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

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Abstract

Background: The 6-minute walking test (6MWT) is a simple and inexpensive way of measuring exercise capacity in patients with heart failure (HF) that predicts morbidity and mortality. However, there are few reports from large multi-centre cohorts assessing the predictive value of baseline and changing walk distance.

Methods: In BIOSTAT-CHF, a 6MWT was performed at baseline (n=1,714) and 9 months (n=1,520). Cox-proportional hazards models were used to assess the associations between 6MWT distance and the composite HF hospitalization and/or death. Median follow-up was 21 months.

Results: The median (pct₂₅₋₇₅) of the 6MWT distance at baseline was 300m (200-388). Independent predictors of a shorter 6MWT distance included greater age, female sex, higher heart rate, NYHA III/IV, orthopnea, ischemic heart disease, a previous stroke, current malignancy, and higher NT-proBNP (all p<0.05). Patients in the lowest baseline 6MWT tertile (≤ 240 m) were less likely to receive guideline-recommended doses of disease-modifying therapies (p<0.05). Compared to patients in the highest baseline 6MWT tertile (>360m), those in the lowest and middle tertiles had a worse prognosis: adjusted HR (95% CI)=1.73 (1.38-2.18). Patients with a decrease in the distance walked had a worse prognosis: adjusted HR (95% CI) for each 50m decrease =1.09 (1.06-1.12). 6MWT distance was not modified by treatment up-titration nor the 6MWT improved the BIOSTAT-CHF prognostic models.

Conclusions: 6MWT distance at baseline and a decline in walking distance were both associated with worse prognosis but did not improve the prognostic models. 6MWT distance was not modified by treatment up-titration and its use for assessing the benefits of pharmacologic treatment up-titration may be limited.

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, 6MWT data from large, international studies are scarce^{5,8,9}, and, to the best of our knowledge, the prognostic implication of the changes in the 6MWT distance was only assessed in one single centre study⁶.

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-titration¹⁰. In BIOSTAT-CHF 1,714 HF patients underwent 6MWT both at baseline and 1,520 patients at the 9-month 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 patients with worsening HF on less than guideline-recommended doses of medication from 69 centres in 11 European countries to investigate factors predicting the response to attempted up-titration of disease-modifying therapies. The design and first results of the study and patients have been published¹⁰. Briefly, patients were aged ≥ 18 years with signs and symptoms of worsening HF managed either in an out-patient clinic or hospital ward. The diagnosis of HF was confirmed either by a left ventricular ejection fraction (LVEF) of $\leq 40\%$ 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 were either treatment naïve with respect to disease-modifying 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^{11,12}. The first three months of treatment were considered to be a treatment optimization phase. Patients were reassessed at 9 months but followed for a median of 21 months. During the optimization phase, initiation or up-titration of ACEi/ARB and/or β -blocker was done according to the routine clinical practice of the treating physicians, who

were encouraged to follow the ESC guidelines^{11, 12}. Patients reaching at least 50% of the recommended dose of ACEi/ARB and/or β -blocker at the 3-month visit 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 (pct₂₅₋₇₅) follow-up was 21 (9-26) 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 has been published and validated¹³.

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 symptoms subsided sufficiently. The participant was allowed to discontinue the test at any time if they wished. Moreover, the test was interrupted by the investigator immediately if one of the following symptoms appeared: chest pain, severe dyspnoea, claudication, loss of balance, 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 them to continue the test. At six minutes, the participant was advised to stop and sit down. The distance walked was measured to the nearest whole metre. The procedure was standardized across centres using 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). The 6MWT full protocol is provided as **Supplemental Data**.

Statistical analysis

Population description and comparison of the 6MWT tertiles was performed using parametric or non-parametric tests, 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 models¹³. Proportional hazard assumption was verified graphically using "log-log" plots. Log-linearity was checked by testing the functional forms of the covariate 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^{14,15}, 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/>)¹³. NT-proBNP is presented as NPX units which are the units used by the Olink Proseek® Multiplex technology - this platform provides normalized protein expression (NPX) data where a high protein value corresponds to a high protein concentration, but not an absolute quantification. 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 rule¹⁶. 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 (194 patients died between the two visits). The comparison of those who performed vs. those who did not perform the 6MWT is depicted in the **Supplemental Table 1**. The 802 (32%) patients who did not perform the baseline 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 (90% of those who did not perform the test) compared to those who did perform the test. **Supplemental Table 1** (legend).

Among the patients who did perform the 6MWT, those in the lower 6MWT distance tertile (≤ 240 m) 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 compared with the intermediate [241-

360m] and the higher [$>360\text{m}$] 6MWT distance tertiles). **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**.

No heterogeneity (*i.e.*, statistical interaction) was present with regards to LVEF ($\leq 40\%$ vs. $>40\%$), sex (male vs. female), atrial fibrillation (yes vs. no), diabetes (yes vs. no) or patient enrolment local (inpatient vs. outpatient) ($p > 0.1$ for all). The results above present can be generalized to the entire BIOSTAT-CHF population.

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, more often treated as inpatients and with more co-morbid conditions. 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 report may have clinical relevance by studying the 6MWT in a contemporary and international HF population, providing insight on the clinical correlates and prognostic associations of the 6MWT both at baseline and respective changes between two time-points. 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 test. In routine practice, performing a 6MWT may provide prognostic information and serve as an objective assessment of patients` exercise capacity, allowing a better monitorization of the clinical course of the disease.

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 output¹⁷. 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 meaningful¹⁸.

In the SOLVD trial⁵, a stratified random sample of 898 patients with symptomatic HF and an ejection fraction $\leq 45\%$ 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, 18}. An analysis from the Efficacy and Safety of Exercise Training in Patients With Chronic Heart Failure (HF-ACTION) trial including 2,054 HF patients also showed that a shorter walked distance in the baseline 6MWT was associated with worse outcomes⁸. An Analysis From the Surgical Treatment for Ischemic Heart Failure (STICH) Trial showed that patients walking less than 300m had higher early mortality and did not seem to benefit from coronary artery bypass grafting⁹. In the Perindopril in Elderly People with chronic Heart Failure (PEP-CHF) study, 6MWT distance improved in patients assigned to perindopril¹⁹. 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 years⁶. In this study, a decrease in the 6MWT distance from the baseline visit to the 1-year visit was independently associated with increased death rates⁶. 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. It 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) trials²⁰. The inconsistent results of the 6MWT as a treatment response measure in pharmacologic drug trials should be considered when using this measure as a trial endpoint.

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 is 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 HF²¹. However, CPX requires specific equipment and personnel adequately trained in the performance and interpretation of the test²², 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, 23}. 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 approval²⁴⁻²⁷. The 6MWT can be used as end-point *per se*, and if aligned with other measures (such as natriuretic peptides and imaging) may be used to assess a treatment effect in HF²⁰.

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. Fourth, 32% of the patients did not perform the baseline 6MWT, these patients were older and more often

hospitalized, which may point to the difficulty for performing this test in patients with limited functional capacity and those in the in-hospital setting. Fifth, as per Olink® technology standard procedures (as stated in the methods section), NT-proBNP was measured in NPX units and not in standard units, however this does not change the interpretation of our findings, where a higher NT-proBNP was linearly associated with shorter distance walked. Sixth, information on “osteoarticular pathology” was not available in the dataset; this information could provide further insight about the factors influencing the 6MWT distance.

Conclusion

6MWT distance at baseline and a decline in walking distance by 9 months were both associated with worse prognosis in patients with HF but did not improve the best BIOSTAT-CHF prognostic model. The 6MWT distance was not increased by treatment up-titration. These findings should be considered when using the 6MWT as end-point in trials, as the distance walked may not reflect the benefits of pharmacologic treatment up-titration.

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Disclosures

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

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