Protective effect of nebivolol against target organ damage in hypertension

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Abstract

Cardiovascular complications (left ventricular hypertrophy, atrial fibrillation, heart failure, coronary events, increased arterial stiffness and atherosclerotic lesions) are the major causes of death among patients with hypertension. Oxidative stress and central aortic pressure play a key role in the pathophysiology of the cardiovascular diseases and complications. Antihypertensive agents may, even within the same class of drugs, exert variable effects on arterial stiffness parameters and endothelial function. Nebivolol is a third-generation β-blocker with vasodilator activity. Its vasodilatory function is mediated by the endothelial L-arginine/NO pathway. Nebivolol increases the bioavailability of NO in the vasculature. Recent studies have demonstrated that nebivolol improves arterial stiffness to a greater extent than conventional β-adrenolytics (atenolol, metoprolol). According to ESH/ESC guidelines, some of the vasodilating β-adrenolytics, such as celiprolol, carvedilol and nebivolol, provide greater reduction in central pulse pressure and aortic stiffness than atenolol or metoprolol.

Key words: nebivolol, hypertension, target organ damage, central aortic pressure

Introduction

According to current standards, the assessment of subclinical target organ damage (TOD) is necessary to determine the risk of cardiovascular mortality and its effective prevention in patients with hypertension [1, 2]. Pathologies such as left ventricular hypertrophy, carotid atherosclerosis, and impaired renal function are commonly considered as an intermediate stage of the vascular disease continuum. Literature data indicate that TOD is present in 61.3% of patients with diagnosed hypertension and 30.8% of patients with high normal arterial pressure [3]. The most important mechanisms leading to organ damage are oxidative stress and increased central aortic pressure [4, 5]. Considering the above data, the selection of an antihypertensive drug that both effectively reduces central aortic pressure and has a proven effect on the reduction of oxidative stress is of utmost importance in cardiovascular prevention.

Such a drug is undoubtedly nebivolol, which is a third-generation β1-blocker with vasodilator activity. In terms of chemical structure, it is a racemic mixture in a 1:1 ratio of the two enantiomers: D-nebivolol (right) and L-nebivolol (left). D-nebivolol has a selective antagonistic effect on adrenergic receptors, whereas β1-adrenergic L-nebivolol directly stimulates endothelial secretion of nitric oxide (NO) and, thereby, NO-mediated vasodilation [6].

Clinical significance of central aortic pressure

A significant difference between the central aortic pressure (measured in the aorta and carotid arteries)

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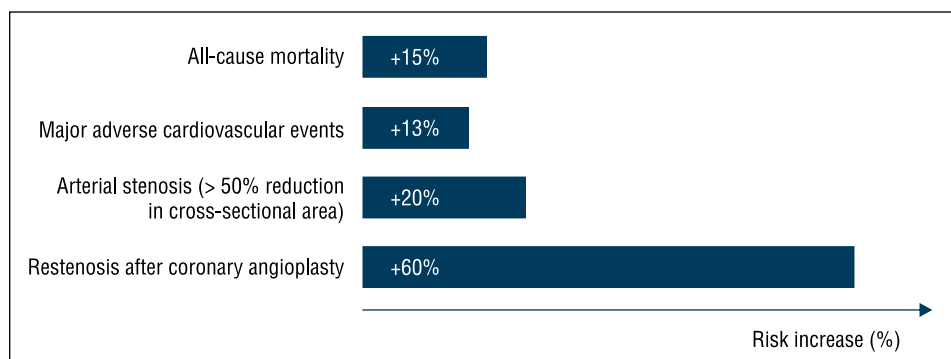71–252 Szczecin; tel.: 91 4253550; fax: 91 4253552; e-mail: widecka@o2.pl

Figure 1. An increase in the central aortic pressure by 10% results in increased risk of death and other cardiovascular complications (modified from: Eur. Heart J. 2010; 31: 1865–1871)

and the peripheral pressure (measured on the brachial artery) is well documented in the literature [7].

It has been shown that the difference between central and peripheral blood pressures depends not only on age, but also on gender, heart rate, presence or absence of cardiovascular disease, diabetes, renal failure, medication used, and hemodynamic cardiovascular status [8].

The central aortic pressure is directly responsible for the left ventricular load, determines the blood supply to the heart and the brain and acts on the walls of the coronary and cervical arteries. Elevated central blood pressure results in atherosclerotic lesions in these areas. Many studies assessed the prognostic value of central aortic pressure and convincing evidence was obtained that this parameter better predicts the risk of stroke, heart attack or cardiovascular death than peripheral blood pressure [5, 9–11]. In a study in patients with renal failure, Safar et al., found a significant correlation between central pulse pressure and the risk of death, but they did not observed such correlation for the pulse pressure measured on the brachial artery [12]. Similar results were obtained in another study in which a group of 320 patients without symptoms of cardiovascular disease was followed-up for 5 years (48% of the study population had diabetes mellitus, 54% had hypertension). It was shown that central pulse pressure (assessed by analysis of the peripheral pulse wave) enables better prediction of cardiovascular complications than peripheral blood pressure [9].

Vlachopoulos et al. [11] published an interesting meta-analysis of 11 prospective studies which assessed the associations of central blood pressure with cardiovascular events and total mortality. Data were collected from 5648 patients; mean follow-up period was 45 months. It has been shown that the increase in central pulse pressure by 10 mmHg increases the risk of all-cause mortality by 14%, risk of major ad-

verse cardiovascular events by 13%, narrowing of the vascular lumen by 20% and restenosis after coronary angioplasty by 60% (Figure 1).

The most important indicators of central blood pressure are: augmentation index (AI), augmentation pressure (AP), arterial compliance (C), arterial distensibility (d) and pulse wave velocity (PWV).

The augmentation pressure is defined as the difference between the pressure produced by the heart and the actual pressure in the aorta. The augmentation index (AIx,) is calculated as the quotient of the augmentation pressure to the pressure in the aorta [13]. Arterial elastic properties are also reflected by arterial compliance and distensibility. The arterial compliance is the ability of the artery to undergo deformation (a change in the lumen of the vessel) under the influence of pressure. The arterial distensibility is calculated as the quotient of arterial compliance relative to the initial volume. Pulse wave velocity is a derivative of the distensibility and compliance of the arteries. The PWV is measured between the common carotid and femoral arteries, using a non-invasive method. A pulse waveform is obtained from specific arterial segments, based on which the pulse wave velocity is calculated at the given distance. A significant problem impeding wider clinical application of PWV is the lack of clearly defined reference values. In normal conditions, the value of the pulse wave velocity is low, and the wave-reflection sites are found mainly at the origin of the peripheral resistance vessels. Ageing of the vessels leads to acceleration of the pulse wave, because the reflection sites are getting closer and a late peak on the pressure curve occurs. This leads to a disproportionately higher increase in systolic blood pressure (SBP) compared with diastolic blood pressure (DBP) and increased pulse pressure [14]. The pulse wave velocity increases with the severity of hypertension in both sexes and has been consid-
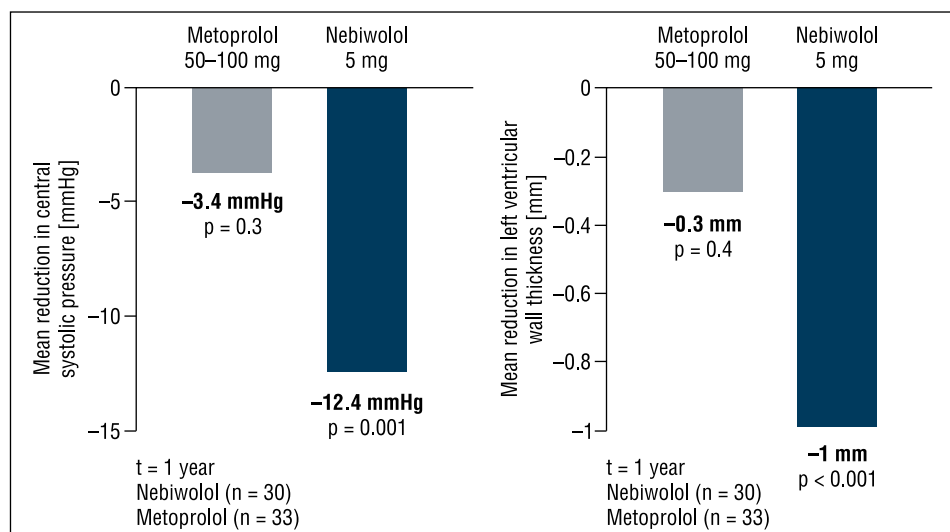
Figure 2. Nebivolol significantly reduces central aortic pressure and left ventricular hypertrophy compared with metoprolol (modified from: Hypertension 2011; 57: 1122–1128)

ered an independent marker of an increased risk of cardiovascular complications [5, 12].

Wider clinical use of PWV also requires clearly defined reference ranges. In children, reference range is usually defined as 5–6 m/s, in young adults (20–50 years old) 7–9 m/s, in people over 50 years of age 9–11 m/s [9, 15, 16]. Although the reference values for PWV are still being discussed, the authors of the European Society of Hypertension (ESH)/the European Society of Cardiology (ESC) guidelines on the management of hypertension published in 2013 have assumed that the values exceeding 10 m/s indicate subclinical organ damage [1].

Comparison of the effects of nebivolol and classic *β*-blockers on central aortic pressure

The literature emphasizes that the beneficial effects of nebivolol on the central pressure is mainly due to its unique vasodilating properties and direct protective effect on the vascular endothelium.

The recently published clinical trials compared the effects of nebivolol and classic *β*-blockers on central blood pressure parameters and significant superiority of nebivolol has been proven [17–19].

Dhakam et al., in a randomized, double-blind clinical trial, compared the effects of nebivolol and atenolol on central pressure in patients with isolated systolic hypertension. There was no difference in the reduction of blood pressure between the two groups of patients during 5-week treatment. However, a significant decrease in aortic pulse pressure measured by

the augmentation index was found only in the group of patients treated with nebivolol. The haemodynamic mechanism of this difference can be explained by the fact that nebivolol causes a smaller heart rate reduction compared with atenolol [17].

These results were confirmed in a 4-week study of hypertensive patients randomized to receive either 5 mg of nebivolol or 50 mg of atenolol. The aortic elasticity was assessed by measuring PWV and AIx. Both drugs equally reduced the peripheral pressure. However, only nebivolol reduced the pulse wave reflection. This can be explained by the direct effect of nebivolol on small, muscular arteries and a decrease in peripheral resistance resulting from an increase in NO level in peripheral vascular endothelium. The authors of the study emphasized that, due to different pharmacological properties, *β*-blockers should not be treated as a homogeneous group of drugs [18].

Similarly, Soanker et al. found that nebivolol (5 mg) used in patients with hypertension not only lowered central pressure, but also had a positive effect on all the parameters of the vessels' elasticity [19].

Recently, Kampus et al. [20] published a study aimed at comparing the vasodilator *β*-blocker, nebivolol, with the classic, selective *β*-blocker, metoprolol, in terms of their effect on central pressure and left ventricle wall thickness. In this randomized double-blind study, hypertensive patients received 12-month antihypertensive treatment: either 5 mg of nebivolol or 50–100 mg of metoprolol. The effect of treatment on heart rate, peripheral arterial pressure, central systolic, diastolic and mean pressure, augmentation index, PWV and echocardiographic pa-

rameters of left ventricular wall thickness were evaluated. Both nebivolol and metoprolol significantly, but to the same extent, reduced peripheral pressure, heart rate and mean central pressure. However, the reduction of central systolic and diastolic pressures and reduction of left ventricular hypertrophy were significantly higher in the group treated with nebivolol. As shown in Figure 2, central systolic pressure in the nebivolol group decreased by 12.4 mmHg and was statistically significant ($p < 0.001$), whereas in the metoprolol group central systolic pressure was reduced by 3.4 mm Hg and was not statistically significant ($p = 0.3$). The left ventricle wall thickness decreased significantly ($p < 0.001$) by 1 mm in the group treated with nebivolol, and remained without significant change (-0.3 mm, $p = 0.4$) in the metoprolol group.

The changes in left ventricular wall thickness significantly correlated with central systolic and diastolic pressures. The results of this study confirm the hypothesis that the new third-generation β-blocker, nebivolol, in contrast to classic preparations, significantly lowers the central pressure, which translates into a significant reduction in cardiovascular complications measured by left ventricular hypertrophy. It is worth noting that in the CAFE (Conduit Artery Functional Evaluation) study, a reduction in central pulse pressure by 3 mmHg in patients treated with amlodipine and an angiotensin-converting enzyme (ACE) inhibitor led to a significant reduction in the incidence of cardiovascular events and mortality [21]. Considering the results of the CAFE study, it should be emphasized that the decrease in the central pulse pressure by nebivolol was 6.2 mm Hg and only 0.3 mmHg in metoprolol-treated patients, and that this difference will certainly have clinical significance in the prevention of cardiovascular events.

Koumaras et al. [22] presented an interesting study which assessed the effect of various groups of antihypertensive drugs on central pressure. The authors assumed that drugs of the same class have different effects on the central pressure. The effects of renin-angiotensin-aldosterone system (RAA) inhibitors (quinapril and aliskiren) and β-blockers (nebivolol and atenolol) on the parameters of arterial stiffness were compared. Patients with stage 1 or stage 2 hypertension were randomized to treatment with quinapril, aliskiren, nebivolol or atenolol. Initially, after 10 weeks of treatment, the parameters of central aortic pressure and arterial compliance were assessed. It was shown that central pulse pressure and augmentation index were significantly reduced only in patients treated with quinapril, aliskiren and nebivolol, but not atenolol. In the final conclusions, the authors

found that despite similar peripheral blood pressure reduction, the classical β-adrenolytic (atenolol) is less effective than nebivolol and RAA inhibitors in improving central pressure haemodynamics.

The role of oxidative stress in the mechanism of target organ damage

Endothelial oxidative stress is an early pathophysiological change in many diseases associated with vascular stenosis. It is characterized by an increased generation of reactive oxygen species (ROS), which exceeds the capacity of the antioxidant defence system. This leads to irreversible damage to the vascular endothelium and the development of such diseases as hypertension, atherosclerosis, and myocardial ischaemia [4].

Reactive oxygen species and a decrease in nitric oxide level lead to increased pro-thrombotic, pro-inflammatory and pro-oxidative activity, and are responsible for the ageing of blood vessels (smooth muscle proliferation, vasospasm and vascular stiffness) [4, 23].

Nitric oxide produced by endothelium is a basic mediator modulating key endothelial vasodilatation functions and is directly involved in the development and progression of cardiovascular diseases. Currently, NO is considered the main therapeutic target of new prevention strategies against these diseases. It has been shown that the decrease in NO level is one of the earliest factors leading to the occurrence and intensification of oxidative stress, especially in the vascular system. The balance between ROS and endothelial vasodilators is maintained thanks to the following systems: nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, xanthine oxidase and nitric oxide synthase (eNOS) [23].

Nitric oxide synthase is a dioxygenase catalysing insertion of two oxygen atoms into the L-arginine molecule, which, using NADPH as an electron donor, is metabolized to NO and citrulline. It was confirmed that an increased amount of ROS leads to a decrease in eNOS activity and, as a result, to a decrease in NO level [24].

The mechanism of antioxidative action of nebivolol

Nebivolol differs from other β-blockers due to its vasodilating effect resulting from the ability to increase the release of nitric oxide by the vascular endothelium. The isomer mainly responsible for the endothelial effect is L-nebivolol. In studies that com-

pared the effects of nebivolol and atenolol in patients with hypertension, nebivolol was more effective than the other drug in reversing endothelial dysfunction and increasing the bioavailability of NO and exerted a significantly greater impact on vasodilation of the microcirculation [25]. Nebivolol is the agonist of $\beta3$ receptors which play a role in the vasodilatation mechanism [26]. Ladage et al. have proved that nebivolol stimulates NO production by affecting β-receptors, activation of NO synthase and, to a lesser extent, by stimulation of oestrogen receptors [27]. Maffei et al. [28] not only confirmed that nebivolol at the therapeutic concentration increases the release of NO, but also found that also the three major metabolites of nebivolol exhibit NO-dependent and NO-independent vasodilatory properties.

The vasodilatory effect of nebivolol is not solely dependent on the production of NO, because after the use of the arginine analogue to suppress eNOS, the vasodilation effect was partially maintained. The effects of nebivolol were observed both in conduit and resistance arteries, also within the vascular outer layer, which is devoid of β-receptors [29]. Nebivolol has the ability to increase NO level not only by stimulating its synthesis, but also by inhibiting oxidative degradation. Cominacini et al. [30] have a theory that the reduction of the level of free oxygen radicals formed under the influence of oxidized LDL cholesterol molecules in endothelial cells may be obtained by reducing NO degradation. The antioxidative properties of nebivolol were also confirmed in studies by De Groota et al. [31] on the animal model and by Mason et al. [32]. In heart failure, circulating free radicals can contribute to disease progression and activation of apoptosis. The L-arginine pathway is present in human platelets and is an endogenous modulator of platelet activation. Adenosine diphosphate (ADP)- and collagen-dependent inhibitory effects on platelet aggregation also result from the ability of nebivolol to stimulate the release of NO [33].

The vasodilatory effects of nebivolol have been demonstrated in *in vitro* and *in vivo* studies in normotensive subjects and in patients with hypertension. In healthy volunteers, nebivolol given by an infusion into the brachial artery caused a significant increase in drug-dependent blood flow. However, intra-arterial administration of atenolol at equivalent doses did not cause a significant change in the blood flow. The vasodilatory effect of nebivolol and carbachol (a compound that causes endothelium-dependent vasodilation) was inhibited by co-administration of intravenous L-NMMA (an NO synthase inhibitor) and restored after intravenous administration of L-arginine. Vasodilation induced by administration
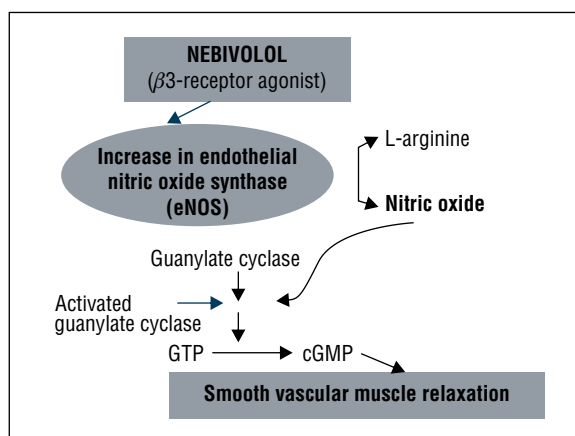
Figure 3. The effect of nebivolol on vascular relaxation *via* L-arginine/nitric oxide pathway

of nebivolol is inhibited by L-NMMA to a similar extent as vasodilation associated with the use of carbachol, which indicates that the action of nebivolol is mediated by the L-arginine/NO pathway [34]. Proven antioxidant properties of nebivolol guarantee the effectiveness of this drug in reducing target organ damage caused by oxidative stress in patients with hypertension. Figure 3 shows the mechanism of vasodilatory effect of nebivolol via the L-arginine/NO pathway.

Evidence-based data confirming cardioprotective properties of nebivolol

Nebivolol is the only third-generation β-blocker which exerts vasodilatory effect by increasing NO release. In this way, it provides a unique dual mechanism of action that clearly distinguishes it from other β-blockers and allows for obtaining additional benefits beyond antihypertensive effects. Clinical trials have proven cardioprotective effects of the drug that were related to heart rate lowering, improvement of left ventricular systolic and diastolic functions and increased coronary reserve. In a clinical trial comparing the effects of nebivolol and atenolol on the coronary reserve, as assessed by the Doppler method, the coronary flow was only increased in the group of patients treated with nebivolol [35]. Another study compared the effects of treatment with nebivolol and metoprolol CR in patients with post-infarction heart failure. Both drugs effectively and similarly reduced the number of acute cardiac events (by 73%), decreased the incidence of ischaemic events (by 68%) and improved exercise tolerance [36].

In the ENECA (Efficacy of Nebivolol in the treatment of Elderly patients with Chronic heart failure
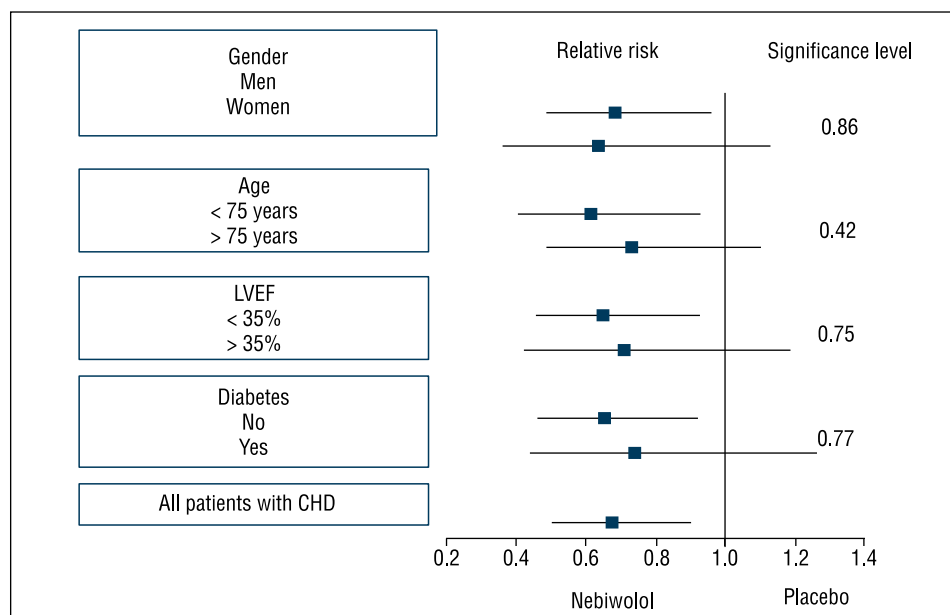
Figure 4. The rate of cardiovascular events in patients with coronary heart disease treated with nebivolol vs. placebo: subanalysis of the SENIORS trial (modified from: Heart 2011; 97: 209–214)
LVEF — left ventricular ejection fraction, CHD — coronary heart disease

as Add-on therapy to ACE inhibitors or angiotensin II receptor blockers, diuretics, and/or digitalis) trial, a significant increase in left ventricular ejection fraction was noted in patients with chronic heart failure [37].

The SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with heart failure) study provided evidence confirming improved prognosis in heart failure patients over 70 years of age treated with nebivolol. There was a 16% reduction in cardiovascular mortality and the incidence of hospitalization due to cardiovascular disease in the nebivolol group. It should be emphasized that this effect was achieved in the population intensively treated with other drugs with proven therapeutic status in heart failure. On average, 83% of patients received ACE inhibitors, 7% sartans, 86% diuretics, 28% aldosterone antagonists and 39% digitalis preparations [38].

Anti-ischaemic effect was demonstrated in the SENIORS study subanalysis including patients with documented ischaemic heart disease. In the group treated with nebivolol, a significant (p = 0.008) reduction in ischaemic events (15.9%) was found compared with the control group (10.7%). As shown in Figure 4, the reduction in the incidence of cardiovascular events in patients treated with nebivolol was found irrespective of sex, age, left ventricle ejection fraction and the presence or absence of diabetes [39].

The results of the studies mentioned above confirmed the usefulness of nebivolol in the treatment of patients with ischaemic heart disease.

Summary

Cardiovascular complications such as left ventricular hypertrophy, atrial fibrillation, heart failure, coronary events, vascular ageing and accelerated atherosclerosis are the leading cause of death in hypertensive patients. The choice of adequate antihypertensive therapy is of key importance for the reduction of mortality and morbidity in these patients. The ideal drug must not only effectively lower blood pressure, but also have pleiotropic effects.

Due to its antioxidant properties, nebivolol is an attractive therapeutic option not only for patients with hypertension, but also for patients with heart failure and coronary heart disease. It has been confirmed that this drug effectively lowers central aortic pressure, slows heart rate, reduces peripheral resistance, improves left ventricular systolic and diastolic functions, has anti-ischaemic effects and increases coronary reserve.

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