

Nebivolol - A Review

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Abstract

Nebivolol is a vasodilating β -blocker, which can be distinguished from other β -blockers by its haemodynamic profile. It combines β -adrenergic blocking activity with a vasodilating effect mediated by the endothelial L-arginine nitric oxide (NO) pathway. The blood pressure lowering effect of nebivolol is linked to a reduction in peripheral resistance and an increase in stroke volume and preservation of cardiac output. Clinical trials have demonstrated that nebivolol reduces blood pressure similarly to atenolol, bisoprolol, amlodipine, nifedipine, lisinopril, and hydrochlorothiazide. The tolerability of nebivolol is similar to or better than that of these agents. In general, response rates to treatment are higher and the frequency and severity of adverse events are either comparable or lower with nebivolol. Endothelium-derived NO is important in the regulation of large arterial stiffness, which in turn is a major risk factor for cardiovascular disease. Therefore, antihypertensive drugs, such as nebivolol, that also improve endothelial function and decrease arterial stiffness, may contribute to a reduction in cardiovascular risk.

Key words: Vasodilating β -blocker, nitric oxide (NO), peripheral resistance, arterial stiffness

Hypertension is one of the major risk factor for cardiovascular disease especially ischemic heart disease and stroke. It impairs left ventricular systolic and diastolic function and thus becomes an important precursor of heart failure. A large number of cardiac death and hospitalization occurring in the elderly are due to hypertension. Pathophysiology of hypertension is characterized by endothelial dysfunction with impaired production of nitric oxide resulting in decreased vasodilatation. Nebivolol, a new highly selective beta blocker and antihypertensive agent has the potential to improve the endothelial dysfunction and improved nitric oxide production. Clinical studies have shown that it is effective and safe in controlling hypertension and chronic heart failure.

Beta-blockers are frequently considered an effective and safe option for the first line treatment of hypertension.¹ However, recently they are no longer be considered for the first line therapy in uncomplicated hypertension because of unfavorable morbidity data.² Rather they should be used in post myocardial infarction, heart failure and atrial fibrillation and may be used in uncomplicated hypertension as a third or fourth line therapy.³ Evidence shows that beta-blockers with or without diuretics were associated with greater number of cases of new onset diabetes mellitus than regimens based on ACE inhibitors, angiotensin receptor blockers or calcium antagonists.⁴ In

addition ASCOT (Anglo Scandinavian Cardiac Outcome Trial) demonstrated an excess of 24% cardiovascular deaths, 14% cardiac events and 23% cerebrovascular events associated with beta blocker atenolol (\pm diuretic) and 30% new onset diabetes compared with calcium antagonist (\pm ACE inhibitors) based therapy.⁵

Nebivolol, a new third generation beta-blocker that differs from other beta-blockers such as atenolol, metoprolol or bisoprolol in that it is a highly selective beta-blocker with additional endothelial nitric oxide (NO)- mediated vasodilating activity.⁶ In addition, it has anti-oxidant properties and favorable metabolic profile on both carbohydrate and lipid metabolism.⁷ It significantly reduces triglycerides, total and LDL cholesterol.⁸ It does not reduce insulin sensitivity like atenolol and it has no effect in the incidence of new onset of diabetes mellitus.⁹ Fatigue, depression, bradycardia, erectile dysfunction worsening of cardiac contractility and bronchospasm are very low with nebivolol.¹⁰

Nebivolol is a new beta blocker. It is a racemic mixture of d-Nebivolol and l-Nebivolol. The former (d-Nebivolol) has selective β_1 -receptor blocking activity and the later (l-Nebivolol) has vasodilating property. Unlike other third generation β -blockers, such as labetalol, carvedilol and bucindolol which mediate vasodilatory effect through alpha-1 adrenoreceptor antagonism, nebivolol mediate

endothelium-dependent arterial and venous dilatation via the L-arginine-nitric oxide (NO) dependent pathway. (L-arginine is a precursor of nitric oxide).^{11,12} Overall antihypertensive effect of nebivolol is exerted by the combination of the activity of both enantiomers. Nebivolol also improves vascular endothelial function. It increases NO-production via stimulation of endothelial NO-synthetase (eNOS) and reduces oxidative inactivation of NO.¹³ Stimulation of eNOS by nebivolol might reduce circulating level of asymmetric dimethylarginine (ADMA), a potent inhibitor of eNOS. It may also stimulate serotonin 5HTA receptors, which in turn stimulate eNOS activity. It decreases oxidative stress in essential hypertension and increases NO by reducing its oxidative inactivation.¹³ Study also shows that nebivolol significantly increased oxidative stress, HOMA index and plasma soluble p-selectin levels, and increased adiponectin levels in hypertensive patients treated with nebivolol.¹⁴ It also possesses anti-proliferative properties that are potentially useful in hypertensive patients.

Comparing with other β -blockers Nebivolol is as effective as atenolol in reducing blood pressure, but has a more homogeneous effect over 24 hours.¹⁵ Moreover it has been associated with a longer reduction in cardiac index and decline in mean pulmonary artery pressure and pulmonary wedge pressure both at rest and with exercise.¹⁶

It does not reduce exercise tolerance, because it does not inhibit the formation of free fatty acids which are a substance for energy expenditures, to the same extent as other β -blockers.^{17,18}

A number of clinical trials have been carried out to see the efficacy and tolerability in patients with hypertension and chronic heart failure. Table-1 shows the summary of clinical studies in hypertensive patients comparing nebivolol with placebo and other beta-blockers. The anti hypertensive effect of nebivolol at different doses (0.5-10 mg per day) was greater than placebo, but similar with other beta-blockers with better tolerability profile. A large multi center, randomized, double-blind, placebo controlled, dose-ranging study of the efficacy and tolerability of nebivolol recruited 509 hypertensive (diastolic blood pressure \geq 95mmHg) patients were allocated to receive nebivolol or placebo once daily for four weeks. Nebivolol 2.5 mg (n=85), 5 mg (n=86), and 10 mg (n=84) were associated with significant, dose dependent decreases in systolic blood pressure and diastolic blood pressure compared with placebo (n=84) (all, $p < 0.05$ vs baseline vs placebo). The efficacy and tolerability of nebivolol were also compared with lisinopril, enalapril, telmisartan, nifedipine and amlodipine in randomized, double-blind clinical trials. The efficacy of nebivolol in reducing blood pressure was comparable with these drugs and well tolerated.²²

Table-I
Clinical studies of Nebivolol in the management of hypertension.

Authors/Design	Population	No of patients	Regimens	Duration	BP Reduction, mm Hg	Adverse Effects
Van Nueten et al MC, R, DB, PC	Essential HTN (DBP 95 mm Hg)	509	Neb: 0.5, 1, 2.5, 5, or 10 mg/d Pla	4wk	Supine (at C _{min}) Nebi 0.5mg:-2.9/-4.0; Nebi 1mg:-6.8/-6.0; Nebi 2.5 mg:-8.6/-7.1 ($P < 0.05$ vs baseline); Nebi 5 mg: -9.2/-9.2 ($P < 0.05$ vs baseline); Nebi 10 mg: -8.2/-10.2 ($P < 0.05$ vs baseline); Pla: -3.1/-3.3	Nebi 0.5 mg: 36%; Nebi 1 mg: 35%; Nebi 2.5 mg: 33%; Nebi 5mg:40%; Nebi 10mg: 35%; Pla: 36%
Van Nuteen et al R, DB, APC, PG	Mild to moderate HTN (DBP 95-115 mm Hg)	364	Nebi 5 mg/d Aten 50 mg/d Pla	4wk	Nebi: -16/-13 ($p < 0.001$ vs Pla); Aten: -14/-12 ($p < 0.001$ vs Pla); Pla: -6/-3	Nebi: 29%; Aten: 31%; Pla: 25%
Kamp et al R, DB	Essential HTN (DBP 90 mm Hg)	25	Nebi 5 mg/d Aten 100 mg/d	2wk	Nebi: -19/-12; Aten: -16/-7 (both, $p < 0.05$ vs baseline)	Not reported
Grassi et al R, DB	Mild to moderate HTN (DBP >90 mm Hg, SBP >140 mm hg)	205	Nebi 5mg/d Aten 100mg/d	12wk	Nebi: -19.1/-14.8; Aten: -18.2/-14.3	Nebi: 20%; Aten: 41% ($P < 0.001$ vs Nebi)
Czuriga et al R, SB	Mild to moderate HTN (DBP 95-110 mm hg, SBP 180 mm Hg)	273	Nebi 5 mg/d Biso 5mg/d	4wk	Nebi: -20.5/-15.7; Biso: -20.0/-16.0	Nebi: 5.8%; Biso: 8.9%

Table-II
Clinical studies of Nebivolol in the management of heart failure

Authors/ Design	Population	No. of Patients	Regimens	Duration	Results for Primary End Points	Adverse Effects
Flather et al R, DB, PC	Patients aged 70 y with chronic stable clinical HF	2128	Nebi 1.25-10 mg/d \ Pla	12mo	All-cause mortality or CV hospitalization: -14%, Nebi vs Pla (HR = 0.86; 95% CI, 0.74-0.99; <i>P</i> = 0.039)	Bradycardia: 11.1% Nebi and 2.6% Pla
Patrianakos et al R, DB	Mild to moderate HF (NYHA Class II-III), LVEF <45%	72	Nebi 1.25-5 mg/d Carv 3.125-25 mg BID	12mo	LVEF: +6.1% Nebi vs +8.8% Carv (<i>P</i> = 0.02, Nebi vs Carv; both, <i>P</i> < 0.05 vs baseline)	Discontinuation rate due to AEs: 16.7% Nebi and 8.6% Carv Exercise capacity: +80 vs +110 min, respectively (<i>P</i> < 0.01, Nebi vs Carv; both, <i>P</i> < 0.01 vs baseline)
Edes et al. (ENECA)	Age >65y; NYHA class II-IV CHF; 35%	134 126	NEB PL	8mo	LVEF: +6.51% (Nebi) vs +3.97% (PL) Both, <i>P</i> < 0.05 vs baseline	
Ghio et al. (SENIORS echocardiographic substudy)	Age 70y; NYHA class I-IV CHF ^b	27 (LVEF35%) 16 27 (LVEF >35%) 34	NEB PL NEB PL	12mo	+4.6% -0.1(p<0.01vs pla) 1.0 1.2	

R = randomized; DB = double blind; PC = placebo controlled; Pla = placebo; CV = cardiovascular; HR = hazard ratio; NYHA = New York Heart Association; LVEF = left ventricular ejection fraction; Carv = carvedilol; AEs = adverse events. ENECA= Efficacy of Nebivolol in the treatment of Elderly patient with Chronic heart failure as Add-on therapy to ACE inhibitors or angiotensin II receptor blockers, diuretics, and/or digitalis. SENIORS= Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure.

Nebivolol has been shown to be safe and effective in the treatment of hypertension in short and long term clinical trials. Recently report from a long-term (9 month) double blind, multicenter clinical trial, which recruited 845 patient with stage I to II hypertension comparing nebivolol monotherapy versus nebivolol in combination with other anti hypertensive therapies for the treatment of hypertension shows that it is safe and effective at doses 5 to 20 mg/day in stage I to II hypertension and provides long term blood pressure lowering effect with favorable tolerability profile.²³

Few clinical studies with nebivolol conducted in chronic heart failure patients. Table 2 summarizes the larger ones. The SENIORS (study of Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with heart failure) trial, a double blind placebo controlled study in the elderly heart failure patients (n=2128) shows that nebivolol (at doses 1.25-10mg/day) was well tolerated and effective in reducing mortality and morbidity in patients of age > 70 yrs with heart failure regardless of the initial ejection fraction.^{21, 22}

In a subanalysis of the SENIORS trial the effect of beta blockade with nebivolol were studied in 2111 elderly heart failure patients with impaired (EF<35%,n=1359) and preserved (EF>35%,n=752) left ventricular ejection fraction. The primary end point was all-cause mortality or cardiovascular hospitalizations. After 21 months follow up the effect of nebivolol was found to be similar in those with impaired and preserve ejection fraction. (HR 0.86: 95% CI 0.72-1.04) in impaired EF and HR 0.81, 95% CI 0.63-0.14 in preserved EF *P*<0.48).¹⁹

A recent study shows that nebivolol also improves coronary micro vascular function (in patients with dilated cardiomyopathy) by increasing coronary flow reserve.¹⁴ This may have benefit in clinical settings like coronary artery disease and hypertension. In addition, nebivolol offers additional benefits by avoiding erectile dysfunction in male hypertensive patients (possibly as a result of its vasodilatory effect mediated by increased nitric oxide release) on long-term β -adrenoreceptor antagonist therapy.¹²

In conclusion, nebivolol is a third generation highly selective β_1 -blocker with vasodilatory properties through enhanced nitric oxide production by vascular endothelium. Clinical studies demonstrated that nebivolol was as efficacious in reducing blood pressure as other β -blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers. Preliminary clinical trials with nebivolol in heart failure also demonstrated beneficial effects in reducing rates of all-cause mortality and cardiovascular hospitalization. In addition, patients with asthma or COPD, or those who experience erectile dysfunction when using other β -blockers may be benefited with nebivolol due to its high selectivity to β_1 receptor and enhanced nitric oxide producing properties.

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