

# NITRIC OXIDE, ERECTILE DYSFUNCTION AND BETA-BLOCKER TREATMENT (MR NOED STUDY): BENEFIT OF NEBIVOLOL VERSUS METOPROLOL IN HYPERTENSIVE MEN

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## SUMMARY

1. Hypertensive men treated with beta-blockers frequently complain of erectile dysfunction. The present study investigated the effects of two  $\beta_1$ -adrenoceptor-selective antagonists, namely nebivolol and metoprolol, on erectile function in hypertensive men.

2. Male out-patients (age range 40–55 years) with newly diagnosed or existing stage 1 essential hypertension (mean seated systolic blood pressure 140–159 mmHg; diastolic blood pressure 90–99 mmHg) were enrolled in the study. All patients lived in a stable, heterosexual partnership and had no history of sexual dysfunction. After a 2 week placebo run-in period, patients were randomized double-blind to either Treatment group A (comprising nebivolol 5 mg once daily for 12 weeks, followed by placebo for 2 weeks and then metoprolol succinate 95 mg once daily for 12 weeks) or Treatment group B (comprising metoprolol succinate 95 mg for 12 weeks, placebo for 2 weeks and then nebivolol 5 mg for 12 weeks). An international index of erectile function (IIEF) questionnaire and a diary documented patients' sexual function and activity.

3. Nebivolol and metoprolol lowered blood pressure to a similar extent. Metoprolol, but not nebivolol, significantly decreased the IIEF erectile function subscore by 0.92 in the first 8 weeks after onset of beta-blocker treatment. In contrast with metoprolol, nebivolol improved secondary sexual activity scores and other IIEF subscores.

4. Despite similar antihypertensive efficacy of the cardioselective  $\beta_1$ -adrenoceptor antagonists nebivolol and metoprolol, nebivolol may offer additional benefits by avoiding erectile dysfunction in male hypertensive patients on long-term  $\beta$ -adrenoceptor antagonist therapy.

**Key words:** erectile function, hypertension, metoprolol, nebivolol.

## INTRODUCTION

Erectile dysfunction (ED) is defined by the National Institutes of Health (NIH) as the inability to achieve or maintain an erection sufficient for satisfactory performance.<sup>1</sup> In numerous controlled trials, ED has been identified as a frequent side-effect of antihypertensive therapy and certain classes of antihypertensive agents (particularly beta-blockers and diuretics) are associated with an increased risk of ED.<sup>2</sup> For example, the Cross-National Survey on Men's Health Issues found that up to 20% of men experiencing ED were being treated with beta-blockers.<sup>3</sup>

Hypertension is highly prevalent; the incidence is lowest in rural communities in developing countries and highest in developed countries.<sup>4</sup> Treatment of hypertension is essential to minimize long-term cardiovascular risk. The importance of maintaining the quality of sexual life when controlling blood pressure is becoming increasingly recognized. For many patients, ED is probably one of the main adverse effects impacting subjective assessment of well-being and quality of life, especially at the beginning of antihypertensive treatment. Therefore, ED may represent one of the major threats to compliance with antihypertensive therapy and resultant poor blood pressure control.<sup>5</sup>

Beta-blockers are among the drugs of choice for the treatment of hypertension.<sup>6</sup> They differ with respect to their mechanisms of action, especially in terms of their  $\beta_1$ -adrenoceptor selectivity and their vasoactive effects. Currently, we differentiate between three generations of beta-blockers (first–third generation). Third-generation beta-blockers have additional effects (e.g. celiprolol, carvedilol and nebivolol are vasodilating drugs). However, only the vasodilating effects of nebivolol can be attributed to additional generation of endothelial nitric oxide (NO; for a review, see Weber<sup>7</sup>).

Recently, Fogari *et al.* performed two studies comparing the effects of lisinopril with those of atenolol and those of valsartan with carvedilol on the frequency of sexual intercourse in hypertensive men.<sup>8,9</sup> These beta-blockers differ in their pharmacological characteristics: atenolol is a second-generation  $\beta_1$ -adrenoceptor-selective antagonist, whereas carvedilol is a non- $\beta_1$ -adrenoceptor-selective third generation beta-blocker. The use of both beta-blockers led to a decrease in the frequency of sexual intercourse compared with the angiotensin-converting enzyme inhibitor lisinopril or the angiotensin receptor antagonist valsartan. However, to date, studies comparing the effects of different beta-blockers on erectile function are lacking.

The present study was designed to evaluate the effects of two widely used adrenoceptor beta-blockers, namely nebivolol (a third-generation beta-blocker with high  $\beta_1$ -adrenoceptor selectivity and

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endothelial NO-dependent vasodilator effects) and metoprolol (a second-generation beta-blocker), on erectile function in hypertensive men. Erectile function was assessed using the international index of erectile function (IIEF), a reliable, validated and widely used self-assessment scale.<sup>10</sup> The IIEF, which incorporates the major aspects of the NIH definition of erectile function, consists of 15 questions with predefined answers that are associated with specific scores. It was developed as a brief, reliable and validated assessment tool of male sexual function in a home setting and is now regarded as the gold standard, being used in most studies evaluating erectile function.

## METHODS

### Patients

Male out-patients aged between 40 and 55 years with newly diagnosed or existing mild (stage 1; systolic blood pressure (SBP) 140–159 mmHg and diastolic blood pressure (DBP) 90–99 mmHg) essential hypertension or taking antihypertensive medication were enrolled in the study. Patients were also required to be living in a stable, monogamous heterosexual partnership for at least 6 months and to have had no symptoms of sexual dysfunction (IIEF erectile function score 25–30), even if they were taking beta-blockers or diuretics. Patients with a history of diabetes mellitus, alcohol and/or drug abuse, major cardiovascular and non-cardiovascular diseases, or those receiving any concomitant treatment related to hypertension and/or ED were excluded from the study. All patients had to provide written informed consent prior to participation.

### Study design

The study was performed in accordance with the Declaration of Helsinki and was approved by the local ethics committee. This pilot study was a double-blind, 1 : 1 randomized, parallel-group cross-over study lasting for a total of 28 weeks (Fig. 1). After a 2 week placebo run-in period, patients were randomly allocated to one of the two treatment groups on the basis of a computer-generated randomization plan in a ratio of 1 : 1. In Treatment group A, patients received once-daily nebivolol 5 mg for the first 12 weeks, then a once-daily placebo for 2 weeks before being crossed-over to once-daily metoprolol succinate 95 mg for a further 12 weeks. In patients randomised to Treatment group B, initial treatment was with once-daily metoprolol

succinate 95 mg for 12 weeks, followed by a 2-week once-daily placebo period and then once-daily nebivolol 5 mg treatment for the final 12 weeks of the study. Patients were examined at the screening visit, at the baseline/randomization visit and every 4 weeks during the active treatment periods (Fig. 1). Clinic visits were generally in the morning and at a similar time on each occasion. Seated blood pressure, measured using a cuff sphygmomanometer, was determined after resting for 10 min and was a mean of three measurements obtained at 2 min intervals. At visits 1–8, patients were issued with a home-use diary to document the frequency of sexual intercourse during the trial. In addition, at each visit, patients were given an IIEF questionnaire with instructions on how to complete the questionnaire.

### Study end-points

The primary measurement of treatment effect on sexual function was the IIEF erectile function subscore at the end of the two active treatment periods (weeks 12 and 26) compared with the respective baseline values (end of placebo run-in period/end of placebo wash-out period). Secondary efficacy variables analysed and derived from the IIEF were changes in orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction after nebivolol or metoprolol treatment. The effects of treatment on blood pressure were also assessed. During the first and second double-blind treatment periods, patients were asked two questions concerning: (i) satisfaction regarding erectile function; and (ii) global satisfaction with therapy. The safety and tolerability of both drugs were assessed in terms of adverse events, heart rate and laboratory parameters.

### Compliance monitoring

Compliance was evaluated by a pill count of returned medication at each clinic visit.

### Statistical analysis

Because of the pilot nature of the study, no formal statistical size estimation was performed. However, the study was planned to enrol 32 patients who could be evaluated with respect to the primary efficacy end-point and it was assumed that 52 patients would have to be randomized to achieve this goal.

Statistical analysis of the data based on the IIEF erectile subscores was performed by analysis of covariance (ANCOVA), with respective baseline values as the covariate. To verify the basic assumptions of the cross-over design, in addition to the evaluation of period effect, the presence of carry over effect (treatment  $\times$  period interaction) was investigated. The primary efficacy analysis was based on the intention-to-treat (ITT) data set and the per-protocol-data set. Secondary efficacy analysis was performed with analysis of variance (ANOVA). All statistical testing procedures were two-sided with  $\alpha = 0.05$ .

## RESULTS

### Study patients

A total of 50 patients were screened for the study. Prior to randomization, two patients in Treatment group B were withdrawn owing to violation of baseline inclusion criteria. All 48 patients randomized to treatment completed the study. The two groups were well balanced with regard to age, height, weight, body mass index, duration of hypertension and SBP and DBP at baseline (Table 1). Comparisons between the treatment groups in terms of erectile function subscores prior to first treatment did not reveal a significant difference between the two treatment groups. Pill counts confirmed that patient adherence to medication was good at between 80 and 120% in both treatment groups.

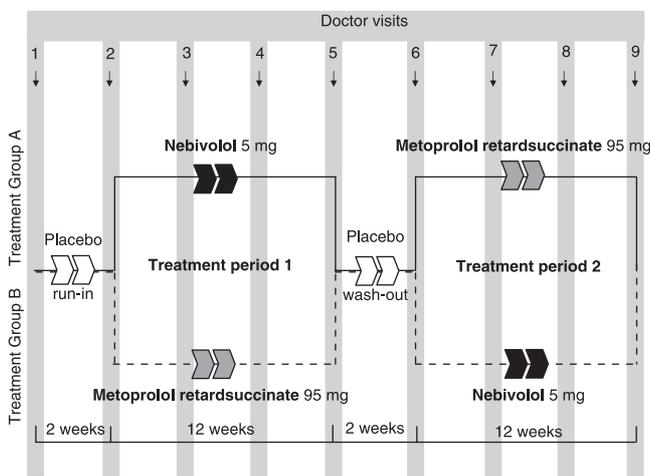


Fig. 1 Study design.

**Table 1** Baseline characteristics of patients

Characteristic	Treatment group	
	A	B
Patients ( <i>n</i> )	25	23
Age (years)	48.4 ± 5.3	47.2 ± 5.3
Height (cm)	176.6 ± 5.5	177.8 ± 4.6
Weight (kg)	87.5 ± 14.4	86.0 ± 7.5
BMI (kg/m <sup>2</sup> )	28.1 ± 4.4	27.2 ± 2.4
Mean duration of hypertension (years)	3.3 ± 3.2	4.0 ± 3.6
SBP (mmHg)	149.4 ± 4.3	148.2 ± 4.8
DBP (mmHg)	92.9 ± 1.9	93.0 ± 1.8
EF subscore*	28.2 ± 1.3	28.1 ± 1.3
Previous antihypertensive therapy ( <i>n</i> )		
Calcium channel blocker	0	1
ACE inhibitor	2	0
ARB	1	0
Diuretic	0	1
Beta-blocker	2	3
No. current smokers (%)	11 (44)	11 (48)

Where appropriate, data are given as the mean ± SD.

Treatment group A: period 1 nebivolol 5 mg once daily, period 2 metoprolol 95 mg once daily; Treatment group B: period 1 metoprolol succinate 95 mg once daily, period 2 nebivolol 5 mg once daily.

There were no statistically significant differences in characteristics at baseline.

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; EF, erectile function; ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

\*Determined before first treatment.

### Blood pressure control

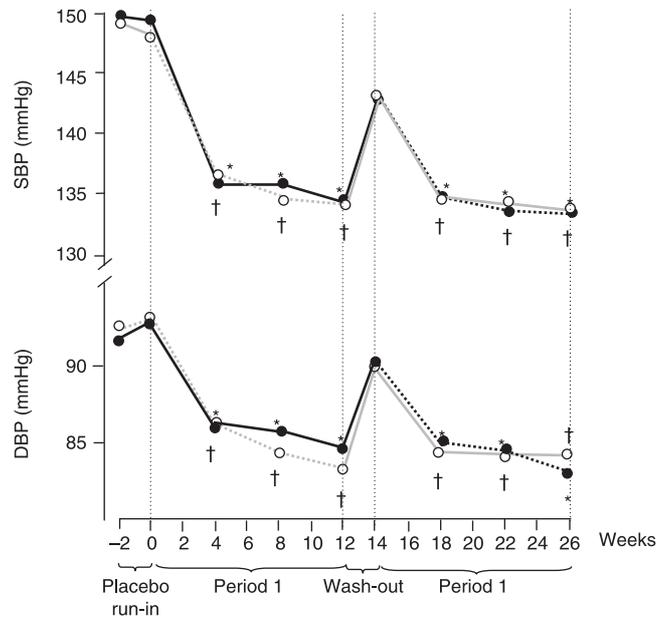
Nebivolol and metoprolol reduced blood pressure to a similar extent, irrespective of the order of treatment (Fig. 2). Because the mean baseline values for SBP and DBP were considerably lower at the end of the placebo wash-out period compared with the end of the placebo run-in period, mean decreases in SBP and DBP were lower in Treatment period 2 than in Treatment period 1. The differences between the treatment groups in terms of the reduction in blood pressure from baseline were not statistically significant (Fig. 2). In both treatment groups, all patients responded to antihypertensive treatment and reached target SBP < 140 mmHg and DBP < 90 mmHg. Accordingly, no patient dropped out owing a lack of efficacy of the antihypertensive treatment.

### Primary sexual end-point

The erectile function subscore showed no significant changes from baseline in patients treated with nebivolol in Treatment period 1 (−0.08 points). This also holds true if nebivolol was administered in Treatment period 2 (+0.35 points; Fig. 3).

In contrast, there was a clear decrease of 1.17 points in patients who received metoprolol during Treatment period 1 and a similarly clear decrease of 0.68 points in patients who received metoprolol after cross-over. During the wash-out period, erectile function only partially recovered in the metoprolol group.

Taking all measurements between the start of the treatment period and the end of the treatment together, nebivolol did not significantly



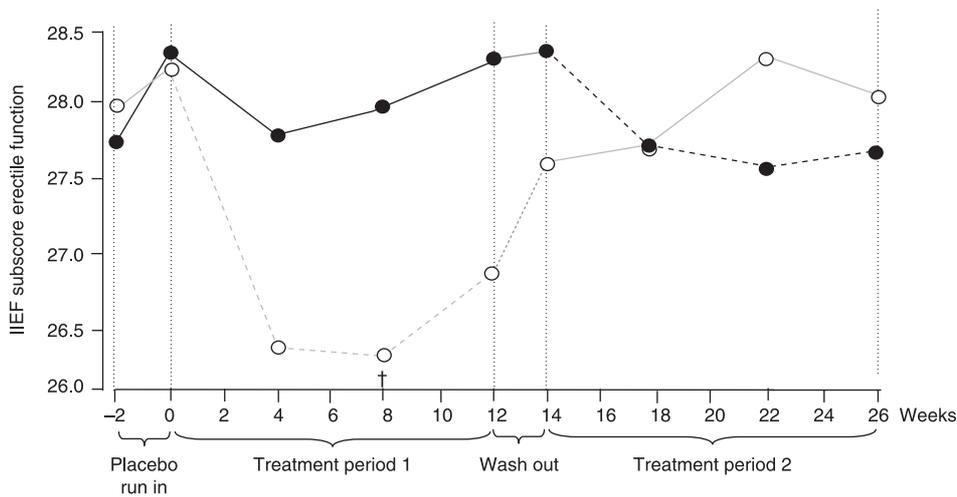
**Fig. 2** Changes in systolic and diastolic blood pressure (SBP and DBP, respectively) in Treatment group A (period 1 nebivolol 5 mg once daily, period 2 metoprolol 95 mg once daily; *n* = 25; ●) and Treatment group B (period 1 metoprolol succinate 95 mg once daily, period 2 nebivolol 5 mg once daily; *n* = 25; ○). Both β-adrenoceptor antagonists similarly decreased SBP and DBP in hypertensive men. \**P* < 0.05 compared with time 0 in Treatment group A; †*P* < 0.05 compared with time 0 in Treatment group B.

alter the mean erectile function subscore (+0.13 points), whereas the mean erectile function subscore decreased significantly under metoprolol by −0.92 points (Fig. 4).

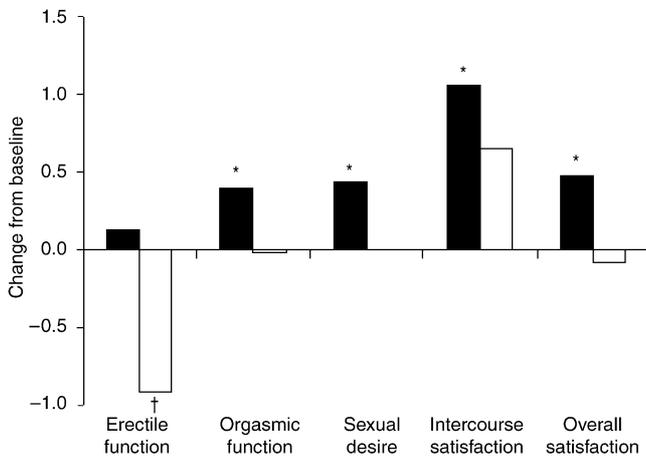
The results for the mean changes from baseline of all secondary efficacy criteria derived from the IIEF (orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction subscores) at the end of treatment were in favour of nebivolol compared with metoprolol (Fig. 4). When other time points were considered, the 5% significance level was achieved for the erectile function subscore after 4 weeks and for the orgasmic function subscore after 8 weeks of treatment (*P* = 0.04 and *P* = 0.038, respectively). The results of the per protocol (PP) analysis were similar to those of the ITT analysis. The only noticeable difference was that the treatment effect for the erectile function subscore after 4 weeks of treatment failed to achieve the 5% significance level in the PP analysis.

### Secondary sexual end-points

With respect to the mean changes from baseline of all individual items of the IIEF, the results were in favour of nebivolol (Fig. 3). The mean frequency of sexual intercourse per month was comparable for the two treatments (nebivolol 5.6; metoprolol 5.8). According to patient ratings, 22.9% considered that nebivolol produced an improvement in their erectile function compared with 14.6% who reported that metoprolol resulted in an improvement. When patients were asked to directly compare the two treatments, 25.0% regarded nebivolol as being better than metoprolol with respect to effects on erectile function, but only 8.3% stated that metoprolol was better than nebivolol. The proportion of patients who were very content with



**Fig. 3** Changes in the international index of erectile function (IIEF) erectile function subscores in Treatment group A (period 1 nebivolol 5 mg once daily, period 2 metoprolol 95 mg once daily;  $n = 25$ ; ●) and Treatment group B (period 1 metoprolol succinate 95 mg once daily, period 2 nebivolol 5 mg once daily;  $n = 25$ ; ○). A significant decline in IIEF was observed in the first 4 weeks of metoprolol treatment. † $P < 0.05$  compared with time 0 in Treatment group B.



**Fig. 4** Effects of 12 weeks treatment with nebivolol 5 mg once daily (■) and metoprolol succinate 95 mg once daily (□) in Treatment periods 1 and 2 combined on changes from baseline in international index of erectile function (IIEF) subscores.

the overall treatment effects was considerably higher for nebivolol than for metoprolol (45.8 vs 29.2%). Regarding the global assessment of treatment satisfaction, 45.8% of patients felt that nebivolol was better than metoprolol, whereas only 20.8% stated that metoprolol was superior.

### Tolerability and safety

No critical findings regarding safety issues occurred during the study. The results of safety analysis confirmed a good safety profile for both study drugs. At least 98% of patients rated the tolerability of the two treatments as good or very good.

## DISCUSSION

The present pilot study investigated the influence of the third-generation  $\beta_1$ -adrenoceptor-selective antagonist nebivolol and another highly  $\beta_1$ -adrenoceptor-selective antagonist, namely metoprolol, on sexual function in middle-aged, hypertensive men. Despite a similar

improvement of SBP and DBP levels, metoprolol significantly decreased the majority of sexual efficacy variables assessed when used to treat middle-aged hypertensive men with no evidence of prior ED, especially in the first weeks after the start of treatment, whereas there was a tendency towards an improvement in the erectile function subscore with nebivolol.

All patients, whether treated with nebivolol or metoprolol, achieved SBP  $\leq 140$  mmHg and DBP  $\leq 90$  mmHg at the end of the study. In everyday circumstances, target blood pressure, even in the absence of additional risk factors requiring more rigorous blood pressure control, often proves difficult to achieve.<sup>11</sup> Insufficient blood pressure control is frequently attributed to patients' poor adherence to the dosing regimen.<sup>12</sup> In the present study, compliance was good and this may be explained, in part, by the good tolerability of the drugs, as well as because of the close monitoring of patients, with regular follow ups.<sup>13</sup>

Normally compliant patients who are, in general, philosophical about any side-effects, may make a conscious decision to stop taking medication at certain times and have a 'drug holiday'.<sup>14</sup> Because many patients are aware that antihypertensives can negatively impact on sexual activity, they may be tempted to discontinue treatment regularly to satisfy themselves and their partners. The perceived short-term benefit from discontinuing antihypertensive treatment may tempt sexually active patients to take longer and longer 'drug holidays' until eventually totally stopping treatment.

The incidence of sexual dysfunction may vary with the age of the study population.<sup>15</sup> To limit the confounding effects of age, we examined a middle-aged, sexually active population. Enrolling subjects with no history of sexual dysfunction allowed us to assess the occurrence of ED related to the medication *per se* and not to other factors.

Differences in the effects of nebivolol and metoprolol on erectile function and other IIEF subscores may be due to their different modes of action. Nebivolol is a potent, highly cardioselective beta-blocker with a unique haemodynamic profile (for a review, see Ignarro<sup>16</sup>) compared with other cardioselective beta-blockers, such as metoprolol. Nebivolol is able to modulate the endothelial NO system,<sup>17</sup> increasing the liberation of NO, resulting in coronary and systemic vasodilation and, thereby, a reduction in peripheral resistance and counteraction of endothelial dysfunction.<sup>18</sup> Nebivolol promotes arterial and venous vasodilation that is independent of its action at

$\beta_1$ -adrenoceptors (for a review, see Ignarro<sup>16</sup>). The endothelial NO effect following nebivolol treatment may be due to an activation of  $\beta_3$ -adrenoceptors<sup>17</sup> or oestrogen receptors.<sup>19</sup> Unique vasodilation effects based on endothelial NO liberation following treatment with nebivolol have been demonstrated in shown in peripheral macro- and in human coronary microvessels.<sup>17,20</sup> In addition, nebivolol has been shown to cause an increase in stroke volume, associated with a reduction in vascular resistance, resulting in a maintained cardiac output despite reduced heart rate.<sup>21,22</sup> These different effects of NO, resulting in increasing blood flow and considerable advantages in terms of the haemodynamic profile on cardiac output, may also contribute to penile erection function.<sup>23</sup>

The second primary parameter investigated in the present study, namely erectile function, was increased following nebivolol treatment and decreased following metoprolol treatment. These opposing results indicate that nebivolol may improve erectile function by increasing perfusion in small and microvessels. Similar effects have been described for sildenafil, a phosphodiesterase 5 inhibitor (for a review, see Moore *et al.*<sup>24</sup>).

Despite the endothelial NO-liberating effect of nebivolol, it is not clear whether nebivolol also increases NO liberation from other cell types in erectile tissue (e.g. corpus cavernosum cells). In contrast with other (vascular) smooth muscle cells, the smooth muscle cells of the corpus cavernosum tissue contain endothelial NO synthase (eNOS)<sup>25</sup> and activation of corpus cavernosum eNOS is also important for erectile function, because it contributes to an increase in penile blood flow.<sup>23</sup> There is evidence that  $\beta_3$ -adrenoceptors are present in the corpus cavernosum.<sup>26</sup> However, whether nebivolol induces NO release from cells other than endothelial cells remains to be investigated in future studies.

In conclusion, the findings of the present pilot study suggest that the cardioselective  $\beta_1$ -adrenoceptor antagonists nebivolol and metoprolol have different effects on erectile function in hypertensive men. Despite similar antihypertensive efficacy, nebivolol may have some advantages in terms of the quality of sexual life, possibly as a result of its vasodilator effect mediated by increased NO release. More evidence is needed to confirm the beneficial effects of nebivolol on erectile function in hypertensive men. If a cross-over design was used to minimize the number patients required, it may be appropriate to extend the placebo wash-out period between treatments. Large-scale trials directly comparing beta-blockers to confirm the benefit of nebivolol in maintaining, or even enhancing, sexual quality of life in hypertensive men seem appropriate.

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