

# Efficacy and Tolerability of Nebivolol Compared with Other Antihypertensive Drugs

## A Meta-Analysis

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### Abstract

**Background and objective:** Lowering BP to normal levels without quality of life deterioration is the most important means of reducing cardiovascular risk. Recent studies have challenged the position of  $\beta$ -adrenoceptor antagonists ( $\beta$ -blockers) as first-line antihypertensive drugs. Nebivolol is a third-generation, highly selective  $\beta_1$ -blocker that causes vasodilation through nitric oxide (NO) release. This meta-analysis investigates the efficacy and tolerability of nebivolol compared with other antihypertensive drugs and placebo in patients with hypertension.

**Methods:** Twelve randomized controlled studies were included in which nebivolol 5 mg once daily was compared with the recommended clinical doses of other antihypertensive drugs (n = 9), placebo (n = 2), and both (n = 1). The clinical studies were selected after a MEDLINE search up to 2007 using the key words 'nebivolol' and 'hypertension.'

**Results:** Antihypertensive response rates (the percentage of patients achieving target BP levels or a defined DBP reduction) were higher with nebivolol than with ACE inhibitors (odds ratio [OR] 1.92; p = 0.001) and all antihypertensive drugs combined (OR 1.41; p = 0.001) and similar to  $\beta$ -blockers, calcium channel antagonists (CCAs) and the angiotensin receptor antagonist (ARA) losartan. Moreover, a higher percentage of patients receiving nebivolol achieved target BP levels compared with patients treated with losartan (OR 1.98; p = 0.004), CCAs (OR 1.44; p = 0.024), and all antihypertensive drugs combined (OR 1.35; p = 0.012). The percentage of patients experiencing adverse events did not differ between nebivolol and placebo; adverse event rates were significantly lower with nebivolol than losartan (OR 0.52; p = 0.016), other  $\beta$ -blockers (OR 0.56; p = 0.007), nifedipine (OR 0.49; p < 0.001), and all antihypertensive drugs combined (OR 0.59; p < 0.001).

**Conclusion:** Results of previous pharmacokinetic studies suggest that nebivolol 5 mg may not conform completely to the definition of a classic  $\beta$ -blocker demonstrating additional antihypertensive effect due to endothelial NO release-mediated vasodilation. This meta-analysis showed that nebivolol 5 mg achieved similar or better rates of treatment response and BP normalization than other drug classes and other antihypertensive drugs combined, with similar tolerability to placebo and significantly better tolerability than losartan, CCAs, other  $\beta$ -blockers, and all antihypertensive drugs combined. Although not definitive, this meta-analysis suggests that nebivolol 5 mg is likely to have advantages over existing antihypertensives and may have a role in the first-line treatment of hypertension.

The role of  $\beta$ -adrenoceptor antagonists ( $\beta$ -blockers) as first-line antihypertensive drugs in uncomplicated hypertension has been questioned, mainly because atenolol<sup>[1]</sup> and some older short-acting

$\beta$ -blockers<sup>[2]</sup> seem to offer less protection than other antihypertensive drugs in reducing mortality in patients with non-complicated hypertension. In particular, results from the LIFE (Losartan Inter-

vention For Endpoint reduction in hypertension) and the ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) studies have shown that atenolol is inferior to losartan<sup>[3]</sup> and amlodipine/perindopril<sup>[4]</sup> in the prevention of major cardiovascular events in patients with hypertension. Whether conclusions from the above studies can be extrapolated to all  $\beta$ -blockers is not clear.

Nebivolol has been classified as a  $\beta$ -blocker; however, some of its BP-lowering effect is not the result of  $\beta$ -blockade,<sup>[5]</sup> but originates from peripheral vasodilation mediated by endothelial nitric oxide (NO) release.<sup>[6,7]</sup> Although several third-generation  $\beta$ -blockers have demonstrated vasodilating properties, only nebivolol has been shown to mediate a vasodilatory effect via NO release, providing a unique dual mechanism of action and clearly differentiating nebivolol from other  $\beta$ -blockers such as atenolol. NO release plays a role in endothelial protection and may, therefore, also provide benefits beyond BP lowering in a variety of cardiovascular conditions, but to date there is no clinical evidence to support this hypothesis.<sup>[8]</sup>

In addition, nebivolol is a highly  $\beta_1$ -selective blocker<sup>[9]</sup> and its pharmacologic profile clearly distinguishes it from classical  $\beta$ -blockers, such as atenolol, metoprolol, and bisoprolol.<sup>[10]</sup> In contrast to classical  $\beta$ -blockers, nebivolol improves insulin sensitivity,<sup>[11]</sup> and has antioxidant effects.<sup>[12]</sup> In addition, nebivolol is generally well tolerated,<sup>[13]</sup> its effect on high-density lipoprotein-cholesterol (HDL-C) did not differ from atenolol in normometabolic patients with mild to moderate hypertension.<sup>[14]</sup> On the other hand, carvedilol, another atypical  $\beta$ -blocker, has been associated with beneficial metabolic and lipid effects including increased HDL-C levels and improved insulin sensitivity<sup>[15,16]</sup> and, like nebivolol, has demonstrated antioxidant effects.<sup>[17]</sup>

The major objectives in the treatment of hypertension are prevention of cardiovascular morbidity and mortality and preservation of quality of life.<sup>[18-20]</sup> The latter will also enhance patients' drug adherence, thereby improving treatment efficacy.<sup>[21]</sup> The pharmacologic properties of a drug used in the treatment of hypertension are important in optimizing clinical outcomes.<sup>[22]</sup> In the LIFE study, properties of losartan<sup>[3]</sup> other than its antihypertensive efficacy resulted in additional benefits including reduced mortality and morbidity. Results from PROGRESS (Perindopril pROtection aGainst REcurrent Stroke Study) showed that the ACE inhibitor perindopril protected both hypertensive and normotensive patients with cerebrovascular disease against acute stroke.<sup>[23]</sup> To achieve BP goals defined by treatment guidelines, often more than one antihypertensive drug has to be used; use of any single antihypertensive drug is unlikely to achieve BP control. However, complicated drug regimens can negatively influence drug adherence.<sup>[24]</sup> It is possible that drugs that provide potent BP-lowering effects without producing major adverse effects may

allow a reduction in the number of tablets needed to achieve the therapeutic goal.<sup>[25]</sup>

The present study is a meta-analysis investigating the antihypertensive effect and tolerability of nebivolol in comparison with other antihypertensive drugs and placebo in patients with hypertension.

## Methods

### Identification and Selection of Clinical Trials

The clinical studies were selected after a MEDLINE search up to 2007 using the key words 'nebivolol' and 'hypertension'. Only studies that used nebivolol 5 mg/day were considered. The search was supplemented by screening bibliographies of identified manuscripts, particularly review articles. We included randomized, controlled studies in patients with essential hypertension where placebo or active drugs ( $\beta$ -blockers, calcium channel antagonists [CCAs], ACE inhibitors, and angiotensin receptor antagonists [ARAs]) were used as controls. The number of patients per study arm had to be at least 25 and the duration of treatment not <1 month. Studies also had to be published in the English language. Those studies without design description or with inadequate reporting of dosage regimen, antihypertensive effect, adverse event incidence, or statistical analysis were excluded. Abstracts, reviews, and studies in which a combination of drugs was used from the start of the study were also excluded. All clinical trials were evaluated by two independent observers and in case of disagreement the trial was not included in the analysis.

### Statistics

The comparison between nebivolol, placebo, and active drugs was made using a meta-analysis (Mantel-Haenszel model) with random effects of the data provided by the individual studies. The following parameters were analyzed: (i) mean change in BP from baseline; (ii) the percentage of responder patients at the end of treatment; (iii) the percentage of patients with normalized BP at the end of treatment; (iv) the percentage of patients with adverse events; and (v) the percentage of patients who withdrew because of drug-related adverse events. Those percentages that were not reported were calculated from absolute numbers. The absolute numbers of patients were calculated where percentages only were reported. For each study, the odds ratio (OR) with 95% CI and p-values were calculated. The OR, relative risk (RR), and rate difference (RD) with 95% CIs and p-values were also calculated for all the studies combined. The absence of heterogeneity between the ORs of the studies was assessed with the  $\chi^2$  heterogeneity test. A significance level of 5% was taken as the  $\alpha$  risk.

## Results

Twelve clinical studies met the inclusion criteria and were selected for the meta-analysis.<sup>[26-37]</sup> The characteristics of these trials are shown in table I.

All studies were double-blind in patients with hypertension except for one which was single-blind.<sup>[34]</sup> Two studies compared nebivolol with placebo,<sup>[26,27]</sup> three with atenolol, metoprolol or bisoprolol,<sup>[32-34]</sup> one with placebo and atenolol,<sup>[28]</sup> one with losartan,<sup>[31]</sup> two with enalapril or lisinopril,<sup>[29,30]</sup> and three with nifedipine or amlodipine.<sup>[35-37]</sup> Overall, 1269 patients were treated with nebivolol, 248 with placebo, and 1136 with an active comparator (table I).

The percentages of responder patients to nebivolol compared with other antihypertensive agents are shown in figure 1. Response rates were reported for nine active comparator studies. Definitions used for response and normalization rates are shown in table I. Response rates were significantly higher ( $p = 0.001$ ) with nebivolol than ACE inhibitors. The differences in response rates between nebivolol and the ARAs,  $\beta$ -blockers, and CCAs were not statistically significant. The OR for all of the studies combined showed a statistically significant difference in favor of nebivolol, with a 6% rate difference (OR 1.41; 95% CI 1.15, 1.73;  $p = 0.001$ ).

Figure 2 shows the analyses of patients with normalized BP in comparative studies. Eight studies reported the percentage of patients with normalized BP. Normalized BP was defined as DBP  $\leq 90$  mmHg in five studies,<sup>[28,31,32,34,35]</sup> as DBP  $< 90$  mmHg in one study<sup>[36]</sup> and as BP  $< 140/90$  mmHg in two studies.<sup>[33,37]</sup> Significantly more patients treated with nebivolol than the ARA losartan or CCAs had normal DBP; differences in DBP between nebivolol and  $\beta$ -blockers were not statistically significant. There were no studies comparing nebivolol with ACE inhibitors for normalized BP. In a combined analysis of all studies, the percentage of patients with normalized BP was significantly higher with nebivolol than other antihypertensive drugs, with a 7% rate difference (OR 1.35; 95% CI 1.07, 1.72;  $p = 0.012$ ).

A meta-analysis of two placebo-controlled studies with tolerability data showed that the percentage of patients experiencing adverse events during treatment with nebivolol was not statistically different compared with placebo (figure 3a).<sup>[27,28]</sup> Data from eight studies<sup>[28-35]</sup> allowed comparison of the incidence of adverse events in patients treated with nebivolol and other antihypertensive drugs (figure 3b). Tolerability between nebivolol and ACE inhibitors was similar, but nebivolol had better tolerability than  $\beta$ -blockers, CCAs, and the ARA losartan. A combined analysis showed that the percentage of adverse events was significantly lower with nebivolol than with the other antihypertensive drugs,

with an 11% rate difference (OR 0.59; 95% CI 0.48, 0.72;  $p < 0.001$ ).

Seven studies<sup>[29-32,34-36]</sup> compared nebivolol with other antihypertensive drugs and measured the percentage of patients who withdrew from treatment as a result of adverse events (figure 4). The incidence of patient withdrawals because of adverse events was significantly lower with nebivolol than with CCAs ( $p < 0.0001$ ); the differences between nebivolol, ACE inhibitors,  $\beta$ -blockers, and the ARA losartan was not statistically significant. Combined analysis of all studies showed fewer patient withdrawals as a result of nebivolol-induced adverse events compared with other antihypertensive drugs, with a rate difference of 4% (OR 0.42; 95% CI 0.19, 0.90;  $p = 0.025$ ). Consequently, patients treated with nebivolol have a statistically lower probability of developing adverse events and of having their antihypertensive treatment interrupted because of adverse events.

## Discussion

The present meta-analysis shows that more hypertensive patients achieved a response or BP normalization and/or achieved normal DBP levels after treatment with nebivolol 5 mg once daily than daily therapeutic doses of other antihypertensive drugs in general, and ACE inhibitors, CCAs, and the ARA losartan in particular. The present meta-analysis also shows that patients treated with nebivolol 5 mg once daily had placebo-level tolerability and experienced less adverse events than those treated with recommended daily doses of other antihypertensive drugs in general, and the ARA losartan,  $\beta$ -blockers, and CCAs in particular.

Patients with hypertension often need more than one antihypertensive drug to achieve the target BP.<sup>[18-20]</sup> These patients are often treated not only with antihypertensive drugs but also with other drugs such as aspirin (acetylsalicylic acid) and lipid-lowering agents, further increasing the number of tablets per day and additionally challenging drug adherence. Although speculative at this stage, it is possible that, with nebivolol, fewer antihypertensive drugs may be required to reach the goal BP because of this drug's antihypertensive efficacy profile, once-daily administration, a long half-life, and dual mechanism of action. This may increase drug adherence in patients, because the daily dosage is known to be an important determinant of patient compliance.<sup>[24,25]</sup> Compliance can also be impacted by costs of medication, an issue which is not covered in this meta-analysis, but should be the subject of a future study. For example, thiazide antihypertensives are associated with low medication costs compared with other antihypertensive drug classes, but have been shown to be less effective in BP lowering than nebivolol 5 mg and 10 mg, respectively.<sup>[38]</sup>

Table 1. A summary of studies included in the meta-analysis

Study	Design and treatment duration	Dosage <sup>a</sup> (mg/day)	No. of patients	Age (mean ± SD)	Baseline BP (mean seated, unless stated otherwise)	BP change from baseline (mmHg)	Response rate (%) <sup>b</sup>	Normalization rate (%) <sup>c</sup>	Adverse events (% patients)
<b>Versus placebo</b>									
Van Bortel et al. <sup>[26]</sup>	db, pc, mc, 4 and 8 weeks	Nebivolol 5	40	54 <sup>d</sup>	165/101 <sup>e</sup>	-17/-10 (4 weeks) -23/-14 (8 weeks)	65	NR	NR
Van Nueten et al. <sup>[27]</sup>	r, db, pc, pg; 4 weeks	Placebo Nebivolol 5	40 86	54 <sup>d</sup> 56 <sup>d</sup>	165/101 <sup>e</sup> 160.3/101.6 <sup>e,f</sup>	-4/-3 (4 weeks) -9.2/-9.2	25 58	NR	NR 40
Van Nueten et al. <sup>[28]</sup>	r, db, mc; 4 weeks	Placebo Nebivolol 5	84 119	56 <sup>d</sup> 55	158.8/101.3 <sup>e,f</sup> 167/102 <sup>f</sup>	-3.1/-3.3 -16/-14	32 NR	NR	36 28
		Placebo	124	55 <sup>d</sup>	168/104 <sup>f</sup>	-6/-7	NR	29	25
<b>Versus ACE inhibitors</b>									
Van Nueten et al. <sup>[29]</sup>	r, db, mc; 12 weeks	Nebivolol 5 Enalapril 10	208 211	54 53	162/105 <sup>f</sup> 163/106 <sup>f</sup>	-15/-12.3 <sup>g,h</sup> -13/-9.9 <sup>h</sup>	70 <sup>g</sup> 55	NR	48.6 55
Agabiti Rosei et al. <sup>[30]</sup>	r, db, mc; 12 weeks	Nebivolol 5 Lisinopril 20	35 30	50.1 ± 8.2 48.3 ± 9.6	161/98 <sup>f</sup> 158/101 <sup>f</sup>	-27.3/-18.9 <sup>i</sup> -21.8/-16.8 <sup>i</sup>	94 90	NR	14 23
<b>Versus angiotensin receptor antagonists</b>									
Van Bortel et al. <sup>[31]</sup>	r, db, pg; 12 weeks	Nebivolol 5 Losartan 50	147 151	56 ± 9 56 ± 8	166/103 165/102	-15/-12 -18/-10	65.3 58.3	50 <sup>i</sup> 50 <sup>i</sup>	19.0 31.1
<b>Versus β-adrenoceptor antagonists</b>									
Van Nueten et al. <sup>[28]</sup>	r, db, mc; 4 weeks	Nebivolol 5 Atenolol 50	119 121	55 55	167/102 <sup>i</sup> 169/104 <sup>i</sup>	-16/-14 <sup>i</sup> -17/-14 <sup>i</sup>	NR NR	59 59	28 31
Uhlir et al. <sup>[32]</sup>	r, db, mc; 12 weeks	Nebivolol 5 Metoprolol tartrate 100 bid	73 67	NR NR	160/106 157/107	-20/-17 -15/-16	82.2 82.8	79.5 65.6	20.0 <sup>g</sup> 34.0
Grassi et al. <sup>[33]</sup>	r, db, mc; 12 weeks	Nebivolol 5 Atenolol 100	105 100	50.1 ± 11.3 49.8 ± 10.9	157.3/100.4 155.2/100.5	-19.1/-14.8 -18.2/-14.6	85.0 79.0	37.0 41.7	20 <sup>g</sup> 41
Czuriga et al. <sup>[34]</sup>	r, sb, mc, pg; 12 weeks	Nebivolol 5 Bisoprolol 5	138 135	50 ± 8.4 49 ± 8.2	153/99 153/100	-20.5/-15.7 -20.0/-16.0	92 90	90.6 87.4	5.8 8.9
<b>Versus calcium channel antagonists</b>									
Van Nueten et al. <sup>[35]</sup>	r, db 12 weeks	Nebivolol 5 Nifedipine SR 20 bid	211 209	54.0 53.0	159/104 <sup>i</sup> 160/105 <sup>i</sup>	-13/-11.7 <sup>h</sup> -14/-10.9 <sup>h</sup>	70 67	54 <sup>g</sup> 42	39 <sup>g</sup> 56.5
Lacourciere et al. <sup>[36]</sup>	r, db, pg; 12 weeks	Nebivolol 5 Nifedipine SR 20 bid	26 25	51.5 ± 10.4 53.0 ± 7.7	153.1/99.2 151.2/99.7	-10.1/-8.9 -10.2/-8.5	69 59	61 59	NR NR
Mazza et al. <sup>[37]</sup>	r, db, mc, pg; 12 weeks	Nebivolol 5 Amlodipine 5-10	81 87	70.1 ± 5.1 70.6 ± 5.1	163/100 <sup>i</sup> 164/101 <sup>i</sup>	-21/-15 -19/-15	88 86	50 47	NR NR

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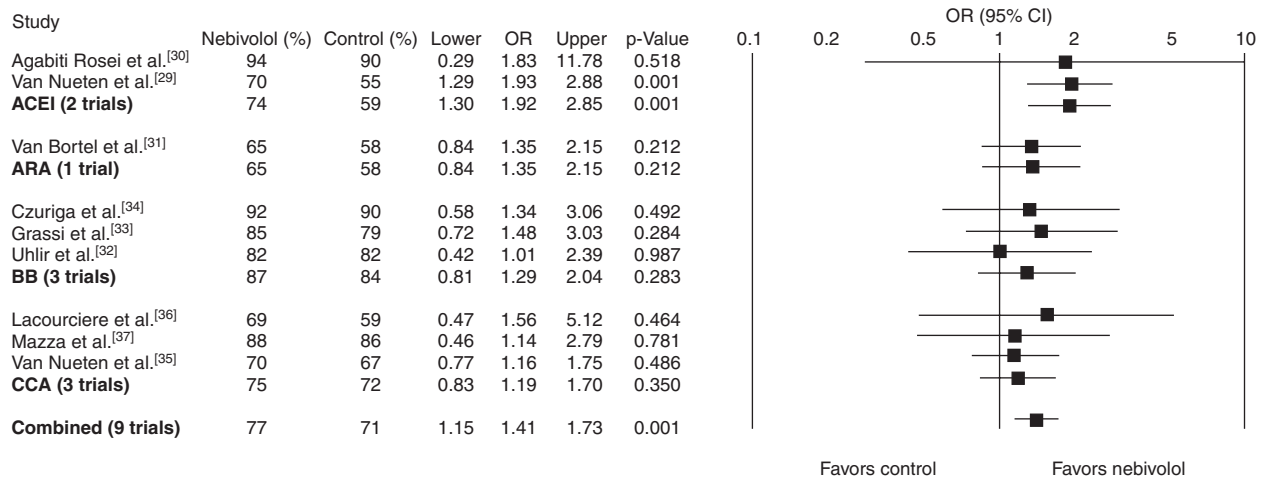
Table 1. Contd

- a All dosages were given once daily unless otherwise indicated.
- b Response rate definitions used in individual studies: percentage of patients with SBP/DBP  $\leq 140/90$  mmHg or RedDBP  $\geq 10$  mmHg;<sup>[30]</sup> percentage of patients with SBP/DBP  $< 140/90$  mmHg or RedDBP  $\geq 10$  mmHg;<sup>[33,37]</sup> percentage of patients with DBP  $\leq 90$  mmHg or RedDBP  $\geq 10$  mmHg;<sup>[27,29,31,34,35]</sup> percentage of patients with DBP  $< 90$  mmHg or RedDBP  $\geq 10$  mmHg;<sup>[36]</sup> percentage of patients with DBP  $\leq 90$  mmHg or RedDBP  $> 10\%$  relative to baseline.<sup>[26,32]</sup>
- c Normalization rate definitions used in individual studies: percentage of patients with SBP/DBP  $< 140/90$  mmHg;<sup>[33,37]</sup> percentage of patients with SBP/DBP  $\leq 140/90$  mmHg;<sup>[30]</sup> percentage of patients with DBP  $\leq 90$  mmHg;<sup>[28,31,32,34,35]</sup> percentage of patients with DBP  $< 90$  mmHg.<sup>[36]</sup>
- d Mean age across all patients.
- e Supine BP.
- f At trough drug level.
- g  $p < 0.05$  vs comparator.
- h Only DBP data provided.
- i Hydrochlorothiazide 12.5 mg/day was administered to nonresponders (BP  $\geq 140/90$  mmHg and RedDBP  $< 10$  mmHg) after 4 weeks.
- j  $p < 0.05$  vs baseline.
- k Hydrochlorothiazide 12.5 mg/day was administered to non-normalized patients (DBP  $> 90$  mmHg) after 6 weeks.
- l Estimated from graph.
- m Hydrochlorothiazide 12.5 mg/day was administered to nonresponders after 8 weeks.
- n Nebivolol 2.5 mg/day was also administered. Cumulative data are reported. Hydrochlorothiazide 6.25–25 mg/day was administered to non-normalized responders (BP  $\geq 140/90$  mmHg and RedDBP  $\geq 10$  mmHg) after 8 weeks.

**AE** = adverse event; **bid** = twice daily; **db** = double-blind; **mc** = multicenter; **NR** = not reported; **pc** = placebo-controlled; **pg** = parallel group; **r** = randomized; **RedDBP** = reduction in diastolic blood pressure; **sb** = single-blind; **SR** = sustained-release.

Another important determinant of patient compliance is the occurrence of drug-induced adverse events.<sup>[21,39]</sup> This is of particular importance in hypertension, because some patients with mild-to-moderate hypertension may be asymptomatic. Adverse events may, therefore, negatively influence the quality of life and drug adherence. In contrast, treatment-related adverse events may have less impact on quality of life in patients with symptomatic disease. Although the studies with nebivolol were up to 3 months' duration only, this meta-analysis indicates that nebivolol is associated with a similar level of adverse events to placebo and similar or better tolerability than other antihypertensive drug classes. As with any treatment selection, the individual benefit-risk ratio should be considered when prescribing. In the SOLVD (Studies of Left Ventricular Dysfunction) study<sup>[40]</sup> of patients with heart failure, the percentage of patients with cough was higher with enalapril than placebo (5% vs 2%) and the percentage of patients discontinuing the drug because of cough was also higher ( $p < 0.0001$ ) in the treated than placebo group. The rates of reported cough were low in this study, most likely because pulmonary edema-induced cough as a result of heart failure was largely replaced by ACE inhibitor-induced cough after treatment. In contrast, in patients with asymptomatic hypertension, ACE-inhibitor induced cough may be less well tolerated and can adversely impact quality of life. In a double-blind study<sup>[41]</sup> investigating quality-of-life issues in patients with mild-to-moderate hypertension, carvedilol and the ACE inhibitor enalapril provided similar BP lowering but a significantly greater incidence of cough was reported in the enalapril group (12% vs 0% with carvedilol;  $p < 0.001$ ). The favorable tolerability profile of nebivolol compared with other antihypertensive drugs in general, and to other  $\beta$ -blockers in particular in this analysis, confirms the results of a recent meta-analysis that showed better tolerability with nebivolol than with other cardioselective  $\beta$ -blockers<sup>[13]</sup> strongly suggesting that  $\beta$ -blockers are not all equal. The present study also supports the results of quality-of-life studies with nebivolol, showing no difference in general well-being with nebivolol therapy versus placebo<sup>[26]</sup> and losartan.<sup>[31]</sup> Nebivolol does not deteriorate particular aspects of quality of life such as erectile function in men<sup>[31,42-44]</sup> and endurance exercise performance in physically active individuals,<sup>[45,46]</sup> which further supports the view that nebivolol is not a classic  $\beta$ -blocker.

Apart from good antihypertensive potency, antihypertensive drugs should also have a steady antihypertensive effect during the full dosing interval. This view is supported by the fact that treatment with amlodipine, a long-acting drug, has shown lower mortality than atenolol.<sup>[4]</sup> In this respect the trough-to-peak ratio, which is the ratio between the smallest and the largest antihypertensive effect, is important. The trough-to-peak ratio for the antihypertensive effect of nebivolol 5 mg once daily is high: 89%<sup>[27]</sup>

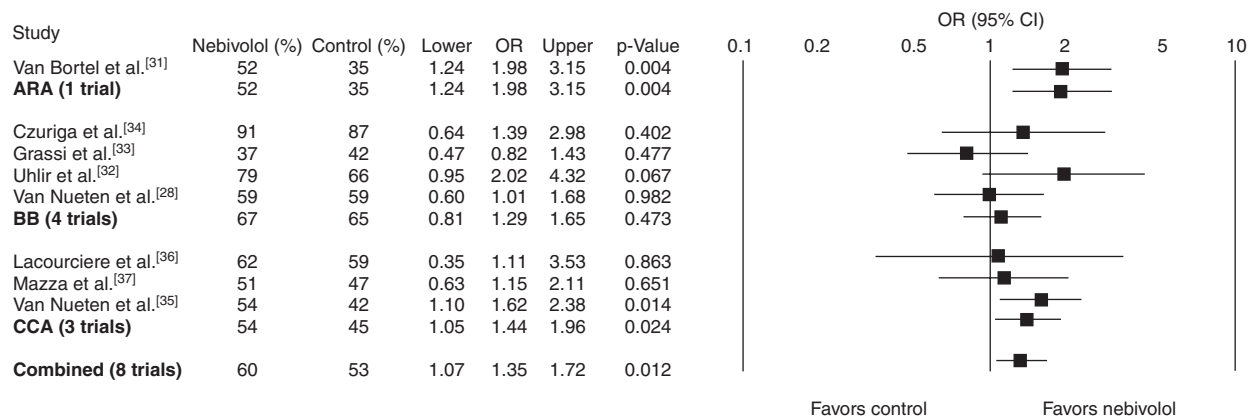


**Fig. 1.** Percentage of responder patients to nebivolol compared with other antihypertensive drugs.<sup>[29-37]</sup> **ACEI** = ACE inhibitors; **ARA** = angiotensin receptor antagonists; **BB** =  $\beta$ -adrenoceptor antagonists; **CCA** = calcium channel antagonists; **combined** = all studies combined; **control** = antihypertensive drug used as comparator drug in that study; **lower** = lower limit of 95% CI of OR; **OR** = odds ratio; **p-value** = p-value of difference between nebivolol and control; **upper** = upper limit of 95% CI of OR.

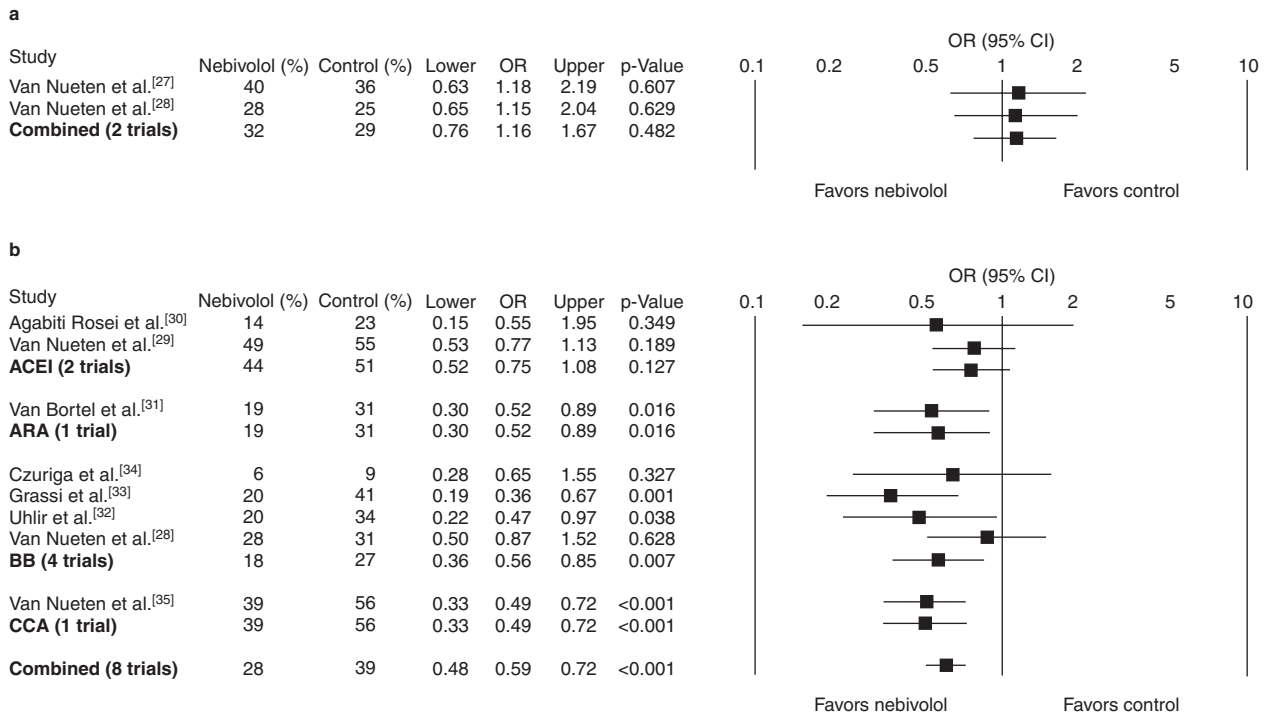
which means that a steady antihypertensive effect is maintained during the full 24-hour dosing interval. In contrast, atenolol has a trough-to-peak ratio of 46% and loses its antihypertensive effect dramatically in the last 6 hours of the 24-hour dosing interval.<sup>[47]</sup> This may, at least in part, explain why atenolol did not show a reduction in mortality<sup>[1]</sup> or why atenolol was associated with a smaller reduction in mortality than comparator drugs in the LIFE and ASCOT studies.<sup>[3,4]</sup> Short-acting antihypertensives can also be harmful because of dramatic changes in hemodynamic parameters such as BP and reflex tachycardia. The hemodynamic effects of nebivolol were compared with those of a short-acting, non-vasodilating  $\beta$ -blocker, metoprolol in patients with left ventricular (LV) systolic dysfunction/systolic heart failure.<sup>[48]</sup> Nebivolol 5 mg/day was associated with reduced systemic vascular resistance and no

deterioration in LV systolic function (as a result of vasodilatory properties) and none of the adverse hemodynamic effects associated with metoprolol in this population.<sup>[48]</sup> Short-acting  $\beta$ -blockers can also produce harmful withdrawal effects with increased sympathetic tone; such withdrawal effects were lower or not observed with long-acting  $\beta$ -blockers.<sup>[49]</sup> These withdrawal effects are not expected with the newer  $\beta$ -blockers such as nebivolol, metoprolol succinate, and carvedilol because of their longer duration of action.

The National Institute for Health and Clinical Excellence (NICE)<sup>[50]</sup> has advocated that  $\beta$ -blockers should be dropped as first-line antihypertensive drugs. Also, the 2007 American Heart Association hypertension guidelines<sup>[19]</sup> state that  $\beta$ -blockers should be reserved primarily for patients with compelling indica-



**Fig. 2.** Percentage of patients with normalized BP treated with nebivolol and other antihypertensive drugs.<sup>[28,31-37]</sup> **ARA** = angiotensin receptor antagonists; **BB** =  $\beta$ -adrenoceptor antagonists; **CCA** = calcium channel antagonists; **combined** = all studies combined; **control** = antihypertensive drug used as comparator drug in that study; **lower** = lower limit of 95% CI of OR; **OR** = odds ratio; **p-value** = p-value of difference between nebivolol and control; **upper** = upper limit of 95% CI of OR.

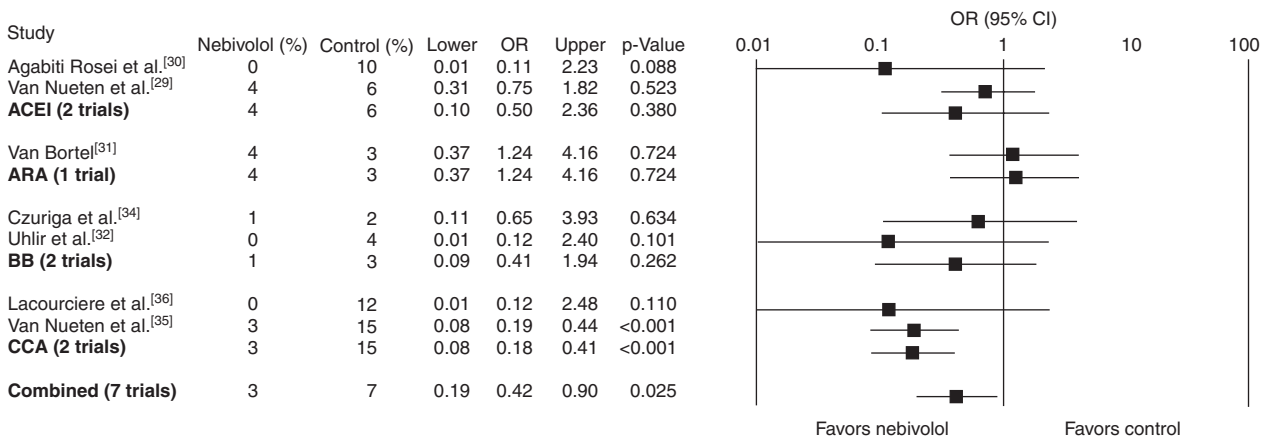


**Fig. 3.** Percentage of patients with adverse events to nebivolol compared to placebo (a) and other antihypertensive drugs (b).<sup>[27-35]</sup> **ACEI** = ACE inhibitors; **ARA** = angiotensin receptor antagonists; **BB** =  $\beta$ -adrenoceptor antagonists; **CCA** = calcium channel antagonists; **combined** = all studies combined; **control** = placebo or antihypertensive drug used as comparator drug in that study; **lower** = lower limit of 95% CI of OR; **OR** = odds ratio; **p-value** = p-value of difference between nebivolol and control; **upper** = upper limit of 95% CI of OR.

tions of angina or coronary artery disease and their use in other hypertensive patients could now be considered controversial. However, long-acting  $\beta$ -blockers have never been used as comparator drugs in outcome studies in patients with hypertension. It is, therefore, debatable whether  $\beta$ -blockers as a class should be dropped as first-line antihypertensive drugs or whether short-acting  $\beta$ -blockers only such as atenolol should be dropped. The

ongoing debate is witnessed by the fact that, in contrast to NICE, the 2007 European Society of Hypertension/European Society of Cardiology guidelines for the management of arterial hypertension recommends  $\beta$ -blockers as first-line antihypertensive drugs.<sup>[18]</sup>

As stated in the introduction, nebivolol is not a classic  $\beta$ -blocker; in addition to BP lowering via  $\beta$ -blockade, it is also thought to produce an antihypertensive effect by virtue of its



**Fig. 4.** Percentage of patients withdrawn because of an adverse event to nebivolol or active comparator drug.<sup>[29-32,34-36]</sup> **ACEI** = ACE inhibitors; **ARA** = angiotensin receptor antagonists; **BB** =  $\beta$ -blockers; **CCA** = calcium channel antagonists; **combined** = all studies combined; **control** = antihypertensive drug used as comparator drug in that study; **OR** = odds ratio; **p-value** = p-value of difference between nebivolol and control; **upper** = upper limit of 95% CI of OR.

vasodilating properties. It has been hypothesized that these properties, mediated via endothelial NO release, may also give nebivolol the ability to protect against atherosclerotic disease independent of BP-lowering effects. This was demonstrated in a comparison of the vasodilatory responses of nebivolol and atenolol. Although nebivolol and atenolol produced statistically similar reductions in seated BP, only nebivolol increased the vasodilatory response.<sup>[7]</sup> This finding also suggests that nebivolol may prove more effective in reducing the risk of cardiovascular events than atenolol, as demonstrated in the LIFE and the ASCOT studies.<sup>[3,4]</sup> In this respect, nebivolol is similar to other vasodilating  $\beta$ -blockers carvedilol and labetalol in that it has a favorable hemodynamic profile, whereas nonvasodilating  $\beta$ -blockers tend to produce unfavorable hemodynamic effects such as increased central aortic BP.<sup>[51]</sup> One hypothesis is that nebivolol slows atherogenesis because of its antioxidant effects,<sup>[12]</sup> improves endothelial function through NO release,<sup>[7]</sup> and inhibits smooth muscle cell proliferation.<sup>[52]</sup> Oxidative stress is an important causal feature of atherosclerosis and is elevated even in healthy individuals. Reducing oxidative stress, therefore, may protect against cardiovascular disease. A double-blind, crossover study in 12 healthy volunteers showed that nebivolol 5 mg/day for 7 days significantly decreased oxidative stress, assessed using 24-hour urinary excretion of 8-isoprostaglandin F<sub>2a</sub>, compared with placebo ( $p = 0.01$ ).<sup>[12]</sup> In a prospective, randomized study in 80 treatment-naïve patients with grade 1 hypertension, nebivolol 5 mg/day, but not metoprolol 100 mg/day, improved oxidative stress.<sup>[11]</sup> Other known cardiovascular risk factors – insulin sensitivity, adiponectin level and plasma soluble P-selectin levels – were also significantly improved with nebivolol treatment but not with metoprolol; neither treatment affected lipid parameters.<sup>[11]</sup> Nebivolol may reduce the risk of atherosclerotic plaque rupture by lowering the stress on the arterial wall<sup>[53]</sup> as a result of decreases in BP, stress frequency (heart rate), and arterial stiffness.<sup>[54]</sup> When a plaque has ruptured, nebivolol may help to decrease the formation of an occluding thrombus by the NO-mediated decrease in platelet aggregation.<sup>[55,56]</sup> Whether these postulated favorable effects at the three levels of atherosclerotic disease are of clinical relevance and would decrease mortality in hypertensive patients treated with nebivolol has yet to be proven.

The present study like all meta-analyses, based on published data, has some limitations. Because of the stringent inclusion criteria and the fact that studies were excluded by either of the two independent observers, the final number of studies included in the meta-analysis ( $n = 12$ ) and the total number of patients are small (~2700). It cannot be excluded that some relevant studies in languages other than English or published in journals not indexed in MEDLINE may have been missed. The designs of the studies

included in the meta-analysis were not homogeneous. In the majority of studies, recommended dosages were used. There were some differences in clinical endpoints – mean change in BP and response rates were most commonly used in older studies, but the clinical relevance of response, usually defined as achievement of target BP or a DBP reduction of  $\geq 10$  mmHg, has been questioned. Consequently, ongoing and planned studies usually include the more clinically relevant BP normalization or control rates as endpoints, but many clinical efficacy studies still use response rates so that they can compare efficacy indirectly with published trials. The current meta-analysis is based on response, BP normalization, and adverse event rates at the end of the study, not on the change from baseline. Hence, the data were not baseline corrected. This could introduce some errors, particularly in the reported results of individual studies. The use of concomitant thiazide medication also varied among studies. In three studies, hydrochlorothiazide 12.5 mg once daily was added to non-normalized patients during the double-blind treatment period. In the nebivolol versus atenolol study,<sup>[33]</sup> hydrochlorothiazide 12.5 mg was added in both arms in 23% and 20% of patients, respectively, and is presumed to have very limited or no influence at all on the comparison between the drugs. In contrast, in the nebivolol versus losartan study,<sup>[31]</sup> hydrochlorothiazide 12.5 mg was added to more losartan (57%) than nebivolol (40%) recipients; and in the nebivolol versus amlodipine study,<sup>[37]</sup> hydrochlorothiazide 6.25–25 mg/day was added to more recipients of nebivolol (20%) than amlodipine (9%). One study<sup>[34]</sup> was not double-blind and may, therefore, introduce some bias; however, its results were not different from the other studies with comparator drugs of the same class.

## Conclusion

This meta-analysis revealed that the long-acting vasodilating  $\beta$ -blocker nebivolol 5 mg once daily had a high antihypertensive efficacy at least as effective as other agents and more effective than older nonvasodilating  $\beta$ -blockers. Nebivolol 5 mg/day also demonstrated equal or better tolerability than recommended daily doses of other antihypertensive drugs, a property expected to result in improved adherence to long-term therapy. Nebivolol has antihypertensive effects beyond  $\beta$ -blockade and may also have additional cardiovascular protecting properties independent of BP-lowering efficacy, but these remain to be demonstrated in controlled clinical trials. Although not definitive, this meta-analysis suggests that nebivolol 5 mg/day is likely to have advantages over existing antihypertensives and, unlike older short-acting nonvasodilating  $\beta$ -blockers, may have a role in first-line treatment of hypertension and in the prevention of cardiovascular events.

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