalization or later, on an outpatient basis, would provide the same prognostic information remains undefined. Because classifying the cause of death by phone interview of patient relatives and/or treating physician could be problematic, we assessed all-cause mortality, which, however, is an objective and unbiased end point. Moreover, it should be acknowledged that patients were on average rather young and the majority were men. Finally, we failed to include other known predictors of prognosis in the analysis such as the degree of neurohumoral activation.

**Conclusions.** In conclusion, our data indicate that repeating a 6MWT after drug intervention provides independent prognostic information in CHF patients with more compromised exercise capacity, thus supporting the usefulness of standardized 6MWT in the process of multiparametric assessment of the effectiveness of therapeutic interventions in clinical practice.

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