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Reviews

# Recent advances in the treatment of renal diseases with nebivolol: A literature review

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ABSTRACT

Reactive oxygen species play an important role in both acute and chronic kidney diseases. Chronic kidney disease is associated with various consequences to the cardiovascular system and metabolic profiles. Nebivolol, a highly cardioselective third-generation β-blocker, has nitric oxide (NO) induced vasodilation and antioxidant properties. Nebivolol affects the endothelial NO pathway in two complementary ways: it increases endothelial mediated NO expression and has antioxidant action, which leads to a decrease in degradation. Central blood pressure can be effectively lowered by nebivolol in the prehypertension phase. Clinically nebivolol's ability to modulate endothelial dysfunction may offer additional vascular protection in treating hypertension. As well, pre-treatment with 5 mg nebivolol every 24 hours for 4 days is protective against nephrotoxic effects of contrast media. The aim of this study is to review the current literature on the efficacy and safety of nebivolol in the treatment of various states of renal diseases.



## 1. Introduction

Beta-blockers are the second line agents in treatment of hypertension excluding patients with coronary artery diseases as well as it has not been received the Food and Drug Administration (FDA) approval in patients with heart failure. Nebivolol is a novel β-blocker that has been available for a number of years for the treatment of hypertension, either taken alone or in combination with other antihypertensive agents. It is a third-generation β-blocker that exhibits highly selective β1-adrenergic receptor blockade and nitric oxide mediated vasodilation. The beneficial effects of nebivolol as an antihypertensive treatment are not associated with the usual side effects of other β-blockers. Nebivolol was also shown to interfere with amyloid-β protein precursor (AβPP) processing in neuronal like cells and exert estrogen like neuroprotective effects. Animal study by Wang et al. showed that chronic application of nebivolol is highly tolerable and safe and can significantly reduce neuropathology in the brain, which is one of the most important parameters for primary prevention of Alzheimer's disease (AD) [1].

## 2. Method

This paper has written in accordance with review of systematic literature search via PubMed from inception to December 2015 and Google Scholar using medical subject headings that combined with terms for acute kidney injury or chronic kidney disease. Then this method supplemented with author's working knowledge and reference lists of review article and textbooks, and with references in articles that author found relevant.

## 3. Pharmacology of nebivolol

### 3.1. Pharmacodynamics

Generally, in pharmacology references beta-blockers are categorized as cardioselective (atenolol, bisoprolol, metoprolol, nebivolol), non-selective (nadolol, propanolol, timolol), intrinsic sympathomimetic activity (acebutolol, carteolol, penbutolol, pindolol) and mixed α- and β-blockers (carvedilol, labetalol). Currently, based on receptor affinity and hemodynamic properties, available β-blockers can be categorized into one of four principle groups: non-cardioselective and non-vasodilatory, cardioselective and non-vasodilatory, non-cardioselective and vasodilatory, cardioselective and vasodilatory. A fifth category is non-selective β-blockade with intrinsic sympathomimetic activity, example of which is pindolol; this latter group has fallen into disfavor because

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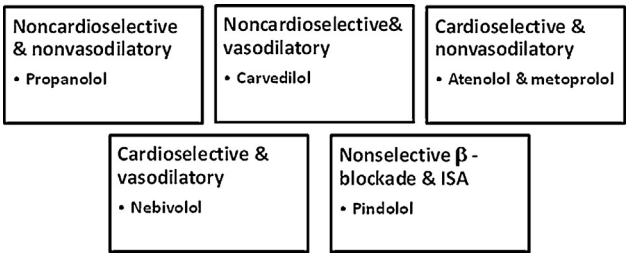


**Fig. 1.** Classification of beta-blockers based on receptor affinity and hemodynamic properties. Nebivolol is a vasodilator, highly selective $\beta_1$-blocker that works by generating and releasing nitric oxide while having a complimentary antioxidant effect without intrinsic sympathomimetic activity. ISA: intrinsic sympathomimetic activity.

data demonstrate that they actually increase peripheral vascular resistance and attenuate the decrease heart rate and cardiac output that may negate any benefit in a cardiovascular disease population (Fig. 1).

Nebivolol has the highest cardioselectivity of any currently available β-blockers, exhibiting a 321-fold higher selectivity for the $\beta_1$-adrenoceptor activity compared with the $\beta_2$-adrenoceptor (this selectivity for propanolol, metoprolol, bisoprolol, celiprolol and carvedilol is 1, 74, 103, 69 and 1 respectively). Nebivolol is a racemic mixture made up of equal amounts of D and L-nebivolol. It is the D-isomer that is primarily responsible for the selective $\beta_1$-adrenoceptor antagonist activity. In addition, vasodilatory properties of nebivolol are not related to $\alpha$-$_1$ receptor blockade but the vasodilation is mediated by its effects on nitric oxide through the stimulation of the endothelial beta$_3$-adrenergic receptor (AR) instead [2]. Nebivolol might also activate the beta$_2$-AR and it is also a G protein-coupled receptor kinase (GRK)/β-arrestin biased agonist.

The beta$_3$-adrenergic receptor has been shown to produce a negative inotropic effect that antagonizes the activity of beta$_1$- and beta$_2$-ARs. The beta$_3$-AR is activated at higher concentrations of catecholamines than required for beta$_1$- and beta$_2$-ARs and is thought to act as a counter-mechanism during sympathetic overstimulation. The beta$_3$-AR-mediated signalling also results in nitric oxide (NO) generation from endothelial nitric oxide synthase (eNOS). Activation of the beta$_3$-AR by nebivolol likely stimulates many cytoprotective signalling cascades, which ultimately result in the cardioprotection. Nitric oxide is synthetized from the amino acid L-arginine by a family of enzymes, the nitric oxide synthases, through a metabolic route namely the L-arginine-nitric oxide pathway. The synthesis of nitric oxide is produced by vascular endothelium for the vasodilator tone that is essential for the regulation of blood pressure [3].

Nebivolol affects the endothelial NO pathway in two complementary ways. It increases endothelial mediated NO expression and has also antioxidant action, which leads to a decrease in degradation. The most interesting and likely clinically relevant property of nebivolol is its ability to cause specific endothelial vasodilation. Although several mechanisms have been proposed for nebivolol-induced relaxations, including estrogen receptor-dependent eNOS translocation and phosphorylation of the serine 1177 or stimulation of serotonin receptors, the most attractive concepts in this regard include activation of eNOS via binding of a nebivolol metabolite to $\beta_2$-receptor, direct binding of nebivolol to the $\beta_3$-receptor, and/or stimulation of endothelial adenosine triphosphate efflux. Immunohistochemistry revealed the presence of β2- but not β1-receptors on endothelial cells. Further, in human and rodent coronary micro-vessels, nebivolol induces vasodilation via endothelium-dependent hyperpolarization and NO, an effect that is abolished by eNOS inhibition, is specifically blocked by $\beta_3$-inhibitors, and is absent in $\beta_3$-knockout animals. Finally, nebivolol stimulates endothelial adenosine triphosphate efflux, increasing endothelial calcium levels via P2Y-receptors and determining calcium-dependent activation of the eNOS in the renal glomerular microvasculature. Nebivolol or its metabolite may also activate $\beta_2$ (in conduit arteries) or $\beta_3$-receptors (in resistance arteries), which also increase intracellular calcium, thereby activating eNOS. Improvement of endothelial (vascular) dysfunction in vivo may thus be secondary to inhibition of superoxide-producing enzymes such as the nicotinamide diphosphate [NAD(P)H] oxidase, mitochondria, or the cyclooxygenase, or to recoupling of the eNOS. Nebivolol also improves endothelial function, reduces vascular superoxide production via prevention of eNOS uncoupling, reduces vascular macrophage infiltration, and inhibits NAD(P)H oxidase-dependent superoxide production in neutrophils isolated from hyperlipidemic rabbits. The antioxidant properties of nebivolol are not mediated by β-AR agonism or antagonism. Nebivolol may scavenge ROS by direct interaction with the free radicals and by acting as a chain breaking antioxidant through proton donation and electron stabilization. Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase is a major source of superoxide anions in the vascular wall. Nebivolol inhibits the association of the NADPH oxidase subunits p67phox and Rac1, probably because of a direct effect on cell membrane fluidity. An increased level of superoxide anions may lead to eNOS uncoupling because of oxidation of both tetrahydrobiopterin, an essential cofactor for eNOS, and the zinc thiolate complex of the enzyme. The uncoupled eNOS produces more superoxide anions than NO does. Superoxide anions can interact with NO to form peroxynitrite, a highly toxic ROS, which further accelerates eNOS uncoupling. This vicious circle may be interrupted by nebivolol due to its antioxidant properties. Indeed, several in vivo and in vitro studies show that nebivolol prevents eNOS uncoupling, increases NO bioavailability, and improves endothelium-derived nitric oxide (EDNO) – mediated vasodilatation. Nebivolol also inhibits the activity of neutrophil NADPH oxidase, implying a broader antioxidant and anti-inflammatory action of this β-blocker [4]. Nebivolol, in NO-dependent ways, also inhibits vascular smooth muscle proliferation, platelet aggregation, oxidative stress and inflammatory leukocyte adhesion. Therefore, nebivolol may inhibit vascular remodelling and ameliorate target organ damage resulting from the hypertensive process [5] (Fig. 2).

Clinically nebivolol's ability to modulate endothelial dysfunction may offer additional vascular protection in treating hypertension. Nebivolol also appears to function as an antioxidant and is able to modify markers of oxidative stress. Oxidative stress is known to play an important role in the development of renal diseases such as glomerulonephritis, drug-induced nephrotoxicity and chronic kidney disease [6]. Chronic kidney disease is associated with mitochondrial dysfunction that leads to an imbalance between reactive oxygen species and the natural antioxidants that normally quench these pathological free radicals. In particular hypertensive nephropathy and proteinuria have been directly linked to salt induced oxidative stress [7]. One report showed that high salt intake activates the renin-angiotensin system, urinary protein excretion and nitro-oxidative markers in rat models. By using of a novel β-blocker with antioxidant function, this study showed that kidney damage associated with oxidative stress is independent of the hemodynamic damage of hypertension induced by the high salt diet [8]. In central nervous system, nitric oxide is a neurotransmitter that underpins several functions including the formation of memory, physiologic role in vision, feeding behavior, nociception and olfaction. In the periphery, there is a widespread network of nerves, previously recognized as nonadrenergic and non-cholinergic, that operate through a nitric oxide-dependent mechanism to mediate some