

## STATE-OF-THE-ART PAPER

# Nebivolol

## The Somewhat-Different $\beta$ -Adrenergic Receptor Blocker

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Although its clinical use in Europe dates almost 10 years, nebivolol is a  $\beta$ -blocker that has been only recently introduced in the U.S. market. Like carvedilol, nebivolol belongs to the third generation of  $\beta$ -blockers, which possess direct vasodilator properties in addition to their adrenergic blocking characteristics. Nebivolol has the highest  $\beta_1$ -receptor affinity among  $\beta$ -blockers and, most interestingly, it substantially improves endothelial dysfunction via its strong stimulatory effects on the activity of the endothelial nitric oxide synthase and via its antioxidative properties. Because impaired endothelial activity is attributed a major causal role in the pathophysiology of hypertension, coronary artery disease, and congestive heart failure, the endothelium-agonistic properties of nebivolol suggest that this drug might provide additional benefit beyond  $\beta$ -receptor blockade. Although lesser  $\beta$ -blocker-related side effects have been reported in patients with chronic obstructive pulmonary disease or impotence taking nebivolol, side effects and contraindications overlap those of other  $\beta$ -blockers. Clinically, this compound has been proven to have antihypertensive and anti-ischemic effects as well as beneficial effects on hemodynamics and prognosis in patients with chronic congestive heart failure. Further studies are now necessary to compare the benefit of nebivolol with that of other drugs in the same class and, most importantly, its prognostic impact in patients with hypertension. (J Am Coll Cardiol 2009;54:1491-9) © 2009 by the American College of Cardiology Foundation

Nebivolol ( $\alpha, \alpha'$ -[iminodimethylene]bis[6-fluoro-2-chrommethanol]) is a third-generation  $\beta$ -adrenergic receptor blocker with vasodilator properties. Unlike those of carvedilol, which are mediated by  $\alpha$ -adrenergic receptor blockade, these hemodynamic effects are in the case of nebivolol primarily mediated by a direct stimulatory effect on the endothelial nitric oxide synthase (eNOS).

This review focuses on the processes underlying endothelial dysfunction in cardiovascular disease and discusses the mechanisms by which  $\beta$ -blockade with nebivolol may improve this condition. Finally, it summarizes the clinical effects of nebivolol treatment in patients with arterial hypertension and chronic congestive heart failure.

### Mechanisms Underlying Endothelial Dysfunction

By releasing a number of different substances, the endothelium modulates not only the tone but also the structure and biology of blood vessels. Produced via 2-step oxidation of the amino acid L-arginine, nitric oxide (NO) has potent antiatherosclerotic properties, and it works in concert with prostacyclin to inhibit platelet aggregation, neutrophil adhesion to endothelial cells, and expression

of inflammatory molecules. In high concentrations, NO inhibits the proliferation of smooth muscle cells. The very short half-life of this highly unstable free radical is primarily determined by its capacity to react with other oxygen-derived free radicals like superoxide to form the highly reactive intermediate peroxynitrite (Fig. 1). Beyond this direct NO scavenging effect, superoxide and peroxynitrite may trigger mechanisms that are opposite to those of NO and, in high concentrations, have cytotoxic effects mediated by direct oxidative damage of proteins, lipids, and deoxyribonucleic acid (1). Therefore, tissue superoxide production and subsequent peroxynitrite formation exert a major influence on vascular homeostasis and NO bioavailability in both experimental models and human disease.

In line with this, we recently reported evidence confirming a direct role of oxidative stress in cardiovascular pathophysiology, as we observed that those patients who show evidence of vascular oxidative stress have a worse prognosis (Fig. 2) (2). Thus, medical treatment of vascular dysfunction should be aimed not only at increasing levels of NO but also at reducing those of vascular superoxide and peroxynitrite. In line with this, a number of studies have shown that substances that simply deliver NO such as organic nitrates will worsen rather than improve endothelial dysfunction via further peroxynitrite formation (3). Different therapeutic approaches therefore need to be sought: in the setting of endothelial dysfunction

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**Abbreviations and Acronyms**

- ACE** = angiotensin-converting enzyme
- eNOS** = endothelial nitric oxide synthase
- NO** = nitric oxide

tion and high oxidative stress, the ideal compound should stimulate NO production and simultaneously reduce oxidative stress within vascular tissues.

In this state-of-the-art review, we describe the pharmacokinetics of nebivolol and the NO-stimulating and antioxidant properties of this compound, and we present results of pre-clinical and clinical studies with respect to treatment of hypertension and heart failure.

**Nebivolol**

Nebivolol is a 1:1 racemic mixture of a D- and an L-isomer and is at present the only  $\beta$ -blocker whose structure differs fundamentally from that derived from propranolol (Fig. 3). A number of mechanisms combine to determine the hemodynamic changes induced by nebivolol. These include a negative chronotropic effect, inhibition of sympathetic outflow from cerebral vasomotor centers, inhibition of peripheral  $\alpha_1$ -adrenoceptors (4), suppression of renin activity, and most importantly, decreased peripheral vascular resistances. Interestingly, although nebivolol's D-isomer appears to possess relevant selective  $\beta_1$ -blocking and mild vasodilatory properties, the L-isomer determines the stimulation of eNOS and subsequent endothelium-dependent vasodilation (5), and

only at suprapharmacologic dosages does it exert  $\beta$ -blocking effects (6).

These differences between isomers might well have clinical implications, and separate administration of 1 of the 2 could be hypothesized for selected patients. In combination, the 2 stereoisomers of nebivolol cooperate in determining the hemodynamic impact of the drug (6,7). The very high selectivity for  $\beta_1$ - versus  $\beta_2$ -adrenergic receptors of the *d*-isomer (Table 1) explains the limited effects on airway reactivity and insulin sensitivity (8,9) as well as the lesser negative inotropic effect of nebivolol in patients with heart failure (10,11). Of note, this selectivity tends to be overcome at dosages >10 mg and in poor metabolizers, causing the loss of this positive characteristic of nebivolol. Although nebivolol has no intrinsic sympathomimetic activity (and actually has  $\alpha$ -blocking properties, like carvedilol), it possesses agonistic activity on  $\beta_3$ -receptors, which may partially contribute to explain its endotheliotropic effects (4).

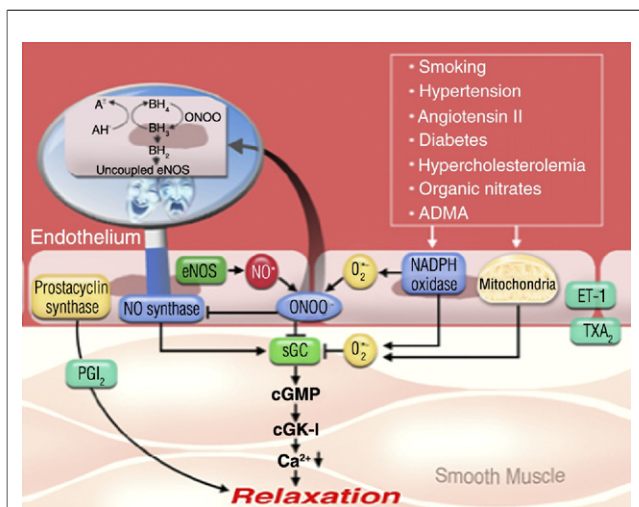
**Electrophysiological Properties**

Like other  $\beta$ -blockers, nebivolol has important electrophysiologic properties because it increases the ventricular fibrillation threshold, therefore reducing ventricular arrhythmias in animal models of ischemia- or drug-induced cardiomyopathy (12), and it reduces QT dispersion, a marker of arrhythmic risk (13). Further, nebivolol reduces P-wave dispersion on the electrocardiogram, which would attenuate the risk of atrial fibrillation, one of the leading causes of death in heart failure and hypertension (14).

**Endothelium-Dependent Vasodilator Effects**

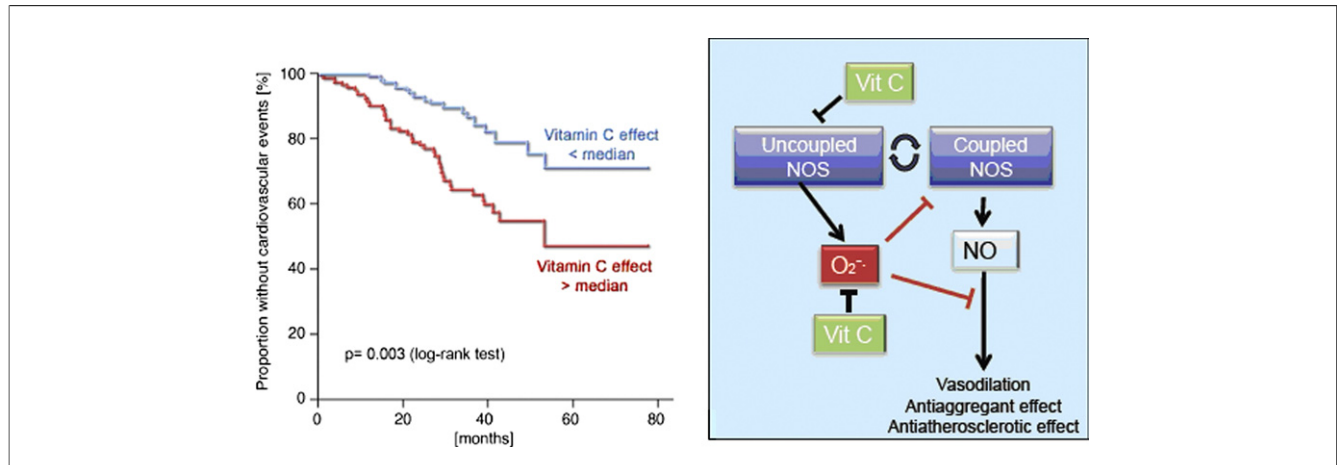
Along with its cardiac effects, the most interesting (and likely clinically relevant) property of nebivolol is its ability to cause specific endothelial vasodilation, as Gao et al. (15) demonstrated that the dose-dependent vasodilation induced by nebivolol is abolished after the removal of endothelium or inhibition of eNOS. Of note, other drugs in the same class, such as celiprolol or bopindolol, have also been shown to exert an eNOS-stimulatory effect similar to that of the L-isomer of nebivolol (15-20). Although several mechanisms have been proposed for nebivolol-induced relaxations, including estrogen receptor-dependent eNOS translocation and phosphorylation of the serine 1177 (21) or stimulation of serotonin receptors (16), the most attractive concepts in this regard include activation of eNOS via binding of a nebivolol metabolite to  $\beta_2$ -receptor (22), direct binding of nebivolol to the  $\beta_3$ -receptor (23), and/or stimulation of endothelial adenosine triphosphate efflux (Fig. 4) (24).

In a study by Broeders et al. (22), nebivolol per se was unable to cause vasodilation at all; however, when allowed to metabolize, the addition to aortic tissue increased endothelial calcium concentrations and doubled NO release in a  $\beta_2$ -receptor-dependent fashion. Immunohistochemistry revealed the presence of  $\beta_2$ - but not



**Figure 1** Mechanisms Underlying Endothelial (Vascular) Dysfunction in Vascular Disease

An unbalanced production of nitric oxide (NO) and superoxide ( $O_2^-$ ) leads to inappropriate formation of peroxynitrite ( $ONOO^-$ ). Peroxynitrite and superoxide cause vascular dysfunction through several mechanisms (reviewed in Forstermann and Münzel [1]). Peroxynitrite is a strong inhibitor of NO and prostacyclin ( $PGI_2$ ) signaling, and it may cause eNOS uncoupling, causing this enzyme to produce superoxide instead of NO. ADMA = asymmetrical dimethylarginine; cGMP = guanosine 3',5'-cyclic monophosphate; cGK = cGMP-dependent kinase; eNOS = endothelial nitric oxide synthase; ET = endothelin; sGC = soluble guanylate cyclase; TXA = thromboxane.



**Figure 2** Oxygen Free Radicals in Cardiovascular Pathophysiology

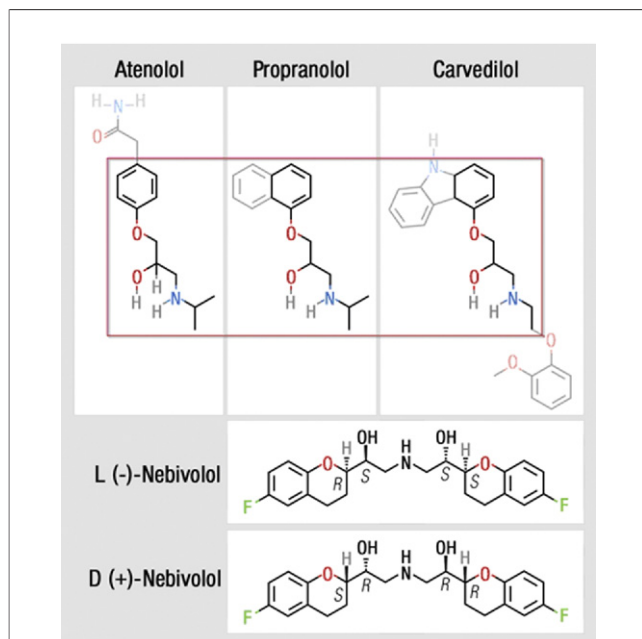
(Left) Kaplan-Meier analysis demonstrating cumulative proportion of patients without cardiovascular events during follow-up. Effect of vitamin C on acetylcholine-induced vasodilation is divided into values **below** and **above** the median. Interestingly, patients who responded well to vitamin C treatment had a worse prognosis compared with patients with a weak response to vitamin C. Thus, a strong vitamin C-induced improvement of endothelial dysfunction may point to increased oxidative stress in coronary arteries as well. (Right) Mechanistic hypothesis: vitamin C may restore eNOS function by either direct scavenging of superoxide (red) or by recoupling of the eNOS. Details in Forstermann and Münzel (1). NOS = nitric oxide synthase; Vit = vitamin; other abbreviations as in Figure 1.

$\beta_1$ -receptors on endothelial cells. Further, in human and rodent coronary microvessels, nebivolol induces vasodilation via endothelium-dependent hyperpolarization and NO (25), an effect that is abolished by eNOS inhibition, is specifically blocked by  $\beta_3$ -inhibitors, and is absent in  $\beta_3$ -knockout animals (23). 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 (24). Thus, the exact

mechanism of nebivolol-induced eNOS stimulation, particularly in humans, remains somewhat controversial.

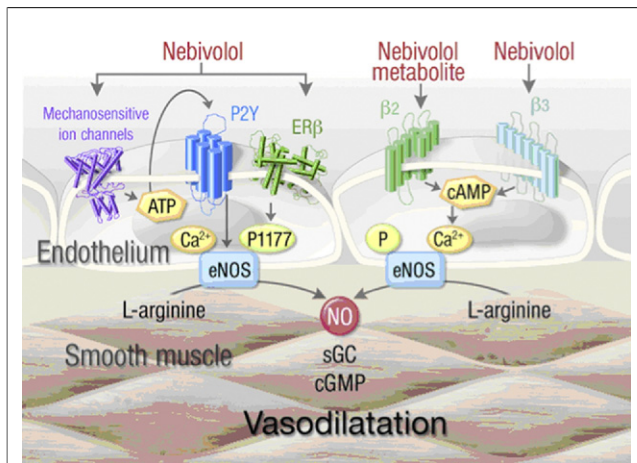
### Human Data

Evidence of eNOS-dependent vasodilator effects of nebivolol was also reproduced in humans in the arterial and venous circulation, where both direct endothelium-dependent vasodilation and increased responsiveness to other specific stimuli such as hyperemia were reported (26–28). Remarkably, the magnitude of this effect was similar across hypertensive patients and healthy volunteers (Fig. 5), which shows that the presence of vascular disease does not limit the endothelium-dependent vasodilator capacity—and hemodynamic benefit—achievable pharmacologically. Of note, similar data also were reproduced with celiprolol, which has been shown to cause direct coronary vasodilation (29). In a double-blind randomized study in hypertensive patients, Tzemos et al. (30) demonstrated that, despite having blood pressure-lowering effects comparable with those of atenolol, nebivolol therapy was associated with a highly significant improvement of NO-mediated endothelial function (Fig. 5). In line with these data, beneficial effects of



**Figure 3** Structure of Nebivolol Compared With Other  $\beta$ -Blockers

Table 1 Differential Selectivity of $\beta$ -Blockers for $\beta$ -Receptor Subtypes		
Compound	$\beta_1/\beta_2$ Selectivity	Additional Effect
Propranolol	1	
Metoprolol	74	
Bisoprolol	103	
Celiprolol	69	$\beta_2$ agonism (lungs, endothelium)
Carvedilol	1	$\alpha_1$ -blockade, antioxidant
Nebivolol	321	$\beta_{2-3}$ agonism (endothelium)



**Figure 4** Mechanisms Underlying Release of NO in Response to Acute Nebivolol Challenges

In renal glomeruli, nebulol activates mechanosensitive ion channels, which subsequently release adenosine triphosphate (ATP) and stimulate P2Y receptors, causing calcium-dependent eNOS activation (24). Nebivolol or its metabolite may also activate  $\beta_2$  (in conduit arteries) (22) or  $\beta_3$ -receptors (in resistance arteries) (23), which also increase intracellular calcium, thereby activating eNOS. cAMP = cyclic adenosine monophosphate; cGMP = cyclic guanosine monophosphate; ER $\beta$  = estrogen receptor beta; other abbreviations as in Figure 1.

nebulol treatment have been demonstrated in smokers (31) as well as in patients with hypertension (32) or coronary artery disease (33). Of note, the observation that the L- and the d-isomer of the drug possess different properties suggests that they could be separately administered to patients who can benefit from one more than the other.

### Nebivolol Reverses Endothelial Dysfunction in Animal Models of Oxidative Stress

As mentioned previously, an important determinant of the half-life of NO is the simultaneous production of reactive oxygen species in vascular endothelial and smooth muscle cells. Improvement of endothelial (vascular) dysfunction *in vivo* may thus be secondary to inhibition of superoxide-producing enzymes such as the nicotinamidediphosphate [NAD(P)H] oxidase, mitochondria, or the cyclooxygenase, or to recoupling of the eNOS (Fig. 1). We recently demonstrated that nebulol, but not other  $\beta$ -blockers, 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 (Fig. 5) (34). Similarly, in a model of angiotensin II-induced oxidative stress (35), we observed that nebulol, but not metoprolol, normalizes endothelial function, reduces superoxide formation, increases NO bioavailability, and inhibits up-regulation of the activity and expression of the vascular NAD(P)H oxidase (35), thus preventing eNOS uncoupling.

The effects of nebulol on endothelial NO, superoxide and peroxynitrite release were studied in human umbilical vein endothelial cells and iliac artery endothelial cells isolated from age-matched black and white Americans (36). The rate of NO release was 5 times slower in black than in white subjects, whereas the rates of release were 2 times faster for superoxide and 4 times faster for peroxynitrite. Pre-treatment with nebulol restored NO bioavailability in endothelial cells from black donors with concurrent reductions in superoxide and peroxynitrite, similar to levels in the endothelium of white subjects. The effects of nebulol were clearly dose dependent and not observed with atenolol. In addition, similar effects were observed with apocynin, an NAD(P)H oxidase inhibitor (36), suggesting that NAD(P)H oxidase activation may subsequently trigger eNOS uncoupling (Fig. 6) as demonstrated by our animal experiments (34,35).

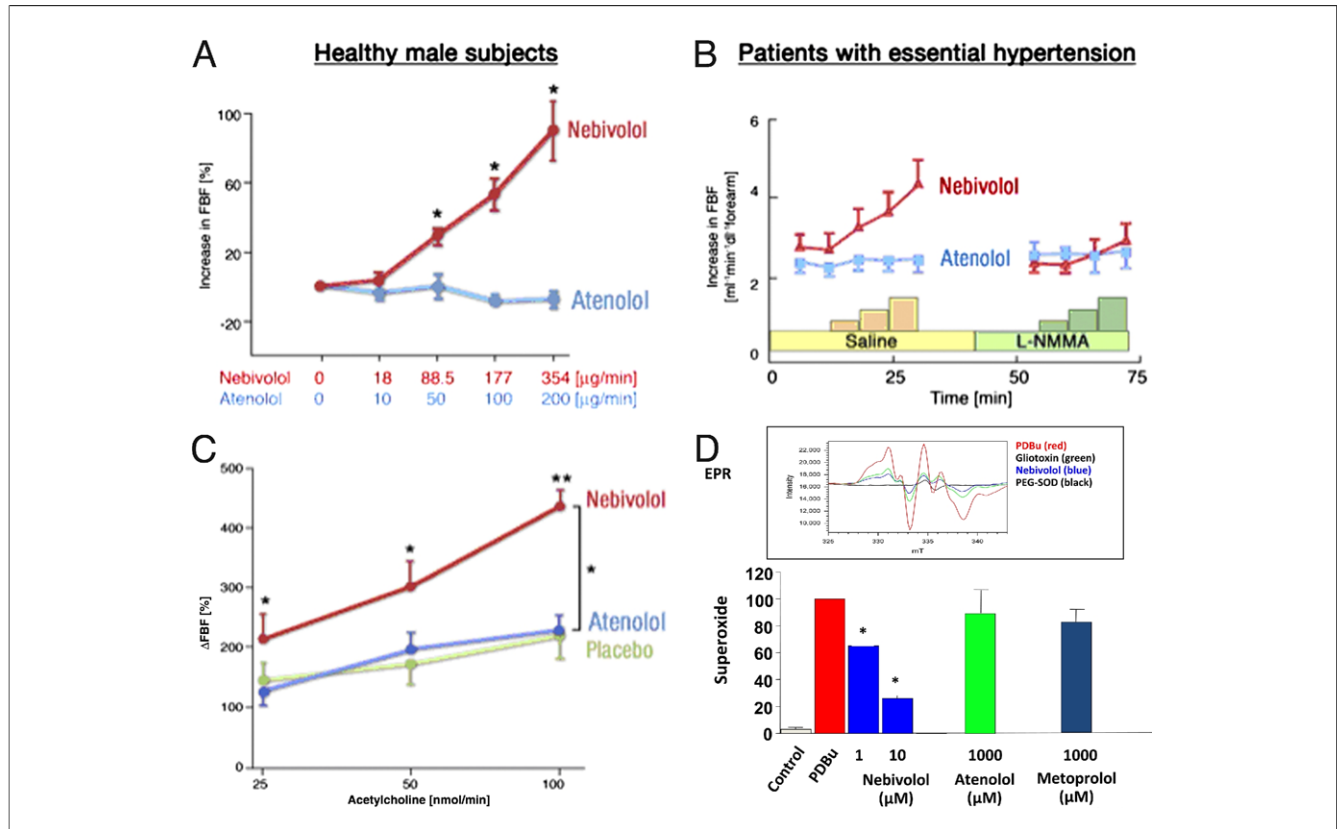
Finally, nebulol treatment has been demonstrated to inhibit the oxidized low-density lipoprotein-induced inactivation of NO (37) and to reduce the levels of the circulating eNOS inhibitor asymmetric dimethyl-arginine, which likely contributes to increase vascular NO bioavailability (38).

### Platelet Aggregation and Thrombus Formation

*In vitro*, nebulol, propranolol, and carvedilol have all been shown to inhibit both adenosine diphosphate- and collagen-induced platelet aggregation; however, the effect of nebulol appears to be significantly greater, and it is lost after inhibition of eNOS (39). Further, therapy with nebulol causes a significant decrease in mean platelet volume and plasma sP-selectin levels and is associated with favorable modifications of hemostatic and fibrinolytic status (40,41), including reduced plasma levels of fibrinogen plasma activator inhibitor-1, homocysteine, and endothelin-1 (41,42).

### Antiproliferative Effects

Nebivolol causes down-regulation of a number of genes involved in inflammatory processes, oxidative stress, and smooth muscle cell proliferation (43–46). Such antiproliferative and proapoptotic effects have obvious potential implications in the prevention and treatment of atherosclerosis. Of interest, this antiproliferative action (along with that of other NO donors), although being NO-mediated, appears to be independent of cyclic guanosine monophosphate (47). In agreement with these findings, nebulol has been shown to inhibit the expression of inflammatory proteins and factors involved in vascular remodeling such as metalloproteinases and protease inhibitor (44,45,48). In hyperlipidemic animals, augmentation of NO with nebulol increased plaque stability (40). Further, nebulol inhibited neointima formation in a murine model of vascular injury (45), and it prevented cardiac and renal modifications in a rat model of insulin



**Figure 5** Impact of Nebivolol on Endothelial Responses and Free Radicals Production

Effects of intra-arterial infusion of nebivolol on forearm blood flow in healthy control subjects (A) and patients with essential hypertension (B) (26,27). In both groups, nebivolol but not atenolol caused vasodilation, an effect that was antagonized by endothelial nitric oxide synthase (eNOS) inhibition. (C) Percent change in forearm blood flow in response to the endothelium-dependent vasodilator acetylcholine after treatment with atenolol or nebivolol, respectively. Nebivolol alone markedly improved endothelial function in hypertensive patients (30). (D) Nebivolol, but not other  $\beta$ -blockers, inhibits phorbol ester (PDBu)-induced superoxide production in neutrophils from hypercholesterolemic rabbits (34). EPR = electron paramagnetic resonance.

resistance (49). Finally, nebivolol inhibited the development of atherosclerosis in cholesterol-fed rats (50).

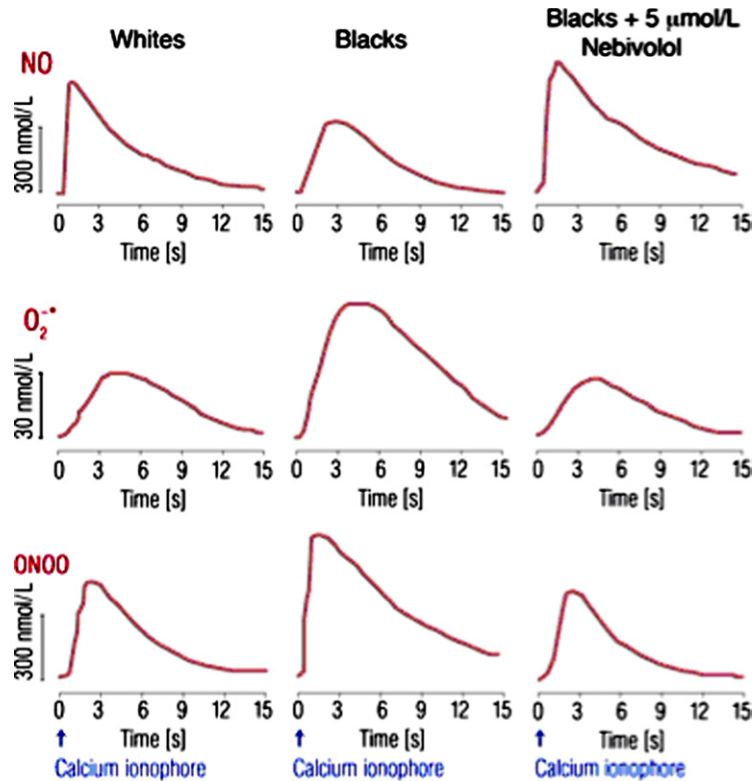
### Clinical Trials

The primary indications for which nebivolol has been developed and studied include systemic hypertension, heart failure, and although less data are available, coronary artery disease.

**Hypertension.** A number of randomized, double-blind, placebo-controlled trials have investigated the efficacy and tolerability of 5 to 10 mg of nebivolol therapy in patients with mild-to-moderate essential hypertension. Nebivolol has a relatively modest impact on diastolic blood pressure (51), a characteristic that is believed to contribute to the safety profile of the drug. In terms of effectiveness on systolic blood pressure, studies (52-54) suggest that nebivolol compares at the same level with other  $\beta$ -blockers and  $\text{Ca}^{2+}$ -antagonists and is somewhat more potent than angiotensin-converting enzyme (ACE) inhibitors (54). The typical onset of maximal nebivolol antihypertensive effect occurs after 2 to 8 weeks of therapy, which is intermediate between ACE inhibitors (slower) and amlodipine (faster).

In recent meta-analyses (55), the percentage of patients who achieved target blood pressure levels was somewhat greater compared with ACE inhibitors and comparable with angiotensin-II blockers or  $\text{Ca}^{2+}$ -channel antagonists. Although these preliminary observations appear promising, it has to be emphasized that outcome data from large studies in isolated hypertension are currently not available and will definitely have to be gathered in the next years, particularly after the recent observations of neutral or comparatively worse effects of  $\beta$ -blockers on mortality and morbidity in hypertension (56). In the absence of such data (and particularly of a comparison of nebivolol with other drugs), the use of any  $\beta$ -blocker as a first-line agent in hypertension remains under discussion.

**Heart failure.** Large randomized trials and meta-analyses (57) have shown that  $\beta$ -blocker administration reduces 5-year mortality and morbidity by approximately 30% in heart failure patients by reducing adrenergic drive, modulating sympathovagal balance and rate variability, and improving cardiac performance.  $\beta$ -blocker therapy, however, is not deprived of side effects in these patients, mostly because of the negative inotropic and chrono-



**Figure 6** Typical Tracings of the Changes in NO, O<sub>2</sub><sup>•-</sup>, and ONOO<sup>-</sup> Concentrations Recorded by Nanosensors From a Single Endothelial Cell Harvested From Age-Matched White and Black Americans

Treatment with nebivolol increased NO and decreased O<sub>2</sub><sup>•-</sup> and ONOO<sup>-</sup> in cells from black patients compatible with recoupling of eNOS in these endothelial cells (36). Abbreviations as in Figure 1.

tropic effects of these drugs. Importantly, although other  $\beta$ -blockers mostly act by reducing stroke volume, nebivolol and carvedilol preserve left ventricular function, cause peripheral vasodilation, maintain stroke volume and cardiac output, and preserve cardiac chronotropism during exertion (58–61). Further, compared to bisoprolol, they do not cause the increase in (or actually improve) (62) pulmonary artery and wedge pressure (63). Whether these differences will translate in a more favorable outcome remains to be studied.

A shortcoming of  $\beta$ -blocker studies in heart failure is that they have enrolled subjects younger than the real-world heart failure population. The mean age of patients included in these previous trials was in the range of 60 years, and only approximately 25% of the patients were older than 70 years. Although trends for benefit were reported in older and more frail patients (64,65), these large studies were not powered to detect statistical significance. More recently, the researchers of the SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure) study enrolled heart failure patients older than 70 years of age and showed a 14% proportional reduction in all-cause mortality as well as an improvement in cardiac diameters and function (66) but not in

hospitalization after nebivolol therapy compared with placebo (67). Although these data appear to be somewhat less favorable than those observed in other  $\beta$ -blocker trials, a nonpre-specified analysis in patients younger than 75 years of age and with an ejection fraction <35% showed a hazard ratio of 0.62, in line with other  $\beta$ -blockers in other studies.

Thus, although the exact mechanism of action in heart failure remains unclear (reduction in ventricular wall stress, favorable left ventricular remodeling, neurohormonal inhibition, protection from ischemic events),  $\beta$ -blockers are invaluable tools in the treatment of heart failure. At present, data on a favorable effect of nebivolol exist; however, given the differences in trial designs, no definitive conclusion can be drawn on the comparison with other  $\beta$ -blockers (selective or nonselective), and further comparative studies are necessary.

**Coronary artery disease.** As reported previously, nebivolol has been shown to have protective effects in experimental models of experimental ischemia and reperfusion injury (68). In humans, it was shown that administration of nebivolol, as compared with atenolol, more effectively improves exercise tolerance and time to onset of angina during exercise test (69). Nebivolol and carvedilol have been shown to increase coronary flow reserve in patients

**Table 2** Effects of Nebivolol as Compared With the Most Commonly Used Drugs in the Same Class; in North America, Nebivolol Is Licensed for Hypertension Only

	Coronary Artery Disease	Heart Failure	Hypertension	Platelet Inhibition	Endothelial Function*
Atenolol	Less effective? (76)	Benefit†	Potent	Very mild	None?
Propranolol	Increased exercise tolerance	Benefit	Comparable with atenolol	Inhibition	Indirect
Metoprolol	Increased exercise tolerance	Benefit. Tartrate likely less effective than carvedilol (77)	Comparable with atenolol	No effect	Milder effect?
Carvedilol	Increased exercise tolerance; improves coronary flow reserve‡	Benefit. Maintains cardiac index (62)	Comparable with atenolol; cardiac and vascular mechanism	Inhibition§	Indirect
Bisoprolol	Increased exercise tolerance	Benefit	Comparable with atenolol	Inhibition	Not well studied
Nebivolol	Increased exercise tolerance; improves coronary flow reserve	Benefit. Comparative data not exhaustive. Maintains cardiac index	Comparable with atenolol; cardiac and vascular mechanism; less potent on diastolic pressure	Inhibition, NO mediated	Direct

Data should be interpreted cautiously because direct comparative trials often are not available. \*A number of studies show improvements in endothelium-dependent vasomotor function in cardiovascular patients treated with all drugs listed in the table. Of these drugs, nebivolol is the only one felt to act by direct stimulation of nitric oxide (NO) synthesis. †Comparative studies tend to show no difference across  $\beta$ -blockers in their beneficial effects in heart failure patients, except, possibly, for metoprolol tartrate (78). Data on the comparison of nebivolol with other  $\beta$ -blockers are not available. ‡The effect of  $\beta$ -blockers on coronary flow reserve is complex. Carvedilol and nebivolol show a more consistent improvement of this parameter (70). §This effect appears to be more modest than that of nebivolol and NO independent (39). ||Impact on mortality and morbidity has not been investigated.

with ischemic heart disease and nonischemic dilated cardiomyopathy more consistently than other  $\beta$ -blockers, which is expected to be associated with a clinically relevant reduction in ischemic threshold (70). Data on the mortality and morbidity impact of nebivolol in coronary artery disease are awaited.

### Side Effects

Nebivolol is contraindicated in patients with severe bradycardia, atrioventricular nodal block greater than first degree, cardiogenic shock, decompensated heart failure, and severe hepatic disease. Warnings also have been issued regarding abrupt cessation of therapy, heart failure, coronary syndromes, bronchospastic diseases, anesthesia and major surgery, diabetes and hypoglycemia, thyrotoxicosis, peripheral vascular disease, nondihydropyridine calcium channel blockers use, and anaphylactic reactions. In patients with asthma and chronic obstructive pulmonary disease, nebivolol's greater selectivity for  $\beta_1$ -receptors results in improved tolerability: in patients with mild asthma, nebivolol induced a mild, clinically insignificant reduction in respiratory parameters that was not different from that of celiprolol, a  $\beta_1$ -blocker and  $\beta_2$ -agonist (71,72). After a 4- and 12-week treatment on hypertensive patients, the use of nebivolol actually increased peak expiratory flow and quality-of-life parameters (73).

Similarly, nebivolol appears to have a minor, if any, effect on libido and sexual performance, which likely ensues from a compensatory effect of the increased NO release (74). In contrast with metoprolol, nebivolol improves secondary sexual activity and erectile dysfunction scores (75), a characteristic that might significantly improve the compliance to this drug.

Common adverse effects reported with nebivolol in clinical trials included fatigue, headache, dyspnea, insomnia,

dizziness, and paresthesia; however, the incidence of these symptoms was not different in placebo-treated subjects (0–5%) (76). Importantly, nebivolol does not appear to modify low-density lipoprotein cholesterol or total cholesterol levels, and it does not seem to precipitate diabetes. Because it is metabolized by CYP450-2P6, nebivolol is potentiated by inhibitors of this enzyme, such as fluoxetine, and any coadministration should be avoided.

### Summary

Nebivolol is a third-generation  $\beta$ -adrenergic receptor blocker with endothelium-dependent vasodilator properties. Available clinical data show an efficacy that is in line with that of other drugs in the same class (Table 2) (39,62,70,77–79). Nebivolol and/or its metabolites possess direct stimulatory effects on eNOS activity as well as potent antioxidant properties, which may have a profound impact on the pathophysiology and progression of cardiovascular disease. Nebivolol has the greatest specificity for  $\beta_1$ -receptors, which explains its high tolerability in patients with lung disease. Although a decade of clinical experience with this drug in Europe provides support to its blood pressure-lowering and anti-ischemic effects, further clinical trial data are necessary. Particularly, comparative trials on the efficacy of nebivolol versus other  $\beta$ -blockers and/or other antihypertensive drugs are awaited.

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**Key Words:** nitric oxide ■ oxidative stress ■ beta-receptor blockade ■ vasodilation ■ nitric oxide synthase.