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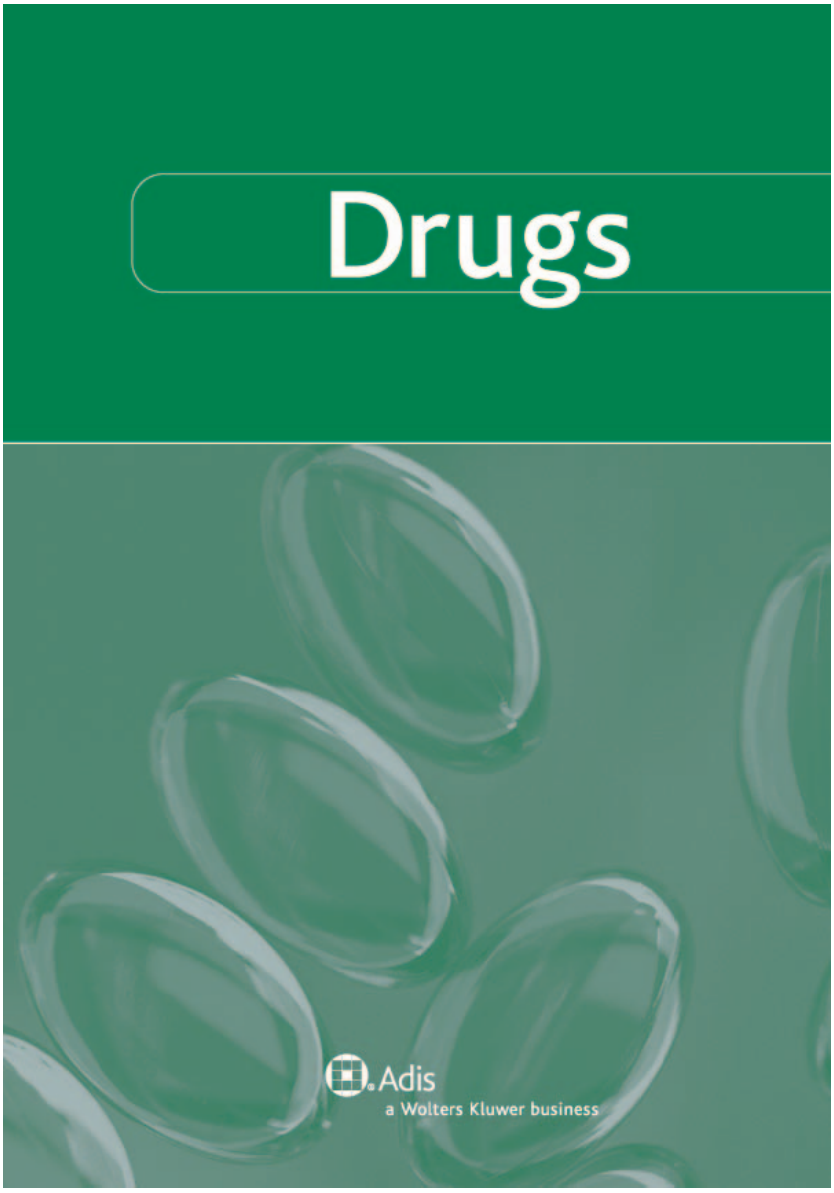

REVIEW ARTICLE

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Nebivolol

Haemodynamic Effects and Clinical Significance of Combined β-Blockade and Nitric Oxide Release

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Abstract

Nebivolol is a third-generation β-adrenergic receptor antagonist (β-blocker) with high selectivity for β_1-adrenergic receptors. In addition, it causes vasodilatation via interaction with the endothelial L-arginine/nitric oxide (NO) pathway. This dual mechanism of action underlies many of the haemodynamic properties of nebivolol, which include reductions in heart rate and blood pressure (BP), and improvements in systolic and diastolic function. With respect to BP lowering, the NO-mediated effects cause a reduction in peripheral vascular resistance and an increase in stroke volume with preservation of cardiac output. Flow-mediated dilatation and coronary flow reserve are also increased during nebivolol administration. Other haemodynamic effects include beneficial effects on pulmonary artery pressure, pulmonary wedge pressure,

exercise capacity and left ventricular ejection fraction. In addition, nebivolol does not appear to have adverse effects on lipid metabolism and insulin sensitivity like traditional β-blockers. The documented beneficial haemodynamic effects of nebivolol are translated into improved clinical outcomes in patients with hypertension or heart failure. In patients with hypertension, the incidence of bradycardia with nebivolol is often lower than that with other currently available β-blockers. This, along with peripheral vasodilatation and NO-induced benefits such as antioxidant activity and reversal of endothelial dysfunction, should facilitate better protection from cardiovascular events. In addition, nebivolol has shown an improved tolerability profile, particularly with respect to events commonly associated with β-blockers, such as fatigue and sexual dysfunction. Data from SENIORS (Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure) showed that significantly fewer nebivolol versus placebo recipients experienced the primary endpoint of all-cause mortality or cardiovascular hospitalization. The benefits of nebivolol therapy were shown to be cost effective. Thus, nebivolol is an effective and well tolerated agent with benefits over and above those of traditional β-blockade because of its effects on NO release, which give it unique haemodynamic effects, cardioprotective activity and a good tolerability profile.

β-Adrenergic receptor antagonists (β-blockers) play an important role in the management of cardiovascular disease, including hypertension, coronary artery disease and chronic heart failure. However, the role of traditional β-blockers in the treatment of hypertension has recently been questioned,[1,2] leading to these agents no longer being recommended as first- or second-line therapy for hypertension.[3] Third-generation β-blockers with β_1-adrenergic receptor selectivity, such as nebivolol, have been used effectively in patients with hypertension,[4-11] heart failure[12,13] and left ventricular (LV) dysfunction.[12,13]

This review focuses on the haemodynamic effects of nebivolol, along with other ancillary mechanisms of action that differentiate it from traditional β-blockers and may contribute to beneficial cardiovascular effects. Haemodynamics and other activity are considered in general initially, then discussed with respect to the use of nebivolol in the treatment of cardiovascular disease.

1. Mechanisms of Action

1.1 Differences Between β-Blockers

β-Blockers vary with respect to several pharmacological properties, including intrinsic sympathomimetic activity, selectivity for β_1- and/or β_2-receptors, and additional properties, including peripheral vasodilatation.[14-16] Intrinsic sympathomimetic activity is not considered to be a desirable feature because increased sympathetic stimulation has adverse effects on the heart. In contrast, receptor selectivity and peripheral vasodilatation are important properties for a β-blocker.

One of the main differences between β-blockers is selectivity for β_1-adrenergic receptors. β_1-Selective agents include metoprolol, bisoprolol, atenolol and, with the greatest degree of selectivity, nebivolol. β_1-Adrenergic receptors are most numerous in the heart, and selectivity for this subtype of β-adrenergic receptor limits adverse effects resulting from blockade of β_2-adrenergic receptors in the lungs and vascular beds. Most, if not all, the negative effects of sympathetic stimulation are mediated by β_1-adrenergic receptors,[17,18] whereas stimulation of β_2-adrenergic receptors may have potentially beneficial effects. These include inhibition of apoptosis and LV remodelling as well as other favourable actions on myocardial cell biology.[14,19,20] However, selectivity is dose dependent, and decreases or disappears when higher dosages are used. On the other hand, the favourable effects of carvedilol, compared with metoprolol, on LV function[21]

and outcomes[22] in patients with heart failure are probably not explained by differences in receptor selectivity but rather by other characteristics of this agent such as its peculiar binding characteristics to the β_1- and β_2-adrenergic receptors, and ancillary antioxidant and anti-proliferative properties.[14,15]

Concomitant peripheral vasodilatation is an important characteristic of third-generation β-blockers such as carvedilol and nebivolol. Vasodilatation may be achieved through concomitant blockade of α_1-adrenergic receptors (in the case of labetalol and carvedilol) or via stimulation of nitric oxide (NO) release (nebivolol).[23] Vasodilatation may allow greater efficacy in the treatment of cardiovascular diseases, such as hypertension, coronary artery disease and heart failure, through a decrease in peripheral and coronary vascular resistance and a lower LV afterload. The presence of peripheral vasodilator activity may also result in better tolerability for patients with concomitant peripheral vascular disease.

1.2 β_1-Adrenergic Receptor Selectivity

Nebivolol is a lipophilic, third-generation β-blocker consisting of a racemic mixture of *d*- and *l*-nebivolol.[24,25] In contrast to other β-blockers, nebivolol offers a unique mix of β_1-selectivity and NO-mediated vasodilatation. Firstly, it is a highly selective β-blocker with high selectivity for β_1-adrenergic receptors. The relative selectivity of nebivolol for the β_1-adrenergic receptor in human myocardium [expressed as $K_i(\beta_2)/K_i(\beta_1)$] is 40.7, which is considerably higher than that of bisoprolol (15.6), metoprolol (4.23), carvedilol (0.73) and bucindolol (0.49).[24,26]

1.3 Nitric Oxide Release

The second major mechanism of action of nebivolol is NO-mediated vasodilatation.[17,23,25-28] This is likely to be mediated by stimulation of β_3-adrenergic receptors.[23,28-31] These receptors have been traditionally related to metabolic effects of sympathetic stimulation (lipolysis in adipocytes, insulin sensitivity). However, more important actions, because of their greater expression in these tissues, have been described in the peripheral vessels and the heart.[23,28-31] In the peripheral vessels, β_3-adrenergic receptors are expressed in the endothelial cells where they stimulate endothelial NO synthase (eNOS) with increased NO release. NO produced at the endocardial level may paracrinally promote cardiomyocyte relaxation and improve left ventricular filling. Other β_3-adrenergic receptors are located in the cardiomyocytes, where they have negative inotropic effects mediated by G-α-I coupling with NOS and NO-mediated inhibition of β_1- and β_2-adrenergic effects on cardiac muscle.[31] Thus, β_3-adrenergic receptor stimulation causes NO-mediated peripheral vasodilatation, increased myocardial compliance (through the paracrine effects of endocardial NO release) and inhibition of the inotropic effects of β_1- and β_2-adrenergic receptor stimulation. These mechanisms are likely to be beneficial as they reduce cardiac load, improve cardiac filling and protect the myocardium from the untoward effects of excessive sympathetic stimulation.

Experimental studies have consistently shown that nebivolol-induced NO release is likely to be mediated by β_3-adrenergic receptor stimulation.[31] Nebivolol has been shown to dose-dependently increase phospholipase A_2 activity and stimulate intracellular cyclic adenosine monophosphate (cAMP) production in endothelial cells.[31] Stimulation of cAMP was not inhibited by either propranolol (a β_1/β_2-adrenergic receptor antagonist) or butaxamine (a selective β_2-adrenergic receptor antagonist).[31] However, bupranolol, an antagonist at β_1-, β_2- and β_3-adrenergic receptors, reduced cAMP in cells treated with nebivolol, implying a role for β_3-adrenergic receptors in the NO-mediated vasodilatory effect of nebivolol.[31] Increased NO release after nebivolol administration causes peripheral vasodilatation, improves endothelial function and has antioxidant effects.

The β_1-selective antagonist and β_3-receptor agonist activity of nebivolol are also associated with beneficial metabolic effects, including increased insulin sensitivity.[32,33] A thorough discussion of these effects goes beyond the aims of this review; however, they further differentiate nebivolol from traditional β-blockers, which may

Table I. Overview of the haemodynamic properties of nebivolol (adapted from Moen and Wagstaff,[38] with permission)

↓ Blood pressure
↓ Heart rate
↑ LVEF (improvement of systolic function)
↑ E/A ratio (improvement of diastolic function)
↑ Stroke volume
Maintenance of cardiac output
↓ LV mass
↓ Vascular resistance
Improves endothelial function
↓ Large artery stiffness
↓ Platelet aggregation
No effect on exercise capacity or oxygen consumption
No effect on glucose or lipid metabolism

E/**A** = ratio of early to late atrial peak filling velocity; **LV** = left ventricular; **LVEF** = left ventricular ejection fraction; ↓ indicates decrease; ↑ indicates increase.

worsen insulin sensitivity and the lipid profile.[34] For example, one double-blind, parallel-group study showed a significant decrease in total cholesterol and low-density lipoprotein cholesterol plasma levels after nebivolol treatment, rather than the increase expected with traditional β-blockers.[35] Similarly, controlled studies have shown that nebivolol, in contrast to conventional β-blockers such as atenolol or metoprolol, can improve insulin sensitivity, oxidative stress, plasma adiponectin and soluble selectin plasma levels in patients with hypertension and/or diabetes mellitus.[32,33,36,37] All these metabolic effects of nebivolol, as well as NO release, appear to be mediated via β_3-adrenergic receptor stimulation.[30] Table I summarizes the mechanisms thought to underlie the beneficial effects of nebivolol.

2. Haemodynamic Effects of Nebivolol

2.1 Heart Rate

Similar to other β-blockers, nebivolol reduces resting and exercise heart rate. Resting heart rate is decreased to a similar or lesser extent[5] by nebivolol than with other β-blockers (e.g. bisoprolol, metoprolol and atenolol). In addition, the decrease in heart rate at peak exercise with nebivolol is of lower magnitude than with other β-blockers.[39-41] Therefore, nebivolol may have fewer unfavourable effects on exercise capacity than other β-blockers.[34,39,41,42] Less bradycardia may also contribute to making nebivolol better tolerated than other β-blockers and assist with the maintenance of cardiac output.[43] In a double-blind, randomized study comparing the effects of nebivolol and atenolol in 25 patients with uncomplicated essential hypertension, stroke volume increased from 72 ± 12 to 87 ± 15 mL, while cardiac output was maintained (from 4.8 ± 0.7 to 5.2 ± 0.5 L/min) in patients receiving nebivolol.[44]

2.2 Peripheral Vasodilatation and Endothelial Function

Experimental studies have shown that nebivolol, in contrast to other β-blockers, may reduce peripheral vascular resistance and blood pressure (BP) even after acute administration.[45] At low doses, the reduction in BP is accompanied by no change, or a slight increase, in cardiac output and stroke volume, whereas these variables are decreased by other β-blockers, such as propranolol and atenolol. When nebivolol is administered at higher doses, β-blockade may prevail with an associated decline in cardiac output and stroke volume, and a slight increase in LV filling pressures.[45]

The vasodilatory effects of nebivolol have also been documented in humans. In a comparative, randomized, double-blind, crossover study, both nebivolol 5 mg/day and bisoprolol 10 mg/day, administered for 2 weeks, reduced systolic BP (SBP) and diastolic BP (DBP) to a similar extent, whereas only nebivolol reduced the systemic vascular resistance index (2854 ± 201 to 2646 ± 186 dyn • sec • cm^{-5} • m^2; $p < 0.05$).[43] Peripheral vasodilatation after nebivolol administration is caused by NO release. It is therefore an indication of improved endothelial function, an important prognostic factor in patients with a wide spectrum of cardiovascular diseases.[28,46-49]

The role of NO release was first shown by Cockcroft et al.[50] In this study, blood flow was measured using venous occlusion plethysmography during brachial artery infusion of different agents. Specifically, the effect of NG-monomethyl

L-arginine (L-NMMA), a competitive inhibitor of NOS, on forearm blood flow (FBF) was compared with that of carbachol (an endothelium-dependent agonist) and sodium nitroprusside (an endothelium-independent vasodilator). It was found that nebivolol increased FBF by 91 ± 18% ($n = 8$; $p < 0.01$) and that this effect was inhibited by L-NMMA (by 65 ± 10%) and carbachol (by 49 ± 8%). Inhibition of the response to nebivolol by L-NMMA was, in turn, abolished by L-arginine. These data show that nebivolol dilates peripheral vascular resistance vessels via the L-arginine/NO pathway (figure 1).[50]

Later studies confirmed these results. In one study in 35 patients with stable coronary artery disease, nebivolol administration for 4 weeks improved flow-mediated dilation (FMD) compared with baseline (5.6 ± 2.9% vs 3.9 ± 2.7%; $p = 0.047$). In contrast, patients treated with atenolol did not show any increase in FMD.[51] In another study, 12 hypertensive patients were randomized in a double-blind crossover fashion to 8 weeks' treatment with either nebivolol 5 mg/day or atenolol 50 mg/day, both in combination with bendroflumethiazide 12.5 mg/day.[52] Stimulated and basal endothelium-dependent NO release were assessed by forearm venous occlusion plethysmography after intra-arterial infusions of acetylcholine and L-NMMA, respectively. Sodium nitroprusside was used as an endothelium-independent control. Nebivolol/bendroflumethiazide and atenolol/bendroflumethiazide both reduced BP to the same extent. The vasodilatory response to acetylcholine was increased with nebivolol/bendroflumethiazide (maximum percentage change in FMD 435 ± 27%; $p < 0.001$) but not with atenolol/bendroflumethiazide (figure 2). Similarly, the endothelium-dependent vasoconstrictive response to L-NMMA was significantly improved only with nebivolol treatment. The response to sodium nitroprusside was not different between treatments, suggesting that the endothelium-independent pathway was unaffected.[52] These data show that the nebivolol/bendrofluazide combination, but not atenolol/bendrofluazide, can increase both stimulated and basal endothelial NO release and improve endothelial function in hypertensive patients.

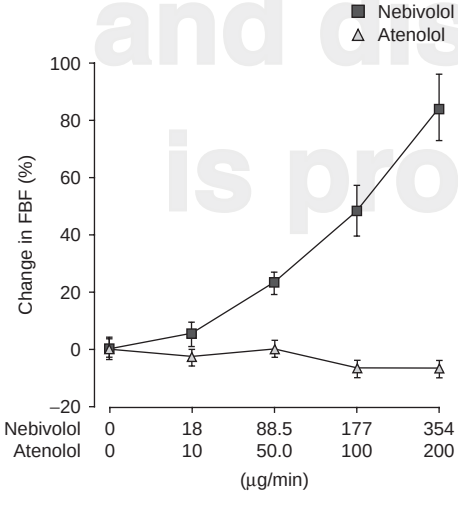

Fig. 1. Nebivolol vasodilates human forearm vasculature in healthy male subjects ($n = 40$). First evidence of an L-arginine/nitric oxide-dependent mechanism (reproduced from Cockcroft et al.,[50] with permission). **FBF** = forearm blood flow.

More recently, a study in 40 hypertensive patients showed that nebivolol, but not atenolol, improved FMD and decreased plasma levels of asymmetric dimethylarginine (ADMA), a naturally occurring amino acid that inhibits eNOS, with a significant correlation between these changes.[53] Moreover, sera derived from patients treated with nebivolol, but not atenolol, decreased ADMA levels and increased dimethylarginine dimethylaminohydrolase 2 (the enzyme that selectively degrades ADMA) expression and eNOS activity.[53] These results confirm that nebivolol can improve endothelial function in hypertensive patients and suggest increased degradation of ADMA, an inhibitor of NOS, as a potential mechanism.

All these data consistently show that nebivolol causes vasodilatation through its effects on endothelial NO release. Endothelial dysfunction is a systemic defect that affects both central and peripheral arteries and has an impact on the cardiovascular event rate.[47] Therefore, it could be hypothesized that nebivolol may further reduce cardiovascular risk compared with traditional β-blockers.

Stimulation of NO release by nebivolol administration may also be associated with favourable effects on sexual function. It has been shown that

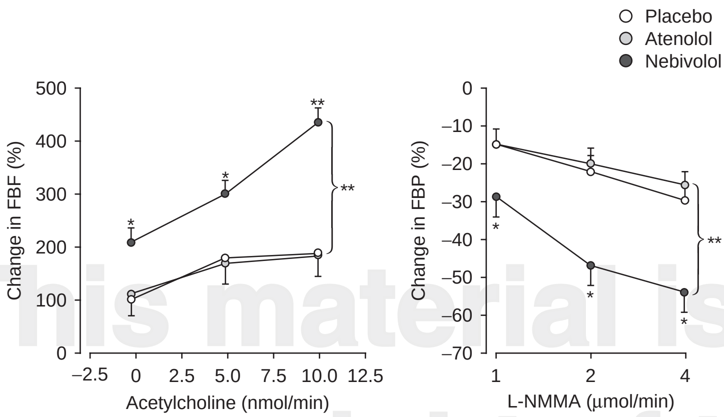

Fig. 2. Nebivolol reverses endothelial dysfunction in hypertensive patients (reproduced from Tzemos et al.,[52] with permission). Values are mean ± standard error of the mean. **FBF** = forearm blood flow; **L-NMMA** = NG-monomethyl L-arginine. * $p < 0.05$, ** $p < 0.001$ for differences between treatments.

nebivolol, but not metoprolol, can induce eNOS activation and NO liberation in murine corpus cavernosum.[54] The reported incidence of erectile dysfunction and worsening of sexual function in hypertensive men is lower during treatment with nebivolol compared with other β-blockers.[55-57] Hence, compliance with nebivolol therapy may be greater than with traditional β-blockers in patients with a variety of cardiovascular diseases.

2.3 Coronary Blood Flow

β-Blockers have multiple effects on coronary blood flow. Bradycardia decreases myocardial oxygen consumption and increases the duration of diastole – the phase of the cardiac cycle during which coronary blood flow is maximal. Secondly, β-blockers have direct effects on coronary circulation. Blockade of β_1- and β_2-adrenergic receptors by nonselective agents may lead to greater stimulation of α_1-adrenergic receptors by noradrenaline (norepinephrine), resulting in coronary vasoconstriction. However, β_1-selective agents such as nebivolol may allow stimulation of vascular β_2-adrenergic receptors without associated vasoconstriction.[58]

The effects of nebivolol administration on coronary flow reserve (CFR) have been studied. CFR represents the capacity of the coronary circulation to dilate following an increase in myocardial metabolic demands. CFR is expressed as the difference between the hyperaemic flow and resting flow curves, and is assessed clinically using perfusion imaging and, more recently, transoesophageal or transthoracic Doppler echocardiography. Using these techniques, CFR of the left anterior descending artery can be measured. Impaired CFR has been noted in patients with diabetes, hypertension and idiopathic dilated cardiomyopathy (IDC), in whom it predicts a poor prognosis.[59] The mechanisms by which arterial hypertension can bring about changes in CFR are numerous, and include increased afterload, LV hypertrophy and endothelial dysfunction.

The potential for nonspecific β-blockers to improve CFR is limited by their tendency to cause vasoconstriction through β_2-adrenergic receptor antagonism. On the other hand, the vasodilatory properties of nebivolol should theoretically preserve CFR. Indeed, clinical studies have confirmed that nebivolol may improve CFR in patients with hypertension without coronary heart disease and in those with IDC. Following treatment with nebivolol, CFR was increased in 14 subjects with newly diagnosed hypertension with or without LV hypertrophy.[60] CFR was measured at baseline and following 4 weeks' treatment with nebivolol 5 mg/day, using low-dose dipyridamole Doppler echocardiography at the level of the distal left anterior ascending artery. Nebivolol administration did not change coronary flow velocity at rest but was associated

with an increase in coronary diastolic peak velocity after dipyridamole (25.8 ± 5.1 vs 47.9 ± 7.3; $p < 0.03$) leading to an improvement in CFR (2.12 ± 0.33 vs 1.89 ± 0.31 at baseline; $p < 0.0001$). In two-thirds of the patients, the increase in CFR was ≥8%, which represents a biologically relevant change in this parameter.

In another comparative trial, the effects of nebivolol 5 mg/day on CFR were compared with those of atenolol 50 mg/day in 63 hypertensive patients using an 8-week, crossover design. Compared with baseline, nebivolol induced a nonsignificant increase in CFR (from 2.45 to 2.56; $p = 0.09$), while atenolol was associated with a significant reduction in CFR (from 2.46 to 2.21; $p = 0.006$).[61]

Thus, unlike other β-blockers, nebivolol has beneficial effects on CFR. This activity is likely to be related to peripheral and coronary NO-mediated vasodilatation, as well as to afterload reduction and reduced LV end-diastolic pressure. These effects may have clinical implications because patients with hypertension often have reduced CFR and exercise-induced subendocardial ischaemia.

Patients with IDC may also have impaired coronary blood flow and CFR. LV dilatation and eccentric hypertrophy, tachycardia, and a reduced pressure gradient for coronary blood flow caused by increased end-diastolic LV pressure and/or lower aortic pressure, may also favour subendocardial ischaemia despite normal coronary arteries. Improving CFR is therefore a potentially important therapeutic target for heart failure treatment. Administration of nebivolol to patients with IDC has been shown to significantly increase coronary velocities after dipyridamole, resulting in a greater CFR (2.02 ± 0.35 vs 2.61 ± 0.43; $p < 0.001$), with an absolute CFR increase of 6% in 17 of 21 patients.[62]

2.4 Left Ventricular (LV) Function

Bradycardia, peripheral vasodilatation and improved endothelial function are accompanied by an improvement in systolic and diastolic LV function after nebivolol administration. This has been shown consistently by many studies conducted in patients with hypertension or heart failure.[63,64]

These effects of nebivolol must be assessed in the context of the effects of β-blocker therapy on LV function. Many β-blockers, without and with ancillary properties (e.g. metoprolol, bisoprolol, carvedilol and bucindolol) have been consistently shown to improve LV systolic function after long-term administration to patients with heart failure.[16,17,21] With nebivolol, the beneficial effects of long-term β-adrenergic blockade may be accompanied by its favourable short- and long-term effects related to NO release.

Vasodilatation caused by NO release in the peripheral vessels may counteract the decrease in myocardial contractility caused by β_1-adrenergic receptor antagonism, so that nebivolol administration may be better tolerated in the short-term, similar to what has been seen with other β-blockers that have associated vasodilatory properties.[65] The cardiac release of NO may also have some effects.

Cardiac NO production may have a profound impact on cardiac function through both vascular-dependent and vascular-independent effects. Vascular-dependent mechanisms include regulation of coronary vessel tone, thrombogenicity, proliferative and inflammatory properties, and angiogenesis.[29] Direct effects of NO on myocardial contractility and diastolic function are mediated by changes in the excitation-contraction coupling, presynaptic and postsynaptic modulation of autonomic signalling, and changes in mitochondrial respiration.[66,67] Nebivolol has been shown to induce NO release in the heart through inducible NOS activation.[68] Thus, nebivolol may also affect cardiac function via these mechanisms, in addition to β_1-adrenergic receptor antagonism.

The results of the main studies investigating the effects of nebivolol on LV function in patients with normal LV function (either healthy subjects or those with essential hypertension) or LV dysfunction will be detailed separately.

2.4.1 Subjects with Normal LV Function

Investigations in healthy subjects and in patients with essential hypertension and normal LV

function have confirmed that nebivolol may reduce BP with no change or an improvement in variables related to LV systolic performance such as the systolic time intervals, ejection fraction and stroke volume.

The ratio of the heart rate-corrected preejection period (PEPc) to the LV ejection time (LVET) is inversely related to LV systolic performance and directly related to peripheral vascular resistance. In a comparative study in healthy volunteers, the PEPc/LVET ratio increased after 1 month of treatment with propranolol or atenolol (consistent with their negative inotropic activity), remained unchanged after pindolol (because of its intrinsic sympathetic activity) and progressively decreased with nebivolol.[69]

Results obtained in patients with arterial hypertension are consistent with these findings. Nebivolol decreased SBP and DBP with no change or a slight increase in cardiac output and stroke volume, and no significant change in right ventricular and LV filling pressures.[69,70]

LV diastolic function may also be favourably influenced by nebivolol administration, via bradycardia, peripheral vasodilatation and afterload reduction, along with stimulation of cardiac NO release. Nebivolol has also been shown to significantly improve variables related to early LV filling, such as the early transmitral peak flow velocity and the LV peak filling rate, both in healthy volunteers and in patients with essential hypertension.[39,44,48,69,70]

2.4.2 Patients with Heart Failure and Preserved LV Systolic Function

One prospective, parallel-group, randomized study in 30 patients with mild arterial hypertension and chronic heart failure secondary to LV diastolic dysfunction, and diagnosed on the basis of high pulmonary wedge pressure, compared the effects of long-term administration of atenolol or nebivolol on exercise capacity, and haemodynamic parameters at rest and during maximal exercise.[40] Both β-blockers improved clinical symptoms of heart failure, and decreased heart rate and BP. However, only nebivolol significantly improved exercise capacity, accompanied by a greater improvement in LV diastolic function compared with atenolol. Cardiac index declined to a lesser extent in nebivolol recipients, and there was a greater increase in stroke volume index and a greater decline in mean pulmonary artery pressure and pulmonary wedge pressure, both at rest and peak exercise. At rest, cardiac index changed from a mean baseline value of 3.62 ± 0.51 to 2.98 ± 0.46 L/min/m^2 at 6 months in atenolol-treated patients and from 3.46 ± 0.45 to 3.20 ± 0.48 L/min/m^2 in nebivolol-treated patients over the same period ($p < 0.01$ for intergroup difference). Systemic vascular resistance at rest, expressed as dyn • s • cm^{-5}, changed from 1405 ± 239 to 1523 ± 352 in atenolol-treated patients and from 1366 ± 228 to 1334 ± 243 in nebivolol recipients ($p < 0.05$). During exercise, the negligible effect of nebivolol versus atenolol on cardiac index was even more apparent than at rest (change from 5.85 ± 1.22 to 5.31 ± 1.26 for atenolol vs 5.84 ± 1.83 to 5.79 ± 1.80 for nebivolol; $p = 0.005$ between groups). Regression of LV hypertrophy and the effects of nebivolol on peripheral resistance and LV diastolic function were suggested by the authors as possible mechanisms to account for the differences observed between nebivolol and atenolol. These haemodynamic improvements and the increase in exercise tolerance after nebivolol could also be ascribed to the ancillary effects of this β-blocker on NO release, which may cause both vasodilatation and a greater improvement in LV diastolic function.

2.4.3 Patients with LV Systolic Dysfunction: Short-Term Studies

The acute haemodynamic effects of nebivolol and atenolol, administered intravenously, have been compared by left heart catheterization in patients with mild post-infarction LV dysfunction.[42] Intravenous nebivolol 2.5 mg was associated with a reduction in heart rate similar to that of intravenous atenolol 15 mg. However, nebivolol did not affect the cardiac index, slightly but significantly increased the stroke volume index and ejection fraction, and reduced the LV end-diastolic pressure and the pressure at the time of mitral valve opening. In contrast, atenolol reduced cardiac index, stroke volume index and ejection fraction, and slightly increased LV

pressures. These different haemodynamic effects may be explained by the vasodilatory action of nebivolol. However, despite a similar reduction in mean LV wall stress, atenolol decreased the ejection fraction, consistent with its negative inotropic action, while nebivolol increased ejection fraction.[42] This difference, despite a similar afterload reduction, may be attributed to increased cardiac NO release after nebivolol administration.

Significant differences between nebivolol and atenolol were also found for effects on LV diastolic function. Nebivolol, but not atenolol, increased the peak filling rate and shifted the LV pressure-volume curve downward, consistent with an improvement in LV compliance.[42] These changes appeared to be the result of peripheral vasodilatation, with venous dilatation causing a smaller right ventricular volume and a secondary improvement in LV filling.[42] Another study compared the acute haemodynamic effects of nebivolol and atenolol, administered orally rather than intravenously, in patients with LV dysfunction after coronary artery bypass grafting.[71] Nebivolol 5 mg and atenolol 50 mg induced a similar decline in heart rate and BP. However, cardiac index and stroke volume index decreased significantly after atenolol, but remained unchanged 6 hours after nebivolol administration and improved significantly after 24 hours. These observations were related to the different effects of the two agents on systemic vascular resistance, which increased after atenolol and declined after nebivolol, with significant changes after 24 hours. The echo-Doppler study showed an increase in the acceleration of aortic flow velocity and a decline of the isovolumic relaxation time, consistent with an improvement in diastolic function, with nebivolol but not with atenolol.[71]

Other studies evaluated the medium term (1–6 weeks) effects and tolerability of nebivolol in patients with symptomatic, New York Heart Association (NYHA) class III–IV[72] or II–III[73] congestive heart failure. When started at a low dose (1 mg/day) with a gradual up-titration to the final dose of 5 mg/day, nebivolol was well tolerated even in patients with advanced, class III–IV disease. In this study, nebivolol significantly reduced heart rate, while all the other haemodynamic variables remained unchanged.[72] In another study, haemodynamic measurements were performed at rest and during bicycle exercise using right heart catheterization, at baseline and after 1 week of treatment. Similar to the other studies, nebivolol was associated with a decline in heart rate and BP, along with an increase in stroke volume and no significant change in any other variables.[73]

All these investigations show that nebivolol is well tolerated even when administered to patients with advanced heart failure. The lack of improvement in haemodynamic variables is likely to be a result of the relatively short (1–6 weeks) duration of these studies. In fact, the effects of β-blockers on LV function are time dependent, and at least 3 months' treatment is necessary to obtain a significant improvement in haemodynamic variables in patients with heart failure.[16,17]

2.4.4 Patients with LV Systolic Dysfunction: Long-Term Studies

Administration of β-blockers has been shown to be the most effective treatment for improving LV function and prognosis in patients with heart failure. Accordingly, a significant improvement in LV function has been observed in studies assessing the medium- to long-term effects of nebivolol administration.

LV function and exercise tolerance were studied at baseline and after 8–10 weeks in 40 patients with post-infarction LV dysfunction (mean ejection fraction 35.6 ± 6.1%) but no overt heart failure, randomized to placebo, nebivolol 2.5 or 5 mg/day or atenolol 50 mg/day.[41] Both β-blockers significantly reduced heart rate, although the effect of atenolol was greater than that of nebivolol. LV pressures during ejection were also significantly reduced by both agents, resulting in reduced mean systolic wall stress. LV ejection fraction significantly improved compared with baseline (+5.3% with atenolol and +4.3% with nebivolol). Regarding the effects on LV diastolic function, both dosages of nebivolol, but not placebo or atenolol, induced a parallel downward shift of the pressure-volume curve

with an increase in the peak filling rate and a reduction in the time to peak filling rate, compared with placebo. These variables tended to worsen after atenolol but these differences were not significant. The improvement in the peak filling rate despite a decrease of the driving pressure after nebivolol implies an improvement in early diastolic compliance, which was greater than that observed by the same investigators with other agents, such as xamoterol or ACE inhibitors.[41] Lastly, peak exercise duration remained unchanged in the placebo- and atenolol-treated patients, while it improved in those receiving nebivolol (+15.4% with 2.5 mg/day and +15.6% with 5 mg/day; $p = 0.0077$).[41] This improvement in exercise capacity seems to be quite a nebivolol-specific effect because it has not been observed with other vasodilating β-blockers, such as bucindolol or carvedilol, in patients with heart failure.[65,74]

Wisenbaugh et al.[75] performed the first controlled study in which follow-up duration was long enough to detect the effects of β-blockade on LV function. This study included 24 patients with idiopathic or ischaemic (n = 2) dilated cardiomyopathy, in NYHA class II (n = 23) or III (n = 1) heart failure, with a mean LV ejection fraction of 24%, and who were treated only with furosemide. Left and right heart catheterization and exercise testing were performed at baseline and after 3 months of therapy with either placebo or nebivolol 1–5 mg/day. In contrast to the findings of Rousseau et al.,[41] exercise tolerance was not altered by nebivolol administration. A significant haemodynamic improvement was detected after 3 months of nebivolol therapy, compared with placebo. Nebivolol induced a significant decline in heart rate with a concomitant increase in LV stroke volume (43 ± 9 to 55 ± 14 mL; $p = 0.003$) and LV ejection fraction (23 ± 8 to 33 ± 12%; $p = 0.002$), and a slight but significant reduction in mean pulmonary artery pressure (34 ± 11 to 28 ± 9 mmHg; $p = 0.05$), LV end-diastolic pressure (21 ± 11 to 15 ± 9 mmHg; $p = 0.03$) and LV mass (228 ± 64 to 199 ± 52 g/m^2; $p = 0.04$). The relationship between the preload-corrected ejection fraction and end-systolic stress was improved by nebivolol administration, consistent with an improvement in myocardial contractility.[75]

These findings differ from those in short-term haemodynamic studies, with an improvement in myocardial contractility and no change in LV afterload after long-term nebivolol administration. It is likely that this difference may be explained by the follow-up duration. Similar to what is observed with other β-blockers with associated vasodilatory activity,[65] it is likely that peripheral vasodilatation is most important in the short-term when it may counteract the negative inotropic effect of β-blockade and contribute to better drug tolerability. However, after long-term treatment, the improvement in myocardial function associated with chronic β-blockade may become more important.

The findings by Wisenbaugh et al.[75] were confirmed by further studies.[12,63,76] Ghio et al.[63] reported the results of an echocardiographic substudy of the SENIORS (Study of the Effects of Nebivolol Intervention on Outcomes and Hospitalisation in Seniors with Heart Failure) trial, designed to evaluate the effects of nebivolol on systolic and diastolic LV function. The substudy included 104 patients, 43 with a LV ejection fraction ≤35% and 61 with a LV ejection fraction >35%, assessed before and after 12 months of treatment. In the patients with a LV ejection fraction ≤35%, nebivolol reduced end-systolic volume by 25.8 mL ($p = 0.016$) and improved LV ejection fraction by 4.6% ($p = 0.008$); no changes were observed in the ratio of early to late atrial peak filling velocity (E/A ratio) or E-wave deceleration time. In the group with LV ejection fraction >35%, no significant changes in either systolic or diastolic parameters were observed.[12]

3. Clinical Effects

3.1 Hypertension

As stated in the recent guidelines from the European Society of Hypertension and the European Society of Cardiology (ESC),[77] β-blockers may still be considered an option for initial and subsequent antihypertensive treatment strategies. However, because they have a tendency to increase bodyweight, have adverse effects on lipid metabolism and increase (compared with other drugs)

the incidence of new-onset diabetes, β-blockers are not the agents of choice for treating hypertension in patients with multiple metabolic risk factors. However, such a recommendation may not apply to β-blockers such as carvedilol and nebivolol,[3] which have little or no adverse metabolic effects and are associated with a lower incidence of new-onset diabetes than traditional β-blockers.[36,37,77,78] According to the US Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure,[79] β-blockers are the agents of choice when a patient has concomitant diseases for which β-blockers have been shown to improve outcomes (i.e. heart failure, post-myocardial infarction, coronary artery disease).

As mentioned previously, stimulation of NO release by nebivolol may be associated with ancillary effects in patients with hypertension compared with other β-blockers. These include antioxidant and anti-inflammatory activity,[32] reversal of endothelial dysfunction,[52] improvement in coronary blood flow[60] and improvement in LV diastolic function during exercise.[40]

Less bradycardia and peripheral vasodilatation with nebivolol may also have other beneficial effects. When bradycardia occurs with traditional β-blockers, the reflected wave reaches the next wave in systole (instead of diastole), and therefore may increase central aortic pressure through dys-synchrony and uncoupling between the outgoing and reflected waves. This mechanism has been used to explain the somewhat paradoxical increase in mortality and cardiovascular event rate with lower heart rate after treatment with traditional β-blockers in hypertensive patients.[80] For example, in the CAFE (Conduit Artery Functional Endpoint) study, central aortic SBP (measured indirectly by radial artery applanation tonometry) was higher by 4.3 mmHg with atenolol than with amlodipine for the same peripheral BP. This was associated with a 14% higher risk of coronary events and a 23% higher rate of strokes in atenolol recipients compared with amlodipine, despite a similar reduction in peripheral BP.[81]

Nebivolol, through its NO release and peripheral vasodilatory action, decreases pulse wave velocity, a measure of arterial stiffness.[82] In a comparative trial, treatment with nebivolol was associated with a lower central aortic pulse pressure compared with atenolol (50 ± 2 vs 54 ± 2 mmHg; $p = 0.02$) despite similar values for peripheral BP.[83] It could therefore be hypothesized that the lower incidence of bradycardia, along with peripheral vasodilatation and NO release, associated with nebivolol administration facilitates better protection from cardiovascular events in hypertensive patients compared with traditional β-blockers.

Antihypertensive therapy not only needs to be effective, but also well tolerated. One major drawback of the currently available β-blockers, particularly the noncardioselective agents, is their adverse effect profile, including sexual dysfunction, fatigue, depression and metabolic abnormalities, such as impaired glucose tolerance and lipid abnormalities. Nebivolol has a favourable adverse effect profile, most notably for events commonly associated with β-blockers, such as fatigue and sexual dysfunction.[55,56,84] Overall, the antihypertensive efficacy of nebivolol appears to be similar to that of other β-blockers, as well as calcium channel antagonists and renin-angiotensin antagonists, but with a better adverse effect profile compared with traditional β-blockers.[8,11]

In a multicentre, nationwide observational study including 6356 patients with mild hypertension, the rate of significant adverse effects during 6 weeks' treatment with nebivolol was only 0.5% and there were no serious adverse effects.[85] One of the largest double-blind, multicentre, randomized, placebo-controlled studies of nebivolol in hypertension was conducted by Weiss et al.[86] in 909 patients with mild to moderate disease. Nebivolol reduced trough sitting DBP by 8.0–11.2 mmHg, compared with 2.9 mmHg for placebo ($p < 0.001$), and trough sitting SBP by 4.4–9.5 mmHg compared with a 2.2 mmHg increase in placebo recipients ($p = 0.002$). The overall incidence of adverse events was similar in the nebivolol (46.1%) and placebo (40.7%) groups ($p = 0.273$). In particular, the incidence of typical β-blocker-induced adverse events was not different from placebo, including erectile dysfunction (0.2% nebivolol vs 0.0% placebo), decreased libido (0.1% vs 0.0%), dyspnoea (1.0% vs 0.0%) and bradycardia (0.7% vs 0.0%).[86]

3.2 Heart Failure

The clinical efficacy and effects of nebivolol on outcomes in patients with chronic heart failure has been thoroughly assessed in the SENIORS trial.[13] Based on the results of this trial, nebivolol is now indicated for the treatment of patients with heart failure in ESC guidelines.[87] In the study, a total of 2128 elderly patients (age ≥70 years) with a clinical history of congestive heart failure (hospital admission within 12 months or LV ejection fraction ≤35%) were randomized to nebivolol or placebo; mean duration of treatment was 21 months. This trial was one of the first to include not only patients with a low LV ejection fraction but also those with preserved systolic function (LV ejection fraction >35%). The primary composite endpoint was all-cause mortality or cardiovascular hospitalization, and secondary endpoints included cardiovascular mortality, cardiovascular hospitalization, and the composite of cardiovascular and all-cause mortality and hospitalization.

Mortality or cardiovascular hospitalization, the primary endpoint, occurred in fewer patients receiving nebivolol compared with placebo (hazard ratio [HR] 0.86; 95% CI 0.74, 0.99; p = 0.039). The cardiovascular mortality or hospitalization rate was also lower in the nebivolol group than the placebo group (HR 0.84; 95% CI 0.72, 0.98; p = 0.027). Prespecified subgroup analyses did not show any significant interaction between sex, ejection fraction, age, diabetes or prior myocardial infarction, and the effects of nebivolol on outcomes. However, the HR for the primary endpoint was 0.79 (95% CI 0.63, 0.98) in patients aged less than the median of 75.2 years and 0.92 (95% CI 0.75, 1.12) in those aged >75.2 years (for interaction test p = 0.51).[13]

In order to assess the effects of nebivolol therapy in patients comparable to those assessed in previous β-blocker trials, the authors assessed the effects of treatment in patients aged less than the median of 75.2 years and with a LV ejection fraction ≤35% (n = 342 for nebivolol and n = 342 for placebo). In this subgroup, the HR for the primary outcome was 0.73 (95% CI 0.56, 0.96) and for all-cause mortality alone the HR was 0.62 (95% CI 0.43, 0.89), which is higher than in the overall study group and comparable to values reported in previous β-blocker trials.[13,16,17,87] Additional analyses also confirmed that the results were consistent with those from other β-blocker trials. There was a significant correlation between achievement of nebivolol target dose (10 mg/day) and a more favourable effect of nebivolol on outcomes (HR 0.73; 95% CI 0.61, 0.87; p < 0.001),[88] and nebivolol treatment was also shown to be cost effective.[89]

SENIORS is the only trial with data regarding the effects of nebivolol on outcomes. A detailed discussion of the significance of its results goes beyond the scope of this article. However, even in this context, some issues should be highlighted. SENIORS was one of the first trials in patients with chronic heart failure that tried to broaden the indications for medical therapy and to assess the effects of treatment in patients with characteristics more similar to real life clinical practice.[89,90] Thus, elderly patients were included and inclusion was not based on LV ejection fraction criteria. These criteria did not show significant interaction with the effects of treatment in subgroup analyses (figure 3).[13] However, results may have been more significant had the study included only patients with characteristics similar to those of previous β-blockers trials.

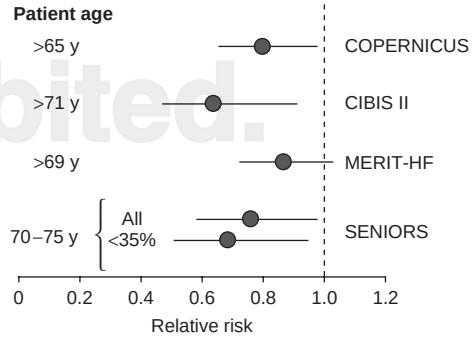

Fig. 3. Effect of β-blockers on all-cause mortality or cardiovascular hospitalization in elderly patients; *post hoc* subgroup analysis from the SENIORS (Study of the Effects of Nebivolol Intervention on Outcomes and Hospitalisation in Seniors with Heart Failure) trial in patients with left ventricular ejection fraction <35%. **CIBIS II** = Cardiac Insufficiency Bisoprolol Study II; **COPERNICUS** = Carvedilol Prospective Randomized Cumulative Survival; **MERIT-HF** = Metoprolol CR/XL Randomized Intervention Trial in Heart Failure.

Thus, as well as showing the beneficial effects of medical treatment in a wider spectrum of patients with heart failure, SENIORS was one of the first trials to show the limitations of large trials in providing evidence for treatment in elderly patients with heart failure and those with preserved LV ejection fraction. Such issues have unfortunately been replicated by subsequent trials with a similar design, although addressing different treatments.[90]

4. Conclusion

Nebivolol is a third-generation β-blocker with a unique haemodynamic profile, combining highly selective β_1-adrenergic receptor antagonism with NO-mediated vasodilatory activity. The actions of nebivolol over and above β-blockade may have important implications with respect to reversal of endothelial dysfunction, improvement in peripheral and coronary blood flow, and antioxidant and anti-inflammatory activity. These pharmacological properties appear to be associated with better tolerability compared with traditional β-blockers and may result in additional protection from cardiovascular events.

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