

## Clinical Research

## Effects of Nebivolol on Left Ventricular Function and Exercise Capacity in Patients with Non-Ischaemic Dilated Cardiomyopathy. A Randomised Placebo-Controlled Study

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**Keywords:** Beta-blocker, heart failure, left ventricular ejection fraction, left ventricular diastolic function, exercise test.

*Manuscript received:*  
December 14, 2004;  
*Accepted:*  
March 18, 2005.

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**Introduction:** This study assessed the effects of Nebivolol on left ventricular (LV) function and exercise capacity in patients with non-ischaemic dilated cardiomyopathy (NIDC).

**Methods:** After enrolment in this double-blind trial, 60 patients, aged  $55 \pm 9.5$  years, with angiographically proven NIDC, LV ejection fraction (EF)  $< 45\%$ , NYHA class II-III, were randomised to either Nebivolol (target dose 5 mg) or placebo and were evaluated using echocardiography and exercise tests over 3 months.

**Results:** There were no baseline differences between the 2 groups regarding NYHA class, heart rate (HR), blood pressure (BP), LVEF or other echocardiographic variables. During follow-up, 4 patients in the Nebivolol and 5 in the placebo group discontinued treatment. After 3-months' treatment a significant decrease in NYHA class ( $p=0.001$ ), resting HR ( $p=0.03$ ), systolic and diastolic BP (both  $p<0.001$ ), left atrial diameter ( $p=0.01$ ) and LV end-systolic volume ( $p=0.046$ ), and an increase in LVEF ( $p=0.01$ ) were observed in the Nebivolol group compared to placebo. The atrial contribution to total LV filling ( $p=0.007$ ) and the pulmonary venous (PV) systolic wave velocity ( $p=0.007$ ) increased, whereas the atrial PV component decreased ( $p<0.001$ ) in the Nebivolol patients compared to placebo. Exercise duration decreased at 3 months ( $p=0.01$ ) compared to placebo, probably as a result of reduced maximal exercise HR ( $p<0.001$ ).

**Conclusions:** Nebivolol is a safe and well-tolerated drug that improves NYHA class, systolic and diastolic LV function in NIDC patients, although it is associated with a lower maximal exercise duration at 3 months.

Certain beta-blockers have been shown to improve cardiac function and symptoms and reduce the risk of death and hospitalisation in patients with heart failure (HF).<sup>1-3</sup>

Although all beta-blockers that prolong survival interact with the  $\beta_1$ -receptor, some agents may have additional properties that can modify the magnitude of sympathetic antagonism and clinical benefit. In the specific case of beta-blockade for HF, a debate concerning the relative efficacy of "second generation"  $\beta_1$ -selective agents (Metoprolol controlled release, or long acting Meto-

prolol) versus the "third generation" non-selective beta-blocker Carvedilol has arisen. The results of the recent COMET trial suggest that Carvedilol has a more beneficial effect on mortality than does Metoprolol.<sup>4</sup>

Nebivolol, a new third generation cardioselective  $\beta_1$ -blocker, which increases endothelial nitric oxide (NO) release thereby inducing peripheral vasodilation,<sup>5-6</sup> has not been adequately studied in the HF syndrome. The aim of our study was to investigate the safety of Nebivolol and its effect on left ventricular (LV) function and exercise capacity in patients with non-ischaemic di-

lated cardiomyopathy (NIDC) and mild to moderate HF.

## Methods

Eligible patients were men or women with symptomatic mild to moderate HF (New York Heart Association [NYHA] functional class II-III) due to angiographically proven NIDC, with at least one cardiovascular admission during the previous year and a clinical history >6 months. Admission requirements included stable HF treatment with angiotensin converting enzyme inhibitors for at least 4 weeks and diuretics, if necessary, for at least 3 weeks. Digitalis, angiotensin II inhibitors, or other vasodilators could be used at the discretion of the investigators. Study patients were referred to our outpatient heart failure clinic for evaluation and none of them were on prior treatment with any other beta-blocker. LVEF had to be <45% measured within the previous 6 months by echocardiography or ventriculography.

Exclusion criteria included the introduction of new drug therapy for HF in the 6 weeks prior to randomisation, primary valvular heart disease or severe secondary mitral regurgitation, history of bronchospasm, asthma or regular medication with inhaled bronchodilators, known hepatic failure (defined as elevation of aspartamine transaminase, alanine transaminase or bilirubin levels to three times the upper limit of the normal reference range), known renal dysfunction (defined as serum creatinine >1.5 mg/ml), any important contraindication for beta-blockers (including second or third degree heart block without a permanent pacemaker, sick sinus syndrome, heart rate <60 beats/min, systolic blood pressure <90 mmHg), previous intolerance to beta-blocker therapy and poor acoustic images.

The hospital's Ethics Committee approved the protocol and all patients gave informed written consent. Eligible patients were randomised in a double blind fashion to either Nebivolol or placebo, using a computer generated random number algorithm, and immediately received the first dose of either placebo or 1.25 mg Nebivolol. The study stipulated that patients attend weekly visits following the initiation of the titration phase. Upon patient evaluation, if tolerance was certified (resting heart rate >50 beats per min, systolic blood pressure >90 mm Hg, drop in systolic blood pressure <30 mmHg on standing upright, no new symptoms of dizziness or increased shortness of breath not alleviated by an increase in diuretics),

the dosage of Nebivolol was increased by 1.25 mg at each visit. Once the target dose was achieved patients were followed up every month for three months. Quality of life was evaluated along with NYHA functional class and any complications, hospitalisation or death during the observation period were noted.

## Echocardiographic study

M-mode, 2-dimensional and Doppler echocardiography were performed in all patients and controls, using a Hewlett-Packard Sonos 2500 echocardiographic device (Andover, Mass.) and a 2/2.5 MHz wide-angle phased-array transducer. All examinations were recorded on videotape for subsequent offline data analysis.

M-mode echocardiographic recordings were obtained from the left parasternal window and all measurements were made according to the recommendations of the American Society of Echocardiography.<sup>7</sup>

LV volumes were measured from the apical 4-chamber view of the 2-D echocardiogram and LVEF was calculated using a modified Simpson's rule algorithm. Data were analysed as the mean of three cardiac cycles.

Spectral Doppler recordings from the mitral inflow were obtained from the apical 4-chamber view to assess LV filling dynamics. The pulsed-wave Doppler sample volume was positioned between the tips of the mitral leaflets to derive the following variables during normal breathing: (1) peak early (E) and late (A) transmitral filling wave velocities in metres per second and their velocity time integrals (VTI); (2) E/A ratio and the atrial contribution to the total LV filling, VTIA/ (VTIE + VTIA); and (3) deceleration time of the E (DTE) velocity in milliseconds (from peak E velocity to baseline). Atrial filling was estimated with the pulsed-wave Doppler sample volume positioned 1 cm into the right upper pulmonary vein and systolic (Spv), diastolic (Dpv) their VTI and the reversal atrial component (Ar) were calculated.

Two independent laboratory investigators performed the measurements. The intra- and inter-observer variability, according to the recommendations of the British Standards Institution,<sup>8</sup> were for LVEF 8.6% and 11.8% respectively, for the calculation of pulsed-wave Doppler peak E and A velocities 5.9, 6.1% and 7.4, 7.6% respectively, and for E and A velocity time integrals VTIE and VTIA 9.8, 10.1% and 13.1, 13.6% respectively.

### Exercise Test

All patients underwent a graded, symptom-limited exercise test, using a Naughton protocol (mean time  $\pm$ 5 days after echocardiography study) on a Marquette treadmill device (Max-1 Marquette treadmill device, GE Medical Systems, Milwaukee, Wisconsin). The exercise test was usually carried out during the morning and after at least 3 hours without food, coffee or cigarettes. A 12-lead ECG was monitored continuously, with recordings every 2 minutes at the end of each stage.

The exercise duration was defined as the time from the start of exercise until its cessation because of dyspnoea or fatigue, and maximal exercise heart rate as the peak heart rate achieved at the end of exercise. The investigators who performed the echo studies and exercise tests were blinded to treatment and previous measurements.

### Statistical analysis

Summary data for continuous variables are expressed as mean  $\pm$  standard deviation. Comparisons between

groups were made using the unpaired Student's t-test or the Mann-Whitney test, as appropriate. The association between continuous variables was assessed using the Pearson correlation method.

An interim repeated measurements ANOVA analysis with one between factor at 2 levels was carried out to assess the differences between the two groups (Nebivolol or placebo) in terms of clinical, functional and echocardiographic parameters at 3 months' follow-up.

A two-tailed p-value less than 0.05 was considered statistically significant. All analyses were performed using a commercially available statistical package (SPSS for Windows 11.0, Chicago, Illinois).

## Results

### Patients' characteristics

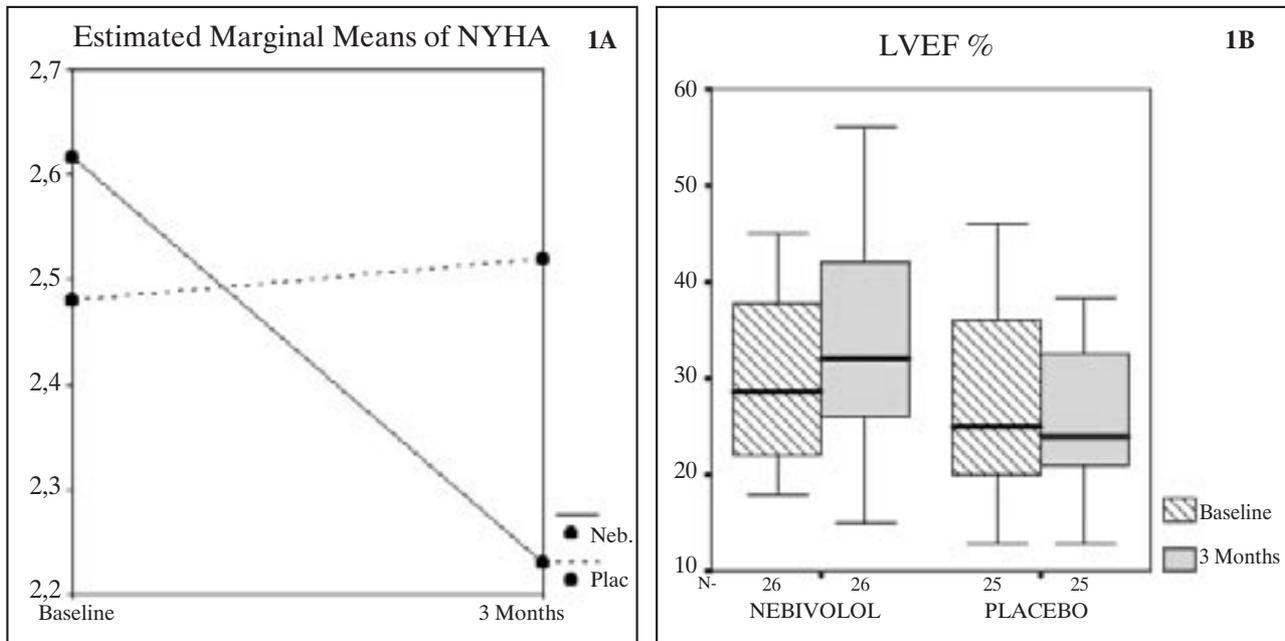
The patients' characteristics and their changes through the 3-month follow-up are shown in Table 1. The study population included 60 patients who were randomised into the Nebivolol group (30 patients) or the control group (30 patients). Most of the patients were on di-

**Table 1.** Patients' clinical characteristics.

Group	Baseline		3 Months	
	Nebivolol (26 pts)	Placebo (25 pts)	Nebivolol (26 pts)	Placebo (25 pts)
Age	56 $\pm$ 8.6	51.2 $\pm$ 11.9	56 $\pm$ 8.6	51.2 $\pm$ 11.9
Men	22	20	22	20
Women	4	5	4	5
NYHA				
II	16	14	20	13
III	10	11	6	12
Heart rate (beats/min)	74.2 $\pm$ 8.1	77.9 $\pm$ 8.1	71.3 $\pm$ 7.5*	77.2 $\pm$ 7.26
Systolic BP (mmHg)	132.2 $\pm$ 17.4	122.7 $\pm$ 8.13	116.9 $\pm$ 11.6*	125.9 $\pm$ 9.2
Diastolic BP (mmHg)	83 $\pm$ 10.4	78 $\pm$ 7.5	75.5 $\pm$ 7.3*	82 $\pm$ 8.1
Sinus rhythm	24	23	24	23
Atrial fibrillation	2	2	2	2
LBBB	8	7	8	7
Pacemaker	4	3	4	3
ACE-inhibitors	23	21	21	21
Digoxin	12	13	9	12
Diuretics	22	23	24	24
Amiodarone	5	6	5	6
AT <sub>1</sub> -blockers	3	4	2	5

\*p<0.05 inter-group (Nebivolol vs. placebo) statistically significant difference between the in-group changes during follow-up.

ACE – angiotensin converting enzyme, AT<sub>1</sub>-blockers – angiotensin II receptor blockers, BP – blood pressure, LBBB – left bundle branch block.



**Figure 1.** A: Mean NYHA functional class in Nebivolol (solid line) and placebo (dotted line) patients at baseline and 3-months' follow-up. B: Left ventricular ejection fraction (LVEF %) in Nebivolol and placebo patients at baseline and 3-months' follow-up.

uretic, digitalis and angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor-1 antagonists in addition to the study medication.

All patients began the study with a 1.25 mg dose of Nebivolol or placebo. If tolerance was good, the dose was titrated up to the intended maximum dose of 5 mg over 4 weeks. Eight patients did not achieve the 5 mg target dosage by week 5 and remained at 1.25 mg (4 patients) or 2.5 mg (4 patients). In 5 patients, low tolerance was due to low blood pressure (systolic blood pressure  $\leq 100$  mm Hg), while in another three it was due to bradycardia, defined as resting heart rate  $< 50$  beats/min.

During the first three months, 4 patients in the Nebivolol group stopped taking the medication, two because of increased shortness of breath not alleviated by increased diuretic dose, another as a result of hypotension and one because of bradycardia. Of the 30 patients in the placebo group 5 patients discontinued treatment (2 due to exacerbation of dyspnoea, two because of dizziness and one at his own request). None of the patients in either group died or needed to be hospitalised. All of them were followed on an outpatient basis.

After 3 months' treatment patients in the Nebivolol group exhibited a significant improvement in NYHA class compared to placebo ( $p=0.001$ , Figure 1A). Patients in the Nebivolol group showed a significant reduction in resting HR ( $-7.2 \pm 11$  vs.  $-1 \pm 6.5\%$ ,  $p=0.01$ ) systolic and diastolic BP (both  $p<0.001$ ) compared to the placebo group after 3 months' treatment.

#### Echocardiographic study

Echocardiographic parameters and their changes during follow-up are shown in Table 2. Nebivolol patients showed a significant decrease in left atrial (LA) diameter ( $p=0.01$ ) and in LV end-systolic volume ( $p=0.046$ ) and an increase in LVEF after 3 months' treatment compared to the placebo group ( $15.3 \pm 17.4$  vs.  $0.49 \pm 25.5\%$ ,  $p=0.01$ ), showing the drug's beneficial effect on LV systolic function in patients with NIDC (Figure 1B). As regards diastolic LV function, the transmitral VTIA ( $p<0.001$ ) and the atrial contribution to total LV filling ( $p=0.007$ ) increased (Figure 2), while the DTE showed a tendency to increase ( $p=0.09$ ) compared to the placebo group.

**Table 2.** Echocardiographic and exercise test parameters at baseline and 3-months' follow-up

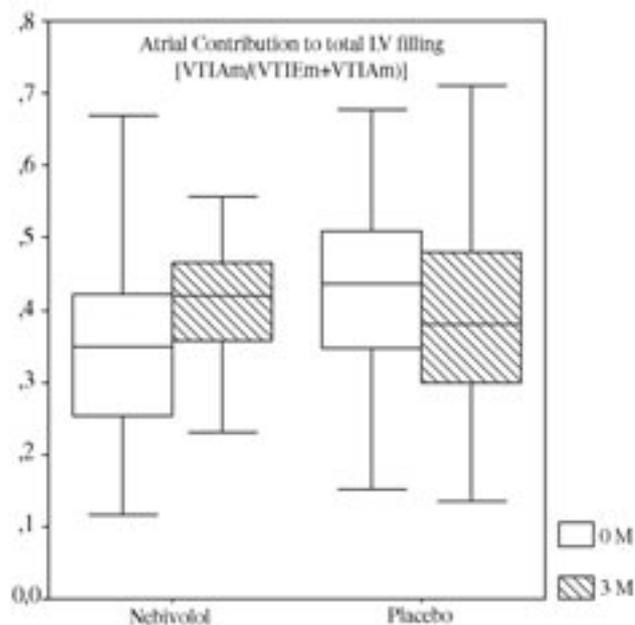
Group	Initial examination		3 Months		p*
	Nebivolol (26 pts)	Placebo (25 pts)	Nebivolol (26 pts)	Placebo (25pts)	
LVDD (mm)	60.6±5.1	62.3±6.6	59.1±5.5	62.8±5.5	0.01
IVS(mm)	10.2±2	9.8±1.1	9.4±1.4	9.58±0.8	0.48
PW(mm)	10.2±1.35	9.9±1	9.6±1.2	9.6±1.1	0.51
LVSD(mm)	47.2±7.1	50.6±8.4	46.3±7.4	50.4±7.7	0.1
LA(mm)	45±2.5	45.1±5.1	42.6±4.5	45.5±3.8	0.01
LVDV(ml)	152.6±53.6	165.9±65.5	142.4±48.4	171.6±73.6	0.1
LVSV(ml)	110±48.8	122.3±63.5	98.7±45.9	130.3±70.3	0.046
LVEF(%)	29.6±8.2	28.4±9	34.3±11.1	27.3±7.3	0.01
E(m/s)	0.74±0.28	0.73±0.27	0.66±0.18	0.78±0.27	0.056
A(m/s)	0.58±0.20	0.57±0.14	0.61±0.17	0.51±0.15	0.19
VTIE (cm)	11.5±4	10.9±3.8	11.2±3.2	10.1±3.5	0.55
VTIA (cm)	5.9±2.2	8.1±2.9	7.8±2.4	7±3.6	<0.001
E/A	1.43±0.88	1.56±0.97	1.16±0.45	1.68±0.85	0.11
VTIAm/(VTIA+VTIE)	35.1±13.5	43.1±12.9	40.8±8.7	40±14.5	0.007
DTE (ms)	187.8±51.8	206.4±50.1	201.7±38	188±65.7	0.09
Spv (m/s)	0.41±0.15	0.44±0.13	0.47±0.08	0.43±0.12	0.007
Dpv (m/s)	0.47±0.14	0.51±0.16	0.45±0.13	0.50±0.1	0.32
VTI <sub>Spv</sub> /(VTI <sub>Spv</sub> +VTI <sub>Dpv</sub> )	0.46±0.13	0.50±0.11	0.51±0.11	0.49±0.11	0.067
Ar (m/s)	0.36±0.07	0.29±0.05	0.30±0.04	0.32±0.05	<0.001
Exercise duration (s)	888.4±404.3	876.8±351	719.2±337.2	873.4±291	0.01
Peak exercise HR (b/min)	135.5±17.4	139.5±29.4	124.3±14.7	143.4±25.6	<0.001

A – atrial transmitral pulsed wave Doppler wave velocity, Ar – atrial reversal wave of the pulmonary venous flow, Dpv – diastolic component of the pulmonary venous flow, DTE – deceleration time of E, E – early transmitral pulsed wave Doppler wave velocity, IVS – interventricular septal thickness, LA – left atrial diameter, LVDD – left ventricular (LV) end-diastolic diameter, LVDV – LV end-diastolic volume, LVEF – LV ejection fraction, LVSD – LV end-systolic diameter, LVSV – LV end-systolic volume, PW – posterior wall thickness, Spv – Systolic component of the pulmonary venous flow, VTI – velocity time integral.

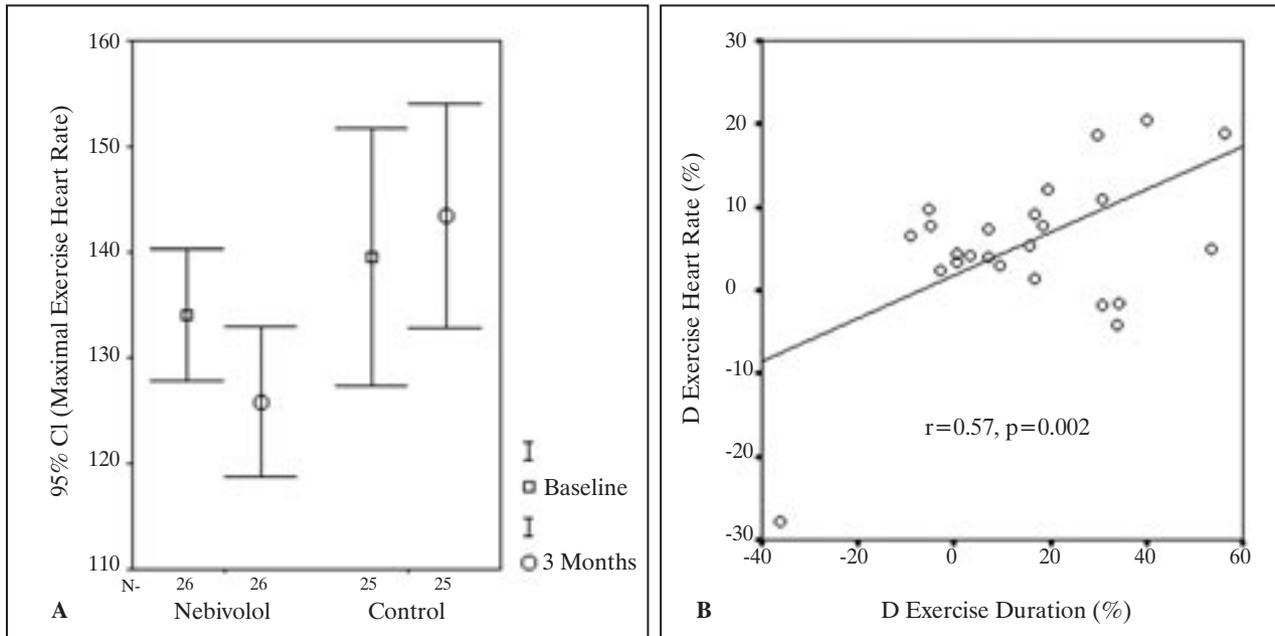
An inverse correlation between changes in HR and the atrial fraction/total LV filling ratio was observed ( $r=-0.44$ ,  $p=0.02$ ) in the Nebivolol group. The peak velocity of the systolic component of PV flow ( $p=0.007$ ) increased and the systolic fraction to total atrial filling ( $VTI_{Spv}/VTI_{S+Dpv}$ ) showed a tendency to increase ( $p=0.06$ ), while the atrial reversal wave decreased ( $p<0.001$ ) compared to the placebo group.

### Effects of Nebivolol on exercise capacity

Exercise test parameters and their changes during follow-up are shown in Table 2. In Nebivolol patient a decrease was seen in exercise duration ( $-16.3\pm 20.9$  vs.  $1.4\pm 20.8\%$ ,  $p=0.01$ , 95% CI:  $(-35.5) - (-7.9)$ ) and maximal exercise heart rate ( $-4\pm 11.7\%$  vs.  $5\pm 9.5\%$ ,  $p=0.001$ , 95% CI:  $0.04 - 0.16$ ) (Figure 3A) compared to placebo after 3 months follow-up. The changes in exercise duration were correlated with the changes in maximal exercise HR in the Nebivolol group ( $r=0.57$ ,  $p=0.002$ ), suggesting that there may be a relationship between these two parameters (Figure 3B).



**Figure 2.** The contribution of the late filling to total left ventricular diastolic filling in Nebivolol and placebo patients at baseline and 3-months' follow-up.



**Figure 3.** A: Maximal exercise heart rate (beats/min) in Nebivolol and placebo patients at baseline and 3-months' follow-up. B: Relationship between the changes in exercise duration (D Exercise Duration %) and exercise heart rate (D Exercise heart rate %) after 3 months of Nebivolol treatment. CI= Confidence Interval.

## Discussion

The aim of this study was to investigate the safety and efficacy of Nebivolol, a new, third generation  $\beta_1$ -adrennergic blocker, in the treatment of patients with chronic mild to moderate HF due to NIDC, by evaluating its effects on LV function and exercise capacity. The hypothesis behind the use of Nebivolol was that the effects of this NO-releasing<sup>5,6</sup>  $\beta_1$ -blocker, combined with the well-proven beneficial effects of beta-blockers in HF, might represent a promising pharmacological tool in the treatment of those patients.

The pathophysiological role of NO in HF is still poorly understood. Although controversy exists, prevailing opinion rejects the current hypothesis of an adverse effect of excessive myocardial NO in HF<sup>9</sup> and instead proposes that loss of NO bioactivity, at least partly related to reduced endothelial NO synthase,<sup>10</sup> contributes to cardiac dysfunction and that NO may confer a cardioprotective effect in HF.<sup>11-12</sup> NO has also been shown to counter the effects of beta-adrenergic stimulation in patients with dilated cardiomyopathy.<sup>10,13</sup>

Our main findings were that Nebivolol, similarly to other beta-blockers used in the treatment of HF, is a safe choice of treatment with many beneficial effects on the NYHA functional class, systolic and diastolic left ventricular function in NIDC patients.

## Tolerability

None of the patients in the placebo or Nebivolol group required hospitalisation during the observational period. Four patients (13.3%) in the Nebivolol group discontinued treatment due to side effects. A similar result was observed in the placebo group (16.6%) and seems comparable to the reported percentage that discontinued Carvedilol (16.6% to 19.6%) or Metoprolol (10.3-13.5%) in other major trials of beta-blockers in HF.<sup>3,14-16</sup>

The target dose of 5 mg was achieved in 17 patients (68%), a percentage quite similar to the reported percentage of patients who received the target dose of Carvedilol (65.1-75%) or Metoprolol (71-78%) in other trials.<sup>14-15,17</sup>

## Nebivolol and LV systolic function

A significant improvement in LVEF was noticed in NIDC patients after 3 months' treatment with Nebivolol compared to placebo.

Previous studies<sup>17-18</sup> with Carvedilol or Metoprolol reported results similar to ours concerning LV systolic function. This improvement in LVEF was associated with a concomitant decrease in LV end-systolic volume, a finding that was also reported by Khattar et al.<sup>19</sup> Those investigators showed that Carvedilol mo-

notherapy produced significant reductions in end-systolic volume at 3 months, while in another study the anti-remodelling effect of Metoprolol was observed after 6 months' treatment.<sup>20</sup>

Apart from its beta-1 blocking effects, Nebivolol, with its additional peripheral vasodilating properties due to NO modulation,<sup>5</sup> may decrease the LV afterload, thereby allowing more effective LV pumping, while an additional NO-dependent mechanism cannot be excluded.<sup>21,22</sup>

### ***Nebivolol and LV diastolic function***

There are conflicting data in the literature concerning the impact of beta-blocker treatment on diastolic function in patients with HF. In our study indices of LV diastolic function showed an improvement after 3 months' Nebivolol treatment compared to placebo.

Andersson et al<sup>23</sup> found an improvement in LV diastolic function after Metoprolol treatment in patients with idiopathic dilated cardiomyopathy, although in a later study<sup>24</sup> the same author failed to show any change in peak filling LV rate measured by radionuclide ventriculography. Quaipe et al<sup>25</sup> reported that 4 months' treatment with Carvedilol did not affect LV diastolic performance, while Clements et al<sup>26</sup> found that an improvement in diastolic function in patients with idiopathic dilated cardiomyopathy treated with Metoprolol was related with heart rate changes.

Capamolla et al<sup>27</sup> observed that Carvedilol administered over 6 months resulted in a change of the diastolic LV filling pattern and was associated with an improvement of diastolic function. Rousseau et al<sup>28</sup> reported that in patients with ischemic cardiomyopathy 8-10 weeks' treatment with Nebivolol resulted in a parallel downward shift of the pressure-volume relationship during early diastolic filling and improved the early peak filling rate, when compared to placebo.

We found a decrease in LA diameter with a concomitant increase in the atrial contribution to total LV filling and the systolic fraction of PV flow to total atrial filling, an index that has been proposed to reflect LA filling pressures.<sup>29</sup> We can hypothesise that the decrease in LA diameter may be related to decreased filling pressures and improved LA systolic function. It cannot be determined whether this improvement is related to HR changes, but it seems that a relationship between them may exist, at least with regard to the improvement in the atrial contribution to total LV filling. However NO has been shown to hasten relax-

ation, improve distensibility and also depress mitochondrial respiration, thereby altering mechanoenergetic coupling.<sup>22</sup>

### ***Nebivolol and exercise tolerance***

After three months' treatment maximal exercise duration showed a reduction despite the improvement in NYHA class. Previous studies have reported contradictory data concerning the effect of beta-blocker treatment on exercise tolerance in patients with HF. Bucindolol,<sup>30,31</sup> Carvedilol<sup>16-17,32-34</sup> and Metoprolol<sup>16,35</sup> failed to demonstrate an improvement in peak exercise in multicenter trials, despite an observed improvement in NYHA class or HF symptoms. Earlier studies with Nebivolol in HF patients have reported a non-significant reduction in maximal ergometer bicycle exercise duration, with a simultaneous improvement in NYHA functional class<sup>36</sup> and improved exercise capacity in patients with ischemic cardiomyopathy.<sup>28</sup>

As in all previous beta-blocker studies, the maximal exercise HR was decreased in our study and the exercise duration changes appear to be related to the changes in HR. The reduced maximal exercise HR in the Nebivolol group, which results in reduced exercise cardiac output, may be a possible explanation for the earlier termination of the exercise test.

### ***Study limitations***

The major limitation of our study was the relatively small number of patients enrolled. We only studied patients with NIDC, so as to obtain a homogeneous group with reliable, comparable results, but these findings cannot be extended to patients with ischemic cardiomyopathy.

We made no invasive measurements, since our primary end-point was the clinical effects of Nebivolol treatment and echocardiographic measurements have proved their value.

We investigated patients with mild to moderate HF and excluded patients with more severe HF. As a result of this, together with the regular follow up, we had a negligible incidence of serious side effects (death or hospitalisation), so we cannot estimate the effect of Nebivolol on mortality or morbidity. Finally, no comparison of Nebivolol with other established beta-blockers used for the treatment of HF, such as Carvedilol or Metoprolol, was attempted. This will be the target of a possible further study, along with the chronic effect of Nebivolol.

## Conclusions

In patients with dilated cardiomyopathy, Nebivolol is a safe and well-tolerated choice of treatment that improves NYHA functional class, systolic and diastolic LV function compared to placebo, despite an initial decrease in maximal exercise duration at 3 months.

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