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Effects of the long-term administration of nebivolol on the clinical symptoms, exercise capacity, and left ventricular function of patients with diastolic dysfunction: results of the ELANDD study

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Aims We hypothesized that nebivolol, a beta-blocker with nitric oxide-releasing properties, could favourably affect exercise capacity in patients with heart failure and preserved left ventricular ejection fraction (HFPEF).

Methods and results A total of 116 subjects with HFPEF, in New York Heart Association (NYHA) functional class II–III, with left ventricular ejection fraction (LVEF) >45%, and with echo-Doppler signs of LV diastolic dysfunction, were randomized to 6 months treatment with nebivolol or placebo, following a double-blind, parallel group design. The primary endpoint of the study was the change in 6 min walk test distance (6MWTD) after 6 months. Nebivolol did not improve 6MWTD (from 420 ± 143 to 428 ± 141 m with nebivolol vs. from 412 ± 123 to 446 ± 119 m with placebo, $P = 0.004$ for interaction) compared with placebo, and the peak oxygen uptake also remained unchanged (peakVO_2; from 17.02 ± 4.79 to 16.32 ± 3.76 mL/kg/min with nebivolol vs. from 17.79 ± 5.96 to 18.59 ± 5.64 mL/kg/min with placebo, $P = 0.63$ for interaction). Resting and peak blood pressure and heart rate decreased with nebivolol. A significant correlation was found between the change in peak exercise heart rate and that in peakVO_2 ($r = 0.391$; $P = 0.003$) for the nebivolol group. Quality of life, assessed using the Minnesota Living with Heart Failure™ Questionnaire, and NYHA classification improved to a similar extent in both groups, whereas N-terminal pro brain natriuretic peptide (NT-pro BNP) plasma levels remained unchanged.

Conclusions Compared with placebo, 6 months treatment with nebivolol did not improve exercise capacity in patients with HFPEF. Its negative chronotropic effect may have contributed to this result.

Keywords Nebivolol • Heart failure • Heart failure with preserved ejection fraction • Exercise capacity • Chronotropic

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Introduction

Approximately 50% of patients with heart failure (HF) have a preserved left ventricular (LV) ejection fraction (EF) and their incidence and prevalence are increasing.[1] Patients with HF and preserved EF (HFPEF) differ from subjects with HF and reduced LVEF (HFREF) with respect to demographic and clinical characteristics.[2–5] However, symptoms, prognostic variables, hospitalization, and mortality rates are similar.[1–3,5–11] Large trials enrolling patients with HFPEF have yielded unsatisfactory results,[10,12–14] and no specific drug regimen is recommended by current guidelines.[15]

Because of their benefits in terms of LV remodelling and outcomes, beta-blockers have become standard treatment in patients with HFREF. However, most studies have either not evaluated or have shown a neutral result for an effect on maximal exercise capacity.[16] From a theoretical standpoint, blood pressure control, increased diastolic filling time, and protection from ischaemia, resulting from beta-blockers, might also be useful for the treatment of HFPEF. In one study, beta-blocker therapy has been associated with decreased myocardial collagen volume fraction, reduced cardiac myocyte diameter, and down-regulated expression of stimulatory G protein, all effects which may improve cardiac diastolic function, in patients with HFPEF.[17]

The Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure (SENIORS)[12] is the only prospective beta-blocker trial which included patients with HFPEF and focused on hard endpoints. The effects of nebivolol on the primary endpoint, as well as secondary endpoints, were similar in patients with LVEF $<35\%$ and those with higher LVEF.[11] The cut-off of 35% for defining the HFPEF group in that study was lower than usually applied.[4] In addition, SENIORS did not include formal exercise capacity as an endpoint.

Nebivolol is a highly selective blocker of beta-1 adrenergic receptors with associated vasodilatory effects mediated by nitric oxide (NO) release and beta-3 adrenergic receptor stimulation.[18–21] NO release has been shown to favour relaxation at the cardiac level so that lower LV pressure is achieved during diastole.[22,23] Haemodynamic studies have confirmed these findings,[19,21,23] and have also shown improved exercise tolerance with nebivolol, compared with traditional beta-blockers.[24]

We therefore hypothesized that a beta-blocker with NO-releasing properties, such as nebivolol, could favourably affect exercise tolerance in patients with HFPEF. This paper presents the results of the effects on exercise capacity of the phase IIIb study: 'Effects of Long-term Administration of Nebivolol on the clinical symptoms, exercise capacity, and left ventricular function of patients with Diastolic Dysfunction (ELANDD)', a randomized, double-blind, multicentre, parallel group, placebo-controlled trial designed to investigate the effects of nebivolol in patients with HFPEF (Study ID MeBN/02/Neb-DHF/001).

Methods

A complete description of the study design and the endpoint definition has been published previously.[25]

Inclusion and exclusion criteria

To be included into the study, patients had to fulfil the following criteria: willing and able to sign the informed consent form and comply with the requirements of the study, aged ≥ 40 years, have a documented history of HF and persistent symptoms during effort [New York Heart association (NYHA) class II–III], an LVEF $>45\%$, and LV end-diastolic internal diameter <3.2 cm/m^2 or LV end-diastolic volume index <102 mL/m^2 by echocardiography, radionuclide ventriculography, or nuclear magnetic imaging, or any abnormality of LV diastolic function documented by echocardiography, according to the guidelines of the European Study Group on Diastolic Heart Failure.[26] This last inclusion criterion was revised in April 2007 following the online publication of the new consensus statement on the diagnosis of HFPEF by the European Society of Cardiology.[4] Accordingly, an E/E' ratio >15 at tissue Doppler echocardiography was required as an inclusion criterion. Patients with an E/E' ratio between 8 and 15 could be included when additional abnormalities of diastolic function were found. These included an E/A ratio <0.5 and/or a deceleration half-time >280 ms in patients older than 50 years, and/or a duration of reverse pulmonary vein atrial systole flow–mitral valve atrial wave flow >30 ms, and/or a left atrial volume index >40 mL/ m^2, and/or an increased LV mass index.[4] Exclusion criteria were also described in detail in the design paper.[25] They included a recent (<3 months) acute coronary or cerebrovascular ischaemic event, exercise-induced myocardial ischaemia, major contraindications to beta-blocker treatment, or ongoing treatment with beta-blockers, verapamil, or diltiazem.

Procedures

Patients were assigned to placebo or nebivolol in a double-blinded manner according to a computer-generated 1:1 randomization scheme. Nebivolol was started at 2.5 mg/day and gradually up-titrated to 10 mg/day over a period of 5 weeks. Down-titration to lower doses was allowed if the higher dose was not tolerated. Treatment at maintenance doses was continued for an additional 21 weeks (6 months of treatment in total). Ongoing treatment with other drugs was maintained throughout the study.

Clinical examination, including blood pressure and heart rate measurements, 6 min walk test (6MWT), cardiopulmonary exercise test, and Doppler echocardiography were performed at baseline, within 1 week before randomization, and after 21 weeks of maintenance treatment with the study drug. Procedures are described in detail in the design paper.[25]

The primary endpoint of the study was the change from baseline in the distance walked during the 6MWT after 6 months of treatment with nebivolol vs. placebo. Additional secondary endpoints are shown in the design paper.[25] The present paper is focused on the primary endpoint and the results on exercise capacity measurements.

Statistics

The size of the study group was calculated assuming a similar impairment of 6MWT distance (6MWTD) and exercise capacity in patients with HFPEF, compared with those with low LVEF,[24] and a similar improvement with nebivolol in patients with HFPEF, compared with that found with other beta-blockers in patients with low LVEF.[27] Thus, assuming a 10% drop-out rate and a 15% difference (70 m) in the increase in the 6MWTD between the nebivolol and the placebo treatment groups, we calculated that a sample size of 118 patients (59 in each group) would have detected a difference of 70 m, at an SD of 140 m, as statistically significant at $\alpha = 0.05$ (two tailed) and

$\beta = 0.20$ (power 80%) for the comparison of the change of the 6MWTD between the two study groups.

Pre-treatment characteristics were compared between the nebivolol and placebo groups by Student's *t*-test and/or analysis of variance (ANOVA) for continuous variables and the Cochran–Mentel–Haenszel test or Fisher's exact test for categorical variables. Efficacy endpoints were evaluated using the intent-to-treat (ITT) method, applying the last observation carried forward method for patients enrolled who were not reassessed after 6 months.

The changes from baseline in the two treatment groups were compared by two-way ANOVAs. Data are presented as mean ± SD unless otherwise specified. Namely, N-terminal pro brain natriuretic peptide plasma levels are shown as median as their distribution was not normal. Analysis was performed using SAS version 9 or higher. The recorded adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA)® terminology and compared for both treatment groups using Fisher's exact test.

Results

A total of 116 subjects were enrolled in 12 centres from eight countries, with 57 patients assigned to nebivolol and 59 to placebo. Due to early withdrawal for side effects, poor tolerance, or lack of compliance, 6 month reassessment was performed in 93 patients (42 on nebivolol and 51 on placebo, *Figure 1*). Ten patients dropped out during the titration phase, two for withdrawal of consent and eight for AEs. All the 93 patients who completed the study achieved the target dose of the study drug which, in the case of the 42 patients on nebivolol, corresponded to 5 mg daily or, if the patient could tolerate it, to 5 mg b.i.d. Seven patients assigned to nebivolol had a dose reduction to 2.5 mg daily on at least one visit because of lack of tolerance but completed the study on nebivolol 5 mg daily. No death or hospitalization occurred during follow-up in any patient.

Patients characteristics

Clinical characteristics of the two study groups are shown in *Table 1*. Mean age was 66 years and most patients were female (65%), with a history of hypertension and with a relatively high body mass index of 30. No differences were found between the two study groups with respect to baseline variables, with the exception of a higher proportion of chronic obstructive pulmonary disease (COPD) among the patients assigned to nebivolol (16% vs. 7%, $P = 0.032$).

Heart rate and blood pressure data, measured during the clinical visits at baseline and at the end of the study, are shown in *Table 2*.

Primary endpoint

The 6MWTD increased numerically from 420 ± 143 m to 428 ± 141 m with nebivolol, with a mean increase from baseline of +7.8 ± 34.5 m ($P = 0.094$). This change was significantly smaller than the observed difference for the placebo group (+33.54 ± 63.8 m, $P = 0.0001$ vs. baseline, and $P = 0.004$ for interaction; *Table 3*).

Cardiopulmonary exercise test

Peak oxygen uptake (peakVO_2) decreased slightly in the nebivolol group, and increased in the placebo group, without reaching statistical significance (*Table 3*). Exercise duration and peak workload did not show any difference between the two groups after 6 months treatment. Resting and peak heart rate, as well as systolic blood pressure decreased significantly from baseline in the nebivolol group, without a change in the placebo arm (*Table 3*).

A significant correlation was found between the change in peak exercise heart rate and the change in peakVO_2 ($r = 0.391$; $P = 0.003$, *Figure 2*) for the patients treated with nebivolol. This did not occur in the placebo group (data not shown).

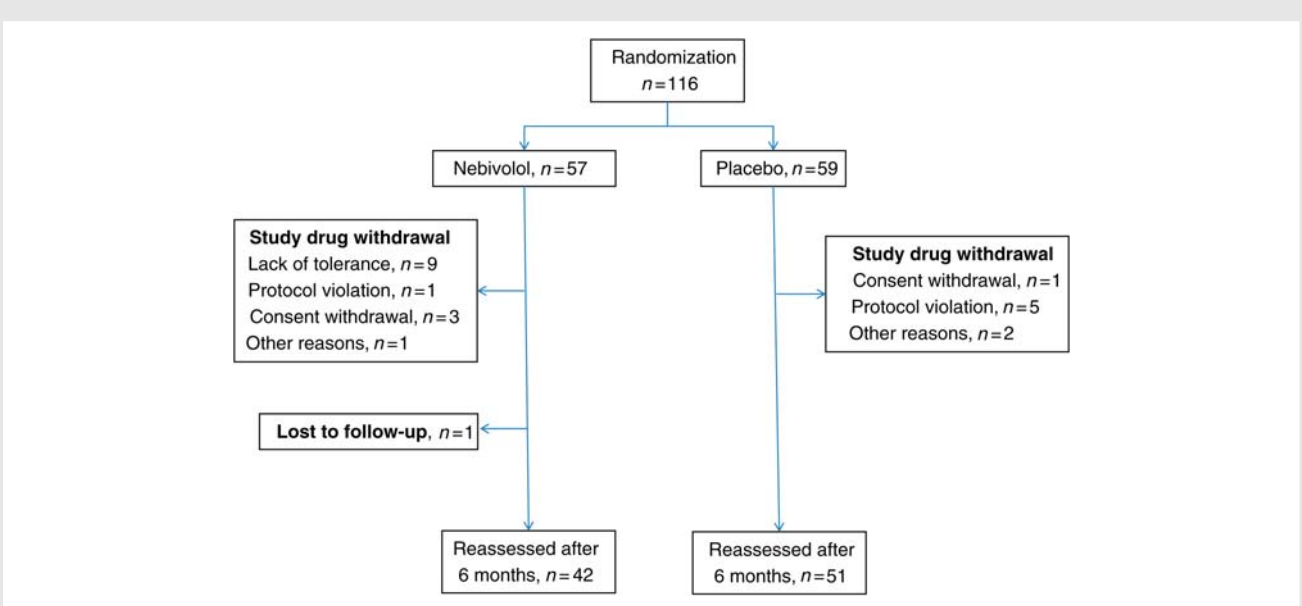

Figure 1 Patient flow diagram.

Table 1 Clinical characteristics of the patients

Variables	Nebivolol ($n = 57$)	Placebo ($n = 59$)	*P*-value
Age (years)	66.5 ± 9.8	65.3 ± 11.3	0.389
Gender, males, *n* (%)	20 (35)	21 (36)	>0.999
Aetiology, *n* (%)			
Coronary artery disease, *n* (%)	10 (17)	12 (20)	0.676
Hypertension, *n* (%)	49 (86)	51 (86.4)	0.981
Body mass index (kg/m^2)	30.3 ± 4.5	30.2 ± 4.9	0.397
Diabetes, *n* (%)	12 (21)	12 (20)	0.999
Hyperlipidaemia, *n* (%)	32 (56)	33 (56)	0.832
Smoking habits, *n* (%)	8 (14)	10 (17)	0.814
COPD, *n* (%)	9 (16)	4 (7)	0.032
NYHA class, II/III, *n* (%)	44 (77)/12 (21)	46 (78)/13 (22)	0.771
Serum BUN, mmol/L	13.6 ± 9.1	12.6 ± 7.9	0.077
Serum creatinine, μmol/L	88.5 ± 33.1	85.8 ± 25.1	0.463
6MWTD, m	420 ± 143	412 ± 123	0.586
Peak VO_2, mL/kg/min	17.02 ± 4.79	17.79 ± 5.96	0.073
LV ejection fraction (%)	61.9 ± 7.8	63.2 ± 9.2	0.428
Left atrial dilatation (% of patients)	56.1	63.4	0.68
E/A ratio	0.8 ± 0.18	0.9 ± 0.21	0.927
E/E' (E': sept + lat mitr ann/2)	11.1 ± 4.2	11.0 ± 4.0	0.707
Concomitant medication			
Diuretics, *n* (%)	28 (49)	32 (54)	0.71
ACE inhibitors/sartans, *n* (%)	43 (75)	47 (80)	0.659
Calcium channel blockers, *n* (%)	11 (19)	21 (36)	0.062
Hypolipidaemic drugs, *n* (%)	26 (46)	31 (53)	0.465
Antidiabetic agents, *n* (%)	12 (21)	12 (20)	>0.999

ACE, angiotensin-converting enzyme; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease.

Table 2 Haemodynamic variables measured at rest during the clinical assessments

Variables	Nebivolol	Placebo	*P*-value
Heart rate at rest, b.p.m.			
Baseline	73 ± 14	73 ± 11	0.397
6 months	67 ± 8	75 ± 13	<0.001
Systolic BP at rest, mmHg			
Baseline	134 ± 21	133 ± 18	0.992
6 months	127 ± 16	129 ± 18	0.390
Diastolic BP at rest, mmHg			
Baseline	81 ± 12	78 ± 10	0.350
6 months	77 ± 9	77 ± 10	0.961

BP, blood pressure.

New York Heart Association class and quality of life

NYHA functional class improved from baseline in both groups (from 2.19 ± 0.44 to 1.93 ± 0.50 for nebivolol: $P = 0.0001$; from 2.22 ± 0.42 to 1.95 ± 0.60 for placebo: $P = 0.0003$) without a significant difference between the two treatment arms ($P = 0.854$ for interaction).

The improvement from baseline in quality of life, measured with the Minnesota Living with Heart Failure Questionnaire, was of a similar magnitude in the nebivolol (from 27 ± 17 tot 23 ± 21, $P = 0.009$) and placebo group (from 29 ± 19 to 24 ± 18, $P = 0.007$). No difference between the two treatment groups was observed ($P = 0.697$ for interaction), both when the overall score was considered and when the physical and the emotional dimension scores were considered separately (data not shown).

N-terminal pro brain natriuretic peptide

NT-proBNP plasma levels slightly increased from baseline in the nebivolol group [median (range) from 147 pg/ mL (9–3577) to 162 pg/ mL (27–5158), $P = 0.228$], whereas they slightly decreased in the placebo group [from 126 pg/ mL (15–2055) to 99 pg/ mL (16–2899), $P = 0.413$], with no significant difference between the nebivolol and placebo arm ($P = 0.878$ for interaction).

Adverse events

The number of subjects who experienced at least one drug-related AE was higher in the nebivolol group (20 subjects, 35.1%),

Table 3 Effects on exercise testing

Variable	Nebivolol		Placebo		*P*-value
	Baseline	6 months	Baseline	6 months	
6MWTD, m	420 ± 143	428 ± 141	412 ± 123	446 ± 119**	0.004
Peak VO_2, mL/kg/min	17.02 ± 4.79	16.32 ± 3.76	17.79 ± 5.96	18.59 ± 5.64	0.63
Exercise duration, s	634 ± 274	564 ± 247	633 ± 250	569 ± 288	0.627
Peak workload, W	98.6 ± 34.6	92.7 ± 30.5	99.5 ± 38.3	103.3 ± 37.4	0.714
Heart rate, b.p.m.					
Rest	76 ± 15	68 ± 10**	78 ± 13	80 ± 16	<0.001
Peak exercise	127 ± 24	17 ± 21*	132 ± 21	134 ± 20	0.065
Systolic BP, mmHg					
Rest	128 ± 17	122 ± 18*	129 ± 23	126 ± 22	0.497
Peak exercise	176 ± 29	167 ± 31*	180 ± 34	182 ± 26	0.382
Diastolic BP, mmHg					
Rest	80 ± 11	76 ± 12**	78 ± 9	78 ± 10	0.07
Peak exercise	90 ± 12	87 ± 12	89 ± 16	87 ± 15	0.797

Asterisks after the numbers indicate *P*-values for changes from baseline: *$P < 0.05$ vs. baseline; **$P < 0.001$ vs. baseline.
P-values in the last column indicate between = group differences with respect to the changes from baseline in each study group.
BP, blood pressure.

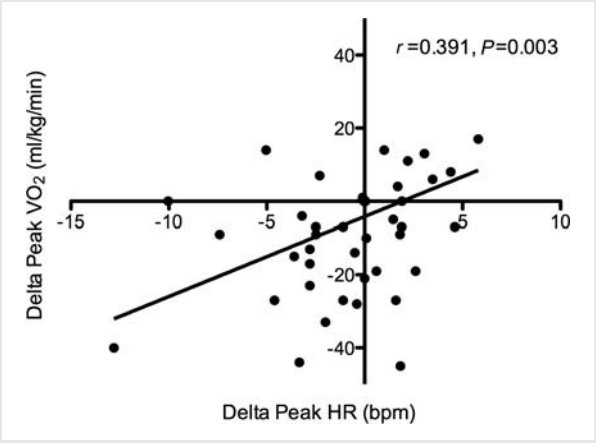

Figure 2 Correlation between changes in peak heart rate (Delta Peak HR) and peak oxygen consumption (Delta Peak VO_2) measured with cardiopulmonary exercise testing after 6 months nebivolol treatment. $r = 0.391$, $P = 0.003$ for intention-to-treat analysis; $r = 0.452$, $P = 0.004$ for on-treatment analysis.

compared with the placebo group (13 subjects, 22.0%). Adverse events caused study drug withdrawal in nine patients in the nebivolol group and none in the placebo group (*Figure 1*).

Discussion

ELANDD is the first prospective double-blind placebo-controlled study to assess the effect of long-term treatment with a beta-blocker, nebivolol, on exercise capacity in patients with HFPEF. Compared with placebo, 6 months treatment with nebivolol had no favourable effect on exercise performance, assessed either by the 6MWTD (primary endpoint of the study) or cardiopulmonary exercise testing, with, actually, a lower increase from baseline in the 6MWTD with nebivolol vs. placebo. The reduction in peak exercise heart rate after nebivolol administration was related to the changes in peakVO_2, thus suggesting that the inhibition of the chronotropic response to exercise is the main cause of the lack of beneficial effects of nebivolol administration on exercise performance.

Nebivolol is a third-generation beta-blocking agent with associated NO-releasing properties. This mechanism causes a concomitant peripheral vasodilation with improved aortic and ventricular compliance and, probably, better LV filling.[6,18,19,21] On the basis of these findings, we hypothesized that nebivolol administration could be associated with an improvement in exercise capacity in patients with HFPEF.[25] Our study has not proven this hypothesis, showing that nebivolol administration has no favourable effect on exercise capacity in patients with HFPEF, compared with placebo. These data with nebivolol are consistent with the findings with beta-blocker therapy in healthy subjects,[28,29] hypertensive patients,[30] and patients with HF.[16,27,31]

The lack of improvement in exercise capacity, despite the beneficial effects on LV function, with beta-blocker therapy in patients with HF is probably caused by the inhibition of the chronotropic response to exercise. A correlation between the decrease in peak exercise heart rate and the change in peak exercise capacity has been shown in HF patients after beta-blocker therapy.[16,31] Our study shows, for the first time, such a correlation also in patients with HFPEF. Patients with HFPEF have an increased dependency on the chronotropic response to exercise,[32–34] and, thus, they could be even more sensitive to the negative chronotropic

effects of beta-blocker treatment. Other mechanisms, unrelated to the inhibition of cardiac chronotropic responsiveness by nebivolol, may have equally contributed to the results of this study. For example, in a recent study it was shown that nebivolol delays the onset of myocardial relaxation, at least in mouse myocardium, thereby prolonging systolic activity, but shortening diastolic filling time.[35] In addition, the higher prevalence of patients with concomitant COPD in the nebivolol group, compared with placebo, may have also partially contributed to these results. Cardiopulmonary exercise testing could be terminated because of either limiting dyspnoea or fatigue. The reason for exercise test termination was not formally assessed in our study. However, no interaction with COPD was found.

Lastly, it must be noted that our patients had only mild LV diastolic dysfunction and only a mild exercise limitation. Namely, 78% of our patients were in NYHA functional class II, mean 6MWTD was 414 ± 135 m, and median NT-proBNP plasma levels were only 131 pg/ mL (range 9–3577 pg/mL). Thus, it may be that our patients were not sick enough to benefit from the beneficial effects of NO release and beta-blockade. Similar limitations have been described in larger studies of patients with HFPEF.[36]

Our results are seemingly in contrast to a previous single-centre study, involving 26 patients, showing an improvement in exercise capacity with nebivolol compared with placebo in patients with HFPEF,[24] as well with data showing a favourable effect of NO release on LV diastolic function,[21] a known determinant of exercise capacity. In the previous study, however, nebivolol was compared with another beta-blocker, atenolol, and, accordingly, the magnitude of the reduction of heart rate at peak exercise was similar with both compounds.[24] Thus, it may be hypothesized that NO release by nebivolol administration may allow a better exercise tolerance compared with other beta-blockers, though not if compared with placebo, or, probably, other classes of drugs.

Nebivolol has been shown to have favourable effects on outcomes in patients with an LVEF >0.35.[11] Our results do not contradict this study. The beneficial effects of beta-blockers on outcomes are mediated by their favourable effects on LV remodelling and the cardiomyocytes, whereas the effects on exercise capacity depend on the heart rate response to exercise.[16]

In our study, 9 of 57 patients (15.7%) randomized to nebivolol were withdrawn from the study for lack of tolerance of the target dose of 5 mg daily (*Figure 1*). This proportion seems large; however, these data compare favourably with recent data in patients aged ≥ 65 years.[37]

In conclusion, long-term nebivolol administration did not favourably affect exercise performance, compared with placebo, in a group of patients with HFPEF. Changes in peak exercise capacity were related to reduced heart rate response to exercise.

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