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ORIGINAL PAPER

Six-minute walk test: prognostic value and effects of nebivolol versus placebo in elderly patients with heart failure from the SENIORS trial

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Abstract

Background There is limited information about the 6-min walk test (6MWT) in elderly patients with heart failure. We evaluated 6MWT and the effect of nebivolol on 6MWT from the SENIORS trial.

Methods and results The SENIORS trial evaluated nebivolol versus placebo on death and hospitalisation in patients aged ≥ 70 years with heart failure. A total of 1982 patients undertook a 6MWT at baseline and 1716 patients at 6 months. Patients were divided into tertiles (≤ 200 m, 201 to ≤ 300 m and > 300 m) and to change in distance walked between baseline and 6 months (< 0 m, 0 to < 30 m and ≥ 30 m). The primary outcome was all-cause mortality and cardiovascular hospital admission. Secondary endpoint was all-cause mortality. Baseline walk distance of ≤ 200 m incurred a greater risk of the primary and secondary outcomes (HR 1.41, CI 95% 1.17–1.69, $p < 0.001$) and (HR 1.37, CI 95% 1.05–1.78, $p = 0.019$). A decline in walk distance over 6 months was associated with increased risk of clinical events. Nebivolol had no influence on change in walk distance over 6 months.

Conclusions The 6MWT has prognostic utility in elderly patients. Those who walked less than 200 m were at highest risk. Nebivolol had no effect on 6MWT.

Keywords Heart failure · Six-minute walk test · Elderly · Prognosis

Introduction

Heart failure (HF) accounts for about 5% of emergency medical admissions in western Europe [1] and is the leading cause of hospitalisation in adults older than 65 years in the USA [2]. The landmark Studies of Left Ventricular Dysfunction (SOLVD) trial showed that the 6-min walk test was an independent predictor of death in patients with chronic heart failure [3] and this has also been shown by others including hospital admissions [3–5]. Heart failure (HF) is more common in the elderly [6] and older patients have higher rates of heart failure with preserved ejection fraction [7]. There is little information on the prognostic utility of the 6-min walk in elderly patients with heart failure, or in those with heart failure and preserved ejection fraction.

In a systematic review of randomised control trials, there was uncertainty about the effects of beta-blockers on functional capacity as measured by the 6-min walk test [8, 9]. We used data from the SENIORS trial to provide additional insights about the prognostic utility and potential influence of the beta-blocker nebivolol on 6-min walk test in elderly patients with heart failure.

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Methods

The SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with heart failure) trial, which has been described previously, randomised elderly, stable, HF patients to the vasodilating ß-1 selective beta-blocker nebivolol or matching placebo [10–12]. To be eligible, patients had to be ≥ 70 years, provide informed written consent and have a clinical history of chronic heart failure with at least one of the following features: documented hospital admission within the previous 12 months with a discharge diagnosis of congestive heart failure regardless of left ventricular ejection fraction (LVEF) or documented LVEF ≤ 35% within the previous 6 months. The main exclusion criteria were: HF primarily due to uncorrected valvular heart disease, contraindication or previous intolerance to beta-blockers, advanced hepatic or renal dysfunction, cerebrovascular accident within the previous 3 months, and other major medical conditions that may have reduced survival during the period of study. Patients were randomised in 11 European countries and followed for a mean of 21 months. The primary outcome was the composite of all-cause mortality or cardiovascular hospital admission (time to first event) and the main secondary outcome was all-cause mortality. Patients underwent a 6MWT at baseline and at 6 months. The SENIORS protocol was designed in 1999, prior to publication of standard American Thoracic Society (ATS) guidelines in 2002 [13]. Participants were given standardised instructions, asking them to walk "as far as physically able within 6 min" along a 30 m course. Verbal encouragement was given every 30 s using standardised phrases. Participants were allowed to rest on a chair during the test. At the end of the 6-min period, distance walked was measured to the nearest meter. Ethical approval was obtained from the relevant Committees or Institutional Review Boards and all patients provided informed written consent to be included in the trial, which was carried out according to the principles of the Declaration of Helsinki.

Statistical methods

In the SENIORS trial, 6-min walk test was a pre-defined secondary endpoint and a statistical analysis plan was developed prior to undertaking this analysis.

Summary statistics of baseline characteristics including demographics, clinical history, cardiac function, laboratory measures and cardiac medications are presented either as mean (standard deviation [SD]), median (interquartile range [IQR]) or *n* (%) as appropriate according to baseline 6-min walk test tertile (tertile 1: < 200 m, tertile 2: 201 to ≤ 300 m and tertile 3: > 300 m) and tertile of change in 6-min walk test from baseline to 6 months (tertile of change 1: < 0 m change, tertile of change 2: 0 to < 30 m change and tertile of change 3: ≥ 30 m change). Tertiles were chosen by first determining the exact tertile cut-off points and then choosing clinically meaningful values to determine the final groups. The main outcomes of interest were the composite of all-cause mortality or cardiovascular hospital admission (primary outcome) or all-cause mortality (secondary outcome). We performed the following analyses:

1. An analysis of clinical outcomes in the overall group stratified by baseline 6MWT tertile.
2. Exploratory analysis of the association between baseline 6MWT tertile and age tertile, ejection fraction and gender.
3. Analysis of clinical outcomes stratified by tertile of change in 6-min walk
4. Exploratory analysis of the association between tertile of change in 6MWT and age tertile, ejection fraction and gender.
5. Effect of nebivolol versus placebo on change in 6MWT between baseline and 6 months.
6. Effect of nebivolol versus placebo on clinical outcomes, stratified by baseline 6MWT tertile and by tertile of change in 6-min walk test

Using baseline 6MWT data, the Cox proportional hazards model was applied to estimate hazard ratios, with associated 95% confidence intervals and *p* values, for the primary and secondary outcomes for tertiles 1 and 2, using tertile 3 as a reference (HR = 1.0), and to calculate hazard ratios to compare the effect of nebivolol vs. placebo on rates of the primary and secondary outcomes within each tertile.

We undertook a paired analysis, using data on change in 6MWT between baseline and 6 months. Only events occurring between 6 months and the study endpoint were included in this analysis. Cox proportional hazards model was used to generate hazard ratios, with associated 95% confidence intervals and p values, for the primary and secondary outcomes for tertile of change 1 and 2, using tertile of change 3 as a reference group (HR = 1.0) and to calculate hazard ratios comparing the effect of nebivolol vs. placebo within each tertile of change. For both the baseline and change in 6-min walk test data, the Kaplan–Meier technique was used to generate survival curves for the primary and secondary outcomes.

Analysis of Variance (ANOVA) was used to generate p values comparing baseline characteristics between 6MWT tertiles, and for the exploratory analysis of the association between 6MWT performance and age, ejection fraction and gender. An independent two-sample t test was used to

compare the mean change in 6-min walk test between the nebivolol versus placebo groups.

Results

Baseline characteristics

In total, 1982 participants (93% of all patients enrolled) underwent baseline 6MWT and 1716 (79% of the total) underwent repeat testing at 6 months. Of the 266 participants who did not undergo repeat testing at 6 months, 85 died before 6 months and 181 dropped out for other reasons. Reasons for drop-out was not recorded but, compared to those who underwent follow-up 6-min walk testing at 6 months, these participants were older (76 vs 75 years, $p < 0.001$) and had more severe disease (NYHA III: 46.6 vs. 38.0% and NYHA IV: 4.5 vs. 1.3%).

Baseline characteristics according to baseline 6MWT tertile are shown in Table 1. Participants who walked ≤ 200 m at baseline, when compared to other tertiles, were mainly female, non-smokers, with a history of coronary artery disease (CAD), peripheral artery disease (PAD), hypertension and atrial fibrillation (AF). They were also more likely to be in NYHA class III–IV, have left ventricular ejection fraction (LVEF) of ≥ 40% and prescribed diuretics or a cardiac glycoside. In contrast, history of percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) was less prevalent, and participants in this group were less likely to be prescribed an angiotensin receptor blocker (ARB), lipid-lowering medication or a vitamin K antagonist.

Baseline 6-min walk test performance and association with outcomes

Mean distance walked at baseline for the overall group was 276.2 m (SD 116.2 m). Participants in tertile 1, 2 and 3 walked a mean distance of 148.3 m (SD 39.9 m), 254.3 m (SD 30.3 m) and 394.3 m (SD 116.2 m), respectively. When stratified by age tertile, those aged > 77 years had a lower mean walk distance than those aged 73 to < 77 years, and those in the group aged < 73 years (mean distance walked of 262.4 m vs. 281.0 m vs. 298.7 m, respectively, $p < 0.001$). Males walked further on average than females at baseline (mean performance 303.3 m vs. 240.6 m, $p < 0.001$). Participants with a LVEF of > 40% had a lower mean walk distance than those with and LVEF of ≤ 40% (257.6 m vs. 288.5 m, $p < 0.001$).

Baseline walk distance of ≤ 200 m incurred a greater risk of the primary outcome (HR 1.41, CI 95% 1.17–1.69, $p < 0.001$) and secondary outcome (HR 1.37, 95% CI 95% 1.05–1.78, $p = 0.019$), when compared to the reference group (tertile 3: > 300 m) (Table 2). Participants with a baseline walk distance of 201 to ≤ 300 m had higher event rates than participants with a walk distance of > 300 m for both the primary outcome (30.5% vs. 29.3%) and secondary outcome (16.2% vs. 14.3%), but this difference was not statistically significant ($p = 0.606$ and 0.417, respectively) (Fig. 1a and b).

Change in 6-min walk test performance and association with clinical outcomes

We classified patients into tertiles according to change in 6MWT from baseline to 6 months: tertile of change 1 ≤ 0 m, tertile of change 2 = 0 to 30 m and tertile of change 3 = ≥ 30 m. Mean walking distances in tertile of change 1, 2 and 3 were 269.4 m (SD 115.8 m), 284.4 m (SD 110.0 m) and 349.4 m (SD 117.1 m), respectively. Mean walk distance in the overall group at 6 months was 301.8 m (SD 119.3 m). Participants with a shorter baseline walk distance (≤ 200 m) were more likely to have improved performance at 6 months (for patients walking ≤ 200 m at baseline: % of patients tertile of change 1 = 20.4%; tertile of change 2 = 32.0% and tertile of change 3 = 33.5%, $p < 0.001$). There was no statistically significant association between mean change in 6-min walk test distance from baseline to 6 months and age tertile ($p = 0.110$), LVEF (≤ 40% vs. > 40%, $p = 0.121$) or gender ($p = 0.326$).

A decrease in distance walked from baseline to 6 months (< 0 m change) incurred a greater risk of both the primary outcome (HR 1.53, CI 95% 1.23–1.90, $p < 0.001$) and secondary outcome (HR 1.49, CI 95% 1.05–2.11, $p = 0.024$), when compared to the reference group (tertile of change ≥ 30 m). There was no statistically significant difference between change in walk distance of 0 to < 30 m on either the primary or secondary outcomes ($p = 0.879$ and 0.347, respectively), when compared to the reference group (Table 3, Fig. 2a and b).

Effects of nebivolol versus placebo on 6-min walk test and clinical outcomes

Mean walk distance at baseline was 282.3 m (SD 116.3 m) in the nebivolol group and 278.1 m (SD 113.4 m) in the placebo group. Mean walk distance increased in both groups at 6 months, but there was no statistically significant difference between the groups (+ 21.0 m in nebivolol group vs. + 22.2 m in placebo group, $p = 0.735$). There was no difference in change in distance walked from baseline to 6 months between nebivolol and placebo stratified by EF ≤ 40% vs. > 40%.

The absolute risk reduction (ARR) for each tertile was calculated as the difference in rates of primary and secondary outcomes in the nebivolol vs. placebo groups. Compared to the placebo group, participants in the nebivolol group

Table 1 Patient characteristics according to baseline 6-min walk test tertile

	Tertile 1 ≤ 200 m (*n* = 601)	Tertile 2 201 to ≤ 300 m (*n* = 616)	Tertile 3 > 300 m (*n* = 765)	Total (*n* = 1982)	*p* value
6MWT (m)—median (IQR)	156 (120, 180)	250 (230, 280)	380 (340, 428)	270 (189, 350)	
6MWT (m)—mean (SD)	148.3 (39.9)	254.3 (30.3)	394.3 (76.1)	276.2 (116.2)	
Demographics					
Age (years)—median (IQR)	76 (73, 79)	75 (72, 79)	75 (72, 78)	75 (72, 79)	< 0.001
Female	294 (48.9%)	244 (39.6%)	186 (24.3%)	724 (36.5%)	< 0.001
Cardiac function					
NYHA I	7 (1.2%)	11 (1.8%)	41 (5.4%)	59 (3%)	< 0.001
NYHA II	248 (41.3%)	343 (55.7%)	521 (68.1%)	1112 (56.1%)	
NYHA III	317 (52.7%)	258 (41.9%)	201 (26.3%)	776 (39.2%)	
NYHA IV	29 (4.8%)	4 (< 1%)	2 (< 1%)	35 (1.8%)	
LVEF (%)—median (IQR)	35 (29, 45)	34 (29, 41)	33 (27, 40)	34 (28, 42)	0.003
LVEF > 40%	198 (33.1%)	163 (26.6%)	174 (23.1%)	535 (27.2%)	< 0.001
Clinical history					
Smoker	19 (3.2%)	30 (4.9%)	53 (6.9%)	102 (5.1%)	0.007
Prior CAD	443 (73.7%)	447 (72.6%)	470 (61.4%)	1360 (68.6%)	< 0.001
Prior MI	254 (42.3%)	258 (41.9%)	346 (45.2%)	858 (43.3%)	0.382
Prior PCI	13 (2.2%)	17 (2.8%)	36 (4.7%)	66 (3.3%)	0.022
Prior CABG	50 (8.3%)	40 (6.5%)	88 (11.5%)	178 (9%)	0.004
PAD	38 (6.3%)	24 (3.9%)	31 (4.1%)	93 (4.7%)	0.076
Prior CVA in last 3 months	1 (< 1%)	0	0	1 (< 1%)	0.317
Hypertension	407 (67.7%)	393 (63.8%)	422 (55.2%)	1222 (61.7%)	< 0.001
Hyperlipidemia	275 (45.8%)	265 (43%)	377 (49.3%)	917 (46.3%)	0.065
Atrial fibrillation	231 (38.4%)	226 (36.7%)	230 (30.1%)	687 (34.7%)	0.002
Diabetes	166 (27.6%)	160 (26%)	181 (23.7%)	507 (25.6%)	0.241
Medications					
ACE inhibitors	511 (85%)	507 (82.3%)	620 (81%)	1638 (82.6%)	0.151
Diuretics	538 (89.5%)	527 (85.6%)	641 (83.8%)	1706 (86.1%)	0.009
Cardiac glycoside	287 (47.8%)	259 (42%)	275 (35.9%)	821 (41.4%)	< 0.001
Aldosterone antagonist	168 (28%)	167 (27.1%)	202 (26.4%)	537 (27.1%)	0.815
Anti-arrhythmic	101 (16.8%)	103 (16.7%)	133 (17.4%)	337 (17%)	0.937
ARB	35 (5.8%)	43 (7%)	84 (11%)	162 (8.2%)	0.001
Lipid lowering medication	115 (19.1%)	115 (18.7%)	198 (25.9%)	428 (21.6%)	0.001
Vitamin K antagonist	107 (17.8%)	128 (20.8%)	225 (29.4%)	460 (23.2%)	< 0.001
Aspirin	306 (50.9%)	314 (51%)	405 (52.9%)	1025 (51.7%)	0.687
Calcium channel antagonist	83 (13.8%)	82 (13.3%)	96 (12.5%)	261 (13.2%)	0.785
Renal function					
Creatinine (umol/L)—median (IQR)	94 (78, 117)	93 (79, 111)	97 (82, 117)	95 (80, 116)	0.043

6MWT 6-min walk test, *IQR* interquartile range, *SD* standard deviation, *NYHA* New York Heart Association, *LVEF* left ventricular ejection fraction, *CAD* coronary artery disease, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass graft, *PAD* peripheral arterial disease, *CVA* cerebrovascular accident, *ACE* angiotensin-converting enzyme, *ARB* angiotensin receptor blocker

who walked ≤ 200 m at baseline had the highest reduction in risk of both the primary (ARR ≤ 200 m: 6.7%; ARR 201 to ≤ 300 m: 4.2% and ARR > 300 m: 3.4%) and secondary outcomes (ARR ≤ 200 m: 4.3%; ARR 201 to ≤ 300 m: 1.1% and ARR > 300 m: 2.3%), but there was no statistical evidence of an interaction (Table 4).

Patients in nebivolol group who had a decline performing 6MWT between baseline and 6 months had the highest nominal reduction in risk; however, this was not statistically significant (Table 5).

Table 2 Primary and secondary outcomes according to baseline 6-min walk test tertile

	Tertile 1 ≤ 200 m *n* = 601	Tertile 2 201 to ≤ 300 m *n* = 616	Tertile 3 > 300 m *n* = 765	Total *n* = 1982
Primary outcome				
C mortality/CV hospitalisation, *n* (%)	232 (38.6)	188 (30.5)	224 (29.3)	644 (32.5)
Hazard ratio (95% CI)	1.41 (1.17, 1.69)	1.05 (0.87, 1.28)	Ref	
p value	< 0.001	0.606	Ref	
Secondary outcome				
AC mortality, *n* (%)	116 (19.3)	100 (16.2)	109 (14.3)	325 (16.4)
Hazard ratio (95% CI)	1.37 (1.05, 1.78)	1.12 (0.85, 1.47)	Ref	
p value	0.019	0.417	Ref	

AC all-cause, *CV* cardiovascular, *CI* confidence interval, *Ref* reference group (hazard ratio 1.0)

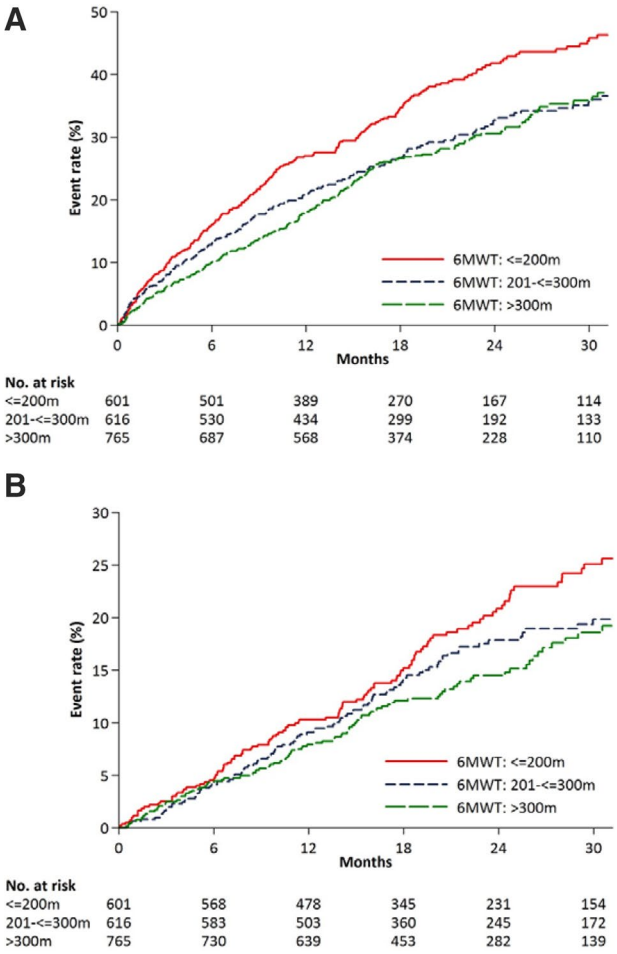

Fig. 1 **a** Kaplan–Meier plot. Effect of 6-min walk test (6MWT) tertile on the primary endpoint. **b** Kaplan–Meier plot. Effect of 6-min walk test (6MWT) tertile on the secondary endpoint

Discussion

SENIORS is the only large-scale trial of beta-blockers in the elderly with heart failure to prospectively incorporate the 6MWT into the study protocol and may provide an additional guide to expected benefits of beta-blockers in heart failure. A lower baseline 6MWT and a decline in distance walked from baseline to 6 months were associated with an increased risk of mortality and hospitalisation. There were no beneficial effects of nebivolol on death or hospitalisation in patients across the tertiles of baseline 6MWT and in patients with a decline 6MWT from baseline to 6 months. Ejection fraction appeared to be inversely associated with distance walked during the 6MWT. Nebivolol has no effect on 6MWTperformance when compared to placebo. Elderly patients with HF and 6MWT ≤ 200 m were at higher risk of death or cardiovascular hospital admissions.

The SENIORS trial is unique since it evaluated an elderly population with heart failure and preserved or abnormal left ventricular systolic function, including a significant proportion of female patients. Previous publication from the SENIORS trial group showed that 6MWT is an independent predictor of mortality in this important cohort of patients, who are often under-represented in previous heart failure trials [14–22]. Ingle et al. studied 1592 elderly heart failure patients (mean age 74 years) with both preserved and reduced left ventricular ejection fraction (mean LVEF 48%) [23]. Distance walked during the 6MWT was found to be an independent predictor of survival, except in the subgroup with normal left ventricular function. In our study, participants with a preserved left ventricular ejection fraction (LVEF > 40%) generally walked shorter distances during 6MWT at baseline and 6 months, probably due to the presence of diastolic dysfunction and increased ventricular filling pressures, which show a more consistent correlation with functional capacity [24–27]. However, we cannot discard the possibility of trial selection bias (more ill patients with

Table 3 Primary and secondary outcomes according to change in 6-min walk test from baseline to 6 months tertile

	Tertile 1 <0 m change *n* = 521	Tertile 2 0 to < 30 m *n* = 616	Tertile 3 ≥ 30 m *n* = 579	Total (*n* = 1716)
Primary outcome				
AC mortality/CV hospitalisation, *n* (%)	179 (34.4)	153 (24.8)	149 (25.7)	481 (28.0)
Hazard ratio (95% CI)	1.53 (1.23, 1.90)	1.02 (0.81, 1.28)	Ref	
p value	< 0.001	0.879	Ref	
Secondary outcome				
AC mortality, *n* (%)	71 (13.6)	67 (10.9)	58 (10.0)	196 (11.4)
Hazard ratio (95% CI)	1.49 (1.05, 2.11)	1.18 (0.83, 1.68)	Ref	
p value	0.024	0.347	Ref	

AC all-cause, *CV* cardiovascular, *CI* confidence interval, *Ref* reference group (hazard ratio 1.0)

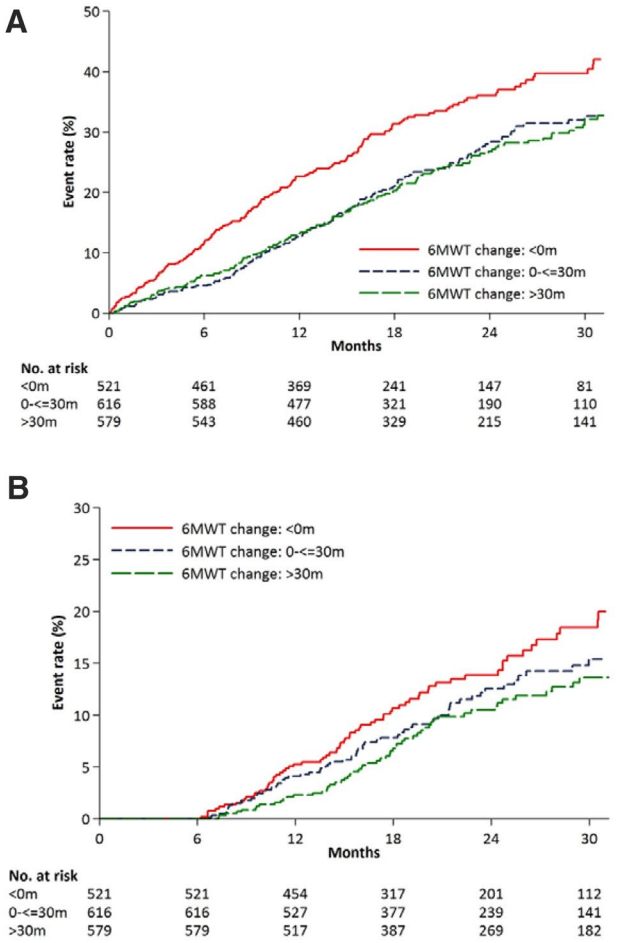

Fig. 2 **a** Kaplan–Meier plot. Effect of tertile of change in 6-min walk test from baseline to 6 months on the primary endpoint. **b** Kaplan–Meier plot. Effect of tertile of change in 6-min walk test from baseline to 6 months on the secondary endpoint

preserved LVEF included). Previous publications regarding 6MWT performance and LVEF revealed inconsistent results. Guazzi et al. [27] evaluated 253 patients (mean age 61.9 years) with heart failure and both preserved and reduced ejection fraction and found no correlation between LVEF and distance walked during 6MWT. This finding was similar to the previous publication by Roul et al. evaluating 121 patients (mean age 59 years) with NYHA class II and III heart failure [18]. Wegrzynowska-Teodorczyk et al. reported a significant positive relationship between left ventricular ejection fraction and 6MWT ($p = 0.004$), although the r value of 0.16 during multivariable analysis suggests a weak correlation [20].

Previous studies of patients with chronic heart failure have demonstrated that patients with 6MWT ≤ 300 m have a poorer prognosis than those walking greater distances. In these studies, follow-up period ranged from 18 to 34 months [17, 18, 21]. The BIOSTAT-CHF was a prospective, observational, European, multicentre, study evaluating 2516 patients with heart failure with an ejection fraction ≤ 40% or with elevated biomarkers for heart failure. Although the mean age in BIOSTAT-CHF is lower when compared to our study, similar to our findings it confirmed 6MWT as a prognosticator for death and hospitalisation for heart failure. Interestingly, the up-titration of evidence-based therapy for heart failure did not impact the distance walked at baseline and at 9 months [28]. In our study, risk of death and hospitalisation was not significantly higher in the tertile walking between 201 and ≤ 300 m at baseline, compared to those walking > 300 m. Given that elderly patients walk shorter distances during 6MWT [29], the cut-off distance for identifying those at high risk of adverse outcome is likely to be lower in older patients. These data are important when risk stratifying elderly individuals with heart failure.

Our study shows that a decline in walk distance between baseline and 6 months is a predictor of poor prognosis. Passantino et al. reported in 476 patients over a 24-month

Table 4 All-cause mortality/CV hospital admission and all-cause mortality according to treatment group, stratified by baseline 6-min walk test tertile

	Event rate		ARR (%)	Hazard ratio	95% CI		*p* value	Interaction *p* value
	Nebivolol	Placebo						
All-cause mortality/CV hospital admission								
≤ 200 m	107 (35.3)	125 (42.0)	6.7	0.79	0.61	1.02	0.076	0.644
201 to ≤ 300 m	87 (28.4)	101 (32.6)	4.2	0.87	0.65	1.16	0.335	
> 300 m	107 (27.6)	117 (31.0)	3.4	0.86	0.66	1.11	0.244	
All-cause mortality								
≤ 200 m	52 (17.2)	64 (21.5)	4.3	0.79	0.55	1.14	0.204	0.843
201 to ≤ 300 m	48 (15.7)	52 (16.8)	1.1	0.95	0.64	1.41	0.806	
> 300 m	51 (13.1)	58 (15.4)	2.3	0.82	0.56	1.20	0.312	

6MWT 6-min walk test, *CI* confidence interval, *CV* cardiovascular, *ARR* absolute risk reduction

Table 5 All-cause mortality/CV hospital admission and all-cause mortality according to treatment group, stratified by change in 6-min walk test from baseline to 6 months

6MWT tertile	Event rate		ARR (%)	Hazard ratio	95% CI		*p* value	Interaction *p* value
	Nebivolol	Placebo						
All-cause mortality/CV hospital admission								
< 0 m	88 (31.9)	91 (37.1)	5.2	0.83	0.62	1.11	0.214	0.958
0 to < 30 m	66 (22.7)	87 (26.8)	4.1	0.85	0.62	1.18	0.336	
≥ 30 m	74 (24.0)	75 (27.7)	3.7	0.84	0.61	1.15	0.273	
All-cause mortality								
< 0 m	34 (12.3)	37 (15.1)	2.8	0.82	0.52	1.31	0.408	0.716
0 to < 30 m	29 (10.0)	38 (11.7)	1.7	0.88	0.54	1.43	0.601	
≥ 30 m	30 (9.7)	28 (10.3)	0.6	0.93	0.56	1.56	0.780	

6MWT 6-min walk test, *CI* confidence interval, *CV* cardiovascular, *ARR* absolute risk reduction

follow-up period that even an improvement in walk distance of < 70 m 15 days after discharge due to a heart failure hospitalisation was a significant predictor of all-cause mortality (HR 2.03, 1.29–3.18, $p = 0.002$) [30]. In 247 patients from FIRST (Flolan International Randomised Survival Trial), 6MWT at baseline was predictive of mortality; however, there was no association with change in walk distance from baseline to 1 month [31]. In our study, participants with a shorter baseline walk distance were more likely to have improved performance at 6 months, even though they did not undergo the same intense therapy as participants in the Passantino and FIRST studies. This finding could be a result of regression to the mean, or patients with severe disease at baseline have greater potential for improvement in functional capacity following intervention. Our study adds important information on the utility of change in 6-min walk distance over 6 months on subsequent longer-term outcomes in elderly patients with heart failure.

A systematic review of the utility of the 6MWT to assess efficacy of heart failure treatments found only 3 out of 15 placebo-controlled trials of beta-blockers reporting a significant increase in distance walked during 6MWT in the beta-blocker group compared to placebo, all with carvedilol. However, 5 other carvedilol studies included in the systematic review did not show a significant effect on 6MWT [8]. The ELANDD study (Effects of Long-term Administration of Nebivolol on the clinical symptoms, functional capacity and left ventricular function of patients with Diastolic Dysfunction) concluded that nebivolol had no effect on functional capacity (measured by the 6MWT) in 116 patients with heart failure with preserved ejection fraction [9]. The findings in our large sample of elderly patients are consistent with these studies and suggest that nebivolol does not improve functional capacity in patients with heart failure, irrespective of ejection fraction. It is possible that other beta-blockers with evidence of benefit in heart failure may influence functional capacity. Moreover, recent results from the CHECK-HF study suggested that evidence-based heart failure treatment is underused in elderly patients [32]

Study limitations

The 6MWT protocol used in SENIORS was written prior to the standardisation of 6MWT protocol by the American Thoracic Society (ATS) in 2002 [13] and therefore does not formally adhere to these standards. Although the 6MWT was

a pre-specified secondary outcome, this specific analysis was not detailed in advance of the original trial. Thirteen per cent did not have a repeat 6MWT at 6 months and this could have influenced statistical analyses. Potential metabolic abnormalities such as iron deficiency and systemic inflammation were not regularly collected [33, 34].

Conclusion

The 6MWT is a useful measure of functional capacity in elderly patients with stable heart failure and has prognostic utility. We demonstrated that in elderly population those who walked less than 200 m are at significant increased risk of death or cardiovascular hospital admission. There was no significant influence of nebivolol on distance walked from baseline to 6 months. The association of 6MWT and quality of life remains an important venue for research and should be further investigated in clinical trials.

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Compliance with ethical standards

Conflict of interest None to declare for this analysis.

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