EXPERT REVIEWS

β-blockers in the management of hypertension: focus on nebivolol

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Hypertension is a major cardiovascular risk factor but most patients remain asymptomatic for many years. Successful therapy not only needs to be effective, it also needs to be well tolerated. β-blockers are well established as effective antihypertensive agents. However, one major drawback to the currently available β-blockers, particularly the noncardioselective β-blockers, is their side-effect profile, including sexual dysfunction, fatigue, depression and metabolic abnormalities such as impaired glucose tolerance and lipid abnormalities. Nebivolol (Bystolic®), a novel, highly cardioselective, third-generation β-blocker that recently received approval by the US FDA for the treatment of hypertension in the USA, is effective in treating blood pressure and has a favorable side-effect profile. Studies conducted in Europe, where nebivolol has been available for some time for the treatment of hypertension, have shown that nebivolol achieves blood pressure reductions comparable to other β-blockers but with fewer side effects. Additionally, nebivolol has demonstrated similar efficacy in blood pressure reduction when compared with calcium channel blockers and inhibitors of the renin–angiotensin system. When combined with hydrochlorothiazide there was an additive antihypertensive effect. Lastly, nebivolol exhibits a vasodilatory property that is related to its effect on nitric oxide, an intrinsic vasodilator produced in the vascular endothelium. Nebivolol enhances nitric oxide bioavailablility. Studies have also demonstrated nebivolol's ability to function as an antioxidant and decrease markers of oxidative stress. These effects are believed to ultimately produce a modulation of the endothelial dysfunction typically seen in hypertension.

KEYWORDS: β-blockers • hypertension • nebivolol • nitric oxide

Hypertension is a major contributor to cardiovascular disease and a leading cause of stroke, myocardial infarction, heart failure and kidney disease. It is estimated that more than 65 million Americans have hypertension [1] and its prevalence is expected to rise. The prevalence of hypertension increases with age and older patients are more likely to suffer from cardiovascular complications of hypertension. Although the benefits of hypertension treatment and control have been well documented, the majority of patients remain undertreated and poorly controlled [2–5]. In the USA, it has been estimated that less than 60% of patients receive any treatment and only 31% are adequately controlled [2]. Although multiple factors contribute to poor patient compliance, medication cost and side effects have frequently been blamed. Hypertension is an asymptomatic disease, and it is important to use effective and well-tolerated regimens as long-term therapy in order to maintain patient compliance.

Multiple medications have been approved for the treatment of hypertension, in general tabulated in one of six categories: diuretics, β-blockers, calcium channel blockers, blockers of the renin–angiotensin–aldosterone system, direct vasodilators and centrally acting agents. Each class of medication has a different mechanism of action and a potentially different side-effect profile. Most patients with hypertension require more than one agent to be controlled and it is logical to combine drugs with different mechanisms of action. The use of β-blockers is well established for the management of cardiovascular diseases [6], and their ability to reduce cardiovascular complications has been shown in many patient populations.

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However, traditional noncardioselective β-blockers have been associated with side effects that often interfere with patient tolerability, such as decreased libido, erectile dysfunction, depression, fatigue, impaired glucose tolerance, insulin resistance and alterations in serum lipid levels [7–9]. Furthermore, trial data summarized in recent meta-analyses suggest that traditional β-blockers, particularly atenolol, may not be as effective as other classes of antihypertensive agents in preventing cardiovascular complications [10,11].

Nebivolol is a novel β-blocker that has been available in Europe for a number of years for the treatment of hypertension and, more recently, for the treatment of congestive heart failure in elderly patients. Nebivolol (Bystolic®) was recently approved (December 2007) by the US FDA for the treatment of hypertension, either taken alone or in combination with other antihypertensive agents. Nebivolol is a third-generation β-blocker that exhibits highly selective β1-adrenergic receptor blockade and nitric oxide-mediated vasodilatation. The beneficial effects of nebivolol as an antihypertensive treatment are not associated with the usual side effects of other β-blockers [12,13].

This article will review evidence from the published literature indicating that nebivolol is an effective and well-tolerated antihypertensive agent, with additional beneficial effects presumed to be related to its attenuation of oxidative stress, increase in nitric oxide levels and improvement of endothelial dysfunction.

Pharmacodynamics

β-blockers exert an antihypertensive effect via several mechanisms of action: central inhibition of sympathetic nervous system outflow, inhibition of the renin–angiotensin system by decreasing renin release from the juxtaglomerular apparatus, decreasing heart rate and myocardial contractility, and a resetting of the baroreceptors [6]. β-blockers differ from one another, however, with regard to many pharmacologic properties, including β1/β2-adrenergic receptor selectivity and vasodilatory capabilities.

Currently, based on receptor affinity and hemodynamic properties, available β-blockers can be categorized into one of four principal groups: noncardioselective and nonvasodilatory, cardioselective and nonvasodilatory, noncardioselective and vasodilatory, and cardioselective and vasodilatory. A fifth category is nonselective β-blockade with intrinsic sympathomimetic activity, examples of which are acebutol and pindolol; this latter group has fallen into disfavor because data demonstrate that they actually increase peripheral vascular resistance and attenuate the decreases in heart rate and cardiac output that may negate any benefit in a cardiovascular disease population [14]. In the first group, noncardioselective β-blockers such as propanolol exert equal blockade of β1- and β2-adrenergic receptors and exhibit no vasodilating effects. In the second group, β-blockers such as metoprolol and atenolol display higher affinity for the β1 receptor and are therefore deemed cardioselective. However, some β2 effects may appear at higher doses [15]; these agents also contain no vasodilatory properties. In the third group is the noncardioselective β-blocker carvedilol, which exerts equal blockade of the β1- and β2-adrenergic receptors, and which exhibits vasodilating properties due to α1-receptor blockade [16]. In contrast to all of these agents is nebivolol, the newest agent in this group, which is both cardioselective and vasodilating. Nebivolol has the highest cardioselectivity of any currently available β-blocker [12], exhibiting a 321-fold higher selectivity for the β1-adrenoceptor compared with the β2-adrenoceptor [17]. Nebivolol is a racemic mixture made up of equal amounts of D- and L-nebivolol (Figure 1). It is the D-isomer that is primarily responsible for the selective β1-adrenoceptor antagonist activity [18]. In addition, nebivolol exhibits vasodilatory properties not related to α1-receptor blockade but instead the vasodilatation is mediated by its effects on nitric oxide (NO) [19]. Specifically, nebivolol exerts its effects via an interaction with the endothelial L-arginine/NO pathway that serves to increase bioavailability of the naturally occurring vasodilator NO. Both isomers, but primarily L-nebivolol, contribute to the vasodilatory action [18]. Lastly, nebivolol seems to be devoid of any intrinsic sympathomimetic effect [13].

Nebivolol affects the endothelial NO pathway in two complementary ways: it increases endothelial-mediated NO expression and has an antioxidative stress action, which leads to a decrease in NO degradation [19–21]. Clinically, nebivolol's ability to modulate endothelial dysfunction may offer additional vascular protection in treating hypertension. In a study by Tzemos *et al.* comparing nebivolol with atenolol in 12 hypertensive patients, both drugs yielded similar blood pressure-lowering effects [22]. However, a detailed evaluation of the drugs' effects on forearm blood flow in these patients with endothelial dysfunction revealed that only nebivolol increased both stimulated and basal endothelial NO release, resulting in enhanced vasodilatation and blood flow. By contrast, for the same level of blood pressure control, atenolol had no effect on NO activity or vasodilatation. The ability of nebivolol to attenuate endothelial dysfunction via

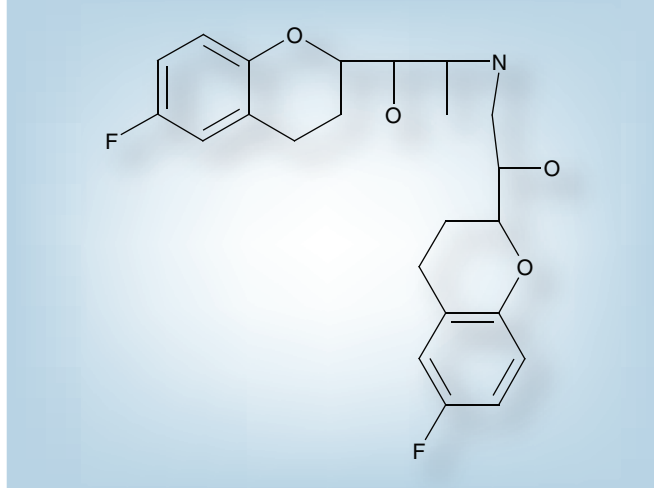

Figure 1. Nebivolol.

Table 1. Nebivolol efficacy compared with other β-blockers.

Study	Trial type	Regimen (duration in weeks)	Patients (n)	Mean sitting baseline BP (mmHg)	Mean sitting BP at study end point* (mmHg)	Response rate‡ (%)	Ref.
Van Nueten *et al.*	Double-blind, randomized, parallel-group	Nebivolol 5 mg q.d. (4) Atenolol 50 mg q.d. (4) Placebo	119 121 124	167/101 169/101 169/102	151/89 152/90.5 163/97.5	59§ 59§ 29	[53]
Czuriga *et al.*	Single-blind, randomized, parallel-group	Nebivolol 5 mg q.d. (12) Bisoprolol 5 mg q.d. (12)	138 135	153/99 153/100	132.5/83.3 133/84	90.6 87.4	[54]
Uhlir *et al.*	Double-blind, randomized, parallel-group	Nebivolol 5 mg q.d. (12) Metoprolol 100 mg b.i.d. (12)	73 67	160/106 157/107	140/89 142/91	79.5 65.6	[55]

All trials had a 4-week placebo run-in period and were multicentered.
*Decrease in baseline BP to study end point was statistically significant in active treatment groups ($p < 0.05$).
‡Defined as achieving diastolic BP ≤90 mmHg.
§Decrease in baseline BP to study end point in active treatment groups compared with placebo was statistically significant ($p < 0.001$).
BP: Blood pressure; q.d.: Daily; b.i.d.: Twice daily.

modulation of NO bioactivity may be of particular importance for African–American patients who, in addition to having a higher prevalence of cardiovascular risk factors such as hypertension and diabetes mellitus [23], also have reduced NO-dependent vasodilatation of the microvasculature when compared with age-matched Caucasians [24]. Not only has nebivolol been shown to increase arterial distensibility *in vivo* [25], but it has also been shown to restore NO bioavailability in endothelial cells from African–American subjects to levels equivalent to those in endothelial cells from age-matched Caucasians [26].

Nebivolol also appears to function as an antioxidant and is able to modify markers of oxidative stress. Pasini *et al.* evaluated the effects of nebivolol on oxidative stress by treating a group of 20 hypertensive patients for 4 weeks with either nebivolol 5 mg daily or atenolol 100 mg daily [27]. Parameters of oxidative stress were measured at baseline and after the 4th week of treatment. It was found that after 4 weeks of treatment, levels of plasma and LDL hydroperoxides, plasma 8-isoprostanes, and plasma oxidized-LDL were significantly decreased and the LDL lag phase to oxidation was significantly prolonged in patients receiving nebivolol compared with the atenolol group [27]. In addition, there was a reduction of reactive oxygen species and superoxide anions in endothelial cells exposed *in vitro* to oxidative stress after incubation of the cells with plasma from patients who received nebivolol but not plasma from patients who received atenolol [27]. Basal and stimulated intracellular NO levels were also significantly lower following incubation with the serum of patients treated with atenolol compared with nebivolol. Lastly, nebivolol has demonstrated the ability *in vitro* to inhibit both platelet aggregation [28] and the proliferation of coronary artery smooth muscle cells [29]. Both of these effects are mediated by NO and play an important role in atherogenesis and particularly in the development of coronary artery disease. Therefore, the aggregate of evidence suggests that nebivolol confers additional benefits beyond that achieved by blood pressure reduction alone, especially when compared with atenolol.

As well as being an effective antihypertensive treatment, nebivolol is not associated with many typical β-blocker-related side effects, such as fatigue, depression, bradycardia or sexual dysfunction [12,30,31]. Patients receiving nebivolol have been shown to have no significant changes in metabolic parameters, including blood lipid levels, insulin insensitivity or impaired glucose tolerance [31]. The neutral effects of nebivolol on a patient's metabolic profile are of particular importance given the rise in the prevalence of diabetes and the metabolic syndrome among the US population. The low incidence of side effects observed with nebivolol compared with other β-blockers may be linked to the high β1-adrenoceptor selectivity and the hemodynamic benefits of NO-mediated vasodilatation that nebivolol provides [30–34].

Nebivolol has also been shown to have fewer adverse effects when used in patients with pulmonary disease. Unlike non-selective β-blockers, which are more likely to cause airway obstruction due to antagonism at the β2-adrenoceptor, nebivolol does not affect airway patency in patients with hypertension and asthma or chronic obstructive pulmonary disease [35,36].

Pharmacokinetics

Nebivolol is absorbed rapidly following oral administration and is not affected by food [18]. Peak unchanged nebivolol plasma concentrations are achieved 1 h after healthy volunteers receive a single dose of oral nebivolol 5 mg [37]. The half-life of D-nebivolol is approximately 12 h in extensive metabolizers and 19 h in poor metabolizers [38]; the volume of distribution is approximately 200 l/kg in extensive metabolizers and 15 l/kg in poor metabolizers and is similar in nonobese and obese patients [39]. Approximately 98% of nebivolol is protein bound [18].

Table 2. Nebivolol efficacy compared with calcium channel blockers.

Study	Regimen	Patients (n)	Mean sitting baseline BP (mmHg)	Mean sitting BP at study end point (mmHg)	Response rate* (%)	Ref.
Van Nueten *et al.*	Nebivolol 5 mg q.d. Nifedipine 20 mg b.i.d.	211 209	159/104 160/105	146/92‡ 145/94‡	70 67	[57]
Mazza *et al.*	Nebivolol 2.5-5mg q.d.§ Amlodipine 5-10mg q.d.§	81 87	163/100 164/101	140/84¶ 139/85¶	88 86	[58]

All trials were 12-week, double-blind, randomized, multicentered, parallel-group, with a 4-week placebo run-in period.
*Defined as achieving a diastolic BP ≤ 90 mmHg or a reduction in diastolic BP ≥ 10 mmHg [57] or a BP <140/90 [58].
‡Decrease in baseline BP to study end point was statistically significant in both groups ($p < 0.001$).
§After 8 weeks of monotherapy at full doses, hydrochlorothiazide (6.25–25 mg q.i.d.) was added in non-normalized responders.
¶Statistical significance for change from baseline BP was not reported.
BP: Blood pressure; q.d.: Daily; b.i.d.: Twice daily.

Metabolism & elimination

Nebivolol is primarily metabolized hepatically by CYP2D6 via multiple processes including: *N*-dealkylation, hydroxylation, oxidation and glucuronidation [40]. When given orally to extensive metabolizers, approximately 38% is excreted in the urine and 44% in the feces. By contrast, when given to poor metabolizers, the primary route of elimination is the urine followed by the feces, 67 versus 13%, respectively [40].

Dosing

The recommended starting dose of nebivolol in most patients with hypertension is 5 mg once daily. The dosage may be increased at 2-week intervals to a maximum of 40 mg once daily if further blood pressure reduction is required. In patients with severe renal impairment or moderate hepatic impairment, it is recommended that the starting dose of nebivolol be reduced to 2.5 mg once daily and that upward titration be performed cautiously. The drug should be used with caution in patients receiving dialysis therapy as studies have not been conducted in this patient population. Nebivolol is contraindicated in patients with severe hepatic dysfunction owing to a lack of clinical data in this patient population.

Drug interactions

There are no significant drug interactions reported in studies of nebivolol when administered with other drugs such as digoxin, warfarin, losartan, spironolactone, ramipril, furosemide, antacids and ranitidine [41–47]. Coadministration of nebivolol with either fluoxetine or cimetidine increases its plasma concentrations [41,48]. It is recommended that caution be used when administering nebivolol with agents that inhibit CYP2D6. When nebivolol and nicardipine are administered together, plasma concentrations of both drugs are slightly increased [41].

Clinical efficacy

Nebivolol has been studied for the management of hypertension both in Europe and the USA, as well as for the treatment of elderly patients with heart failure in Europe. This review will focus on the efficacy data for nebivolol in the treatment of hypertension in European and US trials, as well as comparative data to many standard antihypertensive medications obtained in European trials.

Systemic hypertension

European double-blind, placebo-controlled trials

The antihypertensive efficacy of nebivolol has been evaluated in several European trials. Here we will focus on two double-blind, randomized, placebo-controlled trials [49,50]. Van Bortel *et al.* undertook an 8-week multicenter study to investigate the effect of 4 and 8 weeks of treatment with nebivolol 5 mg daily on blood pressure, heart rate, quality of life and the adverse effect profile [49]. Patients were randomized into three groups. Group one consisted of 40 patients who received nebivolol 5 mg in the first double-blind 4-week period followed by placebo in the second 4-week period. Group two consisted of 40 patients who received placebo in the first double-blind 4-week period followed by nebivolol 5 mg daily, and group three, which consisted of 32 patients, received nebivolol 5 mg daily for the entire 8-week period. Patients were considered responders to therapy if their diastolic blood pressure during double-blind treatment was 90 mmHg or less, or if diastolic blood pressure was decreased by at least 10%. During treatment with nebivolol, statistically significant differences in both systolic and diastolic blood pressure and heart rate were seen compared with placebo. The mean supine blood pressure during placebo was 161/98 mmHg, while the mean supine blood pressure during nebivolol treatment was 150/90 mmHg. Heart rate also decreased from 80 to 68 bpm during active treatment. Quality of life measurement, as determined by the Inventory of Subjective Health questionnaire, did not differ between the double-blind placebo and nebivolol phases. In addition, there were no statistically significant differences in adverse events between placebo and nebivolol.

Van Nueten *et al.* reported on a double-blind, randomized, placebo-controlled, parallel-group, dose-finding trial that included 509 patients with hypertension [50]. Following a 4-week wash-out period patients were assigned to a placebo group or one of several dosing groups of nebivolol (0.5, 1.0, 2.5, 5.0 or 10 mg daily for

1 month). Patients were considered responders if diastolic blood pressure was 90 mmHg or less or fell at least 10 mmHg from baseline. There were significant reductions in supine diastolic pressure from baseline in all treatment groups including placebo. At the two lowest doses of nebivolol therapy there was no significant difference in blood pressure compared with placebo. A significant reduction of blood pressure was seen with the 2.5-mg daily dose. There was no significant difference between the 5 and 10 mg daily dose of nebivolol. Response rates with nebivolol 5 and 10 mg daily were 58 and 57%, respectively. Nebivolol was equally effective in black versus nonblack subjects. Heart rate was significantly lower with nebivolol 5 and 10 mg daily. There were no differences in adverse events between placebo and any dose of nebivolol.

US double-blind, placebo-controlled trials

Two pivotal trials have been conducted in the USA, which were submitted to the FDA and were instrumental in the decision to approve nebivolol for use in the treatment of hypertension in the USA. The first trial by Weiss *et al.* was a double-blind, multicenter, randomized, placebo-controlled study to evaluate the antihypertensive efficacy and safety of nebivolol in patients with mild-to-moderate hypertension [51]. Patients were included in the study if their sitting diastolic blood pressure was 95–109 mmHg, inclusive. A total of 909 patients were randomized to receive either placebo or nebivolol 1.25, 2.5, 5, 10, 20 or 40 mg once daily for up to 84 days. The primary end point was the change in trough sitting diastolic blood pressure from baseline to the end of the study period. Nebivolol significantly reduced the mean sitting diastolic blood pressure compared with baseline (8.0–11.2 mmHg compared with 2.9 mmHg for placebo; $p < 0.001$) and the mean sitting systolic blood pressure compared with baseline (4.4–9.5 mmHg decrease compared with a 2.2 mmHg increase for placebo; $p \leq 0.002$). Patients were considered responders if at the end of the study period the sitting diastolic blood pressure was 90 mmHg or less, or reduced by 10 mmHg or more, compared with baseline. The response rate in the placebo group was 24.7% compared with 45.8–64.5% in the nebivolol groups. The response rates in the nebivolol groups were dose dependent. Additionally, the overall adverse event rate was not significantly different between nebivolol (46.1%) and placebo (40.7%).

The second major US trial, conducted by Saunders *et al.,* was significant as it included only African–American patients, a group that has traditionally responded poorly to β-blocker monotherapy for hypertension compared with Caucasians [52]. This was a double-blind, multicenter, randomized, placebo-controlled study to assess the antihypertensive efficacy and safety of nebivolol in 300 patients. Patients were included in the study if their mean sitting diastolic blood pressure was 95–109 mmHg, inclusive. Patients were randomized to receive either placebo or nebivolol 2.5, 5, 10, 20 or 40 mg once daily for a total of 12 weeks. The primary end point was the change in mean trough sitting diastolic blood pressure compared with baseline. Nebivolol significantly reduced the placebo-subtracted mean trough diastolic blood pressure (4.9–6.1 mm Hg; $p \leq 0.004$) at all doses of 5 mg daily and higher from baseline to study end. Nebivolol also significantly reduced the placebo-subtracted mean trough sitting systolic blood pressure (6–7.3 mmHg; $p \leq 0.044$) at all doses of 10 mg daily and higher from baseline to study end. Patients were considered responders if the average trough sitting diastolic blood pressure was 90 mmHg or less, or decreased from baseline by 10 mmHg or more. The response rate in the placebo group was 26.5% compared with 58–64% in the nebivolol groups at 5 mg daily or higher. Lastly, there was no significant difference in the incidence of adverse events compared with placebo.

European comparative trials

Studies conducted in Europe compared nebivolol with other antihypertensive medications, including: other β-blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, an angiotensin II receptor blocker and hydrochlorothiazide (HCTZ). In the three trials that compared nebivolol with the β-blockers atenolol, bisoprolol and metoprolol, respectively, there was a statistically significant

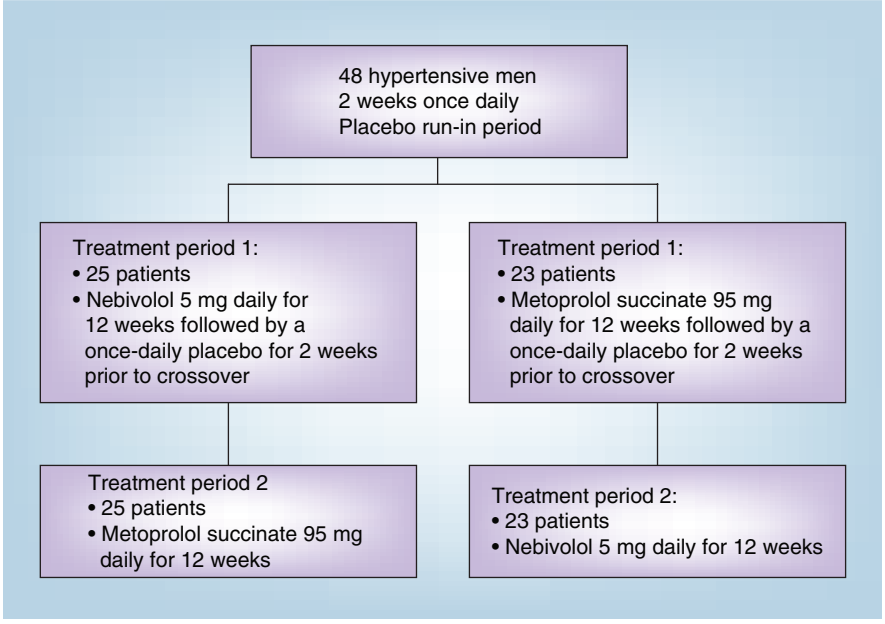

Figure 2. Trial design of Nitric Oxide, Erectile Dysfunction and β-blocker Treatment (MR NOED) study.

Table 3. Nebivolol efficacy compared with angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers.

Study	Regimen	Patients (n)	Mean sitting baseline BP (mmHg)	Mean sitting BP at study end point (mmHg)	Response rate* (%)	Ref.
Van Nueten *et al.*	Nebivolol 5 mg q.d. Enalapril 10 mg q.d.	208 211	162/104.6 163/105.5	147/92.3‡ 151/95.6‡	70 55	[59]
Rosei *et al.*	Nebivolol 5 mg q.d. Lisinopril 20 mg q.d.	35 30	159.3/101 156.4/98.6	132/82.1§ 134.6/81.8§	94 90	[60]
Van Bortel *et al.*	Nebivolol 5 mg q.d. Losartan 50 mg q.d.	147 151	166/103 165/102	151/914,5¶# 147/924,5¶#	65.3 58.3	[61]

All trials were 12-week, double-blind, randomized, multicentered, parallel-group with a 4-week placebo run-in period.
*Defined as achieving a diastolic BP ≤ 90 mmHg or a reduction in diastolic PB ≥ 10 mmHg [59,60] or a BP ≤ 140/90 mmHg [61].
‡Decrease in baseline BP to study end point of the comparison period significantly favored nebivolol ($p = 0.009$).
§Decrease in baseline BP to study end point was statistically significant in both groups ($p < 0.05$).
¶Decrease in baseline systolic BP to study end point was not statistically different between the two groups.
#Decrease in baseline diastolic BP to study end point of the comparison period significantly favored nebivolol ($p < 0.02$).
BP: Blood pressure; q.d.: Daily.

reduction ($p < 0.05$) in blood pressure compared with baseline in all active treatment groups [53–55]. Table 1 summarizes the key points and blood pressure reduction achieved in each of these trials. Patients in the nebivolol arm of each study reported fewer adverse effects. When nebivolol was compared with metoprolol, for example, the adverse effect rate was 23 versus 36%, respectively [55]. The Nitric Oxide, Erectile Dysfunction and β-blocker Treatment (MR NOED) study utilized a crossover design to compare the sexual side effects of nebivolol and metoprolol in hypertensive men with no history of erectile dysfunction [56]. The trial design is shown in Figure 2. There were no statistically significant differences between the treatment groups in terms of blood pressure reduction. However, the effect on sexual function was different as assessed using the international index of erectile function, a reliable, validated and widely used self-assessment scale. The erectile function subscore showed no significant changes from baseline in patients treated with nebivolol in treatment period one. This also was true when nebivolol was administered in treatment period two. By contrast, there was a decrease in the erectile function subscore in patients who received metoprolol in treatment period one and in treatment period two after the crossover phase [56].

As summarized in Table 2, in trials comparing nebivolol to the calcium channel blockers nifedipine and amlodipine there was no statistically significant difference in blood pressure-lowering effect between the active treatment groups at the end of the study period [57,58]. Patients assigned to the nebivolol groups had a statistically significant lower resting heart rate in both studies. However, overall adverse event rates were statistically significantly higher for both nifedipine and amlodipine when compared with nebivolol [57,58]. When nebivolol was compared with amlodipine there were 13 versus 30 drug-related adverse effects, respectively ($p = 0.0358$) [58]. The percentage of patients reporting adverse events in the nebivolol versus the nifedipine group was 39 versus 56.5%, respectively [57]. Additionally, during the comparison period seven patients in the nebivolol group and 32 patients in the nifedipine group stopped therapy because of adverse events ($p < 0.001$) [57].

Nebivolol was also compared with two different ACE inhibitors as well as the angiotensin receptor blocker (ARB) losartan. The data from these trials are summarized in Table 3. When compared with enalapril at 12 weeks, nebivolol demonstrated superior efficacy in blood pressure reduction [59]. By contrast, after a 12-week period nebivolol was equally effective as lisinopril and losartan in its blood pressure-lowering effects [60,61]. However, it should be noted that in the trial comparing nebivolol with losartan, if after 6 weeks of therapy the diastolic blood pressure goal of less than 90 mmHg was not met hydrochlorothiazode (HCTZ) 12.5 mg daily was added. A statistically significant higher number of patients assigned to the losartan group were not at the diastolic goal at the 6-week mark and were therefore started on HCTZ therapy. The larger number of patients in the losartan group on additional HCTZ therapy may have affected the final blood pressure comparison between losartan and nebivolol. Lastly, a symptomatic well-being score was assessed for patients treated in the nebivolol versus losartan trial. The change in general well being did not differ between the two treatment groups [61].

The efficacy of nebivolol in treating hypertension has also been compared with HCTZ in a factorial design study, as seen in Figure 3 [62]. After a 4-week placebo run-in period, patients were randomized to receive either placebo, nebivolol 1, 5 or 10 mg once daily, or HCTZ 12.5 or 25 mg once daily, or one of six possible combinations of nebivolol and HCTZ for 12 weeks. After 2 weeks of therapy, blood pressure was significantly reduced from baseline in all nebivolol, HCTZ and combination therapy groups. Blood pressure reductions were dose dependent in all active treatment groups. However, some differences were noted when comparing the various

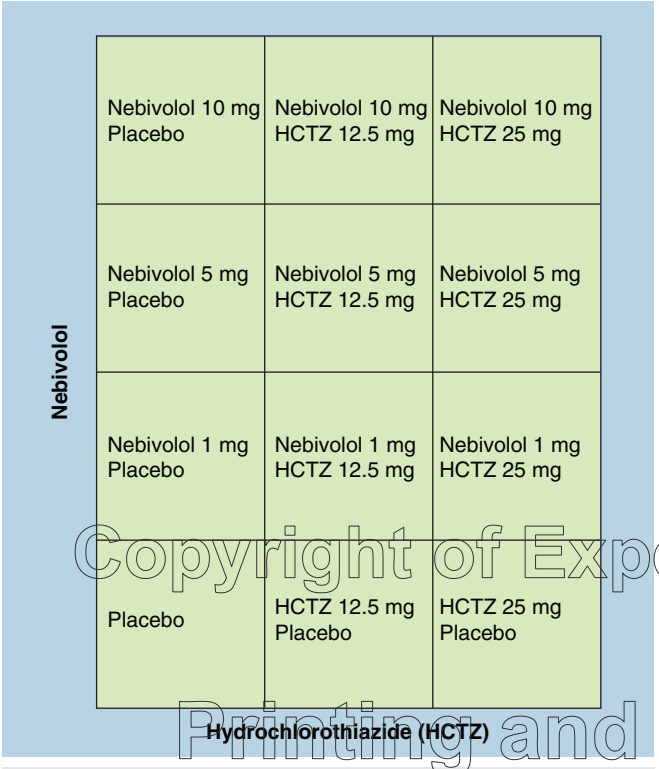

Figure 3. Multifactorial (3 × 4 parallel) study design for the treatment of ambulatory hypertensives with nebivolol or hydrochlorothiazide alone or in combination.

groups in that only nebivolol 5 and 10 mg daily and HCTZ 25 mg daily were statistically superior to placebo. Nebivolol at 1 mg daily yielded blood pressure reduction similar to HCTZ 12.5 mg and placebo but was inferior to HCTZ 25 mg daily. Combination treatment of HCTZ 25 mg daily with nebivolol 5 or 10 mg daily resulted in significantly greater blood pressure reduction than seen with any of these treatments taken as monotherapy. Both nebivolol monotherapy- and combination therapy-treated patients experienced few adverse events. Hypoesthesia (8.3%) was the most commonly reported side effect in the nebivolol monotherapy group, followed by fatigue and dizziness (5% each). The most frequently reported adverse events on HCTZ were fatigue (12%), headache and dyspnea (7.5% each). Adverse event rates were not additive for the combined nebivolol/HCTZ treatments, and were in fact lower than those observed on either monotherapy.

Conclusions

In summary, nebivolol is a third-generation β-blocker that exhibits extremely high β1 cardioselectivity as well as vasodilatory properties that are mediated by the endothelial L-arginine/NO pathway. Several studies have shown its efficacy and safety in treating patients with hypertension. Comparative data have shown similar efficacy results compared with other monotherapies, including other β-blockers, calcium channel blockers, ACE inhibitors and the ARB losartan, often with fewer adverse effects in the nebivolol groups. Used in combination with HCTZ, nebivolol has been shown to have significant additive blood pressure-lowering effects.

Lastly, nebivolol may have the added benefit of acting as an antioxidant and increasing endothelial NO bioavailability. This dual action may help to alleviate the endothelial dysfunction associated with hypertension and oxidative stress, and provide added benefit in patient populations such as African–Americans who appear to express lower levels of NO in their vascular endothelium than Caucasian patients.

Expert commentary

The ability of nebivolol to attenuate endothelial dysfunction and oxidative stress may prove to be its most attractive attribute. Oxidative stress plays a large role in the development of resistant or difficult-to-control hypertension as well as contributing to end-organ damage such as cardiovascular disease, stroke and chronic kidney disease. Further studies will need to be done to further characterize this effect of nebivolol on clinical outcomes.

Five-year view

In our opinion, within the next 5 years, nebivolol will become the β-blocker of choice for the treatment of hypertension. Nebivolol has equivalent antihypertensive efficacy compared with other β-blockers with the added benefit of fewer side effects. Nebivolol's favorable metabolic profile as well as its ability to attenuate oxidative stress and improve NO bioavailability confers additional beneficial qualities as part of its cardiovascular profile.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Key issues

- Nebivolol is safe and effective in the management of hypertension.
- There are generally fewer side effects associated with nebivolol when compared with other β-blockers.
- Nebivolol appears to have the additional benefit of attenuating oxidative stress and reducing endothelial dysfunction.

References

Papers of special note have been highlighted as:
• of interest
•• of considerable interest

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