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Nebivolol

A Review of its Use in the Management of Hypertension and Chronic Heart Failure

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Data Selection

Sources: Medical literature published in any language since 1980 on 'nebivolol', identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Adis International). 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 Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.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: MEDLINE, EMBASE and AdisBase search terms were 'nebivolol'. Searches were last updated 3 July 2006.

Selection: Studies in patients with hypertension or heart failure 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: Nebivolol, hypertension, heart failure, pharmacodynamics, pharmacokinetics, therapeutic use, tolerability.

Contents

Summary

Abstract

Nebivolol is a third-generation β-adrenoceptor antagonist. It differs from other β-adrenoceptor antagonists as it combines highly selective β_1-adrenoceptor antagonist properties with nitric oxide-mediated vasodilatory actions and beneficial effects on endothelial function. Nebivolol is approved in Europe and several other countries for the treatment of essential hypertension and in Europe for the treatment of stable mild or moderate chronic heart failure (CHF) in addition to standard therapies in elderly patients aged ≥70 years.

Nebivolol is an effective antihypertensive agent and is well tolerated in patients with hypertension. The drug also effectively decreased the composite endpoint of mortality and cardiovascular hospital admission in elderly patients with CHF and was generally well tolerated in this population. Nebivolol should be considered as an alternative first-line treatment option for patients with uncomplicated mild to moderate essential hypertension and in elderly patients with CHF.

Pharmacological Properties

Nebivolol is a highly selective β_1-adrenoceptor antagonist that also causes vasodilation via interaction with the endothelial L-arginine/nitric oxide pathway. The drug appears to increase nitric oxide production and release, and to decrease nitric oxide degradation. Nebivolol lowers heart rate and blood pressure (BP), and improves systolic and diastolic function. Nitric oxide-mediated effects of nebivolol include decreasing systemic vascular resistance and large artery stiffness, and nebivolol may also reverse endothelial dysfunction.

Following oral administration, nebivolol is rapidly absorbed. Although metabolism of nebivolol to its numerous metabolites can vary substantially between extensive and poor metabolisers, resulting in a wide range of bioavailability, there appears to be little difference in the clinical outcome between different types of metabolisers.

Dosage adjustments are recommended in patients with renal impairment and a lower starting dosage is recommended for elderly patients. Nebivolol is contraindicated in patients with hepatic impairment.

Therapeutic Efficacy

In randomised, double-blind, parallel-group studies in patients with mild to moderate essential hypertension, nebivolol was at least as effective at lowering BP as other antihypertensive drugs, including other β-adrenoceptor antagonists.

Nebivolol was more effective than placebo in lowering the incidence of the primary composite endpoint of all-cause mortality or cardiovascular hospitalisation in SENIORS (Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure), a study in elderly patients (aged ≥70 years) with CHF. A significantly greater improvement in left ventricular ejection fraction in nebivolol versus placebo recipients was also seen in elderly patients with CHF in the ENECA (Efficacy of Nebivolol in the treatment of Elderly patients with Chronic heart failure as Add-on therapy to ACE inhibitors or angiotensin II receptor blockers, diuretics, and/or digitalis) study and a substudy of SENIORS.

Tolerability

Nebivolol was equally or better tolerated than comparator agents in hypertension trials. The most frequent adverse events in recipients of nebivolol monotherapy were transient headache, dizziness and tiredness.

In elderly patients with CHF, the incidence of most adverse events was similar in nebivolol and placebo recipients. Bradycardia was one of the most common adverse events in nebivolol recipients, but not in placebo recipients.

1. Introduction

β-Adrenoceptor antagonists have held a well established place in the management of hypertension for many years,[1] although recently this has been called into question.[2,3] Several β-adrenoceptor antagonists are also recommended for use in patients with chronic heart failure (CHF).[4] Individual β-adrenoceptor antagonists are distinguished by their selectivity for β_1- or β_2- (and sometimes α-) adrenoceptors and some have other effects such as intrinsic sympathomimetic activity or peripheral vasodilation.[4]

The use of nebivolol, a lipophilic, third-generation β-adrenoceptor antagonist, in the management of essential hypertension has been reviewed previously in *Drugs*.[1] This review provides an update on its use in hypertension and also discusses the potential role of nebivolol in the management of CHF.

2. Pharmacodynamic Properties

This section provides an overview of the mechanism of action of nebivolol and summarises the main pharmacodynamic effects of nebivolol related to the treatment of hypertension and heart failure.

2.1 Mechanism of Action and Receptor Binding

Nebivolol has a dual mechanism of action: it is a selective β_1-adrenoceptor antagonist and it also causes vasodilation via the release of nitric oxide from endothelial cells.[5-8] It is a racemic mixture with equal amounts of *d*- and *l*-nebivolol.[5] Both isomers contribute to the antihypertensive action of the drug; the *d*-isomer is responsible for the β_1-adrenoceptor antagonist activity and both isomers, but particularly *l*-nebivolol,[9] contribute to the vasodilatory action.[6]

Nebivolol binds to β_1-adrenergic receptors with high affinity and selectivity.[7] It is the most selective β_1-adrenoceptor antagonist available. The β_1-adrenoceptor selectivity $[K_i(\beta_2)/K_i(\beta_1)]$ for nebivolol in human myocardium is 40.7.[10] Nebivolol has negligible effects on α_1- or α_2-adrenoceptors,[5] and is devoid of intrinsic sympathomimetic activity or membrane stabilising activity.[7]

The vasodilatory actions of nebivolol occur via interaction with the endothelial L-arginine/nitric oxide pathway.[6] Studies in animals, in healthy volunteers and in patients with hypertension show that nebivolol induces nitric oxide synthase expression, which leads to the production and release of nitric oxide (reviewed by Ignarro[11] and Zanchetti[8]). It

Table I. Overview of the main pharmacodynamic effects of nebivolol

Effect	Subject/study type	References
Cardiovascular effects		
↓ BP	Patients with hypertension	19-22
↓ Heart rate	Patients with hypertension	23-31
↑ LVEF (improvement of systolic function)	Patients with CHF	32,33
	Patients with NIDC	34,35
↑ E/A ratio (improvement of diastolic function)	Patients with hypertension and LV diastolic dysfunction	36
↑ Stroke volume	Patients with hypertension	37
Maintenance of cardiac output	Patients with hypertension	36-38
↓ LV mass	Patients with hypertension	39
Effects of increased nitric oxide availability		
↑ Vasodilation, ↓ vascular resistance	Patients with hypertension	38
Improves endothelial function (reverses endothelial dysfunction)	Patients with hypertension	40
↓ Large artery stiffness	Patients with hypertension	41
↓ Platelet aggregation	*In vitro*	42
↓ Smooth muscle proliferation	*In vitro*	43
Effects during exercise		
No effect on plasma concentrations of nebivolol	Healthy volunteers	44
No effect on exercise capacity or oxygen consumption	Healthy volunteers	45
	Patients with hypertension	46
↑ Exercise duration after initial ↓	Patients with NIDC	34
Effects on airway function		
No effect on airway patency	Patients with hypertension and asthma or COPD	47,48
↑ Peak respiratory flow	Patients with hypertension	49
Metabolic effects		
No effect on glucose or lipid metabolism, or insulin sensitivity	Patients with hypertension	50,51
	Patients with hypertension and type 2 diabetes mellitus	52
	Patients with hypertension and impaired glucose tolerance	53
↑ Insulin sensitivity (↓ insulin resistance index)	Patients with hypertension	54
↓ Total cholesterol	Patients with hypertension	55

BP = blood pressure; **CHF** = chronic heart failure; **COPD** = chronic obstructive pulmonary disease; **E/A** = ratio of early to late atrial peak filling velocity; **LV** = left ventricular; **LVEF** = LV ejection fraction; **NIDC** = nonischaemic dilated cardiomyopathy; ↑ indicates increase; ↓ indicates decrease.

appears that nebivolol also has a complementary anti-oxidative stress action, which leads to a decrease in nitric oxide degradation, thereby also contributing to increased nitric oxide bioavailability.[8,11]

The cellular mechanisms for the increase in nitric oxide bioavailability are not yet fully understood (reviewed by Kuroedov et al.[7]). Several mechanisms have been proposed, including agonist effects at β_2-adrenoceptors,[12,13] β_3-adrenoceptors,[14-16] serotonin 5-HT_{1A} receptors,[17] or interaction with estrogen receptor-mediated pathways.[18]

2.2 Cardiovascular Effects

The blood pressure (BP)-lowering effect of nebivolol is well established (table I). This effect is also seen in patients with concomitant hypertension and diabetes mellitus, and in smokers.[52,56,57] The administration of nebivolol plus hydrochlorothiazide resulted in additive dose-related reductions in

BP.[22] The comparative efficacy of nebivolol versus other antihypertensive agents in patients with hypertension is discussed in section 4.1.1.

Like other β-adrenoceptor antagonists, administration of nebivolol results in a decrease in heart rate (table I). In patients with hypertension, resting heart rate was decreased to a similar extent by nebivolol and other β-adrenoceptor antagonists (bisoprolol, metoprolol, atenolol[23-26]) and to a significantly greater extent by nebivolol than by enalapril, losartan, amlodipine or nifedipine retard[28-31] in studies of 4–12 weeks' duration. A 12-week study of nebivolol versus lisinopril found that heart rate was significantly ($p < 0.05$) lower in the nebivolol group after 8 weeks (66.7 vs 70.4 beats/min), but the between-group difference was not significant after 12 weeks (66.5 vs 70.4 beats/min); however, this was a small study ($n = 65$) and it may have lacked the statistical power to show a difference.[27]

Nebivolol administration significantly improves systolic left ventricular (LV) function, measured by the increase in LV ejection fraction (LVEF) from baseline (table I and section 4.2.2).[32-35] In a small study ($n = 72$) comparing the effects of nebivolol with those of carvedilol on LV function in patients with nonischaemic dilated cardiomyopathy (NIDC), LVEF increased significantly in both treatment groups after 12 months; however, the percentage increase from baseline in LVEF was significantly greater in carvedilol recipients than in nebivolol recipients (35.5% vs 20.7%; $p = 0.02$).[34]

Other studies in patients with hypertension (table I) indicated that nebivolol resulted in significantly greater improvements in diastolic function (measured by the ratio of early to late atrial peak filling velocity [E/A ratio])[36] and increases in stroke volume[37] than atenolol, maintenance of cardiac index[38] or significantly smaller reductions in cardiac output or cardiac index than atenolol,[36,37] and similar reductions in LV mass versus telmisartan.[39]

2.3 Effects of Increased Nitric Oxide Availability

Numerous *in vitro*, animal and human studies have shown that nebivolol causes vasodilation by increasing the availability of nitric oxide at the vascular endothelium (reviewed by Ignarro[11] and Zanchetti[8]).

Systemic vascular resistance is significantly reduced with nebivolol (table I), and this contributes to the BP-lowering effect.[8] Nebivolol decreased systemic vascular resistance significantly ($p < 0.05$) more than bisoprolol in hypertensive patients (≈7% vs ≈2% reduction from baseline), although both drugs reduced BP to a similar extent (both $p < 0.01$ vs baseline).[38]

Nebivolol appears to reverse endothelial dysfunction and also decrease arterial stiffness in patients with hypertension (table I). Endothelial dysfunction, which is characterised by decreased nitric oxide availability, is associated with a number of conditions, including hypertension, diabetes and hypercholesterolaemia.[6,8] It has also been associated with an increased incidence of cardiovascular (CV) events,[8] as has large artery stiffness.[58,59]

The improvement of endothelial function may be particularly important in Black patients. In endothelial cells pretreated with nebivolol, the lower baseline levels of nitric oxide availability in cells from Black patients were increased to levels similar to those in cells from White patients.[60]

Inhibition of platelet aggregation[42] and inhibition of proliferation of smooth muscle cells,[43] which are both mediated by nitric oxide, were significantly increased by nebivolol *in vitro* (table I).

2.4 Effects During Exercise and on Airway Function

Nebivolol does not adversely affect exercise haemodynamics (table I). In hypertensive patients, maximal work capacity and relative oxygen uptake did not change significantly after 6 weeks of nebivolol 5 mg/day ($n = 18$).[46] Compared with placebo, healthy volunteers who received atenolol had a significantly lower maximal workload (263 vs 251W; $p < 0.02$), maximum oxygen consumption (3.40 vs 3.22 L/min; $p < 0.03$) and submaximal endurance time (65 vs 50 min; $p < 0.001$); there were no significant changes in nebivolol recipients ($n = 21$).[45]

In patients with NIDC (n = 72), exercise duration was significantly longer than at baseline after 12 months' treatment with nebivolol (994 vs 894s at baseline) or carvedilol (1124 vs 982s at baseline) [both p = 0.01], despite an initial decrease (not significant versus baseline) in the nebivolol group at 3 months (p = 0.002 vs carvedilol).[34] Exercise duration also decreased significantly (p = 0.01) in nebivolol recipients compared with placebo recipients after 3 months in another study in patients with NIDC (n = 60).[35]

Similar to the reduction in resting heart rate, exercise heart rate decreased significantly from baseline in hypertensive patients who received nebivolol (146.72 vs 168.11 beats/min at baseline; p = 0.0001).[46] In healthy volunteers, both atenolol and nebivolol significantly reduced exercise heart rate compared with placebo (94 and 102 vs 121 beats/min; both p < 0.05 vs placebo); however, exercise heart rate was significantly lower in atenolol than in nebivolol recipients (p < 0.05).[45] Nebivolol and carvedilol reduced exercise heart rate to a similar extent in patients with NIDC (both p < 0.05 vs baseline).[34]

Other β-adrenoceptor antagonists are taken up into adrenergic cells and are released during exercise, resulting in increased plasma concentrations of these drugs during exercise.[44] This effect was not seen with nebivolol or carvedilol (table I).[44]

Unlike nonselective β-adrenoceptor antagonists, which may cause airway obstruction due to antagonist activity at β_2-adrenoceptors, nebivolol did not affect airway patency in patients with hypertension and asthma or chronic obstructive pulmonary disease (COPD) [table I].[47,48] In patients with hypertension, peak respiratory flow increased significantly from baseline after 12 weeks of nebivolol (458.9 vs 448.9 L/min; p < 0.01).[49]

2.5 Metabolic Effects

In contrast to some other β-adrenoceptor antagonists, nebivolol does not adversely affect glucose or lipid metabolism (table I). In patients with hypertension and impaired glucose tolerance, insulin sensitivity was significantly (p < 0.01) reduced in atenolol recipients, but not in nebivolol recipients, compared with placebo.[53] In another study in hypertensive patients with no established insulin resistance, nebivolol, but not metoprolol, significantly improved insulin sensitivity.[54]

A marked increase in plasma triglycerides in two patients who received nebivolol was reported in one study,[28] but this has not been reported elsewhere.

3. Pharmacokinetic Properties

The pharmacokinetics of nebivolol have been reviewed previously.[1] This summary is based on crossover, placebo-controlled studies in healthy volunteers (n = 12)[61] or hypertensive patients (n = 15),[62] a nonblind study in obese and non-obese volunteers (n = 18),[63] reviews[1,64,65] and the UK prescribing information.[66] Pharmacokinetic data on special patient populations and data on drug interactions are mainly from studies in healthy volunteers (reported as abstracts only).[67-75]

Nebivolol is rapidly absorbed following oral administration (food does not affect absorption[66]). The unchanged nebivolol mean peak plasma concentration (C_{max}) of 1.48 ng/mL was reached 1 hour after a single dose of oral nebivolol 5mg in healthy volunteers who were classified as extensive metabolisers of nebivolol.[61] The area under the plasma concentration-time curve (AUC) was 7.76 ng • h/mL. The C_{max} values for *d*- and *l*-nebivolol plus their hydroxylated metabolites were 7.3 and 13.1 ng/mL and they were reached at 2.5 and 2.6 hours following a single oral dose of nebivolol 5mg in patients with essential hypertension (n = 15).[62] The corresponding AUC_{24} values were 65 and 109 ng • h/mL.[62]

Generally, steady-state plasma concentrations are reached within 1 day for nebivolol and within a few days for the active metabolites.[66] The nebivolol isomers are both highly bound (≈98%) to plasma proteins (predominantly to albumin).[66] A study in obese patients reported that the clearance and volume of distribution of unchanged nebivolol at steady state (Vd_{ss}) were increased compared with non-obese patients; however, when expressed per kilo-

gram of bodyweight, there was no significant between-group difference for Vd_{SS}.[63]

Nebivolol metabolism is extensive and results in the formation of numerous metabolites, some of which are active.[64,66] Individuals can be either poor (slow) or extensive (fast) metabolisers, and this results in substantial differences in plasma concentrations of unchanged nebivolol and active hydroxy metabolites between these patient groups.[66] The bioavailability of nebivolol varies from 12% in extensive metabolisers to 96% in poor metabolisers.[64] However, the lower concentration of unchanged drug in extensive metabolisers appears to be compensated for by substantial formation of active hydroxy metabolites, which means there is little clinical difference in outcome between different types of metabolisers.[1,64]

Clearance and elimination half-life ($t_{1/2}$) of nebivolol vary between extensive and poor metabolisers.[64] In healthy volunteers, the clearance was 30 L/h in poor metabolisers and 111 L/h in extensive metabolisers following a single oral dose of nebivolol 5mg (or 0.5mg intravenously).[64] The $t_{1/2}$ values were 27 and 8 hours, respectively.[64]

One week after administration of nebivolol, 38% of the dose was excreted in the urine and 48% was excreted in the faeces; <0.5% of the dose was excreted in the urine as unchanged nebivolol.[64,66]

3.1 Special Patient Populations

The mean AUC was 48.99 ng • h/mL in eight patients with moderate hepatic impairment compared with 11.18 ng • h/mL in eight healthy volunteers after a single dose of nebivolol 5mg.[67] Nebivolol is contraindicated in patients with hepatic impairment (section 6).[66]

The apparent clearance of nebivolol was lower in patients with severe renal impairment than in healthy volunteers (416 vs 891 L/h).[68] Dosage adjustments are recommended in patients with renal impairment (section 6).[66]

Although the pharmacokinetics of nebivolol are not influenced by age, a reduction in starting dosage is recommended for elderly patients (section 6).[66]

3.2 Drug Interactions

Coadministration of fluoxetine (repeat administration) or cimetidine increases the plasma concentration of nebivolol.[65,69] When nebivolol is administered with nicardipine, plasma concentrations of both drugs are increased slightly.[65] Nebivolol has no effect on the pharmacokinetics of digoxin, warfarin, losartan, spironolactone, ramipril or furosemide, and losartan, ramipril, furosemide, antacids, ranitidine, alcohol and hydrochlorothiazide have no effect on the pharmacokinetics of nebivolol.[65,70-75]

4. Therapeutic Efficacy

4.1 In Hypertension

The antihypertensive efficacy of nebivolol has been well established in placebo-controlled trials and has been reviewed previously.[1] A number of randomised, double-blind, comparative trials have evaluated the efficacy of nebivolol compared with other antihypertensive agents; only studies with >60 patients that have been published in full are discussed in detail in this review.[23-31]

The active comparator trials followed similar protocols; there was a 2- to 4-week washout and/or single-blind placebo period, during which other antihypertensive medications were withdrawn, followed by a double-blind treatment phase that lasted 4–12 weeks.[23-31]

Most of the trials included patients with mild to moderate essential hypertension.[23-27,29,30] This was generally defined as diastolic BP (DBP) 95–114mm Hg after the placebo/washout period, although exact definitions varied between trials. Patient numbers ranged from 65 to 420. The two largest studies included only patients with DBP >94mm Hg.[28,31] The mean patient age ranged from ≈49 to 56 years,[23-29,31] except for one study in elderly patients with a mean age of 70 (range 65–89) years.[30]

Nebivolol was administered at the recommended dosage of 5mg once daily (section 6) in most of the studies. Several studies allowed additional treatment with hydrochlorothiazide if a specified level of BP

reduction was not achieved with nebivolol alone.[24,27,30]

The active comparator trials compared nebivolol with other β-adrenoceptor antagonists,[23-26] ACE inhibitors,[27,28] angiotensin II receptor antagonists[29] or calcium channel antagonists.[30,31]

The primary endpoint in most of the trials was change in BP[24,29,30] (or change in DBP[26-28,31]). Secondary efficacy endpoints included response rates (primary endpoint in some trials[23,25,27,30]), and standing systolic BP (SBP) and DBP.

Most of the trials analysed data using an intent-to-treat (ITT) approach.[26-29] Some used a per-protocol analysis,[24] some used both,[23,30] and some did not state the approach used.[25,31] ITT analysis results are reported if available.

An extension of a 12-week randomised, double-blind, multicentre trial of nebivolol versus enalapril[28] compared a further 7-months' double-blind treatment with nebivolol or enalapril.[76] The primary endpoint was sitting DBP at trough.[76]

4.1.1 Blood Pressure

Comparisons with Other β-Adrenoceptor Antagonists

Nebivolol was as effective as the β-adrenoceptor antagonists bisoprolol, atenolol and metoprolol at lowering BP (table II). All treatment groups experienced a statistically significant reduction ($p < 0.05$) in BP from baseline levels; however, the change in BP was not significantly different between groups.[23-26]

Comparisons with Other Antihypertensive Agents

Nebivolol was at least as effective as other classes of antihypertensive agents at lowering BP (table III). BP decreased substantially from baseline in all treatment groups.[27-31] The reduction in BP from baseline was similar in recipients of nebivolol, lisinopril, amlodipine and nifedipine retard.[27,30,31]

Compared with enalapril, the change in DBP was significantly greater in nebivolol recipients by 12 weeks (table III).[28] However, in a subset of patients who continued treatment for a further 7 months, BP did not change appreciably throughout the 7 months and there was no significant difference in BP reduction between nebivolol and enalapril recipients at

Table II. Efficacy of nebivolol (NEB) compared with other β-adrenoceptor antagonists. Summary of randomised, parallel-group, multicentre trials with NEB and bisoprolol (BIS), atenolol (ATE) or metoprolol (MET) in patients (pts) with hypertension. All trials were double-blind except Czuriga et al.,[23] which was single-blind. All trials had a 4-week placebo (PL) run-in period

Study	Regimen (mg) [duration; wk]	No. of pts evaluated	Mean sitting SBP/DBP (mm Hg)		Responders (%)[a]
			baseline	reduction at endpoint[b]	
Czuriga et al.[23]	NEB 5 od [12]	138	153/99	20.5/15.7	90.6[c]
	BIS 5 od [12]	135	153/100	20.0/16.0	87.4[c]
Grassi et al.[24]	NEB 5 od[d] [12]	105	157.3/100.4	19.1[c]/14.8[c]	37.0[e]
	ATE 100 od[d] [12]	100	155.2/100.5	18.2[c]/14.6[c]	41.7[e]
Uhlir et al.[25]	NEB 5 od [12]	73	160/106	20/17	79.5*[c]
	MET 100 bid [12]	67	157/107	15/16	65.6[c]
Van Nueten et al.[26]	NEB 5 od [4]	119	167[f]/101[f]	16†[f]/12†[c,f]	59†
	ATE 50 od [4]	121	169[f]/102[f]	17†[f]/11†[c,f]	59†
	PL	124	169[f]/102[f]	6[f]/4.5[c,f]	29

a Defined as achieving DBP normalisation (≤90mm Hg)[23,25,26] or BP of <140/90mm Hg.[24]

b All decreases from baseline to study endpoint in SBP and DBP were statistically significant ($p < 0.05$) in active treatment groups.

c Primary endpoint.

d Plus hydrochlorothiazide 12.5 mg/day if BP ≥140/90mm Hg or DBP reduction ≤10mm Hg at 8 weeks (23% of NEB recipients and 20% of ATE recipients).

e Statistical analysis not reported.

f Value estimated from graph.

bid = twice daily; **BP** = blood pressure; **DBP** = diastolic BP; **od** = once daily; **SBP** = systolic BP; * $p < 0.05$ vs MET; † $p < 0.001$ vs PL.

Table III. Efficacy of nebivolol (NEB) compared with antihypertensive agents other than β-adrenoceptor antagonists. Summary of randomised, double-blind, parallel-group, multicentre, 12-week trials with NEB and lisinopril (LIS), enalapril (ENA), losartan (LOS), amlodipine (AML) or nifedipine retard (NIF) in patients (pts) with hypertension

Study	Regimen (mg)	No. of pts evaluated	Mean sitting SBP/DBP (mm Hg)		Responders at endpoint (%)[b]
			baseline	reduction at endpoint[a]	
ACE inhibitors					
Rosei et al.[27]	NEB 5 od[c]	35	159.3/101.0	27.3/18.9[d]	94[d]
	LIS 20 od[c]	30	156.4/98.6	21.8/16.8[d]	90[d]
Van Nueten et al.[28]	NEB 5 od	208	162[e]/104.6*	15[e]/12.3**[d]	70**
	ENA 10 od	211	163[e]/105.5	12[e]/9.9[d]	55
Angiotensin II receptor antagonist					
Van Bortel et al.[29]	NEB 5 od	147	166/103	15[d]/12*[d]	65.3
	LOS 50 od	151	165/102	18[d]/10[d]	58.3
Calcium channel antagonists					
Mazza et al.[30]	NEB 2.5–5 od[f]	81	163[e]/100[e]	23[de]/16[d,e]	88
	AML 5–10 od[f]	87	164[e]/101[e]	25[de]/16[d,e]	86
Van Nueten et al.[31]	NEB 5 od	211	159[e]/104.2	13[e]/11.7[d]	70
	NIF 20 bid	209	160[e]/104.5	15[e]/10.9[d]	67

a Decreases in BP from baseline to study endpoint were statistically significant ($p < 0.05$) in active treatment groups where reported.[27,29,31] Statistical significance for changes from baseline were not reported in some trials.[28,30]

b Pts with BP ≤140/90mm Hg[27] or <140/90mm Hg[30] or reduction in DBP ≥10mm Hg,[27,30] or DBP ≤90mm Hg or reduction in DBP ≥10mm Hg.[28,29,31]

c Plus hydrochlorothiazide 12.5 mg/day if BP >140/90mm Hg or change in DBP <10mm Hg after 4, 8 or 12wk (19.4% of NEB recipients and 15.6% of LIS recipients).

d Primary endpoint.

e Value estimated from graph.

f Plus hydrochlorothiazide 6.25–25 mg/day if BP ≥140/90mm Hg and decrease in DBP ≥10mm Hg after 8wk (20% of NEB recipients and 9% of AML recipients).

bid = twice daily; **BP** = blood pressure; **DBP** = diastolic BP; **od** = once daily; **SBP** = systolic BP; * $p < 0.05$, ** $p < 0.01$ vs comparator.

the end of the study.[76] The decrease in DBP was also significantly greater in nebivolol recipients than losartan recipients (table III).[29]

4.1.2 Response Rates

The definition of response varied between trials (tables II and III); however, normalisation of BP was generally defined as a reduction in BP to ≤140/90mm Hg (or reduction in DBP to ≤90mm Hg) and the total response rate definition generally included a reduction in DBP of ≥10mm Hg from baseline.

The response rates for normalisation of BP (DBP ≤90mm Hg) ranged from 37% to 91% in hypertensive nebivolol recipients and total response rates ranged from 48% to 94% during 4–12 weeks' treatment with nebivolol 5 mg/day.[23-31]

Generally, nebivolol recipients had similar response rates with treatment to those seen with other β-adrenoceptor antagonists (normalisation of BP achieved by 37–91% vs 42–87%; table II).[23,24,26] The normalisation rate was significantly higher in nebivolol recipients than in metoprolol recipients (table II).[25]

The percentage of total responders was generally not significantly different between nebivolol recipients and recipients of other classes of antihypertensive drugs (table III). The response rate for nebivolol recipients was significantly higher than that for enalapril recipients after 3 months' treatment ($p = 0.002$; table III),[28] but not after 7 months of treatment (73% vs 64%).[76]

Compared with nifedipine retard, the percentage of normalised responders was significantly higher in nebivolol recipients (42% vs 54%; p 0.007), although there was no between-group difference in the percentage of total responders (table III).[31]

In the studies comparing nebivolol with lisinopril[27] or losartan,[29] the response rates for nebivolol recipients were significantly higher than for the comparators after 6[29] or 8[27] weeks of treatment, but not at the end of the 12-week studies (table III). However, following the 6-week check, significantly more ($p < 0.001$) losartan recipients than nebivolol recipients received additional treatment with hydrochlorothiazide, which may have affected the response rate at 12 weeks.[29]

4.2 In Chronic Heart Failure (CHF)

The efficacy of nebivolol on clinical outcomes in elderly patients with CHF has been evaluated in one double-blind, placebo-controlled study, SENIORS (Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure) [table IV].[77] The primary composite endpoint in this trial was all-cause mortality or CV hospitalisation.[77,78] The ENECA (Efficacy of Nebivolol in the treatment of Elderly patients with Chronic heart failure as Add-on therapy to ACE inhibitors or angiotensin II receptor blockers, diuretics, and/or digitalis) study investigated the change in the surrogate clinical endpoint of LVEF.[32] LVEF was also assessed in an echocardiographic substudy of SENIORS (table IV).[33]

The randomised, double-blind, parallel-group, placebo-controlled, multicentre SENIORS (n = 2128) included patients aged ≥70 years with a clinical history of CHF, determined by either a hospital admission within 12 months prior to the trial for congestive heart failure or documented LVEF ≤35% within 6 months prior to the trial.[77,78]

The mean patient age was 76.1 years and ≈35–38% of patients were female.[77] Most of the patients had New York Heart Association (NYHA) class II (≈56%) or class III CHF (≈39%). LVEF was ≤35% in 64.5% of patients.[77]

Patients were randomised to receive, for a minimum of 12 months, placebo (n = 1061) or nebivolol (n = 1067) at a starting dosage of 1.25 mg/day.[77] The nebivolol dosage was increased every 1–2 weeks to 2.5 then 5 mg/day, up to a maximum of 10 mg/day (within 16 weeks) if tolerated. Other antihypertensive agents, except for other β-adrenoceptor antagonists, were permitted; most patients were also taking diuretics (≈86%) or ACE inhibitors (≈82%). The mean nebivolol maintenance dosage was 7.7 mg/day; the dosage was increased to ≥5 mg/

Table IV. Therapeutic efficacy of nebivolol (NEB) in chronic heart failure (CHF). Summary of randomised, double-blind, parallel-group, placebo-controlled, multicentre trials in elderly patients (pts) with CHF. Pts received NEB at a starting dosage of 1.25 mg/day which was increased gradually to a maximum of 10 mg/day or placebo (PL)

Study (acronym)	Inclusion criteria	Study duration (mo)	Treatment	No. of pts evaluated	Absolute change in LVEF from baseline (%)	Mortality or CV hospitalisation (%)
Edes et al.[32] (ENECA)	Age >65y; NYHA class II–IV CHF; LVEF ≤35%	8	NEB	134	6.51*[a]	
			PL	126	3.97[a]	
Flather et al.[77] (SENIORS)	Age ≥70y; NYHA class I–IV CHF[b]	12	NEB	1067		31.1*[a]
			PL	1061		35.3[a]
Ghio et al.[33] (SENIORS echocardiographic substudy)	Age ≥70y; NYHA class I–IV CHF[b]	12	NEB	27 (LVEF ≤35%)	4.6**	
			PL	16	−0.1	
			NEB	27 (LVEF >35%)	1.0	
			PL	34	1.2	

a Primary endpoint.

b With either a hospital admission with a discharge diagnosis of congestive heart failure within the 12 months prior or documented LVEF ≤35% within the 6 months prior to the study.

CV = cardiovascular; **ENECA** = Efficacy of Nebivolol in the treatment of Elderly patients with Chronic heart failure as Add-on therapy to ACE inhibitors or angiotensin II receptor blockers, diuretics, and/or digitalis; **LVEF** = left ventricular ejection fraction; **NYHA** = New York Heart Association; **SENIORS** = Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure; * $p < 0.05$, ** $p < 0.01$ vs PL.

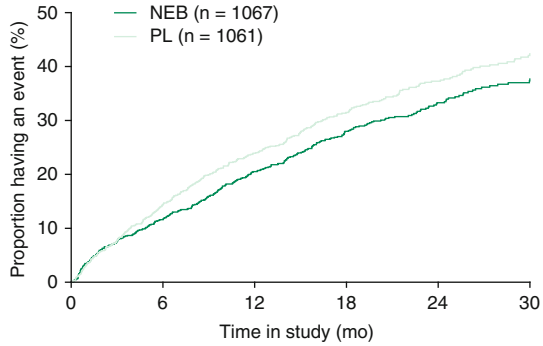

Fig. 1. Time to all-cause mortality or cardiovascular hospital admission (primary endpoint) in SENIORS.[77] Elderly patients with chronic heart failure were randomised to receive nebivolol (NEB) at a starting dosage of 1.25 mg/day, increased gradually to 10 mg/day, or placebo (PL) for a mean duration of 21 months in this double-blind, parallel-group, PL-controlled, multicentre study (reproduced from Flather et al.,[77] with permission from Oxford University Press). **SENIORS** = Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure.

day in 80% of nebivolol recipients.[77] The mean duration of follow-up was 21 months.[77]

Secondary endpoints for SENIORS included all-cause mortality, CV mortality, CV hospitalisation, all-cause hospitalisation and the composites of CV and all-cause mortality and hospitalisation. Functional capacity was also evaluated by assessment of NYHA class and a 6-minute walk test at 6 months. Endpoints were analysed using an ITT approach.[77] Results are reported as hazard ratios (HRs) adjusted for sex, age and LV function.

The randomised, double-blind, parallel-group, placebo-controlled, multicentre ENECA study also evaluated the efficacy of nebivolol versus placebo in treating CHF in elderly patients.[32] Inclusion criteria included hospitalised patients or outpatients aged >65 years; NYHA CHF class II–IV; stable CHF; LVEF ≤35%; and stable CHF medication with ACE inhibitors, angiotensin II receptor antagonists, diuretics and/or digitalis. The treatment regimen used was similar to that in SENIORS; patients were randomised to receive nebivolol at a starting dosage of 1.25 mg/day, which was increased to the maximum tolerated dosage or 10 mg/day (over 8 weeks) [n = 134], or placebo (n = 126) for 8 months.[32] The primary endpoint of the ENECA study, change in LVEF, is discussed in section 4.2.2. Secondary endpoints included change in clinical status and health-related quality of life (HR-QOL); these endpoints are discussed in section 4.2.1.

4.2.1 Clinical Outcomes

In SENIORS, the primary composite endpoint of all-cause mortality or CV hospitalisation occurred in significantly fewer nebivolol recipients than placebo recipients (HR 0.86, 95% CI 0.74, 0.99; p = 0.039) [figure 1 and figure 2; table IV].[77] The interaction tests were not statistically significant for sex, LVEF, age, diabetes or prior myocardial infarction (MI).[77]

The incidence of the secondary composite endpoint of CV mortality or CV hospitalisation was also significantly lower in nebivolol recipients than in placebo recipients (HR 0.84, 95% CI 0.72, 0.98; p = 0.027) [figure 2].[77] There were no significant between-group differences for the other secondary endpoints. Results for functional capacity (NYHA class assessment and the 6-minute walk test) have not yet been reported.

The change in functional status did not differ significantly between nebivolol and placebo recipients in the ENECA study.[32] Similar percentages of patients improved by one class (24.6% vs 27.0%;

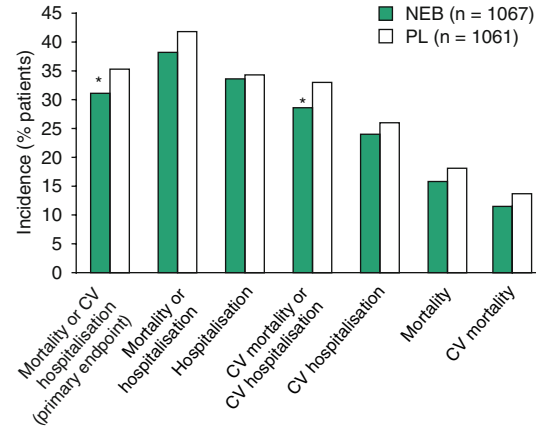

Fig. 2. Primary and main secondary endpoints in SENIORS, a study in elderly patients (aged ≥70 years) with chronic heart failure.[77] This double-blind, parallel-group, placebo (PL)-controlled, multicentre study randomised patients to receive nebivolol (NEB) at a starting dosage of 1.25 mg/day, increased gradually to 10 mg/day, or PL for a mean duration of 21 months. Endpoints shown are all-cause unless otherwise stated. **CV** = cardiovascular; **SENIORS** = Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure; * p < 0.05 vs PL.

Table V. *Post hoc* subgroup analysis of patients who received nebivolol (NEB) 10 mg/day. Relative risk reduction for NEB 10 mg/day versus placebo (PL) for primary and secondary endpoints in SENIORS.[79] Elderly patients with chronic heart failure received PL (n = 1061) or NEB (n = 1067) at a starting dosage of 1.25 mg/day, which was increased gradually to a maximum of 10 mg/day based on tolerability (10 mg/day reached by 68% of NEB and 80% of PL recipients).

Endpoint (time to first event)	Hazard ratio (95% CI)	p-Value
All-cause mortality or CV hospitalisation[a]	0.73 (0.61, 0.87)	<0.001
All-cause mortality	0.76 (0.59, 0.97)	0.027
CV mortality	0.71 (0.53, 0.95)	0.020
CV hospitalisation	0.74 (0.60, 0.90)	0.003
CV mortality or CV hospitalisation	0.70 (0.58, 0.84)	<0.001
All-cause hospitalisation	0.79 (0.67, 0.94)	0.008
All-cause mortality or all-cause hospitalisation	0.75 (0.64, 0.88)	<0.001

a Primary endpoint.

CV = cardiovascular; **SENIORS** = Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure.

nebivolol vs placebo) or two classes (1.5% vs 2.4%). The percentages of patients who remained stable were 60.4% and 53.2% respectively.[32]

The change in HR-QOL score (assessed with the Minnesota Living with Heart Failure Questionnaire) was not significantly different between treatment groups.[32]

4.2.2 Left Ventricular Ejection Fraction

In the ENECA study, the improvement in LVEF from baseline to the end of the study was significantly greater in nebivolol recipients than in placebo recipients (table IV).[32] The mean LVEF increased 6.51% (from 25.41% at baseline to 31.92%) in the nebivolol group compared with an increase of 3.97% in the placebo group (p = 0.027).

In the group of patients with LVEF ≤35% in the SENIORS echocardiographic substudy, nebivolol recipients had a significantly greater change in LVEF from baseline compared with placebo recipients (adjusted difference between treatments 4.6%; 95% CI 1.3, 7.9; p = 0.008) [table IV].[33] In those with LVEF >35%, there was no significant between-group difference.

4.2.3 Exploratory Analyses

Post hoc analyses have been carried out in various subgroups of patients in SENIORS. These non-prespecified analyses should be considered exploratory and hypothesis-generating and may suggest possible areas for future research.

In the subgroup of patients who reached the goal maintenance dosage of 10 mg/day (68% of nebivolol recipients and 80% of placebo recipients), the HR for the primary composite endpoint was 0.73 (95% CI 0.61, 0.87; p < 0.001) [table V; data presented in an oral presentation].[79] The HRs for the secondary endpoints in this subgroup of patients were also significantly in favour of nebivolol recipients. Uptitration of the dosage was based on tolerability; however, the reasons for 32% of patients not reaching the 10 mg/day dosage were not reported.

A *post hoc* analysis of the non-prespecified endpoint of sudden cardiac death reported an HR of 0.62 for nebivolol versus placebo (95% CI 0.42, 0.91; p = 0.014) [figure 3].[77,79,80]

5. Tolerability

5.1 In Patients with Hypertension

5.1.1 General Tolerability

Nebivolol 5 mg/day is generally well tolerated in patients with hypertension.[1] Adverse events tend to be transient and of mild to moderate severity.[1,66]

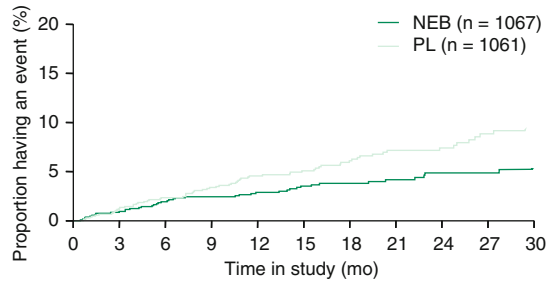

Fig. 3. Effect of nebivolol (NEB) on time to sudden cardiac death (non-prespecified endpoint) in SENIORS.[77,79,80] Elderly patients with chronic heart failure were randomised to receive NEB at a starting dosage of 1.25 mg/day, increased gradually to 10 mg/day, or placebo (PL) for a mean duration of 21 months in this double-blind, parallel-group, PL-controlled, multicentre study. **SENIORS** = Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure.

The most common adverse events (reported by 1–10% of patients) are headache, dizziness, paraesthesia, dyspnoea, constipation, nausea, diarrhoea, tiredness and oedema.[66]

Nebivolol has a tolerability profile similar to or more favourable than that of other β-adrenoceptor antagonists.[81] In a meta-analysis of ten comparative trials of nebivolol versus atenolol, metoprolol or bisoprolol, the rate ratio of adverse events in nebivolol recipients versus recipients of other β-adrenoceptor antagonists was 0.66 (95% CI 0.52, 0.85).

In several double-blind studies, nebivolol was better tolerated than other β-adrenoceptor antagonists.[24-26] In one study involving nebivolol and atenolol, the incidence of drug-related adverse events (e.g. dizziness, bradycardia, asthenia and impotence) was significantly lower in the nebivolol group (6% vs 24%; $p < 0.05$).[24] A significantly higher proportion of metoprolol recipients made newly reported complaints than nebivolol recipients (34% vs 20%; p-value not reported).[25] There was no significant difference in the incidence of spontaneously reported adverse events between nebivolol and bisoprolol recipients in another study (5.8% vs 8.9%).[23]

In double-blind studies that compared nebivolol with antihypertensive agents other than β-adrenoceptor antagonists, the proportion of patients who reported adverse events was 49% for nebivolol versus 55% for enalapril,[28] 19% versus 31% for losartan,[29] 14% versus 23% for lisinopril[27] and 39% versus 57% for nifedipine retard.[31]

Amlodipine recipients had a significantly higher incidence of drug-related adverse events (headache and ankle oedema) than nebivolol recipients ($p < 0.05$).[30] The incidence of potentially drug-related adverse events (cough, headache, tachycardia, vertigo and postural hypotension) was significantly higher in lisinopril recipients than in nebivolol recipients (26.7% vs 5.7%; $p = 0.035$).[27] Cough occurred in significantly more enalapril recipients than in nebivolol recipients (10.0% vs 2.9%; $p = 0.0045$).[28]

Nifedipine retard recipients had a high incidence of peripheral oedema (19.6% vs 5.2%, nifedipine vs nebivolol), headache (18.2% vs 10.0%) and flushing (15.8% vs 2.4%).[31] The incidence of dizziness was numerically higher in nebivolol recipients (5.7%) than in nifedipine retard recipients (2.9%) [statistical analysis not reported].[31]

In a randomised, double-blind 12-week trial investigating the effect of various antihypertensive agents on the sexual function of hypertensive men ($n = 131$), the mean number of episodes of satisfactory sexual intercourse per month was significantly lower than baseline levels in patients who received atenolol 50 mg/day (3.7 vs 7.0; $p < 0.01$) or atenolol 50 mg/day plus chlorthalidone 12.5 mg/day (2.8 vs 6.4; $p < 0.01$); this endpoint did not differ significantly from baseline levels to the end of the study in the nebivolol 5 mg/day group (6.0 vs 6.4).[82]

5.1.2 Health-Related Quality of Life

HR-QOL was generally similar between nebivolol and atenolol or losartan recipients in double-blind studies of hypertensive patients.[26,29] However, atenolol recipients, but not nebivolol recipients, had a significant ($p < 0.05$) deterioration from baseline for 'problems in maintaining interest during sex'.[26] The only significant HR-QOL difference between nebivolol and losartan recipients was that fewer nebivolol recipients than losartan recipients responded positively to 'have you suffered from headaches?' after 6 weeks of treatment (31% vs 40%; $p < 0.05$).[29]

Following 12 weeks of nonblind treatment with nebivolol 5 mg/day, patients reported significant improvements in many HR-QOL variables, notably energy level, breathlessness and libido (all $p < 0.01$ vs baseline).[49]

5.2 In Elderly Patients with CHF

In SENIORS, nebivolol was generally well tolerated with a similar incidence to that of placebo for most adverse events (figure 4).[77] However, the incidence of bradycardia was 11.1% in the nebivolol group compared with 2.6% in the placebo group (no statistical analysis). Lower limb oedema occurred in

5.2% of nebivolol recipients compared with 2.3% of placebo recipients.[77]

Eighteen nebivolol recipients and four placebo recipients withdrew from the study because of bradycardia.[77]

In the ENECA study, drug-related adverse events associated with nebivolol were typical of those associated with β-adrenoceptor antagonists and included bradycardia (9 adverse events reported in the nebivolol group vs 2 for the placebo group), hypotension (8 vs 4) and dizziness (5 vs 2).[32] The total number of drug-related adverse events was 40 in the nebivolol group and 14 in the placebo group ($p < 0.0001$).[32]

6. Dosage and Administration

6.1 In Patients with Hypertension

Nebivolol is approved for the treatment of essential hypertension in Europe and in several other countries outside North America. The recommended dosage of nebivolol in patients with hypertension is 5mg once daily.[66] The daily dose should be taken at the same time each day.[66] Nebivolol can be used with other antihypertensive agents; the coadministration of hydrochlorothiazide 12.5–25mg has been shown to produce an additive effect on BP lowering.[22,66]

In elderly patients (aged >65 years) and in patients with renal impairment, the starting dosage of nebivolol should be reduced to 2.5 mg/day (section 3.1). The dosage may then be increased to 5 mg/day if necessary. Nebivolol is contraindicated in patients with hepatic impairment because of a lack of data in these patients. There is also a lack of data for nebivolol in children and adolescents and use in these patients is not recommended.

Local prescribing information should be consulted for other contraindications, warnings and pre-

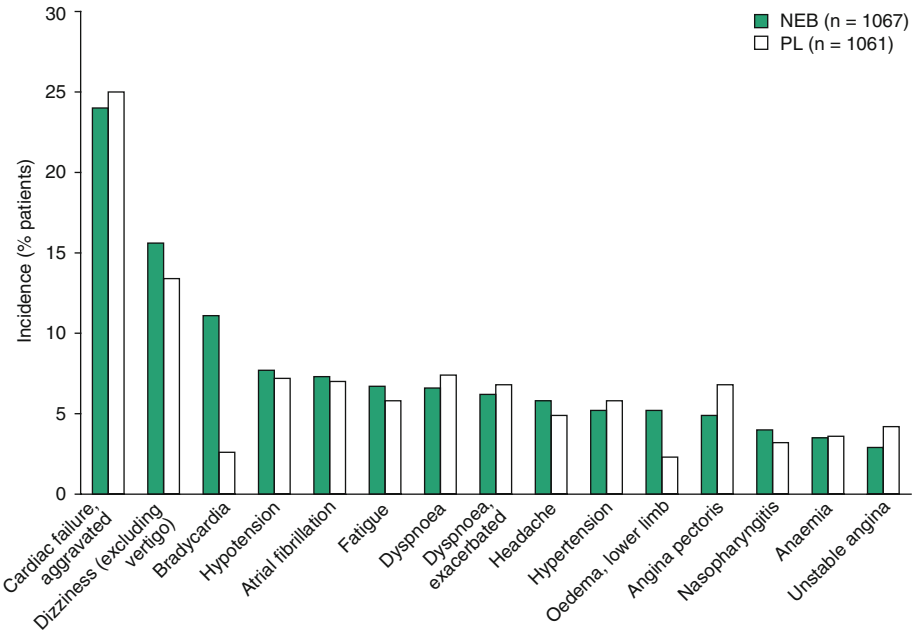

Fig. 4. Tolerability profile of nebivolol (NEB) in SENIORS.[77] In this double-blind, parallel-group, placebo (PL)-controlled, multicentre study in elderly (aged ≥70 years) patients with chronic heart failure, patients were randomised to receive NEB at a starting dosage of 1.25 mg/day, which was increased gradually to 10 mg/day, or PL for a mean duration of 21 months. The 15 most commonly occurring adverse events (by overall incidence) are shown. **SENIORS** = Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure.

cautions, specific dosage recommendations in special patient populations and drug interactions.[66]

6.2 In Elderly Patients with CHF

Nebivolol is approved in Europe for the treatment of stable mild and moderate CHF in addition to standard therapies in patients aged ≥70 years.[66,80] Treatment with nebivolol requires a gradual uptitration of the dosage until an optimal individual maintenance dosage is reached. The recommended starting dosage is 1.25 mg/day; this should be gradually increased at 1- to 2-week intervals to 2.5, 5 and finally 10 mg/day (maximum daily dosage) based on patient tolerability.

Treatment initiation and dosage increases should take place under the supervision of an experienced physician over a period of 2 hours and while monitoring clinical status.[66]

Concomitant treatment with other CV drugs is permitted; however, the dosages of other agents should be stabilised before starting treatment with nebivolol.[66]

7. Place of Nebivolol in the Management of Hypertension and CHF

7.1 Hypertension

Hypertension (SBP ≥140mm Hg or DBP ≥90mm Hg) is an extremely prevalent, treatable condition that is associated with an increased risk of CV events.[83,84] The risks of MI, CHF, stroke and kidney disease increase with increasing BP above 115/75mm Hg.[83] Hypertension is a common comorbidity in patients with diabetes (up to 60% of type 2 diabetics aged 45–75 years have hypertension) and diabetes is an independent risk factor for CV disease.[85]

The recommended target BP for patients with hypertension is <140/90mm Hg[83,86] (or ≤140/85mm Hg[87]). For patients with diabetes, renal disease or established CV disease, the recommended target BP is <130/80mm Hg[83,86] (or ≤130/80mm Hg[87]). Hypertension may be controlled by diet and lifestyle, although many patients will also require pharmacological intervention, often with two or more antihypertensive medications.[83,86,87]

All classes of antihypertensive drugs (β-adrenoceptor antagonists, ACE inhibitors, calcium channel antagonists, diuretics and angiotensin II receptor antagonists) are effective in lowering BP.[86,88] The mechanism of BP lowering varies among the agents, although it is thought that the main benefits of antihypertensive therapy result from lowering the BP rather than from the method of achieving this (i.e. which agent is used).[86] Current guidelines suggest that the choice of which antihypertensive agent to use should be based on compelling indications or contraindications in individual patients.[86]

There is also evidence that some drug classes may be more effective than others for prevention of certain outcomes, such as stroke or CHF, or in special patient groups, such as elderly patients or patients with hypertension and LV hypertrophy.[86]

Another point to consider is the tolerability profile, which varies among drug classes as well as among patients. For example, thiazide diuretics may be associated with hypokalaemia and impaired glucose tolerance, calcium channel antagonists with peripheral oedema, and ACE inhibitors with persistent dry cough.[89]

The β-adrenoceptor antagonists as a class are generally well tolerated, although they are associated with a number of adverse effects.[89] Possible adverse effects include lethargy, headache, bradycardia, atrioventricular block, cold extremities and worsening of peripheral vascular disease.[4,89] β-Adrenoceptor antagonists can also increase airway resistance in asthmatics and patients with COPD and some patients may experience impotence or a loss of libido.[4] Nonselective β-adrenoceptor antagonists may adversely affect lipid and glucose metabolism, which can mask symptoms of hypoglycaemia in diabetics[4] and the incidence of new-onset diabetes may be increased with some β-adrenoceptor antagonists.[89] The frequency and severity of these events vary among the β-adrenoceptor antagonists and among individual patients.[89]

Recently, two meta-analyses have shown that β-adrenoceptor antagonists, particularly atenolol, may

increase the risk of stroke compared with other antihypertensive drugs.[2,3] Atenolol may also increase mortality risk compared with other antihypertension drugs.[3] This has raised some concerns over the use of β-adrenoceptor antagonists as first-line treatment for hypertension; however, these concerns may not be relevant to the newer β-adrenoceptor antagonists with additional vasodilator properties, such as nebivolol.[90]

Nebivolol exerts its antihypertensive effects by selective β_1-adrenoceptor antagonist activity in conjunction with nitric oxide-mediated vasodilation (section 2). In clinical trials, nebivolol has shown equal or better antihypertensive efficacy (section 4.1) and tolerability (section 5.1) to other β-adrenoceptor antagonists and other classes of antihypertensive agents, although the effects of nebivolol on clinical outcomes in patients with hypertension have yet to be investigated. The incidence of drug-related adverse events in nebivolol recipients is low and HR-QOL, including sexual function, does not appear to be impaired (section 5.1).

In contrast to some other β-adrenoceptor antagonists, particularly nonselective β-adrenoceptor antagonists,[85] nebivolol does not adversely affect long-term exercise haemodynamics or airway function (section 2.4). Also, nebivolol does not appear to adversely affect lipid or glucose metabolism (section 2.5), and may therefore be a suitable choice in glucose intolerant, diabetic or dyslipidaemic patients. Moreover, the nitric oxide-mediated effects of nebivolol may provide additional cardioprotective effects, such as decreasing arterial stiffness and improving endothelial dysfunction (section 2.3).[6] The improvement in endothelial dysfunction may be particularly important in some patient groups, such as patients with type 2 diabetes and Black patients.

Although the available data suggest that nebivolol may be particularly useful in certain patient groups, actual clinical data supporting this are limited. A trial assessing long-term clinical outcomes, such as mortality and CV risk, of nebivolol treatment in hypertensive patients would, therefore, be of interest.

7.2 CHF

Hypertension contributes to the development of CHF by causing cardiac hypertrophy and impairment of diastolic function. It is also a risk factor for coronary artery disease which is another contributor to CHF.[91,92] As well as nonpharmacological treatment, such as general advice and exercise, there is a large range of medications (as well as devices and surgical treatments) available to manage CHF.[92] The choice of pharmacological treatment will depend on many factors including the severity of the disorder.[92]

The sympathetic nervous system is activated in patients with CHF to compensate for the failing heart and to help maintain BP.[93] Chronic increased sympathetic activation contributes to cardiac remodelling and progression of CHF.[94] By antagonising the sympathetic nervous system effects, β-adrenoceptor antagonists can slow or reverse the progression of CHF and improve LV function.[93] Although the symptoms of CHF may initially worsen with β-adrenoceptor antagonist treatment (section 2), the long-term benefits outweigh the initial negative inotropic effects.[93,94]

As well as nebivolol, the β-adrenoceptor antagonists recommended (in European guidelines) for treatment of CHF are bisoprolol, carvedilol and metoprolol succinate (controlled-release metoprolol).[92] The large, randomised trials MERIT-HF[95] (Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure), CIBIS-II[96] (Cardiac Insufficiency Bisoprolol Study II) and COPERNICUS[97] (Carvedilol Prospective Randomized Cumulative Survival Study) have shown that these β-adrenoceptor antagonists can reduce the risk of mortality in patients with CHF.

In SENIORS, a study in elderly patients with CHF, nebivolol was more effective than placebo in reducing the risk of the composite endpoint of all-cause mortality or CV hospitalisation (section 4.2) and was generally well tolerated (section 5.2). Many other CHF trials have excluded elderly patients (aged >80 years),[95,97] and, before SENIORS, there was a lack of data from controlled trials of β-adrenoceptor antagonists in elderly patients with

CHF. In addition, elderly patients with CHF are more likely to have preserved systolic function; CHF trials often only include patients with systolic dysfunction (low LVEF), whereas SENIORS included all patients with CHF, including those with preserved systolic function.[77,98]

Although SENIORS demonstrated a benefit of nebivolol over placebo in the treatment of CHF in elderly patients, it is not possible to directly compare outcomes between SENIORS and the other β-adrenoceptor antagonist trials because of the differences in trial design.[99] Other trials included younger patients (and excluded older patients), only included patients with low LVEF (≤40%) and used different study endpoints.[95-97] The authors of SENIORS therefore conducted exploratory analyses (not prespecified) in subgroups that more closely resembled patient groups from other studies.[77]

The risk reduction for all-cause mortality (the primary endpoint in CIBIS-II and COPERNICUS and one of the primary endpoints in MERIT-HF) for nebivolol compared with placebo was 12% in SENIORS compared with risk reductions of 34–35% for bisoprolol, carvedilol and metoprolol CR/XL (controlled-release) versus placebo.[77,95-97] However, in the subgroup of nebivolol recipients from SENIORS aged <75.2 years who had an LVEF ≤35%, the risk reduction for all-cause mortality was 38% (figure 5).[77] Analyses of comparable patient subgroups from the other trials[96,100,101] suggest there may be little difference between these four agents in the treatment of CHF (figure 6).[102]

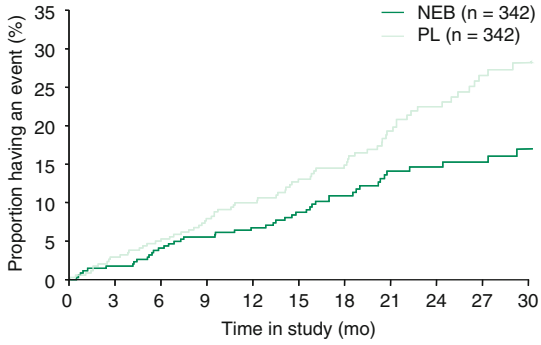

Fig. 5. Time to all-cause mortality in patients aged <75.2 years (median age) with LVEF ≤35% in SENIORS.[80] This *post hoc* analysis examined the effect of nebivolol (NEB; starting dosage 1.25 mg/day uptitrated to 10 mg/day based on tolerability) versus placebo (PL) in a SENIORS[77] patient subgroup that more closely resembled patient groups in previous β-adrenoceptor antagonist studies. The hazard ratio was 0.62 (95% CI 0.43, 0.89; p = 0.011). **LVEF** = left ventricular ejection fraction; **SENIORS** = Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure.

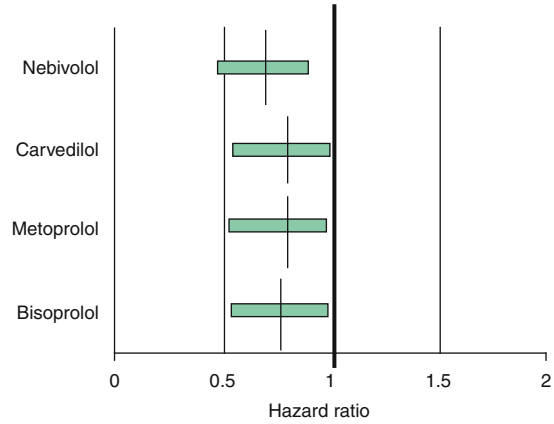

Fig. 6. Hazard ratio plots (with 95% CIs) for total mortality for comparable patient subgroups from the four main β-adrenoceptor antagonist mortality trials, i.e. SENIORS (Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure) [nebivolol];[77] COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival Study Group) [carvedilol];[100] MERIT-HF (Metoprolol CR/XL [Controlled-Release] Randomized Intervention Trial in Heart Failure) [metoprolol];[101] and CIBIS II (Cardiac Insufficiency Bisoprolol Study II) [bisoprolol],[96] using data derived from the trial reports. These data are from published patient subgroups reported by the authors themselves for each trial, and the criteria, therefore, differ between trials. The reported patient age subgroups chosen here are those most similar to each other across the four trials. For nebivolol, this is left ventricular ejection fraction (LVEF) ≤35% and age less than median (70–75.2 years), for carvedilol LVEF ≤25% and age ≥65 years, for metoprolol LVEF ≤40% and age >69 years, and for bisoprolol LVEF ≤35% and age ≥71 years. Reproduced from Coats,[102] with permission.

When carvedilol was compared with metoprolol tartrate (immediate-release metoprolol) in the COMET[103] (Carvedilol Or Metoprolol European Trial), a significantly greater reduction in the risk of all-cause and CV mortality was seen with carvedilol. However, there has been some debate over the dose and formulation of metoprolol used (metoprolol tartrate 50mg twice daily), which may not have been optimal.[104,105] Following on from studies of carvedilol and nebivolol on LV function (section 2.2), a comparative trial of carvedilol versus

nebivolol assessing clinical endpoints would be of interest.

Other *post hoc* analyses from SENIORS suggesting that nebivolol may reduce sudden cardiac death and that greater benefits are achieved in those who reach the target maintenance dosage of nebivolol 10 mg/day (section 4.2.3) require further investigation.

7.3 Conclusion

In conclusion, nebivolol is an effective antihypertensive agent and is well tolerated in patients with hypertension. The drug also effectively decreased the composite endpoint of mortality and CV hospital admission in elderly patients with CHF and was generally well tolerated in this population. In addition to its β_1-adrenoceptor antagonist effects, nebivolol may offer additional benefits, such as improvement of endothelial dysfunction, via interaction with the L-arginine/nitric oxide pathway. Nebivolol should be considered as an alternative first-line treatment option for patients with uncomplicated mild to moderate essential hypertension and in elderly patients with CHF.

Disclosure

During the peer review process, the manufacturer of the agent under review was also offered an opportunity to comment on this article; changes based on any comments received were made on the basis of scientific and editorial merit.

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