Clin Res Cardiol (2010) 99:75–82
DOI 10.1007/s00392-009-0098-x

ORIGINAL PAPER

# Effect of the long-term administration of nebivolol on clinical symptoms, exercise capacity and left ventricular function in patients with heart failure and preserved left ventricular ejection fraction: background, aims and design of the ELANDD study

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Received: 25 May 2009 / Accepted: 8 December 2009 / Published online: 29 December 2009


**Abstract**
*Background* The SENIORS trial demonstrated that nebivolol has beneficial effects in patients with heart failure. However, the role of beta-blocker therapy in patients with heart failure and preserved left ventricular ejection fraction (HFPEF) is still unsettled.
*Objective* To assess the long-term effects of administration of nebivolol, compared to placebo, on the clinical symptoms, exercise capacity and parameters of left ventricular (LV) function in patients with HFPEF.
*Methods* The Effect of Long-term Administration of Nebivolol on clinical symptoms, exercise capacity and left ventricular function in patients with Diastolic Dysfunction (ELANDD) study is a prospective multicenter European trial in 120 patients with HFPEF randomised to nebivolol or placebo. HFPEF is defined as symptoms or signs of heart failure, a LV ejection fraction >45% and evidence of diastolic LV dysfunction by Doppler echocardiography. Procedures include a baseline clinical examination, 6-min walk test (6MWT), electrocardiography, Doppler echocardiography and Minnesota QoL questionnaire. Nebivolol or placebo is started at 2.5 mg/day and gradually uptitrated to 10 mg/day. After initiation of the study, patients are assessed at 1, 2, 5 and 6 weeks (titration phase) and at weeks 12 and 26. The primary endpoint is the change from baseline in the 6MWT distance with nebivolol versus placebo. Sample size calculations are based on an anticipated 15% difference (70 m) in the 6MWT distance between nebivolol and placebo-treated patients. This study will allow the collection of data regarding the possible

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clinical benefits and the effects on LV function of nebivolol administration in patients with HFPEF.

**Keywords** HFPEF (heart failure preserved ejection fraction) · 6 MWT · Nebivolol · Quality of life · ELANDD

## Background and rationale

The prevalence of heart failure (HF) has reached epidemic proportions in Western countries. Approximately 40–60% of patients with HF have a normal or nearly normal left ventricular (LV) ejection fraction (EF) and the main cause of their symptoms and clinical course is LV diastolic dysfunction [1, 2]. These patients may have abnormalities of other indexes of LV systolic function, despite a preserved LVEF. On the other hand, patients with reduced LVEF generally also have diastolic abnormalities. Thus, these patients are currently referred to as subjects with HF and preserved LVEF (HFPEF) [3]. Compared to HF with reduced LVEF, HFPEF is more prevalent in women, black people, elderly, obese patients, patients with diabetes and patients with concomitant hypertension and/or left ventricular hypertrophy [1, 2, 4]. The severity of symptoms and the number of hospital admissions in patients with HFPEF versus those with reduced LVEF seem to be similar [5]. Even mortality rates, initially found to be lower compared to that of patients with reduced LVEF, appear now comparable in some studies [6–9].

Despite its clinical importance, the treatment of HFPEF remains unsettled [10, 11]. In fact, all the controlled trials performed to date, except for the digitalis investigation group, (DIG) trial [12], the study of the effects of nebivolol intervention on outcomes and rehospitalisation in seniors with heart failure, (SENIORS) [8, 13], the candesartan in heart failure: assessment of reduction in mortality and morbidity (CHARM-Preserved) [9], the perindopril in elderly people with chronic heart failure (PEP-CHF) study [14], and the irbesartan in patients with heart failure and preserved left ventricular systolic function (I-PRESERVE) [15], included only patients with reduced LVEF (e.g. <25–40%). Previous studies have shown only slightly favourable [9, 12–14] or neutral [15] effects on outcomes of treatment. A pre-specified analysis of SENIORS, comparing patients with a LVEF ≤35% with those with a LVEF >35%, found a similar effect on outcomes in these two subgroups of patients [8].

Investigations on HFPEF have been hindered by the demographic characteristics of the patients (elderly, with comorbidities, etc.) as well as by difficulties in establishing a definitive diagnosis. In this context, the recently released consensus statement on how to diagnose HFPEF is a major step forward [4]. This statement has allowed a more uniform design of large multicenter trials aimed at the assessment of pharmacological therapy in patients with HFPEF.

The effect of long-term administration of nebivolol on the clinical symptoms, exercise capacity and left ventricular function in patients with diastolic dysfunction (ELANDD) trial was designed before the new consensus statement was issued and was initially based mainly on the document of the European Study Group on Diastolic Heart Failure issued in 1998 [16]. When the new European statement was issued, we recognised its importance and adopted most of its Doppler-echocardiographic criteria for the diagnosis of HFPEF as inclusion criteria for our study [4]. Thus, the present study is among the first using the new criteria for the diagnosis of HFPEF for patient selection.

Nebivolol is a beta-blocker characterised by a high degree of selectivity for the beta-1 adrenergic receptors (ARs), compared to beta-2 ARs, with associated vasodilatory properties mediated by nitric oxide release [17] and probably by beta-3 ARs stimulation of endothelial cells [18]. Nitric oxide release at the level of the myocardium has favourable lusitropic effects with a downward shift of the LV pressure–volume relation in the diastolic phase and lower LV filling pressures [19]. We therefore hypothesised that nebivolol may improve cardiac function in patients with HFPEF through its NO-releasing activity. Previously, we already showed beneficial effects of nebivolol, compared to atenolol, on LV filling pressure and exercise tolerance in a single centre comparison trial [20]. Based on experimental and in vitro analyses and small trials in patients, the hypothesis tested in ELANDD was that nebivolol, compared to placebo, might beneficially affect symptoms and cardiac function in patients with HFPEF.

## Study design and patients' selection

ELANDD is a multicenter, double-blind, placebo-controlled, randomised, parallel group trial involving 12 European centers. The trial is funded by a grant from Menarini.

### Inclusion criteria

Original inclusion criteria were the following:

- Written informed consent to the study.
- Age ≥ 40 years.
- Documented history of HF with persistent symptoms during effort (NYHA class II–III).
- 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 or radionuclide ventriculography or nuclear magnetic imaging.
- Any abnormality of LV diastolic function documented by echocardiography, according to the guidelines of the European Study Group on Diastolic Heart Failure [16]. This inclusion criterion was revised in April 2007 following the online publication of the new European guidelines for the diagnosis of HFPEF [4]. The detection of any abnormality in LV diastolic function was substituted by the detection of an $E/E'$ ratio >15 at tissue Doppler echocardiography. Patients with a $E/E'$ ratio between 8 and 15 had to show additional abnormalities of diastolic function such as an $E/A$ ratio <0.5 and a deceleration half-time >280 ms (patients older than 50 years) or a duration of reverse pulmonary vein atrial systole flow: mitral valve atrial wave flow >30 ms or a left atrial volume index >40 mL/m$^2$ or increased LV mass index [4].

Major exclusion criteria

- Patients unable to perform 6-mi walking test
- Planned invasive cardiac procedures or cardiac surgery during the time of the study
- Recent (<3 months) acute coronary syndrome or stroke
- Exercise-induced myocardial ischaemia as main cause of exercise limitation as shown by symptoms (angina) or by previous exams (exercise test, stress echocardiography or myocardial scintigraphy)
- Concomitant diseases (COPD, peripheral vasculopathy, orthopaedic disease) as main cause of exercise limitation
- Major contraindications to beta-blocker therapy (sinus bradycardia, <50/min; atrio-ventricular block, bronchial asthma sensitive to beta-agonists administration)
- Ongoing treatment with beta-blockers, diltiazem or verapamil
- Systolic blood pressure <100 mm Hg
- Pregnancy, breast feeding or childbearing potential during the study
- History of alcohol or other illicit drug abuse
- Expected poor compliance to drug therapy
- Participation in any other clinical trial with an investigational product or scheduled to receive any such product during the study or in the 4 weeks following the study
- Suffering from any other medical condition that may exclude the patient for safety reasons or interfere with the objective of the study.

## Endpoints

The aim of the ELANDD study is to assess the long-term effects of the administration of nebivolol, compared to placebo, on the clinical symptoms, exercise capacity and parameters of left ventricular function in the patients with HFPEF. The primary endpoint of the study is the change from baseline in the distance walked during the 6-min walking test (6MWT) after 6 months of treatment with nebivolol versus placebo. Additional secondary endpoints are the changes from baseline after 6 months, with nebivolol versus placebo, in the following measurements:

- Symptoms, assessed using a five-level scale (extremely worsened, moderately worsened, unchanged, moderately improved, extremely improved);
- New York Heart Association (NYHA) functional class;
- Minnesota living with heart failure questionnaire [21];
- Maximal exercise duration, peak oxygen consumption, [$VO_2$] and slope of the minute ventilation [VE] to carbon dioxide [$VCO_2$] relation, at cardiopulmonary exercise testing.
- Changes in parameters related to LV diastolic function, including peak $E$ velocity at the Doppler recording of transmitral inflow tracing, peak $E'$ velocity of the mitral valve annulus measured at the level of the septal and lateral wall, respectively, by tissue Doppler recording, and the $E/E'$ ratio.

Lastly, the effects of treatment on major outcomes (death, hospitalization and unexpected visit to the outpatient clinic or heart failure unit) as well as adverse events are assessed.

## Procedures

Screening, titration and maintenance phases

Written informed consent, history and patients' baseline data are collected during the screening phase. Once eligibility has been ascertained, patients undergo baseline clinical evaluation and procedures (e.g. 6MWT, tissue Doppler echocardiography, cardiopulmonary exercise test, laboratory exams) and are then randomised in less than 1 week to either nebivolol (2.5 mg daily) or placebo. Study drug doses are increased during a 5 weeks titration phase: nebivolol or placebo doses are increased to 5 mg daily at 1 week after randomization and are then increased to 10 mg daily after 4 additional weeks if the heart rate is >60 beats/min. If an increase to 10 mg is not tolerated the dose may be reduced to 5 mg once daily. Once adequate dosing has been achieved, patients enter the maintenance

| | Week 0 | Week 1 | Week 5 | Week 6 | Week 12 | Week 26 |
|---|---|---|---|---|---|---|
| **Visit** | **Visit 1** | **Visit 2** | **Visit 3** | **Visit 4** | **Visit 5** | **Visit 6** |
| **Visit Description** | **Screening** | **Step 2** | **Step 3** | **Telephone consult** | **Follow up** | **End of study** |
| **Visit Window** | **Randomization** | **(-2/+2 d)** | **(-7/+7 d)** | **(-2/+2 d)** | **(-6/+6 d)** | **(-14/+14 d)** |
| Informed Consent | X | | | | | |
| In- and Exclusion criteria | X | | | | | |
| Demography | X | | | | | |
| Medical History | X | | | | | |
| Concomitant Drug Treatment | X | X | X | X | X | X |
| Adverse Events/Serious Adverse Events | | X | X | X | X | X |
| Pregnancy Test | X | | | | | |
| Adequate contraception | X | X | X | | X | X |
| NYHA functional class | X | | X | | | X |
| Quality of life (Minnesota) | X | | X | | X | X |
| Physical Examination | X | | | | | X |
| Blood Pressure | X | X | X | | X | X |
| Heart Rate (*pulse on visit 4) | X | X | X | X* | X | X |
| Weight/Height | X | | | | | X |
| Drug Compliance/Accountability | X | X | X | | X | X |
| Blood Sampling for routine analysis | X | | | | | X |
| Sampling NT Pro-BNP | X | | X | | | X |
| 12-lead ECG | X | X | X | | X | X |
| 6 minutes walking test | X | | | | | X |
| $VO_2$ max | X | | | | | X |
| Echocardiography | X | | | | | X |
| Randomization | X | | | | | |
| Titration | X | X | X | | | |
| Dispense study medication | X | X | X | | X | |
| End of Trial | | | | | | X |

**Fig. 1** Summary of baseline and follow-up measurements. *NYHA* New York Heart Association, *NT-proBNP* N-terminal pro brain natriuretic peptide, *ECG* electrocardiogram, $VO_2$ *max* maximal oxygen uptake

phase. During the maintenance phase, patient visits are at 12 and 26 weeks after initiation of the study. Changes in dosing or study drug withdrawal are allowed in case of major changes in the clinical conditions or adverse events throughout the study.

Study ends at the 26 weeks visit. On the day of this visit, patients repeat all the procedures performed at baseline in order to assess the effects of treatment. Baseline and follow-up assessments are shown in Fig. 1.

## Echocardiography

Echocardiography is performed at rest, with the patient in the left lateral position, using commercially available instruments with a multifrequency phased-array transducer of 1.5–2.5 MHz. Echocardiographic measurements are shown in Table 1. Two-dimensional guided M-mode measurements of the left atrial and LV internal dimensions and of the end-diastolic septum and posterior wall thickness are made at the LV minor axis at the level of the chordae tendinae just below the level of the mitral leaflet tips, as recommended by the American Society of Echocardiography (ASE) [22]. LV mass is calculated using the Penn convention [23] according to the equation: LV mass = 1.04 [(LV end-diastolic diameter + posterior wall thickness + interventricular septum thickness)$^3$ − (LV end-diastolic diameter)$^3$] − 13.6 g, normalized for body surface area. The transmitral flow velocity is measured using pulsed-wave Doppler with the sample volume positioned between the mitral leaflet tips during diastole. Relative wall thickness (RWT) at end-diastole and end-systole is calculated as the ratio of the end-diastolic and end-systolic posterior wall thickness (PWT) to the left ventricular internal radius (LVIDd) according to the formula: (2 × PWTd)/LVIDd. The *E*-wave and *A*-wave peak velocities, the ratio of the *E*-wave to the *A*-wave peak velocities (*E*/*A* ratio), *E*-myocardium (of septal wall), and pulmonary veins (*S*, *D*, AR) velocities are measured on three separate beats and then averaged. The isovolumic relaxation time (ms) is measured as the time interval between the end of left ventricular outflow and the start of the left ventricular inflow using simultaneous registrations of outflow and inflow signals by high-pulse repetition frequency pulsed-wave Doppler. The left atrial diameter, mitral valve deceleration time (ms), and atrial filling fraction are measured according to standard methods [24]. The

**Table 1** Echocardiographic measurements of systolic and diastolic left ventricular function

| | | |
|---|---|---|
| LV-ED | Left atrial diameter | MV inflow, *E* and *A* peak VTI |
| LV-ES | Aorta root diameter | PV, peak *S* |
| IVS-ED | Iso-volumetric relaxation time | PV, peak *D* |
| LVPW-ED | MV inflow, peak *E* | PV, peak *A* |
| LVOT, HR | MV inflow, peak *A* | PV, AR duration |
| LVOT, R-R interval | MV inflow, deceleration time *E* | Peak *E*′ septal annulus |
| LVOT, peak | MV inflow, *A*-duration | Peak *E*′ lateral annulus |
| LVOT, TVI syst | MV inflow, diastolic filling period | EDV (biplane Simpson) |
| LVOT, deceleration time | MV inflow, VTI *E* | ESV (biplane Simpson) |
| LVOT diameter | MV inflow, VTI *A* | |

investigators are encouraged to perform the echocardiographic evaluation as complete as possible. A secondary analysis of the echocardiographic parameters is done separately with the data available.

Isovolumic LV relaxation time (IVRT), the ratio of peak early (*E*) to peak atrial (*A*) Doppler mitral valve inflow velocity, deceleration time (DT) of early Doppler mitral inflow velocity and ratio of pulmonary vein systolic (*S*) and diastolic (*D*) flow velocities were originally considered to be indicative of diastolic LV dysfunction if they exceeded specific cutoff values indexed for age groups [16, 25]. Tissue Doppler-derived indices, namely, LV lengthening velocities, were later shown to allow a more accurate assessment of LV diastolic function and filling pressure [25]. Tissue Doppler imaging (TDI) was performed using minimal gain to obtain the best signal/noise ratio. In the apical 4-chamber view, the sample volume was set at 5 × 5 mm and placed 0.5–1 cm over the junction of the LV septal and lateral wall with the mitral annulus. Peak velocities during systole (*S*), early diastole (*E*′), and late diastole (*A*′) were measured. Values represented the average value of the three cycles and the mean values of the septal and lateral wall were used. Thus, the ratio between the early mitral inflow velocity (*E*) and the early diastolic (*E*′) lengthening velocity is nowadays considered as the most accurate parameter to assess LV diastolic function [4]. This measurement has therefore been used as a patient inclusion criterion in 2007, following diffusion of the new guidelines by the heart failure and echocardiography associations of the European Society of Cardiology (ESC).

## Exercise tests

The 6MWT is performed according to standard procedures [26].

Cardiopulmonary exercise testing is performed in all the patients who do not have specific limitations and are able to pedal on a cycle ergometer. Exercise is performed on a cycle ergometer with the patient in the sitting position with simultaneous expiratory gas exchange monitoring. Exercise is started at a work load of 0 W, with further increments of 20 W every 2 min, at a velocity of 50 rpm, up to the appearance of limiting dyspnea or fatigue. Electrocardiographic and respiratory variables are continuously monitored. Peak $VO_2$ is obtained averaging the final 30 s of exercise. The anaerobic threshold and the VE/$VCO_2$ slope are measured by standard criteria [27]. All patients will have performed at least one preliminary exercise test in order to be familiar with the procedure and to ensure stability of the results.

## Data collection and endpoint monitoring

All data will be recorded in the case record forms and will be transferred to the central database at the trial coordination center, which is regularly backed up and password protected. The case record forms are monitored at regular times by the study monitor.

All (possible) endpoints are sent (by fax or mail) to the trial coordination center as soon as they are detected.

## Statistical considerations

The size of the study group has been calculated on the basis of the predicted change in the 6-min walking distance after chronic nebivolol administration. According to previous trials, patients with HFPEF may have a similar impairment of exercise capacity, compared to those with systolic HF [23]. In a previous study in patients with LV systolic dysfunction, we found an increase in the 6MWT from 416 ± 121 to 479 ± 138 m with metoprolol treatment and from 447 ± 136 to 497 ± 126 m with carvedilol treatment (n.s. for differences between the two agents; both $p < 0.001$ for changes from baseline) [28]. We assumed that nebivolol administration may be conservatively associated in the patients enrolled in ELANDD with a similar improvement in 6-min test walk distance from baseline versus no change from baseline in the placebo group. Thus, assuming a 10% dropout rate and a 15% difference (70 m)

in the increase in the 6-min walk distance between the nebivolol and the placebo treatment groups, we have calculated that a sample size of 118 patients (59 in each group) would detect a difference of 70 m, at a standard deviation of 140 m, as statistically significant at $\alpha = 0.05$ (two tailed) and $\beta = 0.20$ (power 80%) in the change of the 6-min walking distance between the two study groups. The planned study sample size was therefore set at 118 patients.

## Discussion and conclusions

Despite the fact that HFPEF accounts for approximately 50% of the admissions for acute HF, its treatment is still unsettled. Only a few trials have included these patients and have often yielded less significant results, compared to trials in patients with reduced LVEF [9, 13, 14]. There are multiple reasons for these findings, including the older age, greater prevalence of comorbidities, as well as the inclusion of patients in whom cardiac dysfunction was likely not the main cause of symptoms [29, 30]. Thus, scrutinized patient selection has become a must for any assessment of the effects of treatment in patients with HFPEF. We have therefore chosen to use the criteria proposed by the ESC [3, 16]. The protocol of the present study has therefore been amended in 2007 according to the definition of HFPEF in the new consensus statement [4]. Because of similarities of the values, the cutoff values for LVEF and LV end-diastolic volume used in the former European document (LVEF $\geq$ 45% and LV end-diastolic volume index $\leq$ 102 ml/m$^2$) [6] have not been changed to the values stated in the new consensus statement (LVEF $>$ 50% and LV end-diastolic volume $<$97 ml/m$^2$) [4].

Our inclusion criteria were mainly based on Doppler and tissue Doppler-echocardiographic measurements. Diagnostic criteria, used in the new consensus statement but not in its former edition, such as atrial fibrillation and natriuretic peptides plasma levels were still not used for our trial. It is possible that BNP and NT-ProBNP measurements may be a valid surrogate to these measurements for screening purposes [3, 4]. However, until the use of these measurements is prospectively validated, tissue Doppler-echocardiographic parameters remain the gold standard, at least for small, mechanistic studies, like ELANDD. ELANDD is actually one of the first studies in which the criteria of ESC were actively used for patient inclusion.

Differently from previous mechanistic studies, however, a clinical endpoint, rather than a Doppler-echocardiography measurement, was chosen as primary endpoint of the study. This was based on multiple considerations. First, Doppler-echocardiographic measurements had not shown major changes with beta-blocker therapy in patients with HFPEF [31]. Second, the 6-min walking test distance is related to symptoms as well as to patients' outcomes [26, 28, 32, 33] and it is less dependent on peak exercise heart rate, a limiting factor for exercise capacity in HFPEF [34]. Third, single center trials have shown that walking distance is responsive to therapeutic changes, including beta-blockers [28]. However, until now, these agents have not been associated with significant benefits in exercise capacity in patients with heart failure in multicenter trials [33]. Nebivolol may have many beneficial effects on exercise performance in patients with HF and, especially, in those with HFPEF. These include a NO-mediated downward shift in the LV pressure–volume relationship [19] with lower LV filling pressure during exercise [20], peripheral vasodilation with increased skeletal muscle blood flow [17, 24], selective beta-1 ARs blockade with reduced heart rate and increased filling time. ELANDD was therefore designed to test the hypothesis that nebivolol can be associated with improved symptoms and exercise tolerance, in patients with HFPEF.

**Acknowledgments** The study is supported by Menarini International Medical Department (Firenze, Italy).

## Appendix

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