



# Use of Nebivolol as an antihypertensive drug: an extensive literature review

## Uso de Nebivolol como medicamento anti-hipertensivo: uma extensa revisão bibliográfica

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### ABSTRACT

Cardiovascular diseases (CVD) are the leading cause of mortality worldwide. In 2019, there were 17.9 million deaths due to CVD, representing 32% of all deaths that occurred this year<sup>1</sup>. As systemic arterial hypertension (SAH) is the main modifiable risk factor for the development of CVD, controlling it is essential to aim for greater survival for a population at risk. Thus, this literature review aimed to evaluate the efficacy of nebivolol in the treatment of SAH, as well as its safety profile, tolerability, and presence of side beneficial effects. To this purpose, the information contained in review articles, randomized clinical trials, and systematic reviews with or without associated meta-analysis, published between 2014 and 2020 in English or Portuguese languages, was compiled. The search for scientific articles occurred in the following databases: PubMed, Cochrane, Medline, and Google Scholar. Twenty-three articles that followed the eligibility criteria were found, and the randomized clinical trials totaled 4,278 patients evaluated. Nebivolol presented controls of systolic blood pressure and diastolic blood pressure comparable to the main drugs used in the treatment of this disease, being well tolerated by patients and also presenting some beneficial side effects such as reduction of inflammatory markers, reduction of vasoactive hormones, reduction of arterial stiffness, reduction of heart rate, increase of GFR, improvement of microvascular function and improvement of metabolic profile. Despite these positive data, further studies are needed to document the increased survival of patients treating SAH with this medication.

**Keywords:** Nebivolol; Nitric oxide; Arterial hypertension.

### RESUMO

As doenças cardiovasculares (DCV) são a principal causa de mortalidade mundial. Em 2019, houve 17,9 milhões de mortes devido a DCV, representando 32% de todas as mortes ocorridas nesse ano<sup>1</sup>. Uma vez que a hipertensão arterial sistêmica (HAS) é o principal fator de risco modificável para o desenvolvimento de DCV, seu controle é essencial para alcançar maior sobrevivência de uma população em risco. Assim, esta revisão de literatura teve como objetivo avaliar a eficácia do nebivolol no tratamento da HAS, bem como seu perfil de segurança, tolerabilidade e efeitos secundários. Foram compiladas informações contidas em artigos de revisão, ensaios clínicos randomizados e revisões sistemáticas com ou sem meta-análise associada, publicadas entre 2014 e 2020 nos idiomas inglês ou português. A busca por artigos científicos foi realizada nas seguintes bases de dados: PubMed, Cochrane, Medline e Google Scholar. Foram encontrados 23 artigos que seguiram os critérios de elegibilidade, e os ensaios clínicos randomizados totalizaram 4.278 pacientes avaliados. Nebivolol demonstrou controle eficaz da pressão arterial sistólica e diastólica, comparável aos principais medicamentos para HAS. Além disso, foi bem tolerado pelos pacientes e apresentou benefícios como redução de marcadores inflamatórios, hormônios vasoativos, rigidez arterial, frequência cardíaca, e melhorias na função renal, microvascular e perfil metabólico. Apesar desses resultados, mais estudos são necessários para confirmar o impacto na sobrevivência dos pacientes tratados com essa medicação.

**Descritores:** Nebivolol; Óxido nítrico; Hipertensão arterial.

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## INTRODUCTION

Systemic arterial hypertension (SAH) is a multifactorial pathological condition dependent on genetic, environmental, and social factors. It can be divided into two distinct classes: primary SAH, also called essential hypertension, which occurs when the permanent increase in blood pressure levels has no defined cause, and secondary SAH, which stems from an identifiable cause, i.e., that arises due to an underlying disease. For example, in adults, the most common causes of secondary SAH are renal parenchymal disease, renovascular hypertension, hyperaldosteronism, obstructive sleep apnea syndrome, and drug-induced SAH<sup>1-5</sup>.

Since cardiovascular diseases (CVD) are the leading cause of death and hospitalizations worldwide<sup>2,4,6</sup>, it is essential to develop and evaluate existing measures capable of reducing blood pressure (BP) since it, when elevated, is the main modifiable risk factor for developing CVD<sup>2</sup>.

The first line of treatment for SAH is non-drug treatment, which consists of adopting a healthier lifestyle and habits. Adopting healthy habits, such as proper diet<sup>7-9</sup> weight loss, and physical exercise, can reduce cardiovascular risk and improve the effect of drug treatment.

Although there is no consensus value about BP, when drug treatment should be initiated, current guidelines recommend that patients with SAH grade 1 should be evaluated and submitted to treatment if there is increased cardiovascular risk, and patients with SAH grades 2 and 3 should generally undergo drug treatment<sup>2-5</sup>. Currently, the first-line classes of medications recommended for BP reduction are thiazide diuretics, calcium channel blockers (CCB), angiotensin-converting enzyme inhibitors (ACEI), and angiotensin receptor blockers (ARBs).

Recommended for many decades as the first line of treatment, beta-blockers (BB) are responsible for preventing the binding of endogenous catecholamines to beta receptors<sup>10</sup>, thus causing a reduction in blood pressure due to decreased heart rate and contractility. However, clinical trials and meta-analyses have questioned the efficacy of BB as the first-line treatment for arterial hypertension, so current guidelines recommend the use of this class in exceptional cases such as the association of SAH with the following pathologies: heart failure, coronary artery disease (CAD), angina and atrial fibrillation (AF) or as an option for young hypertensive women who wish to become pregnant, as an alternative to ACE inhibitors and ARBs<sup>4,6</sup>.

However, it is known that studies that questioned the efficacy of beta-blockers were conducted by first

and second-generation drugs and, therefore, do not correspond to the reality of treatment with third-generation BB such as nebivolol and carvedilol.

Nebivolol is a drug with a better pharmacodynamic and kinetic profile when compared to former beta-blockers. Although it exerts a reduction in blood pressure, very similar to other BB, nebivolol is also able to perform nitric oxide (NO)-mediated vasodilation, improve arterial stiffness and biochemical parameters, decrease oxidative stress (OE), reduce chronic inflammation and improve microvascular and erectile function in men. In addition, nebivolol is currently the beta-blocker with greater selectivity for  $\beta$ -1 receptors, which avoids side effects common to other BBs, such as fatigue, exercise intolerance, and bronchospasm. It has a good dosage, with single daily administration ranging from 5 to 40mg. Therefore, nebivolol can exert the same reduction in systolic blood pressure (SBP) and diastolic blood pressure (DBP) as other BBs, with fewer side effects and more beneficial side effects.

Since beta-blockers are indicated in the treatment of SAH under special conditions, according to recent treatment protocols, this review aims to evaluate the use of nebivolol in the treatment of primary SAH by analyzing randomized clinical trials, reviews, and relevant publications on the subject.

## METHODOLOGY

The search and reading of articles occurred between August 7, 2020, and January 15, 2021, and was performed through the following databases: PubMed, Cochrane, Medline, and Google Scholar. Reviews, meta-analyses, and randomized clinical trials published between 2014 and 2020 were included. The most recent hypertension guidelines were also used to obtain data. The terms used to search for articles are listed in table 1.

**Table 1.** Terms used to search for articles in the selected databases

Terms
Beta blocker
Nebivolol
Neblock
Bystolic
Byvalson
Beta 1 selective blocker
"Nebivolol" AND "hypertension"
"Nebivolol" AND "erectile dysfunction"
"Bystolic" AND "hypertension"
"Neblock" AND "hypertension"
"Byvalson" AND "hypertension"
"Beta 1 selective blocker" AND "hypertension"

Source: own authorship.

Inclusion criteria were randomized clinical trials, reviews, meta-analyses, and guidelines written in Portuguese or English that compared nebivolol with other antihypertensive drugs or placebo, written from 2014 onward and published in journals of the selected databases. Only articles that worked with adult patients were included.

The exclusion criteria were articles that did not attempt to treat systemic arterial hypertension in its various aspects with nebivolol, or that discontinued its use during the clinical trial were also excluded. Articles before December 2014 were also excluded, except the JNC8 guideline. Furthermore, after the pre-selection of articles, which was accomplished by reading the title and abstract, we researched the impact factor of the journals where these articles were published. This review did not include articles with inaccurate data or low methodological quality.

Regarding literature reviews, only those that were substantiated and of good methodological quality were included. Simple reviews were not included.

Articles that followed the inclusion criteria and had no exclusion criteria were considered eligible.

## RESULTS

A total of 23 articles were included in this review, including seven review articles, 12 double-blind randomized clinical trials, one single-blind clinical trial, and three unblinded clinical trials.

In all, the clinical trials totaled 4,278 patients evaluated. A summary of the clinical trials contained in this review, with the main aspects of each article, is included in table 2.

Regarding the clinical trials included in this review, nebivolol was compared with other BBs in 53.3% of the articles and the other 46.6% with other classes of drugs. Graph 1 shows the number of times nebivolol was compared with each drug.

The drug under study proved to be effective in reducing SBP and DBP, both in ABPM and on an outpatient basis. In some clinical trials, nebivolol was more effective, or at least similar, to drugs currently considered first-line antihypertensive treatment<sup>12,13,14,15,16</sup>. As expected, nebivolol was more effective than placebo at reducing blood pressure levels<sup>17</sup>.

Nebivolol also showed some beneficial side effects, which will be described below. These are reduction of vasoactive hormones<sup>14-17</sup>, reduction of inflammatory markers<sup>15,18</sup>, improved metabolic profile<sup>11,15,18</sup>, reduction of arterial stiffness<sup>17,19,20</sup>, increased GFR<sup>14,21</sup>, improvement of microvascular function, due to NO-mediated vaso-

dilation<sup>22,23,24</sup> and reduced heart rate, which was reduced in all clinical trials that evaluated these parameters, except with Farag et al. (2018)<sup>25</sup>. According to the author, this may have happened because the CF of patients at baseline was no longer high. However, the real reason for this finding remains uncertain.

## DISCUSSION

Cardiovascular diseases are a set of diseases that affect the heart and blood vessels, especially CAD and cerebrovascular disease. These are the leading causes of mortality in the world, and systemic arterial hypertension corresponds to the main modifiable risk factor for CVD.

In 2015, the global prevalence of SAH in the population was estimated at 1.13 billion people<sup>4,26</sup>. This number tends to increase in the coming years, totaling 1.5 billion in 2025. In Brazil, the prevalence in the Brazilian population is 32.3%, and in the population over 70 years old, this number is 71.7%<sup>2</sup>.

Because it is usually a silent disease, most of the diagnoses of SAH occur by chance after years of increased BP levels. This period is enough to do organic damage and structural changes that may end up culminating in several diseases, such as heart failure, stroke, acute myocardial infarction, chronic kidney disease (CKD), CAD, OS, endothelial dysfunction, arterial stiffness, diabetes mellitus, AF and sudden cardiac death<sup>2,3,4</sup>.

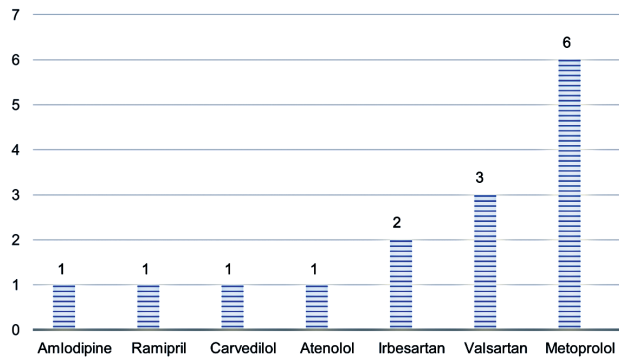
In addition to SAH and cardiovascular diseases being the leading cause of death worldwide, totaling an average of 10.4 million deaths per year<sup>3</sup>, the impact of these diseases on public health systems is such that by 2030, an estimated expenditure of US\$200 billion in health care resources for the treatment of SAH in the U.S is expected<sup>25</sup>. With this in mind, Chen et al. (2015)<sup>25</sup> sought to evaluate the financial impact of switching from metoprolol to nebivolol in hypertensive patients for the American public health system. Such a switch led to fewer cardiovascular-related outpatient and emergency department visits, causing an average cost reduction of US\$40 per month for each patient. In this scenario, we chose to evaluate the treatment of SAH with nebivolol.

Since it is a group of drugs with very discrepant treatment outcomes in treatment, propranolol, a 1st generation BB, should not have the same levels of recommendations as nebivolol, a 3rd generation BB, for example. Therefore, this review aims to evaluate the effects of nebivolol in the treatment of SAH.

**Table 2.** Table containing a brief summary of the clinical trials used as a basis for the development of this review.

Author/year/ country	Characteristic of the population and time of study	Trial design
Giles <i>et al.</i> <sup>(16)</sup> 2015 USA	797 patients completed this randomized, double-blind clinical trial. Among them were men and women over 18 years old, with a mean age of 51 years.	To evaluate the effect of nebivolol (10 or 40mg) and valsartan (160 or 320mg) treatments alone and in combination on the renin-angiotensin-aldosterone system by dosing plasma renin and aldosterone. The N/V doses used were 5/80, 5/160 and 10/160mg.
Hayek <i>et al.</i> <sup>(19)</sup> 2014 USA	30 hypertensive patients with a mean age of 55 years completed this 12-week, double-blind, randomized clinical trial.	To evaluate whether treatment with nebivolol (5-10mg), or with metoprolol (50-100mg), could improve arterial stiffness, increase the amount of circulating progenitor cells, and reduce OS.
Mende <i>et al.</i> <sup>(14)</sup> 2016 USA	2,692 (male and female) hypertensive patients completed this 8-week randomized, double-blind, placebo-controlled clinical trial. Among them, 1,832 were obese and 847 were non-obese.	To evaluate BP, CF, ABPM, plasma aldosterone and glomerular filtration rate (GFR) in obese and non-obese patients with SAH after treatment with nebivolol (10 and 40mg), valsartan (160 and 320mg) and nebivolol/valsartan (N/V) combination. N/V doses: 10/160, 10/320 and 20/320mg.
Diehl <i>et al.</i> <sup>(32)</sup> 2015 USA	42 patients (26 men and 16 women) with hypertension completed this randomized, double-blind, placebo-controlled, 3-month clinical trial.	To evaluate whether nebivolol (5mg) or metoprolol (100mg) can reduce endothelin-1 (ET-1) levels.
Santos <i>et al.</i> <sup>(21)</sup> 2015 USA	29 hypertensive patients post renal transplantation participated in this 12-month randomized clinical trial. The mean age was 53 years in the nebivolol group (n=14) and 46 years in the metoprolol group (n=15).	To evaluate the treatment with nebivolol and metoprolol in patients with recently transplanted kidney in terms of blood levels of NO, GFR, and BP.
Neuman <i>et al.</i> <sup>(22)</sup> 2015 USA	19 hypertensive African-Americans (13 men and 6 women), aged 22 to 80 years, completed this 12-week double-blind randomized clinical trial.	To evaluate the impact of nebivolol (10mg) and metoprolol (100mg) on endothelial function in hypertensive African-American patients.
Velasco <i>et al.</i> <sup>(24)</sup> 2016 USA	25 hypertensive patients (11 men and 14 women) participated in this 12-week, double-blind, randomized clinical trial.	To analyze by ultrasonography, the perfusion in the forearm muscles at rest and after hand-grip in two different groups (nebivolol 10mg and metoprolol 150mg).
Duprez <i>et al.</i> <sup>(23)</sup> 2017 USA	60 patients (men and women) with borderline BP between 18 and 80 years old completed this randomized, double-blind, 9-month trial.	To evaluate the treatment of SAH with nebivolol (5-10mg) and atenolol (25-50mg). On the following aspects: elasticity of small and large arteries, BP at rest and during exercise, retinal analysis, electrocardiography, left ventricular mass, microalbuminuria and NT-proBNP.
Grassi <i>et al.</i> <sup>(12)</sup> 2016 ITALY	122 hypertensive patients (61 men and 61 women) with a mean age of 69.1 years completed this 12-week, double-blind, randomized clinical trial.	To evaluate the treatment of SAH, through the following parameters: SBP, DBP, ABPM, CF, BP change and treatment tolerance. One group received the combination nebivolol/hydrochlorothiazide (5/12.5mg), another group received irbesartan/hydrochlorothiazide (150/12.5mg).
Mose <i>et al.</i> <sup>(17)</sup> 2014 DENMARK	24 patients (14 men and 10 women) completed this 5-day randomized, double-blind, placebo-controlled clinical trial. The mean age was 60 years.	To evaluate nebivolol (5mg) vs placebo treatment in hypertensive patients on a standardized diet. Systemic NO dosage, BP, pulse wave velocity (PWV), central BP (CBP), GFR, vasoactive hormones, plasma nitrite/nitrate concentration, fraction excretion of sodium (FEna) and arterial stiffness were evaluated.
Ozyıldız <i>et al.</i> <sup>(11)</sup> 2015 TURKEY	80 patients (45 men and 35 women) with hypertension completed this 4-month randomized clinical trial. The mean age was 52.6 years in the carvedilol group (n=40) and 50.1 years in the nebivolol group (n=40)	To compare the effect of carvedilol (25mg) and nebivolol (5mg) on some parameters, such as: insulin resistance (IR), lipid profile, blood glucose and CF.
Walczak-Gąteżewska <i>et al.</i> <sup>(35)</sup> 2018 POLAND	57 hypertensive patients (all men), completed this 12-week randomized clinical trial. Ages between 16 and 28 years.	To evaluate the treatments with nebivolol (5mg) and ramipril (5mg) on the arterial stiffness index (ASI), BP on ABPM and some biochemical parameters such as: lipid profile, insulinemia, glycemia and high-sensitivity c-reactive (hsCRP).
Bikos <i>et al.</i> <sup>(15)</sup> 2018 GREECE	38 hemodialysis patients (23 men and 15 women) with intradialytic hypertension completed this randomized, single-blind, cross-over clinical trial. The mean age was 60.4 years.	To evaluate the effects of nebivolol (5mg) and irbesartan (150mg) on the peridialytic and intradialytic period and on ambulatory BP in patients with intradialytic hypertension. One group received the medication for 1 full week and another group received the medication only before hemodialysis.
Hussain, Mazhar <i>et al.</i> <sup>(18)</sup> 2017 PAKISTAN	100 hypertensive patients completed this 12-week, double blind, randomized clinical trial. The age of the patients was 32 to 56 years.	To evaluate the effect of nebivolol (5-10mg) compared to metoprolol (50-100mg), on the neutrophil lymphocyte ratio (NLR). BMI, BP, blood glucose, lipid profile, and lymphocyte count were also evaluated.
Farag <i>et al.</i> <sup>(20)</sup> 2018 EGYPT	137 patients (44 men and 93 women) completed this 12-week randomized clinical trial. The mean age was 55.4 in the A/V group (n=75) and 57.5 in the N/V group (n=62)	To compare the efficacy of anlodipine/valsartan (A/V) with nebivolol/ valsartan (N/V) combinations in reducing BP. Central and peripheral BP, pulse wave velocity and arterial stiffness were evaluated. The doses used were: A/V: 10/160mg and N/V: 5/160mg

Source: own authorship.



**Graph 1.** Overview of the number of times nebulolol was compared with other drugs in the randomized clinical trials contained in this review. Thus, it was compared six times with metoprolol, three times with valsartan, two times with irbesartan, one time with atenolol, one time with carvedilol, one time with ramipril, and one time with amlodipine. Source: own authorship.

## BETA-BLOCKERS

The beta-blocker class of drugs, also called beta-adrenergic blockers, prevents the binding of catecholamines, epinephrine, and norepinephrine by competitive inhibition of beta-adrenergic receptors.

All beta-adrenergic receptors use G protein for intracellular signaling, which, once activated, increases cyclic AMP (cAMP) and activates kinase protein, which will perform several functions, depending on the classification of the beta receptor and its location. Beta receptors can be divided into  $\beta$ -1,  $\beta$ -2, and  $\beta$ -3, according to their affinity for catecholamines. The  $\beta$ -1 receptors respond similarly to epinephrine and norepinephrine and can be found in the heart and renal juxtaglomerular cells. On the other hand,  $\beta$ -2 receptors are more sensitive to epinephrine than norepinephrine and are located mainly in vascular smooth muscle, liver, and bronchi. The  $\beta$ -3 receptors are located in the adipose tissue and respond better to norepinephrine than epinephrine.

The binding of catecholamines to  $\beta$ -1 receptors can increase BP through two distinct mechanisms: one by increasing cardiac output due to the positive chronotropic and inotropic effect, and the other by increasing systemic vascular resistance (SVR), which occurs after the secretion of renin by juxtaglomerular cells that activates the renin-angiotensin-aldosterone system (RAAS), causing peripheral vasoconstriction.

In cardiac tissue, the stimulation of  $\beta$ -1 receptors activates G protein that promotes an increase in cAMP, then activates protein kinase A. This, in turn, is responsible for increasing the concentration of intracellular  $\text{Ca}^{2+}$  through the phosphorylation of

dihydropyridine calcium channels and ryanodine receptors. The increase of intracellular  $\text{Ca}^{2+}$  increases its binding to troponin, which displaces tropomyosin, generating contractility.

Therefore, blocking  $\beta$ -1 receptors means reducing BP through the mechanisms of reduced cardiac output, reduced PVR, readaptation of baroreceptors, and decreased catecholamines in nerve synapses<sup>1</sup>.

According to selectivity, BBs can be distributed into three different categories: non-selective, cardioselective, and vasodilator action. Non-selective BB (propranolol) blocks both  $\beta$ -1 and  $\beta$ -2 adrenergic receptors. Consequently, they list significant side effects with formal contraindications in pneumopathic patients. On the other hand, Cardioselective BB (metoprolol) blocks only  $\beta$ -1 receptors and, therefore, has fewer side effects than non-selective BB. BB with vasodilator action, antagonizes alpha-1 receptors and can stimulate nitric oxide release, such as nebivolol. Thus, besides being highly selective to  $\beta$ -1 receptors and having fewer side effects related to  $\beta$ -2 receptor blockade, BB vasodilators also further reduce PVR due to the peripheral vasodilation they promote.

Beta-adrenergic blockers can also be classified as fat solubility. It consists of the ability of the drug to cross the blood-brain barrier. Highly fat-soluble agents, such as metoprolol, easily cross the blood-brain barrier and focus on brain tissue, causing side effects related to the central nervous system (CNS), such as mental confusion, lethargy, depression, nightmares, seizures, and coma. Water-soluble drugs, such as atenolol, have low CNS penetration and longer half-life, causing fewer adverse effects.

Due to heterogeneity and the wide range of drugs within this class, it is impossible to talk about BB excretion and metabolism in a generalized way. For example, water-soluble BB, such as atenolol and nadolol, have renal excretion and require adjustments in patients with chronic kidney disease. On the other hand, fat-soluble BBs such as metoprolol and carvedilol have hepatic metabolism and should be adjusted in patients with liver disease.

The same considerations made above are valid about contraindications. They depend on each specific drug (their cardioselectivity and liposolubility). However, in general, more adverse effects are expected in older generations. Bronchospasms, bradycardia, atrioventricular conduction disorders, and peripheral vasoconstriction are some of the main adverse effects<sup>2</sup>. It should be avoided in patients with pneumopathies and second and third-degree atrioventricular blocks<sup>2</sup>.

Although beta-blockers have been recommended as first-line treatment for SAH for several decades,

recent randomized clinical trials and meta-analyses have shown low effectiveness in preventing encephalic vascular accident (EVA)<sup>24</sup>, also presenting a 16% higher relative risk than other antihypertensive classes in patients with primary hypertension, of this event occurring<sup>8</sup>. This is the main reason why BB currently has specific indications. However, we still lack data comparing the efficacy of stroke prevention between first and third-generation beta-blockers.

## NEBIVOLOL

Nebivolol is a third-generation beta-blocker with nitric oxide-mediated vasodilator action, which has the highest cardioselectivity among beta-blockers, being 321 times more selective for  $\beta$ -1 receptors than for  $\beta$ -2<sup>27</sup> receptors, which makes its use safer and with fewer side effects when compared to other beta-blockers. It also differs from previous generations of BB by its positive impact on biochemical parameters and protective effect against oxidative stress<sup>11,28</sup>. It has a good dosage, usually administered only once a day, due to its high half-life, which commonly ensures better compliance with its treatment. It positively impacts the reduction of central blood pressure and DBP<sup>12,13,17,20</sup>.

It is a racemic mixture composed of enantiomers d-nebivolol and l-nebivolol. The beta-blocker effect of nebivolol results from l-nebivolol isomer activity, while d-nebivolol is responsible for NO release.

## PHARMACOKINETICS

The usual dose of nebivolol is 5mg/day and can reach 40mg/day. In patients older than 65 years, the recommended starting dose is 2.5mg/day, which is a general recommendation for any antihypertensive treatment in elderly patients, which should initially be done with reduced doses. It should be used preferably between meals, even if food intake does not affect its absorption. The antihypertensive effect has its average peak after 6 hours of ingestion.

Approximately 98% of nebivolol concentration in the bloodstream is linked to albumin. Bioavailability depends from patient to patient, ranging from 12% to 96%, depending on the health conditions of each patient. Similarly, the half-life varies depending on the patient, with numbers between 11 and 40h<sup>29,30</sup>.

Nebivolol is highly liposoluble and has hepatic metabolism through glucuronidation, direct N-Dealkylation, and direct hydroxylation, the latter two of which are the last routes by the CYP2D6 enzyme<sup>30,31</sup>. Its metabolites are excreted mainly by urine.

## PHARMACODYNAMICS

Although the release of nitric oxide by the vascular endothelium by stimulation of d-nebivolol is well established<sup>21,22</sup>, the exact mechanism behind this stimulation remains uncertain. The main hypothesis is that nebivolol increases the bioavailability of NO in the vascular endothelium through the L-arginine/nitric oxide pathway. In addition, nebivolol has been shown to reduce endothelial-1 peptide levels and, therefore, able to perform an anti-vasoconstrictor effect<sup>32</sup>.

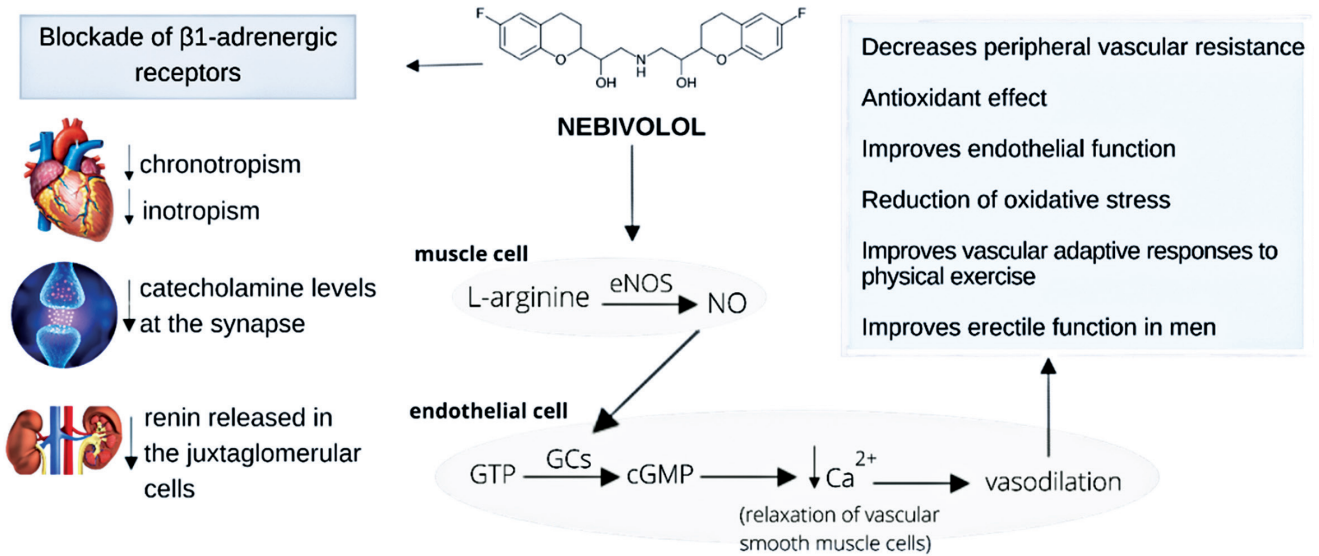
Nebivolol has a very high affinity for  $\beta$ -1 receptors, which confers a low list of adverse effects on lung tissue and is well tolerated in pneumopathic patients.

The chemical structure of nebivolol, as well as its antihypertensive mechanisms and its beneficial effects secondary to vasodilation, are detailed in figure 1 - Overview of the effects caused by nebivolol. By inhibiting  $\beta$ -1 adrenergic receptors, nebivolol performs its actions in cardiac, nervous, and renal tissue. In cardiac conduction tissue, d-nebivolol reduces chronotropism and inotropism, eventually reducing systemic blood pressure. In peripheral nervous tissue, it reduces the amount of catecholamines in the nerve synapses. In the kidneys, the secretion of renin by the juxtaglomerular apparatus is reduced, causing a reduction in the SRAA and BP. Regarding the capacity for NO release, l-nebivolol can stimulate the enzyme endothelial nitric oxide synthase (eNOS), which catalyzes nitric oxide production from L-arginine, NADPH, and molecular oxygen. Once produced, NO activates guanylate cyclase, which converts guanosine triphosphate (GTP) into cyclic guanosine monophosphate (cGMP), which ultimately reduces the amount of intracellular Ca<sup>2+</sup>, causing endothelium smooth muscle cell relaxation, ensuring the effects cited in the image.

## NEBIVOLOL AND BLOOD PRESSURE REDUCTION

All the clinical trials in this review showed the ability of nebivolol to reduce both SBP and DBP. In some studies, nebivolol had better results than some antihypertensive drugs, such as the combination nebivolol/hydrochlorothiazide, which was more effective than irbesartan/hydrochlorothiazide in reducing both SBP and DBP on ABPM<sup>12</sup>. It was also more effective than valsartan in reducing BP on ABPM, regardless of the patient's BMI<sup>14,16</sup>. It was also more effective than placebo and valsartan in lowering SBP and DBP on DBPM<sup>16</sup>.

In other trials, it was similarly effective to metoprolol<sup>15,19,21,22,24,32</sup>, carvedilol<sup>11</sup>, atenolol<sup>23</sup>, ramipril<sup>15</sup>, and valsartan, reducing both brachial and central BP<sup>13</sup>.



**Figure 1.** Overview of the effects caused by nebivolol. By inhibiting  $\beta$ -1 adrenergic receptors, nebivolol performs its actions in cardiac, nervous, and renal tissue. In cardiac conduction tissue, d-nebivolol reduces chronotropism and inotropism, eventually reducing systemic blood pressure. In peripheral nervous tissue, it reduces the amount of catecholamines in the nerve synapses. In the kidneys, the secretion of renin by the juxtaglomerular apparatus is reduced, causing a reduction in the SRAA and BP. Regarding the capacity for NO release, L-nebivolol can stimulate the enzyme endothelial nitric oxide synthase (eNOS), which catalyzes nitric oxide production from L-arginine, NADPH, and molecular oxygen. Once produced, NO activates guanylate cyclase, which converts guanosine triphosphate (GTP) into cyclic guanosine monophosphate (cGMP), which ultimately reduces the amount of intracellular Ca<sup>2+</sup>, causing endothelium smooth muscle cell relaxation, ensuring the effects cited in the image. Source: own authorship.

However, Farag et al. (2018)<sup>20</sup> showed that nebivolol was less effective than amlodipine in the amlodipine/valsartan vs nebivolol/valsartan combination in both ABPM and central BP.

The SBP and DBP reduction and the safety profile of nebivolol were studied in a systematic review with associated meta-analysis, which compiled the information contained in 34 randomized clinical trials, totaling 12,465 hypertensive patients studied. In this meta-analysis, nebivolol performed better in controlling SBP than placebos and diuretics. It also achieved an SBP reduction similar to the ARB class. Compared to ACE inhibitors and CCBs, nebivolol was more effective or at least similar in SBP control. Nebivolol showed excellent control of DBP, showing superiority over ARBs, DIU, and other beta-blockers (atenolol, carvedilol, metoprolol, and atenolol)<sup>33</sup>.

When administered immediately before a dialysis session in patients with intradialytic hypertension, nebivolol reduced SBP and DBP in the intradialytic period. In the post-dialysis period, it reduced SBP but not DBP. When continuously administered, nebivolol kept the results described above, with the advantage of maintaining BP reduction also in the nighttime in ABPM and reducing DBP in the post-dialysis period<sup>15</sup>.

## NEBIVOLOL AND NITRIC OXIDE

The ability to cause endothelium-dependent vasodilation of nebivolol guarantees beneficial effects in its treatment, such as reduction of peripheral vascular resistance, antioxidant effect, improvement of endothelial function, reduction of oxidative stress, improvement of the adaptive response to exercise, and improvement of erectile function in men.

This review article contains five clinical trials that evaluated the amount of NO in plasma, either directly, through direct quantification, or indirectly, through a nitric oxide inhibitor, L-NMMA.

Neuman et al. (2015)<sup>22</sup> showed that in African-American hypertensive patients, nebivolol increased the bioavailability of NO in plasma. In addition, the use of NO inhibitor (L-NMMA) caused higher vasoconstriction in the group that received nebivolol, suggesting a more significant presence of plasma NO in this group. This study also showed a higher exercise-induced vasodilation in the nebivolol group. Santos et al. (2015)<sup>21</sup> showed that, after 12 months of treatment, nebivolol caused a significant increase in plasma NO in patients under 50 years who underwent kidney transplantation. In the group over 50, there was not so much difference.

Duprez et al. (2017)<sup>23</sup> indirectly visualized the increase in NO caused by nebivolol through the increase in elasticity of small and large arteries, measured through pulse contour analysis. Velasco et al. (2016)<sup>24</sup> analyzed, through ultrasound imaging, the perfusion in forearm muscle tissue at rest and after handgrip exercise. After the treatment, metoprolol significantly reduced the increase in microvascular blood volume induced by handgrip exercise, which was not observed in the group treated with nebivolol.

Unlike the results obtained in the four clinical trials mentioned above, Mose et al. (2014)<sup>17</sup> did not detect a significant change in NO during nebivolol treatment. However, this result may be due to the study time being only five days. In addition, the method used to evaluate NO was indirect. In the entire treatment period, patients received amlodipine together, which may have masked the effect of nebivolol on NO.

## NEBIVOLOL AND ARTERIAL STIFFNESS

Increased arterial stiffness is characterized by changes in elasticity and distensibility of large arteries, which occurs due to an imbalance in the production and degradation of elastin and collagen in a pro-inflammatory scenario that may occur in conditions such as SAH and diabetes mellitus, for example. The replacement of elastin by collagen in the artery wall may result in increased arterial stiffening, related to the pathogenesis of cardiovascular and non-cardiovascular diseases, such as cerebral white matter lesions, Alzheimer's, and kidney damage.

Due to nebivolol's ability to perform nitric oxide-mediated vasodilation, increase circulating progenitor cell levels, and reduce oxidative stress, arterial stiffness might be reduced with its treatment. To evaluate this hypothesis, randomized clinical trials were conducted, so in this review, four studies that evaluated this theme are included.

Hayek et al. (2014)<sup>19</sup> evaluated the impact of nebivolol on arterial stiffness, and the result was positive only in patients who had never used beta-blockers before the clinical trial. Mose et al. (2015)<sup>17</sup> showed a positive impact of nebivolol on the reduction of arterial stiffness through pulse wave velocity (PWV), a gold standard method for diagnosing arterial stiffness. However, there was no change in the augmentation index, an indirect evaluation method of arterial stiffness. Farag et al. (2018)<sup>20</sup> evaluated changes in arterial stiffness using the nebivolol/valsartan combination after 6 and 12 weeks of treatment. This combination reduced arterial stiffness in PWV and the augmentation index at the end of the 6th and 12th weeks.

Therefore, in this review, two articles showed no alteration of nebivolol in arterial stiffness<sup>12,15</sup>, and two others did<sup>17,20</sup>. To better elucidate this theme, more clinical trials and reviews are needed.

## NEBIVOLOL AND OXIDATIVE STRESS

Although nebivolol achieved positive results in reducing oxidative stress compared to other beta-blockers, Hayek et al. (2014)<sup>19</sup> did not identify a significant impact of nebivolol on oxidative stress, assessed through plasma levels of aminothiols. According to the author, it may have been due to the marker used. In addition, another reason for the lack of effect in OS is that patients at the beginning of the trial already used antihypertensive drugs. In this assay, the following parameters were evaluated: arterial stiffness, oxidative stress, and amount of circulating progenitor cells.

No significant differences were obtained in the three parameters evaluated in both treatments. However, nebivolol significantly reduced pulse wave velocity in an analyzed subgroup of patients who had not yet used beta-blockers. In addition, nebivolol increased the circulating CD34+/CD133+ in this subgroup, suggesting improved regenerative capacity.

## NEBIVOLOL AND METABOLIC PROFILE

Due to the pathophysiology of SAH and the lifestyle adopted by most of these patients, there is a greater tendency to develop metabolic disorders in hypertensive patients. This population presents a 2.5 times greater risk of developing type 2 diabetes mellitus when compared to normotensive patients<sup>34</sup>.

Because it is a vasodilator beta-blocker, nebivolol might cause fewer side effects related to the metabolic profile, such as increased peripheral insulin resistance and worsening lipid profile, commonly occurring with traditional beta-blockers. To evaluate this hypothesis, we compiled the information from 2 randomized clinical trials and one literature review that evaluated the impact of nebivolol on metabolic markers.

Ozyıldız et al. (2016)<sup>11</sup> showed the ability of nebivolol to reduce fasting blood glucose, insulin levels, HOMA-IR, LDL-cholesterol, total cholesterol, apolipoprotein B, and increase HDL. However, there was no change in triglyceride and apolipoprotein A1 dosage. Hussain et al. (2017)<sup>18</sup> also found positive effects of nebivolol on fasting blood glucose, lipid profile, and BMI. Also, to reduce the neutrophil-lymphocyte ratio (NLR), a marker of systemic inflammation is defined as the neutrophil

count divided by lymphocyte count. This reduction in NLR suggests great potential to reverse subclinical inflammation in hypertensive patients.

Gałęzewska et al. (2018)<sup>35</sup> did not obtain expressive results in HDL, fasting blood glucose, and C-reactive protein.

In their review, Maria et al. (2017)<sup>34</sup> demonstrated nebivolol's positive or neutral impact on lipid profile. Nebivolol had a positive effect on glucose metabolism. It showed no inferiority compared to ACEIs regarding insulin sensitivity, even though this class is considered the first line for treating SAH in diabetic patients due to its positive impact on glucose metabolism. These positive results caused by nebivolol were well documented in this review, demonstrating a reduction in BP and good treatment tolerance, with a low incidence of adverse effects and high patient satisfaction.

### NEBIVOLOL AND THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM AND OTHER RENAL PARAMETERS

Plasma-renin activity is one of the biomarkers of the pathophysiology behind systemic arterial hypertension, via RAAS. Moreover, SAH is one of the leading causes of CKD, and endothelial dysfunction with NO deficiency is one of the pathophysiological mechanisms behind some diseases, such as some nephropathies, for example. Furthermore, the progression of CKD has been associated with NO deficiency<sup>21</sup>. With this in mind, researchers would evaluate the impact of nebivolol on some renal parameters, such as RAAS, GFR, sodium excretion fraction, urine output, and renal NO bioavailability.

Nebivolol had no significant impact on GFR<sup>14,17,19</sup>. Mose et al. (2015)<sup>17</sup> also found no increase in renal NO bioavailability nor changes in urine output and sodium excretion fraction. However, the duration of their clinical trial was only five days, and the effects of nebivolol on NO bioavailability were assessed indirectly through L-NMMA infusion. Regarding vasoactive hormones, nebivolol performed well. Being able to reduce aldosterone<sup>14-17</sup>, noradrenaline<sup>15</sup>, angiotensin-2<sup>17</sup> and renin<sup>16,17</sup>, even with a dose-dependent effect<sup>16</sup>.

Lawrence et al. (2017)<sup>36</sup>, in their review with meta-analysis, compiled the information contained in 39 clinical trials, totaling 3987 patients, to evaluate the impact of vasodilator beta-blockers on renal function in hypertensive patients. The conclusion was that vasodilator beta-blockers, although they did not affect GFR and creatinine, were able to decrease proteinuria and renal vascular resistance.

### NEBIVOLOL AND TOLERANCE AND LIFE QUALITY

Beta-blockers should inhibit only  $\beta$ -1 adrenergic receptors to reduce adverse effects since they act only on cardiac tissue. However, the reality is that first and second-generation beta-blockers cause some degree of inhibition of  $\beta$ -2 receptors and can cause bronchoconstriction, exercise intolerance, weight gain, and worsening metabolic parameters.

However, nebivolol is the beta-blocker with the highest cardioselectivity, reducing adverse effects on other tissues. In addition, its ability to perform NO-mediated vasodilation ensures an excellent metabolic response to exercise and improved erectile function in sexually active men.

Although well tolerated and safe, nebivolol is not free of adverse effects like any other medicine. Headache and fatigue are the most commonly reported in the studies. Some clinical trials have directly evaluated the safety and tolerability of nebivolol, as in the NEHIS study<sup>12</sup> clinical trial, which observed good treatment support for the nebivolol/hydrochlorothiazide combination without the need for drug removal. However, out of 61 allocated in the group receiving this combination, five patients reported fatigue as the main adverse reaction.

Other clinical trials, however, have evaluated the quality of life of patients undergoing treatment with nebivolol indirectly, through NO-mediated vasodilation, which can perform positive functions in patients, such as improved erectile function in men<sup>34</sup> and improved microvascular response to exercise<sup>22,24</sup>. Neuman et al. (2015)<sup>22</sup> showed nebivolol's ability to increase NO's bioavailability at rest and adaptive vasodilation to handgrip exercise in hypertensive African American patients. Velasco et al. (2016)<sup>24</sup> found that nebivolol did not cause impairment in microvascular recruitment during handgrip exercise in hypertensive patients.

Another important aspect of quality of life is related to sexual satisfaction. Erectile dysfunction, defined as the inability of men to initiate or maintain a penile erection that enables satisfactory sexual activity, affects about 100 million men<sup>34</sup>, and the prevalence is even higher in hypertensive patients. In addition, some medications are related to an increased risk of developing erectile dysfunction, such as traditional beta blockers and thiazide diuretics. Due to the vasodilator property of nebivolol, this adverse effect of earlier-generation beta-blockers might be mitigated and perhaps even partly solved. Randall et al. (2017)<sup>3</sup> compiled the information obtained from 4 researchers that evaluated the effect of nebivolol on erectile function in hypertensive men. The drug positively impacted two studies and was neutral in

the other two. It is therefore concluded that nebivolol may be helpful in hypertensive men with erectile dysfunction or at risk of developing it.

## CONCLUSION

Nebivolol proved to be as effective as the drugs currently considered first-line for antihypertensive treatment. It was also safe and well tolerated by patients. It also showed beneficial side effects, such as reduction of peripheral vascular resistance, improvement of microvascular function, reduction of arterial stiffness, positive or neutral impact on metabolic profile, and improvement of erectile dysfunction.

Despite these positive data, further studies are needed to document the increased survival of patients who treat SAH with this medication, especially in the prevention of acute coronary syndromes and stroke.

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## CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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