

# Six-minute walk test distance and outcome in patients with chronic heart failure

## Valeur pronostique du test de marche de six minutes dans l'insuffisance cardiaque chronique

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### Résumé

**Introduction :** L'insuffisance cardiaque (IC) chronique est caractérisée par une altération de la capacité fonctionnelle pouvant être évaluée par des tests d'effort.

**Objectif :** Evaluer la valeur pronostique de la distance parcourue lors du test de marche de six minutes (TDM6) en termes de mortalité dans l'IC chronique.

**Méthodes :** Il s'agissait d'une étude de cohorte prospective chez les patients hospitalisés pour IC aigue et qui avaient réalisé un TDM6 à la sortie.

**Résultats :** Soixante et un patients [52% féminin, âge moyen :  $46,9 \pm 14,1$  ans, fraction d'éjection ventriculaire gauche (FEVG):  $32,4 \pm 8,2$  %, distance du TDM6:  $336,3 \pm 65$  mètres] étaient suivis sur une période de  $277,6 \pm 129,8$  jours. Quatorze patients (30,2 pourcent personne-années) étaient décédés et 21 patients (45,3 pourcent personne-années) réadmis. Les patients dont la distance du TDM6 était  $\leq 300$  m ( $n = 21$ ) avaient une mortalité de 57,1% contre 5% chez ceux dont la distance était  $> 300$  m ( $p < 0,001$ ) et la réadmission était de 57,1% contre 22,5 % respectivement ( $p = 0,02$ ). L'analyse multivariée selon le modèle Cox montrait que la distance  $\leq 300$  m (adjusted HR = 16.75, 95% CI = 3.42 - 81.94,  $p < 0.001$ ), le stade III de la New York Heart Association ( $p = 0.03$ ), la FEVG abaissée ( $p = 0.002$ ) étaient indépendamment associés au décès.

**Conclusion :** Une faible distance de marche à la sortie d'hospitalisation est un facteur prédictif de mortalité dans l'IC chronique.

### Summary

**Introduction:** Chronic heart failure (CHF) is characterized by impaired functional capacity that can be evaluated by exercise tests.

**Aims:** To assess the value of the six-minute walk test(6-MWT) distance in predicting mortality in patients with CHF

**Methods:** We did a prospective cohort study in patients hospitalized with acute decompensated heart failure and who underwent a 6-minute walk test at their discharge. Outcome of interest was death.

**Results:** Sixty-one patients (52% females, mean age  $46.9 \pm 14.1$  years, mean left ventricular ejection fraction  $32.4 \pm 8.2\%$ , mean 6-MWT distance  $336.3 \pm 65$  meters) were followed-up for a  $277.6 \pm 129.8$  days' period. Fourteen patients (30.2 percent person-years) died and 21 patients (45.3 percent person-years) were readmitted. In patients whose 6-MWT distance was  $\leq 300$  m ( $n= 21$ ), the mortality rate was 57.1% versus 5% in those who walked  $> 300$  m ( $p < 0.001$ ), and readmission was 57.1% versus 22.5 % respectively ( $p = 0.02$ ). Multivariate Cox regression analysis showed that 6-MWT distance  $\leq 300$  meters (adjusted HR = 16.75, 95% CI = 3.42 - 81.94,  $p < 0.001$ ), NYHA class III ( $p = 0.03$ ), lower LVEF ( $p = 0.002$ ) were independent predictors of death.

**Conclusion:** A lower six-minute walk distance at hospital discharge is an independent predictor of mortality in patients with CHF.

### Mots-clés

Test de marche de six minutes ; insuffisance cardiaque ; mortalité ; réadmission ; Afrique.

### Keywords

Six-minute walk test; heart failure; mortality; readmission; Africa.

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## INTRODUCTION

Chronic heart failure (CHF) is a major public health concern [1,2] and remains a severe disease with poor outcome despite huge progress in its management [2,3]. Its prognosis is strongly correlated with the functional capacity [4,5]. Assessing functional capacity is a key step for cardiac rehabilitation intervention which contributes to reduce cardiovascular events and re-hospitalizations in patients with CHF. Cardiopulmonary exercise test is known as the 'gold standard' method to assess the functional capacity. [6]. The value of peak oxygen uptake (VO<sub>2</sub>) derived from the cardiopulmonary exercise testing provide an important prognostic information in patients with CHF [7]. Data have demonstrated the important prognostic value of both peak VO<sub>2</sub> and six-minute walk test (6-MWT) in predicting cardiac morbidity and mortality in patients with CHF [8-10]. Moreover, it has been shown that CHF patients with a 6-MWT distance < 300 meters had an increase in mortality and morbidity [11-14]. However, peak VO<sub>2</sub> is more difficult to perform in the field, expensive and not available particularly in some low-income countries with less equipped health facilities. Conversely, the 6-MWT which is safe, simple, well accepted by the patients, and probably better correlate with patient's symptoms [15-17] could be a low-cost alternative for the prescription of aerobic exercise in patients with HF [18]. The assessment of the prognostic importance of 6-MWT distance is not common in Sub-Saharan African (SSA) patients with CHF. Thus, the present study aims to assess for the first time the value of the 6-MWT distance in predicting mortality in those patients in Burkina Faso.

## METHODS

### Study population

From december 1, 2013 to march 31, 2014, we prospectively enrolled into the study, patients with CHF who attended the inpatients' unit of the department of cardiology, Yalgado Ouédraogo University Hospital. Patients hospitalized for congestive heart failure regardless of the etiology, with left ventricular ejection fraction (LVEF) ≤ 45% and under 70 years old and who were in stable clinical condition at discharge, were included. Non-inclusion criteria comprised acute coronary syndrome (< one month), decompensated heart failure, uncontrolled hypertension (BP > 180/100 mmHg), musculoskeletal and neurologic disorders forbidding physical exercise. We did an age cut-off of 70 years due to the fact that patients >70 years old have more frequent physical and mental disabilities and other comorbidities which preclude walk. Enrolled patients received individualized medical treatment of heart failure accordingly [angiotensin-converting enzyme

inhibitors/angiotensin receptor blockers (93.4%), digoxin (36.1%), spironolactone (100.0%), loop diuretic (100.0%), beta blockers (4.9%), amiodarone (14.8%), antiplatelet (42.6%), vitamin K antagonists (57.4 %)] including dietary prescriptions.

### Six-minute walk test

We used the American Thoracic Society's guidelines [19] to obtain the 6-MWT distance measurements at the time of hospital discharge. The 6-MWT was administered on a flat rectangular floor with a track length of 82 meters. The track was marked every three meters so that the total distance walked can be easily calculated. Patients were instructed to walk as far as possible at their own pace according to their tolerance to exercise in the allotted time of six minutes. The 6-MWT was performed under the control of a study physician who provided encouraging comments to the patients during the test. They were allowed to stop and rest or reduce their walking speed in case of discomfort. Prior to the test, patients observed a 10-minutes rest sitting near the starting point of the walk. The test procedures were explained to all patients in advance. After six minutes had elapsed, patients were instructed to stop walking and the total distance walked was recorded to the nearest meter (m) forward.

### Study process

On the eve of their discharge from hospital and prior to enrollment into the study, an oral informed consent was obtained from all study subjects. Thereafter, patients were assessed clinically. LVEF was obtained by echocardiography using either the Teichholz's method or Simpson's 2D formula as appropriate. A pre-test was performed in order to familiarize patients with the floor. On discharge day, an enrollment 6-MWT was performed. Patients were counselled on their health and given more information on their illness and therapeutic prescriptions. Outpatient's follow-up appointments were scheduled by cardiologists every one to three months' period (depending on the severity of their symptoms) during which clinical check-ups were done and treatment adjusted as needed. The primary endpoint was mortality during the observational follow-up period. Data on death were collected prospectively by checking the in-hospital admission registry and patients' healthcare records. In some cases, phone contact was used to catch this information from the patients or their relatives.

### Statistical analysis

Data were analyzed through EPI INFO version 7 and R version 3.2.2 software. Continuous variables were reported as means ± SD and categorical data as percentages. Differences between variables were determined using Fisher's exact, Chi square and Student

tests accordingly. Kaplan-Meier method was used to construct curves and log-rank test to compare survival between stratified groups. Cox proportional hazards regression models were used to estimate the relative risk of death. We used Martingales and Schoenfeld residuals tests to assess respectively the log-linearity and proportional hazard assumptions. Statistical significance was defined as a two-tailed p-value of  $< 0.05$ .

### Ethical aspects

The study protocol was approved by The Research Ethics Committee of Yalgado Ouédraogo University Hospital and was conducted in accordance with the internationally established principles for Good Clinical Practice, which had their origin in the Declaration of Helsinki of the World Medical Association.

## RESULTS

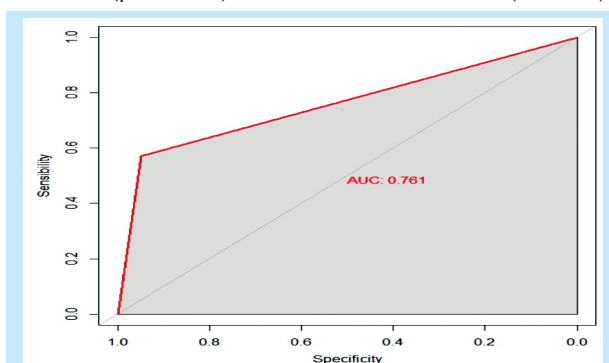
Overall, sixty-one patients with CHF were included in analysis process. Two patients discontinued the test due dyspnea and fatigue associated with cramps. No serious adverse event occurred during the 6-MWT process and one patient was lost to follow-up. The mean age was  $46.9 \pm 14.1$  years (extremes: 21 - 70). Thirty-two patients (52 %) were female. The mean LVEF was  $32.4 \pm 8.2$  % (extremes: 13 - 45). The mean 6-MWT distance was  $336.3 \pm 65$  meters (extremes: 194 - 480). Patients' baseline characteristics are shown in Table 1.

**Table 1:** Baseline characteristics of all 61 patients with chronic heart failure

Characteristic	Values
Number of patients	61
Age (years) mean $\pm$ SD	$46.9 \pm 14.1$ (21 - 70)
Female sex (%)	32 (52)
NYHA class (%)	
II	46 (75.4)
III	15 (24.6)
Atrial fibrillation (%)	15 (24.6%)
LVEF (%) mean $\pm$ SD	$32.4 \pm 8.2$ (13 - 45)
TAPSE (mm) mean $\pm$ SD	$16.16 \pm 4.28$ (9 - 27)
SPAP (mmHg) mean $\pm$ SD	$52.1 \pm 12.4$ (25 - 98)
Primary heart disease (%)	
Ischemic heart disease	10 (16.4)
Hypertensive heart disease	20 (32.8)
Peripartum cardiomyopathy	10 (16.4)
Rheumatic valvular heart disease	12 (19.6)
Others*	9 (14.8)
<b>6-MWT distance (m) mean <math>\pm</math> SD</b>	<b><math>336.3 \pm 65</math> (194 - 480)</b>

ventricular ejection fraction; TAPSE: tricuspid annulus plane systolic excursion; SPAP: systolic pulmonary arterial pressure; \* Including idiopathic dilated cardiomyopathy and myocarditis; 6-MWT: 6-minute walk test.

The mean follow-up period was  $277.6 \pm 129.8$  days (extremes: 2 - 403 days) with a total follow-up time of 16932 days (46.4 years). At the end of follow-up, 14 patients (30.2 percent person-years) had died (worsening heart failure = 5; ventricular tachycardia = 3; sudden death = 6) and 21 patients (45.3 percent person-years) were readmitted to hospital for heart failure decompensation. Receiver operating characteristic curve analysis of the relation between the 6-MWT distance at discharge and mortality at the end of follow-up is shown in figure 1. For this covered distance [area under the curve (AUC) = 0.76; 95% CI = 0.65 - 0.87;  $p < 0.001$ ], the optimal cut-point for predicting mortality was 300 m with sensitivity of 0.86 and specificity of 0.81. Patients who died were older and had higher New York Heart Association (NYHA) functional class, lower LVEF, higher ischemic heart disease, lower TAPSE and lower 6-MWT distance ( $p < 0.001$ ) than those who survived (Table 2).



**Figure 1:** Receiver operating characteristic curve showing value of 6-MWT distance for predicting mortality. Area under the curve (AUC) = 0.76; 95% CI = 0.65 - 0.87;  $p < 0.001$ . The optimal cut-point distance = 300 m with a sensitivity of 0.86 and specificity of 0.81

**Table 2:** Clinical characteristics of all 61 patients with chronic heart failure according to death

Variable	Alive patients	Deceased patients	p-value
Number of patients	47	14	
Age (years) mean $\pm$ SD	$44.4 \pm 13.97$	$55.0 \pm 11.49$	0.02
Male/female (%)	23/24	6/8	NS
NYHA functional class II/III (%)	40 (87) / 7 (46.7)	6 (13) / 8 (53.3)	0.004
Ischemic heart disease (%)	10.6	37.7	0.06
Atrial fibrillation (%)	11 (23.4)	4 (28.6)	NS
LVEF (%) mean $\pm$ SD	$34.1 \pm 7.4$	$26.6 \pm 8.3$	0.002
TAPSE (mm) mean $\pm$ SD	$16.74 \pm 4.32$	$14.21 \pm 3.66$	0.05
SPAP (mmHg) mean $\pm$ SD	$52.9 \pm 12.6$	$49.5 \pm 11.9$	NS
6-MWT distance (m) mean $\pm$ SD	$354.5 \pm 60.83$	$275.4 \pm 34.99$	$< 0.001$
6-MWT distance $\leq$ 300 meters (%)	9 (19.2)	12 (85.71)	$< 0.001$

NYHA: New York Heart Association, SD: standard deviation, LVEF: left ventricular ejection fraction; TAPSE: tricuspid annulus plane systolic excursion; SPAP: systolic pulmonary arterial pressure; 6-MWT: 6-minute walk test

In patients whose 6-MWT distance was  $\leq 300$  m ( $n = 21$ ), the mortality rate was 57.1% compared with 5% in those who walked  $> 300$  m (RR = 11.43, 95% CI = 2.83 - 46.38,  $p < 0.001$ ), and hospital readmission due to acute heart failure was 57.1% compared with 22.5 % in those who walked  $> 300$  m (RR = 2.54, 95% CI = 1.28 - 5.03,  $p = 0.02$ ).

In univariate Cox proportional hazards regression analysis, the risk of death was significantly higher in patients with 6-MWT distance  $\leq 300$  m than in those whose 6-MWT distance was greater than 300 m (HR = 17.01,  $p < 0.001$ ).

Other parameters significantly associated with death comprised age, NYHA functional class III, lower LVEF and ischemic heart disease (Table 3).

**Table 3:** Univariate Cox regression analysis predictors of death in patients with chronic heart failure

Variables	Wald test	HR	95% CI	p-value
Age (years)	4.65	1.047	1.004 - 1.093	0.032
Sex (female)	0.18	0.81	0.279 - 2.326	0.691
NYHA functional class (II/III)	11.67	6.46	2.218 - 18.81	$< 0.001$
Ischemic heart disease (%)	3.87	3.003	1.004 - 8.984	0.049
Atrial fibrillation (%)	0.23	1.326	0.415 - 4.230	0.634
LVEF (%)	9.14	0.88	0.80 - 0.950	0.002
TAPSE	3.52	0.89	0.78 - 1.01	0.06
SPAP	0.68	0.98	0.93 - 1.03	0.4
6-MWT distance	13.9	0.97	0.96 - 0.98	$< 0.001$
6-MWT distance $\leq 300$ m	13.44	17.011	3.791 - 76.34	$< 0.001$

HR: hazard ratio; CI: confident interval; NYHA: New York Heart Association, LVEF: left ventricular ejection fraction; TAPSE: tricuspid annulus plane systolic excursion; SPAP: systolic pulmonary arterial pressure; 6-MWT: 6-minute walk test

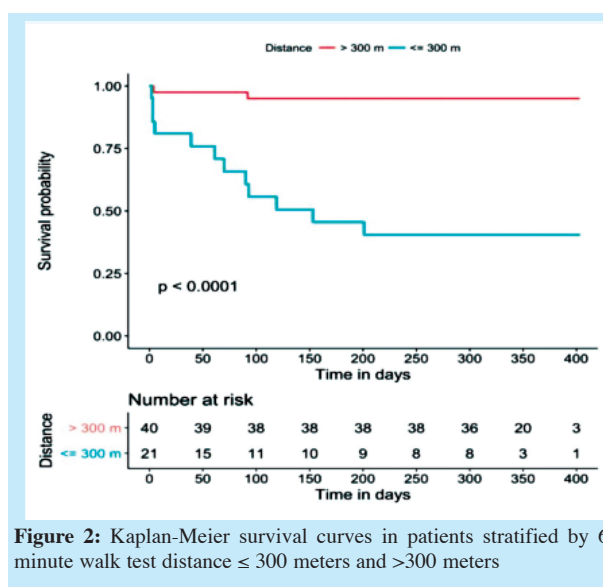
In multivariate Cox proportional hazards model including all variables associated with death in univariate analysis, there was a violation of proportional hazard assumption

**Table 4:** Multivariate Cox proportional hazards ratio regression analysis predictors of death in all 61 patients with chronic heart failure

Variables	Death (AIC = 80.79)		Death with 6-MWT distance as continuous variable (AIC 82.90)	
	HR (95% CI)	P value	HR (95% CI)	p value
6-MWT distance $\leq 300$ m	16.75 (3.42 - 81.94)	$< 0.001$	0.98 (0.96 - 0.99)	$< 0.001$
NYHA class (II/III)	4.02 (1.16 - 14.29)	0.028	4.51 (1.31-15.53)	0.016
Age (years)	1.034 (0.99 - 1.07)	0.19	1.04 (0.99-1.08)	0.053
LVEF	6.599 (1.97 - 21.97)	0.002	5.23 (1.63-16.71)	0.005
Ischemic heart disease	-	-	-	-

HR: hazard ratio; CI: confident interval; NYHA: New York Heart Association, LVEF: left ventricular ejection fraction; 6-MWT: 6-minute walk test, p: p value, AIC: Akaike's information criterion

with ischemic heart disease variable when death was dependent variable. Due to collinearity between this latter and LVEF, we excluded it on the Cox model. Then, we have used the backward elimination procedure according to Akaike's information criterion (AIC) [20] to remove the potential confounding variable and to determine in fine the best model. Six-minute walk test distance  $\leq 300$  m (adjusted HR = 16.75, 95%CI = 3.42 - 81.94,  $p < 0.001$ ), NYHA functional class III and lower LVEF independently predicted mortality (Table 4). For survival analysis, the Kaplan-Meier curves indicate survival rates in patients stratified by 6-MWT distance  $\leq 300$  m versus  $> 300$  m as presented in figure 2.



**Figure 2:** Kaplan-Meier survival curves in patients stratified by 6-minute walk test distance  $\leq 300$  meters and  $> 300$  meters

## DISCUSSION

The current work is one of the first studies in sub-Saharan Africa to describe the prognostic value of the 6MWT distance in patients with CHF. We have demonstrated that 6-MWT  $\leq 300$  m at the time of

hospital discharge was a significant independent predictor of death in patients with CHF. This finding is consistent with data from studies with various cut-off levels of 6-MWT distance depending on CHF patients' clinical characteristics. The SOLVD sub-study [10] was the first to show in 898 patients with NYHA class II and III heart failure that 6-MWT distance and ejection fraction were strongly connected with death and heart failure hospitalization rates during follow-up. The mortality was 3.5-fold higher in subjects covering less than 350 meters in the 6-MWT than in those who walked over 450 meters in this study. In another prospective study of 43 patients (6 women and 37 men) with chronic heart failure secondary to ischemic heart disease (39.5%) or idiopathic cardiomyopathy, LVEF  $\leq 0.40$  in stable NYHA functional class II or III, Arslan et al.[12] found that the death risk was significantly higher in patients with a 6-MWT distance of  $\leq 300$  m ( $p = 0.005$ ) and also higher in patients whose left ventricular ejection fraction was  $\leq 0.30$  ( $p = 0.02$ ). They concluded that a 6-MWT distance  $\leq 300$  m is a simple and useful prognostic marker of subsequent cardiac death in patients with mild-to-moderate heart failure. In 1996, Cahalin et al.[21] conducted a study in 45 patients with advanced heart failure (age =  $49 \pm 8$  years; LVEF =  $0.20 \pm 0.06$ ) who underwent a 6-MWT during cardiac transplant evaluation and demonstrated a significant correlation ( $r = 0.64$ ,  $p < 0.001$ ) between peak VO<sub>2</sub> and the walking distance. Moreover, they noticed that a 6-MWT distance ambulated less than 300 m predicted an increased likelihood of death or pre-transplant hospital admission within six months. Similar data reported prognostic value of a shorter 6-MWT distance in the literature [22-27]. Alahdab et al. [14] prospectively evaluated the usefulness of the 6-MWT in predicting mortality and heart failure re-hospitalization in 200 American African patients with acute decompensated heart failure and found that 6-MWT distance  $\leq 200$  m was the strongest predictor of mortality (adjusted HR = 2.14, 95% CI = 1.20 - 3.81;  $p = 0.01$ ) and heart failure re-hospitalization (adjusted HR = 1.62,  $p = 0.015$ ). More recently a randomized controlled trial conducted by Stewart et al. [28] in 1212 patients with ischemic left ventricular dysfunction showed that, patients unable to walk more than 300 m had higher mortality rate during the first 60 days with coronary artery bypass graft compared to medical therapy (HR = 3.24, 95% CI = 1.64 - 6.83,  $p = 0.002$ ). Furthermore, in a Japanese study including 252 patients with CHF, Tabata et al.[29] observed that a 6-MWT distance  $< 390$  meters at discharge is considered as a strong clinical indicator for hospital readmission. Thus, a shorter 6-MWT distance could help to stratify the severity of heart failure. However, some conflicting observations have been raised regarding the usefulness of 6-MWT in predicting outcomes in heart failure patients. In a population of 315 patients with moderate to severe heart failure, Opasich

and co-authors [30] reported that the 6-MWT distance does not provide prognostic information (even when using the discriminatory  $\leq 300$  m distance cut-off) that can complement or replace oxygen consumption (VO<sub>2</sub>) or the classic clinical functional class grading system. Hence, they concluded that the test is of limited usefulness as a decisional indicator in clinical practice. Data from Guazzi et al.[31] showed that 6-MWT distance does not predict survival either as continuous or dichotomized variable ( $\leq 300$  m), supporting findings of Opasich et al.[30]. However, in this Italian study [31] of 253 patients, findings included patients with heart failure with preserved LVEF and did not apply to patients with advanced HF. Nevertheless, a recent updated Cochrane review including 33 trials with 4740 patients (with predominantly reduced ejection fraction) has shown a trend towards a reduction in long-term mortality with exercise in trials [32]. To us, the 6-MWT distance remains an interesting tool that could help to evaluate outcomes in patients with CHF despite discrepancies between series.

Our study has some limitations. The small size of our study population and the lack of some variables in the analysis process such as NT-proBNP, hemoglobin concentration, renal dysfunction and [23,25] may have affected the statistical power of our findings. However, these results gave a prognostic importance of the 6-MWT distance in Sub-Saharan African patients with CHF.

## CONCLUSION

In Sub-Saharan African patients with CHF, 6-MWT distance less than 300 meters at the time of hospital discharge strongly predicted mortality. Thus, the 6-MWT distance can be an indicator of the evolution of CHF patients. Those patients could greatly benefit from cardiac rehabilitation program at least to improve their quality of life. Therefore, setting-up such cardiac rehabilitation programs in SSA health facilities is needed.

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