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# Nebivolol in the Management of Essential Hypertension

## A Review

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**Data Selection**

**Sources:** Medical literature published in any language since 1966 on nebivolol, identified using AdisBase (a proprietary database of Adis International, Auckland, New Zealand), Medline and EMBASE. Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

**Search strategy:** AdisBase search terms were 'nebivolol' and 'hypertension'. Medline and EMBASE search terms were 'nebivolol' and 'hypertension'. Searches were last updated 12 May 1998.

**Selection:** Studies in patients with hypertension with or without comorbid conditions who received nebivolol. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

**Index terms:** hypertension, nebivolol, pharmacokinetics, pharmacodynamics, therapeutic use.

## Contents

## Summary

**Abstract**

Nebivolol is a lipophilic $\beta_1$-blocker. It is devoid of intrinsic sympathomimetic or membrane stabilising activity but appears to have nitric oxide-mediated vasodilatory effects. Nebivolol is administered as a racemic mixture of equal proportions of *d*- and *l*-enantiomers. The drug does not significantly influence glucose or plasma lipid metabolism and appears to have a protective effect on left ventricular function.

At the recommended dosage (5mg once daily) nebivolol reduces resting diastolic blood pressure as effectively as standard therapeutic dosages of atenolol, metoprolol, lisinopril and nifedipine, as shown in comparative trials. Nebivolol reduced blood pressure significantly more than enalapril 10mg daily in the short but not the long term, although the enalapril dose may not have been optimal. Nebivolol has an additive effect in combination with hydrochlorothiazide.

Standing blood pressure and/or mean 24-hour ambulatory blood pressure is significantly and similarly reduced with nebivolol, atenolol or nifedipine. Nebivolol tended to prevent increases in early morning blood pressure better than nifedipine.

Overall response rates to nebivolol therapy (a decrease in sitting/supine diastolic blood pressure to ≤90mm Hg or a 10% or ≥10mm Hg fall in diastolic blood pressure) ranged from 58 to 81% after 4 to 52 weeks' treatment. In comparative studies, response rates were greater in nebivolol than in enalapril or metoprolol recipients, but not significantly different from those in atenolol or nifedipine recipients.

Nebivolol 5mg once daily is well tolerated in patients with hypertension. Adverse events are infrequent, transient and mild to moderate. Those reported most often include headache, fatigue, paraesthesias and dizziness. Several studies reported no signs of orthostatic hypotension with nebivolol.

Comparative trials revealed no significant differences between the frequency and severity of adverse events in patients receiving nebivolol, atenolol, enalapril or placebo; however, the overall incidence of adverse events was greater with nifedipine or metoprolol. Some atenolol or enalapril, but not nebivolol, recipients reported impotence or decreased libido during therapy.

**Conclusion:** Current evidence indicates that nebivolol 5mg once daily is a well tolerated β-blocker, which is as effective as once daily atenolol and other classes of antihypertensive agents. It may therefore be recommended as a useful alternative first-line treatment option for the management of patients with mild to moderate uncomplicated essential hypertension.

## Pharmacodynamic Profile

Nebivolol is a lipophilic $\beta_1$-blocker administered clinically as a racemic mixture of equal proportions of its *d*- and *l*-enantiomers. The drug is devoid of intrinsic sympathomimetic or membrane stabilising activity but appears to have a nitric oxide-mediated vasodilatory effect. Unlike atenolol, nebivolol causes dose-related endothelium-dependent vasodilation in human dorsal hand or forearm vessels.

Available data suggest that nebivolol has a protective effect on left ventricular function. The drug appears to reduce preload and maintain or decrease afterload. Total peripheral vascular resistance did not increase in any study of nebivolol. Heart rate and left ventricular end-diastolic pressure are decreased, whereas stroke volume is increased and cardiac output is generally maintained, notably in patients with heart failure. Nebivolol reduced left ventricular mass in hypertensive patients with left ventricular hypertrophy.

Decreases in the ratio of pre-ejection period to left ventricular ejection time (PEP/LVET) were the result of significant shortening of PEP and lengthening of LVET periods ($p \leq 0.05$ for both) in patients with hypertension treated with nebivolol for 1 year.

Resting heart rates were reduced similarly with nebivolol 5mg and atenolol 50mg once daily, but resting and 24-hour ambulatory heart rates were reduced to a significantly greater extent with nebivolol than with nifedipine 20mg twice daily ($p < 0.05$) or enalapril 10mg once daily ($p < 0.001$).

Single or multiple doses of nebivolol reduced exercise-induced tachycardia and attenuated exercise-induced increases in blood pressure in patients and volunteers to a similar or lesser extent than atenolol, propranolol or pindolol. Submaximal endurance time decreased with atenolol but was unchanged with nebivolol.

Nebivolol does not appear to significantly influence glucose or plasma lipid metabolism although there have been rare instances of increases in triglyceride levels. The drug was associated with reductions in plasma renin levels and increased plasma atrial natriuretic peptide levels but did not alter renal haemodynamics in hypertensive patients with or without renal artery stenosis when administered for 4 weeks.

## Pharmacokinetic Profile

The metabolism of nebivolol is subject to genetic polymorphism; phenotypically, individuals may be characterised as 'poor' (slow) or 'extensive' (fast) metabolisers.

After a single 5mg oral dose, peak plasma drug concentrations ($C_{max}$) for unchanged *d*,*l*-nebivolol were 1.48 μg/L in fast metabolisers and for active fractions of *d*- and *l*-nebivolol plus their corresponding hydroxylated metabolites were 7.3 and 13.1 μg/L, respectively, in hypertensive patients. Repeated doses increased the $C_{max}$ values for the individual *d*- and *l*-enantiomers and their respective metabolites.

Time to $C_{max}$ after oral administration of nebivolol is reported to be about 0.5 to 2.0 hours and is not significantly affected by the presence of food. Generally,

steady-state plasma concentrations are achieved within 1 day for nebivolol and within a few days for the active metabolites.

Obesity does not appear to affect the total distribution volumes and total body clearance rates (per kilogram bodyweight) of unchanged nebivolol (racemate or each enantiomer).

Extensive first-pass metabolism after oral administration of nebivolol produces active β-blocking hydroxy-metabolites. Elimination half-lives for the unchanged compound (racemate or each enantiomer) average about 10 hours, but are reported to increase by up to 5 times in poor metabolisers. Elimination half-lives for the hydroxy-metabolites of both enantiomers average about 24 hours in extensive metabolisers, but are almost doubled in poor metabolisers.

One week after administration, 38 and 48%, respectively, of the nebivolol dose is excreted in urine and faeces; unchanged nebivolol accounts for <0.05% of the amount recovered in the urine.

Plasma concentrations of nebivolol (both enantiomers) and its hydroxy metabolites are elevated in patients with renal disease.

## Therapeutic Efficacy

Nebivolol 5mg once daily (the recommended dosage; see Dosage and Administration summary) significantly reduces mean sitting or supine diastolic blood pressure (DBP) [by about 10mm Hg]. Significant reductions are maintained during continued therapy with no sign of rebound hypertension or tolerance. In the following discussion the nebivolol dosage is 5mg once daily.

Nebivolol produced similar reductions in resting DBP to atenolol 50 or 100mg once daily for up to 24 weeks and metoprolol 100mg twice daily for 12 weeks in hypertensive patients with or without comorbidities (concomitant type 2 diabetes mellitus or left ventricular hypertrophy).

In addition, nebivolol reduced sitting DBP in patients with hypertension to a similar extent to nifedipine 20mg twice daily after 12 weeks or lisinopril 40mg once daily after 8 weeks. Nebivolol was more effective than enalapril 10mg once daily (usual dosage is 10 to 20mg once daily) after 4 or 12 weeks but not after 28 weeks of treatment. The drug had an additive effect when combined with hydrochlorothiazide 12.5 or 25mg once daily but not with enalapril.

Nebivolol significantly reduced sitting/supine systolic blood pressure (SBP) compared with baseline or placebo. Standing SBP/DBP was also significantly reduced compared with baseline or placebo and to a similar extent to reductions with atenolol, enalapril or nifedipine.

Nebivolol 5 mg/day and atenolol 100mg once daily, nifedipine 20mg twice daily or lisinopril ≤40mg once daily similarly and significantly reduced mean 24-hour ambulatory blood pressure. However, nebivolol tended to prevent increases in early morning blood pressure better than nifedipine. In addition, nebivolol reduced blood pressure loads by about 50% from baseline.

Trough to peak ratios of about 0.9 for supine or sitting DBP have been reported for nebivolol 5mg once daily, which is the same as that for nifedipine sustained release 20mg twice daily but higher than for enalapril 10mg once daily.

Overall response rates (a decrease in sitting/supine diastolic blood pressure to ≤90mm Hg or a 10% or ≥10mm Hg fall in diastolic blood pressure) to treatment with nebivolol 5mg once daily ranged from 58% after 4 weeks' therapy to 81% after 52 weeks' therapy. Response rates in nebivolol recipients were significantly greater than in those receiving enalapril early (≤12 weeks), but not later (7 months), or metoprolol but did not differ between patients receiving nebivolol,

atenolol or nifedipine. More nebivolol than nifedipine recipients responded to treatment after 2 weeks.

**Tolerability**

Nebivolol 5mg once daily is well tolerated in patients with hypertension. Adverse events are typically transient and mild to moderate; the type, severity and frequency are not dose-related. Adverse events experienced most often include headache, fatigue, paraesthesias and dizziness. Importantly, several studies reported no signs of orthostatic hypotension with nebivolol.

In comparative trials the frequency and severity of adverse events reported in patients receiving once daily nebivolol 5mg or atenolol 50mg, enalapril 10mg or placebo were not significantly different. However, the overall incidence of adverse events was greater with nifedipine 20mg twice daily or metoprolol 100mg twice daily than with nebivolol. More atenolol or enalapril than nebivolol recipients reported impotence or decreased libido during therapy. In addition, the incidence of fatigue increased from baseline in atenolol recipients but remained constant in nebivolol recipients during a 4-week treatment period.

**Dosage and Administration**

The recommended dosage of nebivolol is 5mg once daily taken with or without food, preferably at the same time of day.

Use of the drug in children and patients with hepatic insufficiency is not recommended. A reduced starting dose of 2.5mg (with upward titration where necessary) is recommended in the elderly and in patients with renal insufficiency.

Nebivolol may be used alone or in combination with other antihypertensive agents. To date, additive antihypertensive effects have been seen only during combination therapy with hydrochlorothiazide.

## 1. Introduction

In the treatment of essential hypertension, there are numerous classes of drugs to choose from and disparate mechanisms of action to consider when tailoring treatment to the patient's needs. β-Blockers as a class have for many years had an established place as first-line therapy in the management of this disease.[1-3]

Nebivolol, a β-blocker, has an apparent modulatory effect on nitric oxide that may play a part in its antihypertensive efficacy. This review focuses on the effects of nebivolol in patients with mild to moderate essential hypertension.

## 2. Pharmacodynamic Profile

Nebivolol is a lipophilic $\beta_1$-blocker.[4-8] The ratio of $\beta_1$- to $\beta_2$-blockade, as demonstrated in isolated guinea-pig atria or trachea or other models, was about 290. This was 19-fold higher than that of atenolol and 3- to 12-fold higher than those of metoprolol and bisoprolol.[8,9] The octanol/water distribution coefficient is log P = 4.03 at pH 11.8, indicating high lipophilicity.[10]

The drug has no or negligible binding affinity for serotonin 5-$HT_2$, dopamine, $\alpha_1$- or $\alpha_2$-receptors (reviewed by Janssens et al.[4]) and has no intrinsic sympathomimetic or membrane stabilising activity.[9] In rat brain, nebivolol binds to 5-$HT_{1A}$ binding sites with a $K_i$ (receptor binding inhibition constant) of 20 nmol/L[7] but appears to cause no 5-$HT_{1A}$ agonist or antagonist effects.[4]

### 2.1 Effects of the Individual Enantiomers

Clinically, nebivolol is administered as a racemic mixture of equal proportions of its *d*- and *l*-isomers (*d*,*l*-nebivolol). As nebivolol has 4 asymmetric centres, *d*-nebivolol refers to *(S,R,R,R)*-nebivolol and *l*-nebivolol to *(R,S,S,S)*-nebivolol. The separate enantiomers have unequal potency with respect to β-receptor activity[6,7] and nitric oxide-mediated vasodilation (see section 2.2.4) but the combination appears to have greater antihypertensive activity than either enantiomer alone.[11] The

effects of nebivolol on blood pressure in patients with hypertension are discussed in section 4.

Initial *in vitro* studies indicated that the β-blocking effects of the drug resulted from the activity of the *d*-enantiomer rather than the *l*-enantiomer.[12] This was borne out by data in volunteers[13] and patients with mild to moderate hypertension.[14] In these trials the *d*-enantiomer had beneficial effects on haemodynamic parameters, including blood pressure and heart rate during rest and exercise, which were greater than those of the *l*-enantiomer[13] and similar to those of the *dl*-racemic mixture.[13,14] However, a study in patients with coronary artery disease concluded that the presence of both enantiomers (i.e. as the racemic mixture) was required to effect significant changes in the haemodynamic parameters assessed (e.g. heart rate and ejection fraction; blood pressure was not considered).[15]

## 2.2 Cardiovascular Effects

### 2.2.1 Effects on Left Ventricular Function

Available data suggest that nebivolol has a protective effect on left ventricular function. Generally small trials have been conducted in healthy volunteers,[16-18] patients with hypertension with[19] or without[20-24] left ventricular hypertrophy (LVH) and patients with mild to moderate heart failure (due to coronary artery disease or cardiomyopathy).[15,25-28] Treatment durations ranged from 7 days to 6 months. The nebivolol daily dosage was 5mg in healthy volunteers and patients with hypertension and 1 to 5mg in patients with heart failure.

Nebivolol appears to reduce preload and maintain or reduce afterload. Heart rate is decreased (see section 2.2.2) as is left ventricular end-diastolic and systolic pressure in patients with left ventricular dysfunction.[26] Once daily nebivolol increased stroke volume or stroke index in healthy volunteers[16,29] and patients with hypertension[23] or heart failure[25,27,28] and increased peak filling rate in hypertensive patients.[24]

In volunteers receiving nebivolol 5mg once daily for 7 days[18] and patients with hypertension receiving the drug for 1 year,[21] improvements (decreases) in the ratio of pre-ejection period to left ventricular ejection time (PEP/LVET) were the result of significant shortening of PEP[18,21] (by up to 9%[18]) and lengthening of LVET periods[18,21] (by up to 7%;[18] $p \leq 0.05$ for both). Significant reductions in PEP/LVET were seen as early as 8 hours after initial drug administration in patients ($p \leq 0.05$ *vs* baseline),[21] and the ratio remained significantly reduced compared with baseline values for up to 2 days after treatment cessation in volunteers ($p < 0.03$).[18]

Cardiac output was not significantly affected in healthy volunteers,[16] but in hypertensive patients resting cardiac output was reduced to a similar extent with nebivolol 2.5 to 5mg or atenolol 50 to 100mg ($p < 0.05$ *vs* baseline or placebo).[22,23] During exercise, however, only atenolol significantly reduced this parameter ($p < 0.05$).[22] In patients with heart failure, ejection fraction was increased[20,26,28,30] while cardiac output and pulmonary artery and wedge pressures were maintained.[25,27,28]

Most studies showed total peripheral resistance (TPR) to be unaffected by nebivolol 5mg during rest[16,22,23] or exercise in healthy volunteers[16] or patients with hypertension[22,23] during once daily administration of the drug for 1 to 12 weeks. TPR was reduced by 18.5% versus placebo in 15 hypertensive patients given the drug for 4 weeks[31] and was also decreased in patients with left ventricular dysfunction.[27,28] Nebivolol 5mg, unlike atenolol 50mg,[23] did not increase TPR in any of the studies.

Nebivolol 5 mg/day for 6 months decreased left ventricular mass index to a similar extent to atenolol 100mg once daily in hypertensive patients with LVH.[19]

### 2.2.2 Effects on Resting Heart Rate

Like other β-blockers, nebivolol at therapeutic dosages decreases resting heart rate in patients with hypertension. Sitting,[21] supine[32,33] and/or standing[33,34] heart rate measured at trough plasma drug concentrations (23 to 25 hours after last drug intake) was reduced by nebivolol 5mg once daily for

4 to 52 weeks. At this time, reductions in resting supine/sitting heart rate ranged from 7 to 16 beats/ min (9.5 to 15%; $p < 0.01$ *vs* baseline or placebo)[21,32] and standing heart rate was reduced by 10 to 12 beats/min[33,35] ($p < 0.01$ *vs* baseline).[33]

Marked reductions in heart rate were evident after 4 weeks and were maintained thereafter during 8[32] or 52 weeks[21] of continued nebivolol therapy.

Nebivolol 5mg and atenolol 50mg once daily produced similar reductions in resting (supine and standing) heart rate after 2 to 24 weeks ($p < 0.001$ *vs* baseline or placebo).[36,37] Nebivolol reduced sitting,[38,39] standing[39] and 24-hour ambulatory[39] heart rates to a greater extent than nifedipine sustained release 20mg twice daily ($p < 0.05$)[39] or enalapril 10mg once daily ($p < 0.001$)[38] during treatment periods of up to 24 weeks. In addition, after 12 weeks, nebivolol 5 or 10mg alone or in combination with hydrochlorothiazide 12.5 or 25mg significantly reduced sitting heart rate (by up to 12.4 beats/min; $p < 0.05$ *vs* baseline).[40]

#### 2.2.3 Effects on Exercise-Induced Changes in Haemodynamic Parameters and Endurance Time

Many patients taking β-blockers experience reduced exercise capacity.[41] However, nebivolol 2.5 to 10mg as a single or daily dose reduces exercise-induced tachycardia to a lesser extent than equivalent therapeutic doses of atenolol, propranolol or pindolol, as demonstrated in comparative studies in patients treated for 4 months[22] and volunteers given nebivolol as a single dose[42] or for 7[18,41,43] or 14[44] days.

Exercise-induced increases in systolic blood pressure (SBP) were also attenuated to a similar or lesser extent with nebivolol than with the same comparator agents.[18,22,42] Nebivolol and atenolol increased stroke volume during exercise, and whereas nebivolol tended to increase cardiac output and significantly reduced total peripheral resistance, atenolol had no such effects.[44]

Submaximal endurance time was significantly lower with atenolol (50 minutes) than with placebo (65 minutes, $p < 0.001$) but was maintained with nebivolol (61 minutes). The perceived exertion rating did not differ among treatments during maximal exercise testing but was increased with atenolol during endurance exercise ($p < 0.02$).[44]

#### 2.2.4 Nitric Oxide-Mediated Vasodilatory Effects

Both *d*- and *l*-nebivolol induce vascular relaxation but *l*-nebivolol is more potent, as shown *in vitro* in canine coronary arteries[45] and by increased forearm blood flow in healthy volunteers.[46] This effect is endothelium-dependent: arterial relaxation is antagonised *in vitro* by $N^G$-monomethyl-L-arginine (L-NMMA), a competitive inhibitor of nitric oxide synthase,[45,47] and by removal of the endothelium from porcine arteries.[47] As well, L-NMMA antagonised the dose-related venodilation caused by nebivolol, but not atenolol,[48,49] in preconstricted dorsal hand[49] or forearm[48,50] vessels in healthy volunteers[48,49] and patients with essential hypertension.[50]

The vasodilatory effects of nebivolol do not appear to be the result of α-adrenergic blockade in humans. Nebivolol induced a similar degree of venodilation in prostaglandin $F_{2\alpha}$- or phenylephrine-constricted vessels (74 *vs* 85%)[49] and had no effect on the phenylephrine dose-response test.[43]

In a series of studies, each in 8 healthy male volunteers, nebivolol, carbachol (an endothelium-dependent vasodilator) and nitroprusside (an endothelium-independent vasodilator, which acts via nitric oxide) all significantly increased forearm blood flow (by 68, 111 and 173%, respectively, compared with control).[48] Coinfusion of L-NMMA decreased these responses by 65.1, 48.7 and 22%, respectively ($p < 0.05$ for nebivolol and carbachol *vs* nitroprusside). L-NMMA-induced antagonism of the vasodilatory effects of nebivolol were abolished by the addition of L-arginine (a precursor of nitric oxide).[48]

Collectively, these data suggest that nebivolol has an endothelium-dependent vasodilatory effect which is mediated via the L-arginine/nitric oxide pathway in this vascular bed. The clinical relevance of this mechanism of action remains to be confirmed.

### 2.3 Metabolic Effects

#### 2.3.1 Effects on Glucose

Nebivolol appears to lack any influence on glucose metabolism. Compared with placebo, nebivolol 5mg once daily for 4 to 8 weeks had no significant effects on plasma glucose levels in hypertensive patients without diabetes.[32,33]

In hypertensive patients with glucose intolerance, atenolol 50 to 100mg but not nebivolol 2.5 to 5mg once daily for 16 weeks significantly reduced insulin sensitivity compared with placebo ($p = 0.01$).[51] Atenolol, compared with nebivolol or placebo, also significantly reduced glucose clearance rates in these patients ($p < 0.05$ for both comparisons).

However, in 30 hypertensive patients with type 2 diabetes mellitus, neither nebivolol 5mg nor atenolol 50mg once daily for 24 weeks affected mean whole body glucose utilisation or insulin sensitivity.[36]

#### 2.3.2 Effects on Lipids

Nebivolol generally does not adversely affect parameters of plasma lipid metabolism. In a number of studies in patients with hypertension, including a 6-month trial in patients with type 2 diabetes mellitus,[36] nebivolol 5mg once daily for 4 to 24 weeks had no significant effects on total cholesterol, low density lipoprotein (LDL)-, very low density lipoprotein (VLDL)- and high density lipoprotein (HDL)-cholesterol or apolipoproteins A1 and B.[32,33,36,38,40] Indeed, reductions in total cholesterol levels (by 4.6 and 2.5%) and LDL-cholesterol levels (by 7.4 and 2.6%) were evident in patients with essential hypertension receiving nebivolol 5mg once daily or nifedipine 20mg sustained release twice daily for 12 weeks in 1 study ($p < 0.05$ *vs* baseline for all).[39]

Plasma triglyceride levels were generally not affected in hypertensive patients with[36] or without[33,39,40] diabetes. However, rare increases in triglyceride levels have been reported in isolated patients.[38]

#### 2.3.3 Renal Effects

Nebivolol 5mg once daily for 4 weeks was associated with reductions in plasma renin (by 52%; $p < 0.001$) and aldosterone levels [by 28% after 2 weeks ($p < 0.01$) and by 11% after 4 weeks] in 18 patients with hypertension and normal renal function[33] and a 33% decrease in plasma renin level in 10 hypertensive patients with renal artery stenosis.[52] Serum aldosterone levels were not altered in the latter group.

Renal haemodynamics (renal vascular resistance, glomerular filtration rate, renal plasma flow, filtration fraction) were unchanged in hypertensive patients with[52] or without[53] renal artery stenosis after 3 or 4 weeks of treatment with nebivolol 2.5 to 10 mg/day.

Plasma levels of atrial natriuretic peptide (ANP; a potent vasorelaxant) were increased by 60% after 2 weeks ($p < 0.001$ *vs* baseline) but by only 28% after 4 weeks in patients with hypertension.[33]

## 3. Pharmacokinetic Profile

Stereoselective radioimmunoassay methodology has been used to measure active fractions of *d*- and *l*-nebivolol and hydroxylated metabolites.[11] The metabolism of nebivolol is subject to genetic polymorphism;[11,54] individuals may be phenotypically characterised as 'poor' (slow) or 'extensive' (fast) metabolisers.[11,54]

Table I summarises results of 2 studies investigating the pharmacokinetics of oral nebivolol in patients with hypertension[31] and in volunteers who were extensive metabolisers.[55] Other information has been obtained from reviews,[54] the manufacturer's prescribing information[9] and unpublished data.[56,57]

### 3.1 Absorption and Distribution

After single dose oral nebivolol 5mg, the mean peak plasma drug concentration ($C_{max}$) for unchanged *d*,*l*-nebivolol was 1.48 μg/L in healthy volunteers who were extensive metabolisers[55] and those for the active fractions of *d*-nebivolol and *l*-nebivolol plus their corresponding hydroxylated metabolites were 7.3 and 13.1 μg/L in hypertensive patients.[31]

**Table I.** Summary of mean pharmacokinetic data in patients with hypertension or volunteers after single dose oral nebivolol 5mg

| Parameter | Patients[31](n = 15)[a] | | Volunteers[55] (n = 12)[b] |
|---|---|---|---|
| | *d*-[c] | *l*-[c] | *d,l*- |
| $C_{max}$ (μg/L) | 7.3 | 13.1 | 1.48 |
| $t_{max}$ (h) | 2.5 | 2.6 | 1.0 (median) |
| AUC[d] (μg/L • h) | 65 | 109 | 7.76 |
| $t_{½}$ (h) | | | 11.2 |

a Supine diastolic blood pressure 95 to 110mm Hg.

b All individuals were extensive metabolisers.

c Unchanged drug plus corresponding hydroxylated metabolites.

d AUC 0-24h[31] or 0-∞.[55]

**AUC** = area under the plasma concentration-time curve; **$C_{max}$** = peak plasma concentration; ***d-*** = *d*-nebivolol; ***d,l-*** = *d,l*-nebivolol; ***l-*** = *l*-nebivolol; **$t_{max}$** = time to $C_{max}$; **$t_{½}$** = elimination half-life.

Repeated doses (5mg once daily for 4 weeks) in patients increased $C_{max}$ values for the individual *d*- and *l*-enantiomers plus their corresponding metabolites by about 25 and 45%, respectively.[31]

Nebivolol is rapidly absorbed after oral administration: time to $C_{max}$ for the racemic mixture is reported to be about 0.5 to 2.0 hours[9,55,58] and is not significantly affected by the presence of food.[9,54]

For most individuals, steady-state plasma concentrations are achieved within 1 day for nebivolol and within a few days for the active metabolites.[54] Plasma protein binding for each enantiomer is about 98%.[9]

Because of the high lipophilicity of the drug (section 2), a study in obese individuals was performed. The total distribution volumes and total body clearance rates of unchanged nebivolol (racemate and each enantiomer) were about 30 to 40% greater in obese [body mass index (BMI) 34.6] than in non-obese (BMI 21.4) individuals after a single intravenous dose of the drug (0.073mg of base/kg initial bodyweight).[10] Values for *d,l*-nebivolol were 898 *vs* 673L for volume of distribution and 71.6 *vs* 51.6 L/h for total clearance (both $p < 0.05$).

However, when these parameters were expressed per kilogram bodyweight there was no significant difference between the 2 groups. Thus, the investigators concluded that there was no difference between the tissue distribution of the drug in obese and lean individuals.[10]

### 3.2 Metabolism and Elimination

After oral administration nebivolol undergoes extensive first-pass metabolism, which produces active β-blocking hydroxy-metabolites.[54] Absolute oral bioavailability is significantly lower in extensive metabolisers than in poor metabolisers (12 *vs* 96%; no p value provided).[11] Poor metabolisers are unable to adequately hydroxylate the aromatic moiety of the drug and so retain a relatively high concentration of unchanged drug. In extensive metabolisers there is substantial formation of the active hydroxy metabolites, which appears to compensate for the low concentration of unchanged drug in these individuals.[11,54] Therefore, no overall difference is apparent in the antihypertensive activity of the drug in each phenotype.[54]

Elimination half-lives of *d,l*-, *d*-, and *l*-nebivolol averaged about 10 hours,[9,10] but were stated to increase by up to 5 times in poor metabolisers.[9,11] Elimination half-lives for the hydroxy-metabolites for both enantiomers averaged about 24 hours in extensive metabolisers but were almost doubled in poor metabolisers.[9]

One week after administration of a 15mg dose,[11] 38% of the dose was excreted in urine and 48% in the faeces in a radiolabelled mass balance study.[9,11,54] Unchanged nebivolol accounted for <0.05% of the dose recovered in the urine.[9,54]

### 3.3 Special Populations

The mean $C_{max}$ value for unchanged nebivolol after a single 5mg dose was 5.12 μg/L in 8 patients with chronic liver disease,[56] which is slightly lower than that seen for either enantiomer in patients with hypertension without this disease (table I). At present, use of nebivolol in this group is not advised (section 6).

The pharmacokinetics of unchanged *d*- and *l*-nebivolol in 16 hypertensive patients with moderate to severe renal disease did not differ substantially from those in 8 hypertensive patients without

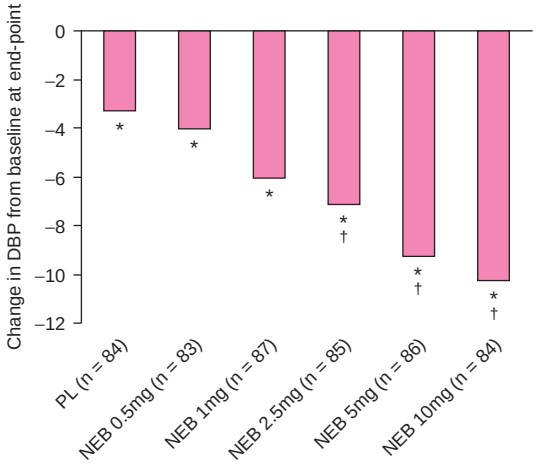


**Fig. 1.** Effects of nebivolol (NEB) or placebo (PL) on trough supine diastolic blood pressure (DBP).[34] NEB in various dosages or PL was given once daily for 4 weeks to a total of 509 patients with mild to moderate essential hypertension (defined as supine DBP ≥95mm Hg after a 4-week placebo run-in period). * $p \leq 0.05$ *vs* baseline; † $p \leq 0.05$ *vs* placebo.

renal insufficiency. However, plasma concentrations of the separate enantiomers plus the hydroxylated metabolites increased significantly in patients with renal disease.[57] A dose reduction is therefore recommended in this population (section 6).

## 4. Therapeutic Efficacy

A number of clinical trials have investigated the effects of nebivolol in patients aged 18 to 78 years (mean age range about 52 to 59 years) with essential hypertension. Generally, patients were without concomitant disease. One small study was conducted in hypertensive patients with type 2 diabetes mellitus [defined as an average glycosylated haemoglobin ($HbA_{1c}$) ≥8% during the previous 6 months with stable diet and oral treatment of at least 6 months].[36] Another examined the effects of nebivolol in patients with hypertension and left ventricular hypertrophy.[19]

Except for the noncomparative trials,[21,32] the design of the studies reviewed was randomised, double-blind[19,33,34,36-39,59-64] and, where necessary, double-dummy.[37,39,59,63] Clinical trials commonly followed a similar protocol, i.e. a 2- to 4-week washout and/or single-blind placebo period in which current antihypertensive medications were withdrawn, followed by a double-blind treatment phase.

Patient numbers per treatment group ranged from 14 to 211, with almost half of the studies including >100 patients. Where stated, patients had mild to moderate hypertension (defined as supine/sitting DBP ≥95 and ≤120mm Hg after washout/placebo run-in period).[21,32,33,36-39,60-62]

The 5mg once daily dosage of nebivolol (the recommended therapeutic dosage; section 6) was most commonly used in clinical trials of the drug, which were 4 to 52 weeks in duration.

The effects of nebivolol have been compared with placebo, (sections 4.1.1 and 4.2.1) the β-blockers atenolol and metoprolol (sections 4.1.2 and 4.2) and other classes of antihypertensive agents including calcium antagonists and angiotensin converting enzyme (ACE) inhibitors (sections 4.1.3 and 4.2). The drug has also been investigated in combination with hydrochlorothiazide and enalapril (section 4.1.4).

The primary efficacy end-point was the change from baseline in supine or sitting DBP. Other end-points included change from baseline in supine or sitting SBP[21,32-34,36-39] and changes in standing DBP and/or SBP, which were generally assessed after 2 minutes in the upright position and after the sitting/supine measurement had been taken.[21,32-34,36-39,64] In most studies measurements were taken at trough (i.e. 23 to 25 hours after the last dose of test medication).[21,34,36,37,39,59,61] There is some information on rebound hypertension and tolerance (section 4.2.4).

Where stated, response to therapy was defined as a reduction in sitting/supine DBP to ≤90mm Hg or a fall from baseline values of 10% or of ≥10mm Hg.[21,32,34,37-39,59,61]

The effects of nebivolol on heart rate and trough to peak ratios of the drug for supine/sitting DBP were also measured in some trials; these aspects are discussed in sections 2.2.2 and 4.1.3, respectively.

## 4.1 Effects on Supine Diastolic Blood Pressure

### *4.1.1 Noncomparative Trials and Comparisons with Placebo*

Once daily nebivolol produces a dose-related reduction in mean supine DBP in patients with hypertension.[34] Figure 1 shows that, compared with placebo, once daily nebivolol 2.5, 5.0 and 10.0mg, but not 0.5 or 1.0mg, for 4 weeks significantly reduced mean supine DBP (by 7.1 to 10.2mm Hg; $p \leq 0.05$); there was no significant difference in efficacy between the nebivolol 5mg and 10mg groups[34] (table II).

Significant reductions from baseline in mean supine DBP and SBP were evident as early as after 1 week of treatment with nebivolol 5mg once daily ($p < 0.01$ for both).[33] In a noncomparative study in 37 patients,[21] reductions were maintained during therapy for up to 12 months ($p \leq 0.0001$ *vs* baseline; fig. 2). This is confirmed by collated unpublished data in 204 patients treated for 3 years.[52]

### *4.1.2 Comparisons with Other β-Blockers*

Table III shows that nebivolol 5mg and atenolol 50mg once daily for 4[37] or 24[36] weeks produced similar and significant reductions ($p < 0.001$ *vs* baseline or placebo) in resting supine[36] or sitting[37] DBP in hypertensive patients with ($n = 30$)[36] or without ($n = 364$)[37] diabetes mellitus. As well, reductions in supine DBP did not differ significantly in patients with left ventricular hypertrophy given nebivolol 5mg or atenolol 100mg once daily for 6 months.[19] In the largest study, conducted in patients without comorbidities,[37] DBP was reduced after 2 weeks in each treatment group compared with placebo and fell further during the remaining 2 weeks of treatment.

Overall, sitting SBP/DBP was reduced to a similar extent with nebivolol 5mg once daily and metoprolol 100mg twice daily for 12 weeks (table III). Reductions in supine, seated and standing blood pressure were apparent as early as 4 weeks after the start of therapy in both groups (no statistical analysis provided).[61]

Table II

**Table II.** Summary of trials comparing once daily nebivolol (NEB) with placebo (PL) for 4 weeks in patients with mild to moderate essential hypertension[a]

| Reference (study design) | No. of evaluable patients | Regimen (mg/day) | Effects on sitting or supine SBP/DBP (mean mm Hg)[b] | | Effects on standing SBP/DBP (mean mm Hg)[b] | | Response rates[c] (% of patients) | Overall efficacy |
|---|---|---|---|---|---|---|---|---|
| | | | baseline | end-point | baseline | end-point | | |
| van Nueten et al.[34] (db, mc, r)[d] | 83 | NEB 0.5 | 157.7/100.9 | 154.8/96.9* | | | 31 | |
| | 87 | NEB 1 | 160.9/101.8 | 154.1/95.8* | | | 38 | |
| | 85 | NEB 2.5 | 161.2/101.8 | 152.6/94.7*† | | | 43 | NEB 2.5 ≡ NEB 1 > NEB 0.5 |
| | 86 | NEB 5 | 160.3/101.6 | 151.1/92.4*† | | | 58 | NEB 5 ≡ NEB 10 > NEB 2.5 |
| | 84 | NEB 10 | 157.9/101.2 | 149.7/91*† | | | 57 | |
| | 84 | PL | 158.8/101.3 | 155.7/98* | | | 32 | NEB 2.5-10 > PL |
| Chan et al.[33] (db, r) | 18 | NEB 5 | 153.8/99.0 | 131.4†††/83.4††† | 154/102.7 | 131.7†††/84.8††† | | NEB > PL |
| | 14 | PL | 162.9/104.1 | 151.5*/96.6* | 162.0/107[e] | 151.9*/105[e] | | |
| DeCrée et al.[21] (db, r, co) | 23 | NEB 5 | 158/100 | 144††/90†† | | | | NEB > PL |
| | | PL | 158/100 | 159/100 | | | | |

a Defined as supine/sitting DBP ≥95 and ≤120mm Hg after a 2- to 4-week placebo run-in period.

b Assessed at trough (23 to 25 hours after last dose).

c Defined as standing DBP ≤90mm Hg and/or a fall in DBP of ≥10mm Hg.

d Intent-to-treat analysis.

e Estimated from a graph.

**co** = crossover; **db** = double-blind; **mc** = multicentre; **r** = randomised; > indicates more effective than; ≡ indicates equally as effective as; * $p < 0.05$ *vs* baseline; † $p < 0.05$, †† $p < 0.01$, ††† $p < 0.001$ *vs* PL.

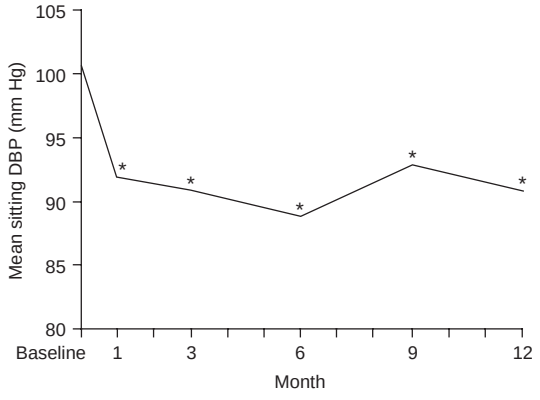


**Fig. 2.** Long term effects of nebivolol (NEB) on trough sitting diastolic blood pressure (DBP).[21] In a noncomparative study, nebivolol 5mg was given once daily for 12 months to 37 patients with mild to moderate essential hypertension (sitting DBP ≥95 and ≤114mm Hg after a 4-week washout period). * $p \leq 0.0001$ *vs* baseline.

#### 4.1.3 Comparisons with Antihypertensive Agents Other Than β-Blockers

Nebivolol has been compared with a number of antihypertensive agents other than β-blockers (table IV). At the dosage of 5mg once daily nebivolol has been shown to reduce sitting DBP to a similar extent to the calcium antagonist nifedipine in a 12-week study.[59]

In comparisons with ACE inhibitors, nebivolol was as effective as lisinopril 10 to 40mg for 8 weeks[62] and was more effective than enalapril 10mg once daily (the usual maintenance dose is 10 to 20 mg/day) after 4[63] or 12[38] weeks (table IV). The difference between nebivolol and enalapril was not sustained during a further 7-month treatment period in a subset of patients from the 12-week study.[64] In the other, a small crossover trial that enrolled 21 patients with mild hypertension, nebivolol for 4 weeks reduced sitting and standing SBP and DBP to a greater extent than placebo ($p \leq 0.001$) and enalapril 10mg ($p < 0.012$).[63]

It should be noted that baseline sitting DBP values were slightly, but significantly, lower in the nebivolol versus the enalapril group (by 0.9mm Hg; $p = 0.032$) in the 12-week study and the dose of enalapril may have been low in both trials.

Trough to Peak Ratios

Nebivolol 5mg once daily produced trough to peak ratios of about 0.9 for sitting or supine diastolic blood pressure,[34,35] which is the same as for nifedipine sustained release 20mg twice daily[35] but higher than that for enalapril 10mg once daily (0.84 *vs* 0.6; $p = 0.02$).[38] These data suggest that nebivolol 5mg once daily is a suitable dosage to provide adequate antihypertensive control throughout a 24-hour period. However, there is debate regarding the importance of this parameter as a relative or absolute measure of sustained antihypertensive efficacy after once daily drug administration.[65,66]

#### 4.1.4 In Combination

Combination therapy may be used in an attempt to maintain or improve efficacy with lower dosages and/or fewer associated adverse events of either or both drugs.[1] Nebivolol has additive effects with hydrochlorothiazide but not enalapril.

Nebivolol 5 or 10mg plus hydrochlorothiazide 25mg reduced sitting DBP more than monotherapy (nebivolol 1 to 10mg or hydrochlorothiazide 12.5 and 25mg) after 12 weeks in patients with mild to moderate hypertension.[60] Combination therapy produced an additive dose-related reduction in mean sitting DBP ranging from 9.4mm Hg for nebivolol 1mg/hydrochlorothiazide 12.5mg to 15.3mm Hg for nebivolol 10mg/hydrochlorothiazide 25mg ($p = 0.0001$ *vs* baseline for all).

After 12 weeks, monotherapy with either agent produced significant, dose-related reductions in mean sitting DBP from baseline (by 5.5 to 13.8mm Hg with 1 to 10mg nebivolol and 4.6 and 5.8mm Hg with 12.5 and 25mg hydrochlorothiazide; $p < 0.001$ for all). Compared with placebo, only monotherapy with nebivolol 5 or 10mg or hydrochlorothiazide 25mg produced statistically significant reductions in mean sitting DBP; combination therapy was not compared with placebo.

Nebivolol 5mg plus enalapril 10mg for 4 weeks did not reduce blood pressure more than nebivolol monotherapy in a small crossover trial.[67] DBP values after treatment were 87mm Hg with nebivolol, 94mm Hg for enalapril and 86mm Hg for the combination (table IV).

## 4.2 Effects on Other End-Points

### 4.2.1 Systolic Blood Pressure and Standing Blood Pressure

Nebivolol 5mg once daily for 4 to 52 weeks significantly reduced sitting[21,37,39,60] or supine[33,36] SBP ($p < 0.01$ for all) compared with baseline or placebo. In comparative trials, supine/seated SBP was reduced to a similar extent with nebivolol and standard dosages of atenolol,[19,36,37] metoprolol,[61] nifedipine[59] or enalapril[38,64] (tables III and IV).

Mean standing SBP and/or DBP was reduced with nebivolol 5mg once daily for 4 to 24 weeks compared with baseline[33,36,38,39] ($p < 0.001$ for all) or placebo[37] (tables II to IV). Similar reductions were seen with atenolol,[36,37] nifedipine[59] and enalapril.[38]

### 4.2.2 Response Rates

Overall response rates to treatment with nebivolol 5mg once daily ranged from 58% after 4 weeks' therapy[34] to 81% after 52 weeks' therapy[21] in patients without comorbidities. One study demonstrated a dose-related increase in response rate (31 to 58%) over the dosage range 0.5 to 10mg once daily (table II) but there was no difference between the 5 and the 10mg doses.[34]

In comparative trials, there was no difference in response rates between patients treated with nebivolol and atenolol for 4[37] and 24[19] weeks or nifedipine for 12 weeks.[39,59] However, compared with nifedipine, more nebivolol than nifedipine recipients responded to treatment after the first 2 weeks of therapy (65.8 *vs* 50% for nebivolol and nifedipine; $p = 0.001$) [table IV].[35] In addition, a greater proportion of nebivolol than nifedipine recipients had a trough sitting DBP of ≤90mm Hg after 12 weeks (54 *vs* 42%, $p = 0.007$).[59]

Although response rates in nebivolol 5mg once daily recipients were greater than in those receiving enalapril 10mg once daily for 4 (65 *vs* 40%, no p value given)[63] and 12 weeks (70 *vs* 55%; $p < 0.01$),[38] there were no significant differences between the 2 drugs at 7 months.[64] Response rates

**Table III.** Summary of randomised, double-blind, parallel comparative trials with once daily nebivolol 5mg (NEB) and once daily atenolol (ATE) 50 or 100mg or twice daily metoprolol 100mg (MET) in patients with mild to moderate essential hypertension[a] with or without comorbidity

| Reference | No. of evaluable patients | Regimen (duration in wk) | Effects on sitting or supine SBP/DBP (mean mm Hg)[b] | | Effects on standing blood SBP/DBP pressure (mean mm Hg)[b] | | Response rate[c] (% of patients) | Overall efficacy |
|---|---|---|---|---|---|---|---|---|
| | | | baseline | end-point | baseline | end-point | | |
| **Hypertensive patients without comorbidity** | | | | | | | | |
| van Nueten et al.[37]d | 119 | NEB (4) | 167/101 | 151*/89* | 165/102 | 151*/90* | 59* | NEB ≡ ATE > PL |
| | 121 | ATE 50 (4) | 169/102 | 152*/91* | 166/103 | 152*/92* | 59* | |
| | 124 | PL (4) | 169/102 | 163/97.5 | 166/104.5 | 160/100 | 29 | |
| Uhlir et al.[61] | 73 | NEB (12) | 160/106 | 140/89 | | | 79.5‡ | NEB ≥ MET |
| | 67 | MET (12) | 157/107 | 142/91 | | | 65.6 | |
| **Hypertensive patients with comorbidities** | | | | | | | | |
| Coto et al.[19] | 24 LVH | NEB (24) | 168.8/103.3 | 146.3/86 | | | 100 | NEB ≡ ATE |
| | 24 LVH | ATE 100 (24) | 169.8/102.9 | 147.7/85.8 | | | 100 | |
| Fogari et al.[36] | 15 DM | NEB 50 (24) | 164.9/103.2[c] | 139.2†/90.3† | 162.3/105.7 | 136.7†/87.7† | | NEB ≡ ATE |
| | 15 DM | ATE (24) | 165.9/103.3[c] | 137.2†/84.5† | 161.9/105.5 | 134.2†/86.8† | | |

a Defined as sitting[37] or supine[36] DBP ≥95 and <116mm Hg after a 4-week placebo run-in period.

b Assessed at trough (23 to 25 hours after last dose).

c Defined as a reduction of sitting DBP to ≤90mm Hg.

d All blood pressure values estimated from graphs.

**DM** = type 2 diabetes mellitus; **LVH** = left ventricular hypertrophy; **PL** = placebo; > indicates more effective than; ≡ indicates as effective as; ≥ indicates at least equivalent efficacy; * $p < 0.001$ *vs* PL; † $p < 0.001$ *vs* baseline; ‡ $p = 0.04$ *vs* MET.

**Table IV.** Summary of double-blind, randomised, comparative trials with once daily nebivolol (NEB) 5mg and other antihypertensive agents in patients with mild to moderate hypertension[a]

| Reference | No. of evaluable patients | Regimen (mg) [duration in wk] | Effects on seated SBP/DBP (mean mm Hg) | | Effects on standing SBP/DBP (mean mm Hg) | | Response rates[b] (% of patients) | Overall efficacy |
|---|---|---|---|---|---|---|---|---|
| | | | baseline | end-point | baseline | end-point | | |
| **Angiotensin converting enzyme (ACE) inhibiting agents** | | | | | | | | |
| Chalmers et al.[63] | 19[c] | NEB 5 od [4] | 170.1/101.7 | 147.5††/86.5†† | 166.2/103.2 | 148.6††/88.9†† | 65 | NEB ≡ NEB + ENA > ENA |
| | 17[c] | ENA 10 od [4] | As above | 158.8/92.9 | As above | 156.0/97.8 | 40 | |
| | 20[c] | NEB + ENA [4] | As above | 149.9††/85.4†† | As above | 149.8††/92.3†† | 81‡ | |
| | 16[c] | PL | As above | 165.4/97.5 | As above | 161.3/100.8 | 37 | |
| Lacourciere et al.[62] | 29 in total[c] | NEB 2.5-10 od [8] | 158/104.7 | 142†/94.9† | | | | NEB ≡ LIS |
| | | LIS 10-40 od [8] | 158/104.7 | 140†/94.1† | | | | |
| van Nueten et al.[38] | 208 | NEB 5 od [12] | 162[d]/104.6* | 147[d]/92.3** | 162[d]/107[d] | 148[d]/96[d] | 70** | NEB > ENA |
| | 211[d] | ENA 10 od [12] | 163d/105.5 | 151[d]/95.6 | 162[d]/107[d] | 151[d]/98[d] | 55 | |
| van Nueten et al.[64] | 82[e] | NEB 5 od [28] | 162/103.8 | 150.9/92.2 | 162[d]/106.5[d] | 149.5d/96[d] | 73 | NEB ≡ ENA |
| | 81[e] | ENA 10 od [28] | 161.9/104.2 | 151.9/94.6 | 163[d]/107[d] | 150.5[d]/96[d] | 64 | |
| **Calcium antagonist** | | | | | | | | |
| van Nueten et al.[59] | 211 | NEB 5 od [12] | 159.5[d]/104.2 | 146.2[d]/92.5† | 158.5[d]/106[d] | 145d/194[d] | 2wk: 65.8***[35] 12wk:70 | NEB ≡ NIF |
| | 209 | NIF 20 bid [12] | 160.3[d]/104.5 | 145.3[d]/93.3† | 160.5[d]/106.5[d] | 144[d]/195.5[d] | 2wk: 50.0[35] 12wk:67 | |

a Generally defined as sitting DBP 95 to 114mm Hg after a 2- to 4-week placebo run-in period.

b Defined as reduction in sitting DBP to ≤90mm Hg or by ≥10mm Hg.

c Crossover study. 21 patients were enrolled in the study of Chalmers et al.[63]

d Estimated from a graph.

e Subset of patients from van Nueten et al.[38] who were randomised to a 1-month double-blind 'run-out' period on placebo or continuation of nebivolol or enalapril for the month and who then, in double-blind fashion, continued the treatment they were receiving or returned to their original treatment (if previously randomised to placebo) for an additional 7 months.

**bid** = twice daily; **ENA** = enalapril; **LIS** = lisinopril; **NIF** = nifedipine sustained release; **od** = once daily; **>** indicates significantly more effective than; ≡ indicates as effective as; * $p < 0.05$, ** $p < 0.01$, *** $p = 0.001$ *vs* comparator agent; † $p < 0.001$ *vs* baseline; ††$p \leq 0.05$ *vs* placebo and ENA (standing SBP *vs* PL only); ‡$p = 0.008$ *vs* PL and ENA.

were higher with nebivolol plus enalapril 10mg daily (81%) than with enalapril alone after 4 weeks ($p < 0.008$).[63]

Nebivolol was reported to normalise DBP (to ≤90mm Hg) in more patients than metoprolol 100mg twice daily for 12 weeks (79.5 *vs* 65.6%, $p = 0.04$).[61] The number of partial responders (DBP reduced by 10% but not normalised) was greater with metoprolol (17.2 *vs* 2.7%, $p = 0.01$) and about 17% of patients in each group did not respond to treatment.

Although race had no significant effect on response rates in 1 study,[34] an overview analysis of the combined efficacy results for nebivolol showed Black patients to have a slightly smaller decrease in DBP than other patients.[52] Older age and cigarette smoking did not influence the antihypertensive effects of nebivolol.[52]

#### *4.2.3 24-Hour Ambulatory Blood Pressure*

Decreases in 24-hour ambulatory blood pressure (ABP) with nebivolol resembled those seen with comparator agents.

Nebivolol 2.5 to 10mg daily and lisinopril 10 to 40mg daily for 8 weeks reduced 24-hour ABP to a similar extent,[62] as did nebivolol 5mg daily and enalapril 10mg daily for 4 weeks,[67] atenolol 100mg daily for 8 weeks[24] or nifedipine 20mg twice daily for 12 weeks[39] ($p < 0.01$ for systolic and diastolic values for all drugs *vs* baseline or placebo).

Both nebivolol and nifedipine caused significant reductions in working (0800 to 1800 hours), awake (1800 to 2300 hours) and sleeping periods (2300 to 0600 hours; $p = 0.0001$ *vs* baseline for all time periods). However, nebivolol tended to prevent increases in early morning blood pressure better than nifedipine (results presented in a graph).[39]

Similar effects were observed in a study in which once daily nebivolol 5 and 10mg, but not 1mg, significantly reduced overall mean 24-hour ABP as well as daytime (dose time to 2000 hours), sleep (2200 to 0700 hours) and early morning (0400 to 0800 hours) periods in a dose-related manner ($p < 0.01$ for all).[60]

In this study, hydrochlorothiazide 12.5 and 25mg once daily also significantly reduced these ABP parameters, but to a lesser extent than nebivolol 5 or 10mg. However, the effects of combined therapy with hydrochlorothiazide 25mg and nebivolol 5 or 10mg was superior to the respective monotherapies ($p < 0.001$ *vs* baseline for all, but no p values for active treatment comparisons; results presented in a graph).[60]

Blood pressure loads (defined as the percentage of readings >140/90mm Hg awake and >120/80mm Hg asleep during the 24-hour period[39,60]) were reduced from baseline by about 50% by nebivolol 5mg once daily for 8[62] or 12[39,60] weeks.

#### 4.2.4 Rebound Hypertension and Tolerance

No rebound hypertension was noted in studies specifically examining this effect.[38,59] Blood pressure increased gradually[59] or did not change appreciably[38] during a 1-month 'run-out' period following discontinuation of nebivolol and nifedipine[59] or enalapril.[38]

Tolerance has not developed to the antihypertensive effects of nebivolol in patients treated for up to 3 years.[52,64]

## 5. Tolerability

Nebivolol 5mg once daily is well tolerated in patients with hypertension, and adverse events are infrequent. This has been shown in clinical trials of up to 1 year[32-34,36-39,60] and confirmed by a combined safety analysis of all placebo-controlled dose-finding (≤30mg) and short term therapeutic trials and in long term studies in patients treated for up to 4 years.[52] Adverse events were transient and mild to moderate;[36,39] the type, severity and frequency were not dose-related.[34,52,60]

Adverse events reported most often during nebivolol therapy are headache, dizziness, fatigue and paraesthesias (fig. 3). The overall incidence of adverse events during treatment for ≤3 months was similar for nebivolol and placebo in the combined analysis of therapeutic trials.[52] Importantly, several studies reported no signs of orthostatic hypotension with nebivolol.[21,32,34,38] Some studies also reported abdominal pain,[34,36] rash/pruritus,[34,60] cold extremities and/or chest pain in generally small numbers of patients.[32,34]

Generally, in comparative trials there were no statistically significant differences between the frequency and severity of adverse events reported

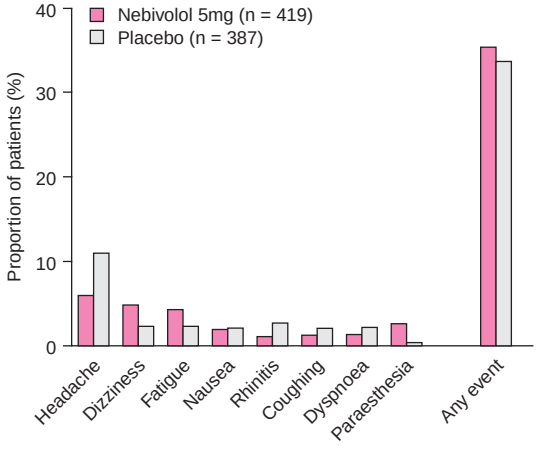


**Fig. 3.** Tolerability of nebivolol. Incidence of adverse events with nebivolol or placebo during ≤3 months of treatment as reported in a combined safety analysis of placebo-controlled therapeutic trials.[52]

in patients receiving once daily nebivolol 5mg (20 to 48.6% of recipients reported adverse events), placebo (25 to 36%),[32-34,37] atenolol 50mg (13%)[36,37] or a low dose of enalapril 10mg (55%).[38]

However, 1 study reported a greater overall incidence of adverse events in patients receiving nifedipine 20mg twice daily (n = 22) than in nebivolol recipients (n = 26) [43 *vs* 25 reports of adverse events, no statistical analysis provided for these values].[39] In particular, peripheral oedema, insomnia and frequent urination were more common in nifedipine than in nebivolol recipients ($p < 0.05$). In another study, 16 of 82 (20%) and 25 of 73 (34%) patients reported adverse events while receiving nebivolol 5mg once daily or metoprolol 100mg twice daily, respectively.[61] This difference was reported as significant but no p values were provided.

In 2 separate comparative studies, more atenolol[37] or enalapril[38] than nebivolol recipients reported impotence or decreased libido during therapy. Furthermore, the incidence of fatigue increased from baseline in atenolol recipients (from 1 to 8 of 121 patients) but remained constant in nebivolol recipients (4 of 119 patients) during a 4-week treatment period.[37]

## 6. Dosage and Administration

In patients with mild to moderate essential hypertension nebivolol is recommended at a once daily dose of 5mg taken with or without food, preferably at the same time of day.[9]

Use of the drug in children and patients with hepatic insufficiency is not advised. In the elderly and in patients with renal insufficiency, a reduced initial dose of nebivolol 2.5mg is recommended, with subsequent upward dose titration if necessary.[9]

Nebivolol may be used alone or in combination with other antihypertensive agents. Additive antihypertensive effects have so far been observed only during combination therapy with hydrochlorothiazide 12.5 to 25mg.[9]

## 7. Place of Nebivolol in the Management of Mild to Moderate Essential Hypertension

It is commonly acknowledged that essential hypertension is associated with an increased risk of stroke, coronary artery disease and congestive heart failure. However, there does not appear to be a universal consensus on the first-line treatment option for essential hypertension; this debate is comprehensively documented elsewhere.[68-70]

Numerous classes of antihypertensive agents are available, and β-blockers are among those currently recommended as a first-line treatment option in patients with uncomplicated, mild to moderate essential hypertension.[1,71-73]

Nebivolol is a selective β-blocker with a possible novel mechanism of antihypertensive activity. The drug has vasodilatory properties that have been attributed to an endothelium-dependent effect mediated via the L-arginine/nitric oxide pathway. The extent of the contribution of this mechanism to the drug's antihypertensive activity remains unclear.

If this effect on nitric oxide is shown to be clinically important, nebivolol could theoretically be of value in managing hypertensive patients with endothelial dysfunction such as those with diabetes mellitus and hypercholesterolaemia. Nebivolol has not shown detrimental effects on glucose or lipid metabolism, apart from rare instances of increased triglyceride levels. At present, however, clinical data in these groups are very limited: 1 small trial showed similar antihypertensive efficacy for nebivolol and atenolol in patients with type 2 diabetes.

The drug also appears to have effects on left ventricular function that could potentially benefit patients with hypertension and/or congestive heart failure. Nebivolol reduces preload while maintaining or reducing afterload and has been shown to decrease left ventricular mass in hypertensive patients with left ventricular hypertrophy (section 2.2.1).

In patients without comorbidities, clinical trials have shown once daily nebivolol to reduce DBP as

effectively as once daily atenolol and twice daily metoprolol and to produce a higher response rate than the latter drug. In comparisons with other classes of antihypertensive agents, nebivolol was as effective as nifedipine and lisinopril and had an additive effect when combined with low doses of hydrochlorothiazide but not with enalapril. Available clinical trials suggest a better effect with nebivolol than with enalapril 10mg daily in the short term but not the long term, but it should be noted that the enalapril dose used (10mg) may not have been optimal.

Black patients show a slightly lower response to nebivolol than other patients, but older age and cigarette smoking do not appear to affect the drug's efficacy.

Nebivolol is generally well tolerated, as demonstrated in clinical trials and by unpublished long term data. Comparative trials revealed no significant differences between the frequency and severity of adverse events in patients receiving nebivolol or atenolol, enalapril or placebo. However, the overall incidence of adverse events was reported to be greater with nifedipine or metoprolol than nebivolol in single studies.

Fatigue, especially on increased physical activity, is a common complaint with use of β-blockers. Fewer nebivolol than atenolol recipients developed fatigue in the largest comparison.[37] The reduction in exercise-induced tachycardia observed with nebivolol was less pronounced than that seen with other β-blockers, including atenolol, propranolol and pindolol. Again, if confirmed in larger trials in patients, these effects could theoretically improve quality of life in some patients.

In summary, currently available evidence indicates that nebivolol 5mg once daily is a well tolerated β-blocker, which is as effective as once daily atenolol and other classes of antihypertensive agents. It may therefore be recommended as a useful alternative first-line treatment option for the management of patients with mild to moderate uncomplicated essential hypertension.

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