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THE ROLE OF "NEBIVOLOL" IN THE MANAGEMENT OF HYPERTENSIVE PATIENT

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INTRODUCTION

Nebivolol

According to the most recent international guidelines, β-blockers maintain a central role in the management of hypertension, being recommended at any treatment step when there is a specific indication, such as heart failure, angina, postacute myocardial infarction, atrial fibrillation or pregnancy.

However, β-blockers are not a homogeneous class: individual molecules differ in terms of pharmacological and clinical profile and are therefore suitable for different patient subtypes. In particular nebivolol, third generation β1-selective β-blocker with vasodilating properties, neutral metabolic effects and good tolerability, proved to have advantages over other β-blockers, which makes the drug suitable in a wide variety of hypertensive patients with or without comorbidities.

Lay abstract: β-blockers are the main class of antihypertensive agents currently available. Nebivolol is one of the most recent β-blocking agents and it has vasodilating effects which may be Useful in hypertensive patients with heart disease of ischemic (restriction in blood supply) origin or with erectile dysfunction. It has a good tolerability profile which makes it safe to use in patients with metabolic abnormalities (such as diabetes or dyslipidemia) or chronic obstructive pulmonary diseases.

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KEYWORDS: coronary artery disease • heart failure • hypertension •

Recommendation.	Class of Recommendation	ESD level of evidence of drug
Drug treated strategy for uncomplicated hypertension		
Among all antihypertensive drugs, ACE inhibitors, ARBs, - blockers, CCBs and diuretics (thiazides and thiazide-like drugs such as chlorhexidine and indicative) have demonstrated effective reduction of BP and CV events in RCTs, and thus are indicated as the basis of antihypertensive treatment strategies	1	A
It is recommended that - blockers are combined with any of the other major drug classes when there are specific clinical situations, for example, angina, postmyocardial infarction, heart failure or heart rate control	1	A
A Drug treatment strategy for hypertension and coronary artery disease	1	A
n In patients with HFrEF, it is recommended that BP-lowering treatment comprises an ACE inhibitor or ARB, and a -blocker and diuretic and/or MRA if required I	1	A
Drug treatment strategy for hypertension and heart failure with reduced ejection fraction		
n In patients with HFrEF, it is recommended that BP-lowering treatment comprises an ACE inhibitor or ARB, and a -blocker and diuretic and/or MRA if required	1	A
Drug treatment strategy for hypertension and atrial fibrillation		
A beta blocker or nondihydropyridine CCB should be considered as part of the treatment of hypertension if rate control is needed	1	A
B ESC Classes of recommendations: Class I = evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective; Class IIa = weight of evidence/opinion is in favor of usefulness/efficacy. ESC Levels of evidence: Level A = data derived from multiple randomized clinical trials or meta-analysis; Level B = data derived from a single randomized clinical trial or large nonrandomized studies. ACE: Angiotensin-converting enzyme; ARB: Angiotensin receptor blocker; BP: Blood pressure; CCB: Calcium channel blocker; CV: Cardiovascular; ESC: European Society of Cardiology;	11a	B

HFrEF: Heart failure with reduced ejection fraction; MRA: Mineralocorticoid receptor antagonist; RAS: Renin–angiotensin system; RCT: Randomized controlled trial. Adapted from.[1]		

Key points

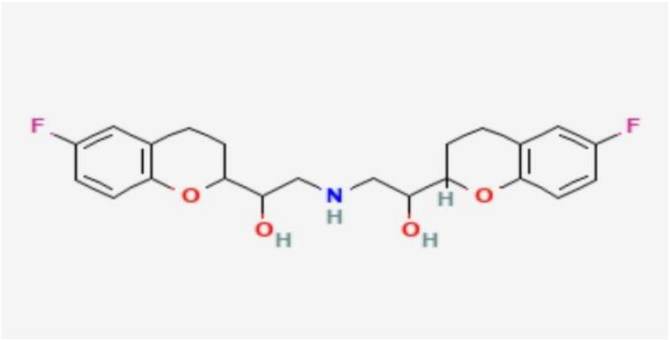
- Nebivolol is the only vasodilating B1- selective blocker the vasodilating effect is nitrite oxide mediated and activated via B3- agonism
- Nebivolol effectively lowers blood pressure either alone or in combination with other antihypertensive drugs
- The unique pharmacology profile of nebivolol coupled with clinical evidence suggests potential utility in the treatment of hypertension and heart failure with reduced ejection fraction

1. Mode of action of Nebivolol

Nebivolol is a unique, third-generation, highly receptor antagonist that reduces blood pressure and heart rate. It works through a dual mechanism: potent -blockade (via the isomer) combined with nitric oxide (NO)-mediated vasodilation (via the l-isomer), which improves endothelial function and reduces peripheral vascular resistance.

 # Key Mechanisms of Action:

- **Highly Selective B1-Antagonism:** It blocks -receptors in the heart, decreasing resting/exercise heart rate, cardiac output, and blood pressure, while minimizing - mediated adverse effects in the airways.
- **Nitric Oxide (NO) Vasodilation:** Unlike traditional -blockers, nebivolol stimulates endothelial nitric oxide synthase (eNOS) through -adrenergic receptor agonism, leading to vasodilation and increased vessel compliance
- **Reduced Peripheral Resistance**: The modulation of endothelial NO release helps decrease systemic vascular resistance, making it effective for hypertension, often with better tolerability than traditional blockers.
- **Cardio protective and Antioxidant Effects**: It reduces oxidative stress and can enhance left ventricular function, beneficial in managing chronic heart failure



2. Literature Search Methodology.

Discussion of safety and efficacy was limited to hyper-tension heart failure and erectile dysfunction literature searches conducted in the period of October – December 2014were performed using the PubMed database looking for terms “nebivolol” hypertension, BP , heart failure in title and abstract and restricted the results to studies in human and non review article in English language Both authors examine the resulting list of abstract and excluded those that did not fit the scope of the article.

3 Pharmacology of The Nebivolol

b-Blockers are a heterogeneous class of compounds that jave evolved from first – generation nonselective agent (eg propranolol) to second generation non selective cardio selective b1 selective(atenolo) to third generation compound that combines l b blocker with vasodilating effect (nebivolol)

The distinct pharmacologic profile of the Nebivolol is associated with a number of hemodynamically systolic and diastolic blood pressure (2)NO- medicated vasodilation that results in a decrease in peripheral vescular resistance an increase in stroke volume and ejection fraction and maintenance of cardiac output vasodilation and reduced oxidative strss that are through to contribute to the neutral and possibly beneficial effects of Nebivolol on glucose and lipid metabolism and reduced platelets volume and aggression these attributes suggest a potentially broad usefulness for Nebivolol in the treatment of hypertension and chronic heart failure.

4. Clinical Pharmacokinetics of Nebivolol

The absolute bioavailability of nebivolol is unknown. The drug is 98%protein bound primarily to albumin and reaches a peak concentration after 1.5-4h Nebivolol is metabolized in the liver mainly via direct glucuronidation and secondarily through cytochrome P450 2D6

(CYP450 2D6) the active metabolites hydroxyl and glucuronides contribute to the b-blocking effect of nebivolol. As with other drugs metabolized via CYP450 2 D6 genetic difference can impact metabolism, elimination half Life, excretion, and clinical and adverse effect of Nebivolol It should however, be noted that data suggests that in. CYP450 2D6 poor metabolizer, no dose adjustment is needed as the clinical effect and safety profiles are similar to that of extensive metabolizer The elimination half- life of Nebivolol is typically 12h, but is prolonged to 19 h in those who are poor metabolizer. Excretion of nebivolol is 35 %through urine and 44% via feces in average metabolizers; of who are poor metabolizers excrete 67% of the drug in the urine and 13%in feces.

5 Endothelial and Hemodynamic Effects

Endothelial dysfunction caused by oxidative stress has been implicated in the development of hypertension a number of studies have demonstrated favorable endothelial effect of Nebivolol verses non- vasodilating B1- selective blocker (atennol)for eg Nebivolol was shown to be superior to atennol in improving small artery distensibility index, parameters of plasma concentration of asymmetric dimethyl arginine (ADME) an endogenous inhibitor of NO production that has been associated with cardiovascular risk compared with metoprolol, Nebivolol reduces plasma ADME levels and the augmentation index (Aix) a surrogate measure arterial stiffness that is also associated with cardiovascular risk.[21] However, the AIxbenefits compared with metoprolol may not extend to individuals with hypertension and diabetes mellitus who are receiving maximal tolerated doses of renin-angiotensin-aldosterone system (RAAS) blockers.[22] Of note, a12-month randomized trial that compared the effects nebivolol and metoprolol on a number of hemodynamic and biochemical parameters found no difference in AIx and ADMA levels between the two groups, but demonstrated that only nebivolol had a beneficial effect on oxidative stress[23] and significantly reduced central systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse 1. pressure (PP) and left ventricular wall thickness.[24] Whether these positive effects translate to improvement of clinical outcomes remains to be seen. Despite the absence of data from large outcome studies with nebivolol, the vascular effects and hemodynamic profile suggest potential advantages of nebivolol compared with non-vasodilating b1-selective and nonselective-blockers in the treatment of hypertension. Central hemodynamic effects are important to highlight, because they are independent predictors of cardiovascular morbid-ity and mortality[25, 26] and because they may be a key reason why traditional b-blockers (e.g., atenolol) have been associated with smaller reductions in cardiovascular mor-bidity and mortality than other

antihypertensive classes(e.g., calcium channel blockers).[27] For example, studies have shown that, relative to ate-nolol and metoprolol succinate, nebivolol improves central hemodynamics and reduces arterial stiffness in patients with hypertension, regardless of similar reductions in peripheral DBP and SBP.[24, 28–30] In one study, 40individuals with untreated essential hypertension were randomized to atenolol 50 mg/day or nebivolol 5 mg/day for 4 weeks; treatment with nebivolol reduced aortic PP toa significantly greater extent than atenolol (-16 vs-11 mmHg; p = 0.04).[29] Though both compounds significantly reduced aortic pulse wave velocity (PWV)from baseline, only nebivolol treatment was associated with a significant reduction from baseline in Axis (from 35to 28 %; p\0.05). Furthermore, PP amplification, a hemodynamic indicator inversely associated with large artery stiffness and peripheral arterial resistance[27], was significantly increased with nebivolol treatment and sig-nificantly decreased with atenolol. Similar results were obtained in a randomized, cross-over study of 16 patients with untreated isolated systolic hypertension (ISH)[28] who received atenolol 50 mg/day, nebivolol 5 mg/day, and placebo for 5 weeks each. The significant reductions in aortic PWV compared with placebo were similar between nebivolol and atenolol, but nebivolol treatment was associated with a smaller increase in Axis compared with ate-nolol (6 vs 10 %; p = 0.04). The aortic PP after treatment with nebivolol was similar to that, but was significantly lower compared with treatment with atenolol(50 vs 54 mmHg; p = 0.02).[28] A few more recent publications also provided evidence of improvement in central hemodynamics with nebivolol. For example, in a trial that randomized 45 patients with stage I hypertension to nebivolol (10 mg/day), lifestyle modifications, or the combination of nebivolol and lifestyle modifications for 12 weeks, the b-stiffness index, a blood-pressure-independent measure of arterial stiffness, decreased (p\0.01), and arterial compliance increased(p = 0.02).[31]

Another trial randomized 138 patients with mild to moderate hypertension to atenolol (50–100 mg/day) or nebivolol (5 mg/day) for 10 weeks, with hydrochlorothiazide 25 mg/day added on if necessary to control blood pressure. After adjusting for heart rate, the mean between-group difference in AIx was 2.4 %(p = 0.041), with nebivolol increasing AIx to a lesserextent than atenolol.[30] Lastly, in a trial that compared nebivolol (5 mg/day) with metoprolol succinate(50–100 mg/day) in patients with mild to moderate hypertension, nebivolol reduced mean central PP from baseline significantly more than metoprolol (-6.2 vs-0.3 mmHg; p = 0.01), with no difference from baseline with either agent in PP amplification, PWV, or AIx.[24] The differential effects on aortic PP between nebivolol and atenolol or

metoprolol succinate observed in these studies are similar in magnitude to those between the amlodipine-and atenolol-based therapies reported in the Conduit Artery Function Evaluation (CAFE) study[32], a sub study of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT;N = 19, 257), which demonstrated a greater reduction in major cardiovascular events and mortality with the amlodipine-based than atenolol-based regimen, despite a similar decrease in brachial blood pressure.[33] The question of whether the more favorable effects of nebivolol central aortic pressure versus those of non-vasodilation-blockers translate into improved clinical outcomes would have to be tested in large primary or secondary preventiontrials. As mentioned previously, nebivolol is a b1-selectiveblocker that exerts a vasodilatory effect through stimulations of endothelial NOS.[1] The contribution of vasodilation to the overall antihypertensive effect of nebivolol was recently assessed in a small, double-blind, placebo-controlled cross-over study of 20 patients with autonomic failure[34], who are devoid of adrenergic input in blood pressure control and are therefore char-acterized by an impaired baroreceptor function, as manifested through orthostatic hypotension and supine hypertension. In that trial, nebivolol (5 mg) but not metoprolol (50 mg) lowered night-time SBP (p = 0.036)and DBP (p\0.001) versus placebo, effects that were driven by the subgroup of individuals who also responded to sildenafil (25 mg).[34] This reduction in blood pressure that is independent of b1-antagonism is consis-tent with the hypothesis that NO-mediated vasodilation contributes significantly to an overall antihypertensive effect of nebivolol. While nebivolol's NO-mediated vasodilatory effects may be favorable, there is concern about the develop-ment of nitrate tolerance and the adverse endothelial effects that are associated with the continuous long-termplacebo for 8 days, forearm blood flow was measured before and after 5 min of intravenous nitroglycerin administration (4 lg/kg body weight/min). The blood flow increase in those receiving nebivolol (96 %) was significantly greater than the increase observed in those receiving placebo (54 %; p\0.05).[35] This reduction in nitrate tolerance following nebivolol treatment remains to be confirmed in larger trials.

6 Nebivolol for the Treatment of Hypertension

Nebivolol at doses of 1.25–40 mg/day has been evalu-ated for the treatment of hypertension, both as monotherapy and in combination with other classes of antihypertensive agents (Table 1). It is provided in tablets of 2.5, 5, 10, and 20 mg; for most patients, it is recommended to start with a dose of 5 mg daily, which can be titrated up to 40 mg/day at 2-week intervals.[13] A lower initial dose of 2.5 mg/day is recommended inpatients with moderate hepatic and/or severe renal impairment. However, nebivolol should be avoided inpatients with severe hepatic

impairment and has not been studied in patients who are receiving dialysis.[13]

While nebivolol monotherapy is approved in the US for low-ering blood pressure, recent treatment guidelines from the American Society of Hypertension and the Interna-tional Society of Hypertension[36], as well as the Panel Members Appointed to the Eighth Joint National Com-mite (JNC 8)[37], do not recommend first-line use of b-blockers in patients with essential hypertension. The rationale provided by JNC 8 is based on results from several randomized controlled trials in which either-blockers performed similarly to the recommended therapies of thiazide-type diuretics, calcium channel blockers (CCBs), angiotensin-converting enzyme inhibit-tors (ACEIs), or angiotensin II receptor blockers (ARBs)or firm conclusions could not be made from the evidence.[37] Additionally, the results of one trial comparing ab-blocker (atenolol) and an ARB (losartan) showed that despite similar reductions in blood pressure, losartan prevented more cardiovascular morbidity and mortality than atenolol.[38]

One meta-analysis and one systematic review, which were not included as supporting evidence for recommendations in JNC 8, have also shown no benefit of b-blockers compared with other antihypertensive in reducing cardiovascular morbidity and mortality, along with an increased risk of stroke.[39, 40] It has-been noted that atenolol, a non-vasoligating b1-selectiveblocker, was used in the large majority of studies included in these meta-analyses, and the finding may not be generalizable to third-generation, vasodila-tory b-blockers such as carvedilol and nebivolol.

6.1 Monotherapy Data

6.1.1 Pivotal Trials

The approval of nebivolol for the treatment of hypertension in the US was based upon evidence of its efficacy in three large, randomized, placebo-controlled dose-ranging studies in adults with hypertension.[42–44] In each study, patients were randomized to 12 weeks of double-blind treatment with various fixed doses of nebivolol or placebo following 4- to 6-weeksingle-blind, placebo washout period. The primary efficacy parameter was change from baseline in mean trough DBP; secondary parameters included change from baseline in mean trough SBP and a response rate at endpoint, defined as the proportion of patients with meant rough DBP \ 90 mmHg or an absolute reduction ofC10 mmHg from baseline. In total, over 2000 patients were included, with one trial consisting of black participants only.[43] Results from each study consistently showed significant reductions in DBP with nebivolol doses

ranging from 5 to 40 mg daily and reductions in SBP at higher daily doses (10–20 mg), as well as significantly higher response rates compared with placebo. A dose-re-sponge effect in terms of both SBP and DBP reduction was observed.[42–44]

6.1.2 Pooled Analyses

Post-hoc, pooled analyses from the three pivotal trials (N = 2016) discussed above were conducted to assess efficacy, safety, and tolerability with a greater statistical power[45], as well as to explore the effects of nebivolol on patients by age[46] and body mass index (BMI).[47] The pooled data demonstrated a significant effect of nebivolol placebo on both DBP and SBP for all clinically rec-commended dosages (5–40 mg/day), and show edthatnebivolol is generally safe and well tolerated.[45] The discontinuation rate due to adverse events (AEs) amongnebivolol-treated patients (all dosages) was low (2.6 %)and comparable to that observed with placebo (2.0 %). The most common AEs in patients receiving nebivolol were headache (7.1 vs 5.9 % for placebo), fatigue (3.6 vs 1.5 %),and dizziness (2.9 vs 2.0 %).Similar efficacy results were reported in a pooled anal-lysis of 205 placebo-treated patients and1380 patients treated with nebivolol dosages of 5, 10, or 20 mg/day, stratified by age (22–46, 47–53, 54–62, and 63–84 years).[46] In all age groups, each nebivolol dose significantly reduced DBP compared with placebo. All dosages nebivolol in all age groups significantly lowered SBP versus placebo, with the exception of the oldest age group, in whom a significant effect was observed only with the20 mg/day dosage.[46] A pooled analysis examining the Effects of nebivolol treatment on patients stratified by Baseline BMI [\30 kg/m2 (non-obese) or BMI C30 kg/m2And B35 kg/m2 (moderately obese)] demonstrated that Nebivolol at doses ranging from 5 to 40 mg/day significantly reduced DBP and SBP versus placebo in both BMI Categories.[47] Response rates at the end of treatment were Significantly higher for all nebivolol dosages C2.5 mg/day In the non-obese group and C5 mg/day in the moderately Obese group.[47]

6.1.3 Monotherapy Trials in Special Populations

Placebo-controlled trials of nebivolol monotherapy in Specific patient populations include one conducted in Younger patients (age range, 18–54 years; mean age, 45.3 years) with stage 1 or stage 2 hypertension in which Nebivolol significantly reduced DBP (change from base-Line: -11.8 mmHg vs -5.5 mmHg; p\0.001) and SBP(change form baseline: -13.7 mmHg vs -5.5 mm Hg;p\0.001), compared with placebo.[48] A trial conducted in self-identified Hispanics also demonstrated a significant decrease in DBP (change from baseline: -11.1

mmHg vs-7.3 mmHg; p\0.0001) and SBP (-14.1 mmHg vs-9.3 mmHg; p = 0.001) with nebivolol treatment, com-Pared with placebo.[49] Finally, in the pivotal trial con-Ducted in African-Americans, nebivolol significantly Reduced both DBP at all doses C5 mg (5 mg, p = 0.004;10, 20, and 40 mg, p\0.001) and SBP at all dosesC10 mg (10 mg, p = 0.044; 20 mg, p = 0.005; 40 mg, P = 0.002) compared with placebo.[43]

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