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Metabolic Profile of Nebivolol, a β-Adrenoceptor Antagonist with Unique Characteristics

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Abstract

β-Adrenoceptor antagonists (β-blockers) have historically been considered an effective and safe option for first-line treatment of hypertension. However, very recently, it has been proposed that β-blockers should no longer be considered suitable for first-line therapy in the patient with uncomplicated hypertension because of unfavourable morbidity and mortality data.

New evidence from recent clinical studies of nebivolol, a third-generation highly selective β_1-blocker with additional endothelial nitric oxide (NO)-mediated vasodilating activity, confirms previous findings that this drug differs from other β-blockers. The combined mechanisms of β-adrenoceptor antagonism and NO-mediated vasodilation may potentiate the blood pressure-lowering effect of this agent, and confer a broader favourable metabolic profile, which may be clinically relevant for hypertensive patients. The antioxidant properties of nebivolol and its neutral or even favourable effects on both carbohydrate and lipid metabolism are well documented. These properties consistently differentiate nebivolol from nonvasodilating β-blockers such as atenolol, metoprolol or bisoprolol.

Therapeutic indications for β-blockers include a wide range of co-morbidities found in hypertensive patients, including ischaemic heart disease, tachyarrhythmias and heart failure. Given that the majority of hypertensive patients require more than one drug to control blood pressure, the multiple mechanisms of action and favourable metabolic profile of nebivolol could make it an alternative therapeutic option for hypertensive patients requiring β-adrenoceptor therapy.

β-Adrenoceptor antagonists (β-blockers) are generally considered among the drugs that can be safely and effectively used as a first step in the treatment of hypertension.[1] However, very recently, new hypertension treatment guidelines from the National Institute for Health and Clinical Excellence (NICE) and the British Hypertension Society (BHS) have proposed that, in the patient with uncomplicated hypertension, β-blockers should no longer be considered suitable options for first-line therapy.[2] Instead, it is suggested that these agents be used in postmyocardial infarction patients and those with heart failure and atrial fibrillation, and that they should be reserved for third- or fourth-line therapy in patients with uncomplicated hypertension.[2,3]

Two main considerations contributed to this proposal. The first issue was the accumulating evidence that treatment regimens based on β-blockers, with or

without diuretics, were associated with a greater number of cases of new-onset diabetes mellitus than regimens based on ACE inhibitors, angiotensin II type 1 receptor antagonists (angiotensin receptor blockers [ARBs]) or calcium channel antagonists. The second issue was related to the results of the ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) study,[4] which demonstrated an excess of 24% cardiovascular deaths, 14% cardiac events and 23% cerebrovascular events associated with a therapeutic regimen based on the β-blocker atenolol, with or without a diuretic, compared with a regimen containing a calcium channel antagonist with or without an ACE inhibitor. In the same study, patients treated with atenolol (± diuretic)-based therapy also had a 30% excess of new onset diabetes compared with those receiving calcium channel antagonist (± ACE inhibitor)-based therapy.

The view of the NICE-BHS guidelines update[2] was that the increased risk of new-onset diabetes with β-blocker therapy (particularly in combination with diuretics) would inevitably confer an increase in long-term cardiovascular risk, with associated adverse health and economic consequences. The NICE-BHS guideline development group concluded that omitting β-blockers from the routine treatment algorithm was justified given the morbidity and mortality data available, but noted that compelling indications still existed for use of β-adrenergic receptor antagonists. However, atenolol was the main β-blocker investigated in clinical studies reviewed for the NICE-BHS guideline update. As a result, concerns have been raised about the generalisability of the recommendations to all β-blockers. Because recent data indicate that the effects of β-blockers on carbohydrate and lipid metabolism are far from homogeneous, the relative lack of clinical outcome data from hypertension trials with the newer β-blockers with additional vasodilating properties, such as nebivolol or carvedilol, may have had an impact on the recommendations.

Nebivolol is a relatively new β-blocker. It is a racemic mixture of *d*-nebivolol, which has selective β_1-receptor blocking activity, and *l*-nebivolol, which causes vasodilation.[5] Once-daily administration of nebivolol results in a dose-dependent antihypertensive effect.[6] The usual therapeutic dose is 5 mg/day, and at this dose the achieved trough-to-peak antihypertensive ratio is around 90%.[7]

Two clinical studies suggested that nebivolol does not negatively affect lipid or carbohydrate metabolism.[8,9] A recently published analysis[10] of metabolic data from the SENIORS (Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with heart failure) trial[11] in elderly heart failure patients also supports the earlier data. Furthermore, other studies[12,13] have found that nebivolol reduces oxidative stress in patients with hypertension. In view of these important new findings on the metabolic profile of nebivolol and its potentially protective effects on oxidative stress, the present narrative review discusses these effects of nebivolol in comparison with those of other antihypertensive agents.

1. Effect of Nebivolol on Endothelial Function and Oxidative Stress

Similar to other third-generation β-blockers, nebivolol has been shown to possess vasodilatory properties. However, unlike other third-generation β-blockers, such as labetalol, carvedilol and bucindolol, that mediate a vasodilatory effect through α_1-adrenoceptor antagonism, nebivolol mediates endothelium-dependent arterial and venous dilatation via the L-arginine-nitric oxide (NO)-dependent pathway.[14-16] These additional properties of nebivolol were first demonstrated in animal models[17,18] and subsequently confirmed in healthy volunteers[19] and patients with essential hypertension.[16] These effects are thought to be due to the *l*-nebivolol enantiomer, whereas the blood pressure-reducing properties of nebivolol appear to be provided by the *d*-enantiomer.[20,21] Thus, the overall antihypertensive effects of the drug would appear to be exerted by the combination of the activity of both enantiomers.

Nebivolol improves endothelial function both by increasing NO production via stimulation of endothelial NO-synthase (eNOS) and by reducing oxidative inactivation of NO.[22,23] Ladage et al.[24] sug-

Table I. Blood pressure (BP) values and oxidative parameters in essential hypertensive patients before and after 4 weeks' treatment with nebivolol and atenolol, and after the wash-out period (data are means ± SD) [reproduced from Fratta Pasini et al.,[12] with permission from Lippincott, Williams & Wilkins]

Parameter	Nebivolol-treated group			Atenolol-treated group		
	baseline	4 weeks	washout	baseline	4 weeks	washout
Systolic BP (mm Hg)	156.5 ± 6.1	136.2 ± 5.2*	150.5 ± 5.4	158.6 ± 5.4	140.2 ± 5.1*	147.4 ± 5.7
Diastolic BP (mm Hg)	95.5 ± 2.4	84.0 ± 2.3*	94.1 ± 2.4	97.5 ± 2.2	86.5 ± 2.2*	94.1 ± 2.6
Heart rate (beats/min)	74.6 ± 5.6	64.0 ± 5.1*	72.2 ± 5.4	76.6 ± 4.9	61.6 ± 4.8*	74.0 ± 5.0
Plasma LOOH (ng/mL)	0.89 ± 0.10	0.63 ± 0.007*	0.85 ± 0.08	0.91 ± 0.10	0.89 ± 0.09	0.91 ± 0.008
LDL LOOH (ng/mg protein)	1.32 ± 0.09	1.01 ± 0.09*	1.28 ± 0.10	1.28 ± 0.09	1.27 ± 0.08	1.25 ± 0.09
Plasma 8-isoprostanes (pg/mL)	80 ± 10	66 ± 8**	78 ± 10	76 ± 12	74 ± 11	77 ± 10
Plasma ox-LDL (U/L)	70 ± 10	52 ± 7*	66 ± 9	74 ± 11	77 ± 10	73 ± 11
LDL lag phase (min)	103.2 ± 4.2	125.9 ± 6.0*	104.5 ± 5.7	101.2 ± 5.6	105.3 ± 5.1	104.8 ± 4.3
LDL tocopherol (vitamin E) [mg/mg protein]	6.9 ± 0.4	7.0 ± 0.5	6.8 ± 0.4	7.2 ± 0.5	7.1 ± 0.4	7.3 ± 0.5

LDL = low-density lipoprotein; **LOOH** = lipid hydroperoxides; **ox-LDL** = oxidised LDL; * $p < 0.01$; ** $p < 0.05$ vs baseline.

gested that stimulation of eNOS by nebivolol may involve β_3-adrenoceptors and estrogen receptors. Alternative hypotheses have been proposed, such as that nebivolol might reduce circulating levels of asymmetric dimethylarginine (ADMA), a potent inhibitor of eNOS.[12] Additionally, nebivolol might stimulate serotonin 5-HT_{1A} receptors,[25] which, in turn, stimulate e-NOS activity.

In 2000, Troost et al.[26] demonstrated that nebivolol administration is associated with statistically significant reductions in urinary excretion of 8-iso-prostaglandin $F_{2\alpha}$ (a marker of systemic oxidative stress) in healthy volunteers. Subsequently, Fratta Pasini et al.[12] showed that nebivolol decreases oxidative stress in essential hypertension and increases NO by reducing its oxidative inactivation. This study also showed that, in 20 hypertensive patients, both nebivolol and atenolol significantly reduced blood pressure values after 4 weeks of treatment. However, plasma and low-density lipoprotein (LDL) cholesterol, hydroperoxides, plasma 8-isoprostanes, plasma oxidised LDL and LDL lag phase (and index of susceptibility of LDL to oxidation) were significantly improved only in patients receiving nebivolol (table I). Similarly, there was a reduction in reactive oxygen species and superoxide anion concentrations in cultured endothelial cells incubated with plasma of patients treated with nebivolol then exposed to oxidative stress, whereas no effect was seen in cells incubated with plasma from patients treated with atenolol. Furthermore, the reduction in NO production by endothelial cells induced by oxidative stress was significantly lower in patients receiving nebivolol compared with those given atenolol. These findings strongly support the hypothesis that nebivolol may increase NO by reducing its oxidative inactivation. Thus, the available data suggest that nebivolol may exert relevant protective actions on the endothelium by increasing NO bioavailability. However, it is not entirely clear to what extent this effect is related to nebivolol-induced increases in NO production as opposed to nebivolol-induced reductions in NO oxidative breakdown.

2. Metabolic Effects of Nebivolol

Despite being a selective drug for β_1-adrenoceptors, atenolol has been shown to have adverse effects on both carbohydrate and lipid metabolism, as well as on insulin sensitivity.[2,4] Conversely, clinical studies of nebivolol[8,9] and other third-generation β-blockers, such as celiprolol[27] and carvedilol,[28] have almost uniformly demonstrated different characteristics in this regard.

Dedov et al.[8] investigated the metabolic effects of treatment with nebivolol versus placebo in hypertensive diabetic patients. A significant reduction in serum triglycerides was observed, while no change in serum total cholesterol, LDL cholesterol, blood glucose level or bodyweight could be detected. In

Table II. Metabolic parameters (mean ± SD) in the SENIORS trial.[10] Laboratory values are expressed as descriptive statistics by presence/absence of baseline diabetes mellitus in the intent-to-treat population

Parameter		Diabetic patients				Nondiabetic patients			
		placebo	nebivolol			placebo	nebivolol		
			≤5mg	10mg	overall		≤5mg	10mg	overall
Total cholesterol (mmol/L)									
Baseline	n	253	88	178	266	756	234	508	742
	Mean	5.45	5.06	5.47	5.33	5.35	5.42	5.51	5.48
	SD	1.21	0.94	1.35	1.24	1.15	1.24	1.17	1.19
Glucose (mmol/L)									
Baseline	n	251	88	178	266	753	233	503	736
	Mean	8.82	8.27	9.38	9.02	5.61	5.33	5.58	5.50
	SD	3.56	3.28	3.41	3.40	1.15	1.12	1.13	1.13
Triglycerides (mmol/L)									
Baseline	n	253	88	178	266	756	234	508	742
	Mean	2.15	1.91	2.22	2.11	1.58	1.63	1.68	1.67
	SD	1.36	1.11	1.82	1.62	0.89	0.94	0.92	0.92
Uric acid (μmol/L)									
Baseline	n	253	88	178	266	756	234	508	742
	Mean	406.60	417.72	387.49	397.49	394.75	407.37	388.60	394.52
	SD	143.55	129.44	123.17	125.84	119.11	128.34	112.18	117.75

another trial,[9] nebivolol was administered for 6 weeks to physically active patients with essential hypertension. Blood pressure was well controlled by the drug at rest and during exercise. Again, nebivolol did not negatively affect lipid or carbohydrate metabolism or substrate flow.[9]

However, as previously mentioned, one of the arguments supporting the proposal of the NICE-BHS hypertension guideline update to remove β-blockers from the list of drugs suitable for first-line therapy in hypertension was the observation of a higher incidence of new-onset diabetes during treatment with these agents (particularly in combination with diuretics), compared with other classes of drugs, namely ACE inhibitors and calcium channel antagonists.[2] This was justified by the fact that atenolol was the β-blocker investigated in most studies; however, the guideline authors noted that the generalisability of their guidelines to all β-blockers was questionable.

Useful information on this topic for nebivolol has been obtained from a recent re-analysis of data[10] from the SENIORS trial.[11] The SENIORS study assessed the effects of nebivolol versus placebo in 2128 patients >70 years of age with heart failure, regardless of ejection fraction. The mean duration of treatment was 36 months, with patients being followed up for 21 months. Very recently, the effects of nebivolol and placebo on the metabolic profile of SENIORS patients were specifically analysed.[10] Table II shows baseline total cholesterol, serum glucose, triglyceride and uric acid levels in diabetic and non-diabetic patients. Changes in fasting serum glucose (mmol/L) in diabetic patients were −0.32 and −0.11 in the overall nebivolol and placebo groups, respectively, while the corresponding changes in non-diabetic patients were 0.03 and 0.05, respectively. Most interestingly, there was a tendency to observe fewer new cases of diabetes during treatment with nebivolol than with placebo, although the difference did not reach statistical significance (figure 1).[10] Therefore, treatment with nebivolol, at least in elderly patients with heart failure, was not associated with an increase in the frequency of new-onset diabetes.

It has been suggested that the duration of treatment in previous studies of antihypertensive agents was insufficient to show a difference in the frequen-

cy of new onset diabetes. In the SENIORS study, patients were treated for 36 months and followed for 21 months, and a difference in the incidence of new onset diabetes between nebivolol and placebo groups was evident; however, larger prospective studies are required to show whether this difference is statistically significant. Also, no increase in weight or body mass index was observed in patients treated with nebivolol compared with placebo.[10] This could be expected since patients with heart failure often have decreased appetite and a decrease in oedema as a result of improved heart failure could cancel out any increase in bodyweight. However, in hypertensive patients with type 2 diabetes and no heart failure, no increase in bodyweight (or adverse effects with respect to lipid or glycaemic control) with nebivolol treatment was seen.[29]

2.1 Comparison with Other β-Adrenoceptor Antagonists (β-Blockers)

Poirier et al.[30] compared the effects of 16 weeks treatment with nebivolol or atenolol on insulin sensitivity, as evaluated by euglycaemic-hyperinsulinaemic clamp, in 25 patients with essential hypertension. Although blood pressure was decreased to the same extent by both drugs, insulin sensitivity was not significantly modified by nebivolol, whereas it was clearly reduced by atenolol. Fogari et al.[31] applied this assessment to patients with type 2 diabetes and confirmed that treatment with nebivolol neither further deteriorates insulin sensitivity or glycaemic control nor adversely affects lipid profile. The effect of nebivolol versus metoprolol was explored in high-risk patients with hypertension, type 2 diabetes and ischaemic heart disease.[32] No unfavourable changes in carbohydrate or lipid metabolism parameters were seen with either drug. Again, a pronounced reduction in serum triglycerides was observed only in nebivolol-treated patients.

Hypertensive patients commonly exhibit lipid abnormalities and frequently require treatment with HMG-CoA reductase inhibitors (statins) in combination with antihypertensive therapy. Rizos et al.[33] conducted a trial to clarify the effect on the metabolic profile of β-blocker therapy with atenolol or nebivolol, administered alone or in combination with pravastatin. Atenolol significantly increased triglyceride levels by 19% and increased lipoprotein(a) by 30%, whereas nebivolol showed a trend to increase high-density lipoprotein cholesterol and to decrease triglyceride levels. Glucose levels remained unchanged with nebivolol, whereas insulin levels were reduced by 10% and the HOMA (Homeostasis Model Assessment) index (fasting glucose levels multiplied by fasting insulin levels and divided by 22.5) was reduced by 20%. The effects on triglycerides and HOMA index were significantly different between the two treatments. Therefore, nebivolol seems to be a more appropriate drug than atenolol for the treatment of hypertensive patients with hyperlipidaemia and carbohydrate intolerance.

Other studies[9,11,12] comparing nebivolol with atenolol have shown that the effects of nebivolol on glucose or lipid metabolism and insulin sensitivity are almost uniformly neutral or positive, whereas a worsening of metabolic parameters was observed with atenolol. Similar results were obtained in a study comparing nebivolol with metoprolol.[32] In addition, nebivolol maintained a more favourable metabolic profile than atenolol when a statin was added.[13]

A possible explanation for the different effects of nebivolol compared with other β-blockers on carbohydrate and lipid metabolism could be related to the modulation of oxidative stress by the drug.[12,13] Celik et al.[13] explored this aspect in 80 hypertensive patients treated with nebivolol or metoprolol for 6 months. Blood pressure, heart rate, oxidative stress (as evaluated by malonyldialdehyde concentrations), insulin resistance (as tested by HOMA index), adiponectin and plasma soluble P-selectin levels were measured before and after treatment. At the end of treatment, nebivolol and metoprolol significantly decreased blood pressure and heart rate. Nebivolol, but not metoprolol, also significantly lowered oxidative stress, HOMA index and plasma soluble P-selectin levels, and increased adiponectin levels (table III).

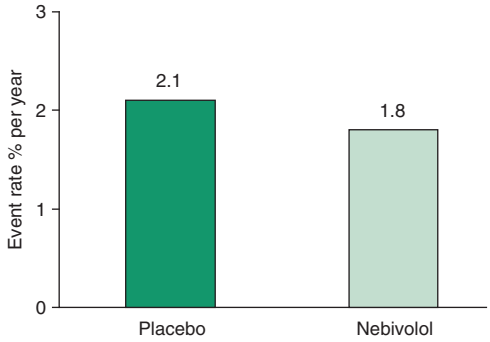

Fig. 1. Patients without diabetes mellitus at baseline who developed new onset diabetes (event rate % per year) in the placebo (17/793) and nebivolol (14/780) groups during the SENIORS trial.[10]

Although carvedilol and nebivolol have demonstrated similar effects on heart rate and blood pressure in healthy volunteers,[34,35] carvedilol treatment has been associated with significantly worse quality-of-life outcomes compared with nebivolol ($p < 0.05$).[35] Furthermore, compared with carvedilol, nebivolol has been shown to exert a greater inhibitory effect on platelet aggregation,[14] and as platelets can be directly implicated in the pathogenesis of vessel wall complications in hypertensive patients,[36] nebivolol may be a safer choice in this setting. Nebivolol may also possess antiproliferative properties that are potentially useful in terms of

Table III. Comparison of effects of nebivolol and metoprolol on plasma soluble P-selectin, adiponectin, malonyldialdehyde, insulin and glucose levels, and on insulin sensitivity (values are mean ± SD) [reproduced from Celik et al.,[13] with permission from Lippincott, Williams & Wilkins]

Parameter	Nebivolol (n = 37)	Metoprolol (n = 35)	p-Value
Malonyldialdehyde (mmol/L)			
Before	0.61 ± 0.46	0.64 ± 0.37	0.75[a]
After	0.47 ± 0.30	0.64 ± 0.34	0.03[a]
p-Value	0.007[b]	0.76[b]	
Adiponectin (mg/mL)			
Before	2.56 ± 0.89	2.52 ± 0.77	0.84
After	2.81±0.91	2.46 ± 0.75	0.04
p-Value	<0.001	0.08	
Soluble P-selectin (ng/mL)			
Before	1.29 ± 0.46	1.45 ± 0.46	0.16[a]
After	1.21 ± 0.36	1.46 ± 0.39	0.008[a]
p-Value	0.002[b]	0.59[b]	
Glucose (mg/dL)			
Before	93.67 ± 9.17	95.14 ± 11.38	0.54[a]
After	94.43 ± 7.13	97.17 ± 7.83	0.12[a]
p-Value	0.71[b]	0.36[b]	
Insulin (mU/mL)			
Before	12.19 ± 5.20	11.51 ± 4.75	0.56[a]
After	9.72 ± 5.13	11.84 ± 1.62	0.001[c]
p-Value	0.006[b]	0.69[b]	
HOMA-IR			
Before	2.79 ± 1.16	2.67 ± 1.07	0.66[a]
After	2.29 ± 1.24	2.83 ± 0.42	0.003[c]
p-Value	0.008[b]	0.39[b]	

a Indicates independent samples t-test.

b Indicates paired t-test.

c Indicates Mann-Whitney U test.

HOMA-IR = Homeostasis Model Assessment of Insulin Resistance.

regression of the vascular structural changes frequently observed in hypertensive patients.[37]

2.2 Comparison with Other Antihypertensive Drugs

We have compared the effects of 12 weeks of treatment with nebivolol or lisinopril on blood pressure and serum glucose and lipids.[38] The two drugs were equally effective in terms of reducing blood pressure and equally well tolerated. No adverse effects on carbohydrate and lipid metabolism were observed with either nebivolol or lisinopril.

The metabolic effects of nebivolol were evaluated versus sustained-release nifedipine in another trial.[39] Total plasma cholesterol and LDL cholesterol levels decreased significantly by 5% and 8%, respectively, after nebivolol treatment, compared with a reduction of approximately 3% after nifedipine treatment. These data suggest that both drugs may have favourable effects on the lipid profile; however, controlled data are required to confirm this.

The effects of nebivolol and hydrochlorothiazide, given as monotherapy or in combination, on blood pressure and plasma lipids, lipoproteins and apolipoproteins were compared with placebo in a parallel 3×4 factorial design study.[40] After an 8-week washout period, 240 patients with primary hypertension were randomised to receive either placebo, nebivolol 1, 5 or 10mg, hydrochlorothiazide 12.5 or 25mg, or one of six possible combinations of nebivolol and hydrochlorothiazide. After 12 weeks of treatment, there was a significant dose-related reduction in blood pressure among the active treatment groups. Apart from a slight and isolated increase in triglycerides with hydrochlorothiazide 12.5mg, lipoprotein and apolipoprotein levels and related lipoprotein and apolipoprotein ratios were not significantly modified by active treatment compared with placebo.[40]

The metabolic effects of nebivolol treatment in studies discussed in this section are summarised in table IV.

3. Haemodynamic Effects of Nebivolol

3.1 Comparison with Other β-Blockers

Several studies have directly compared the haemodynamic effects of nebivolol with those of other β-blockers.[30,38,41-46] Nebivolol is as effective as atenolol in reducing office blood pressure,[41] but has a more homogeneous effect over 24 hours, as documented by a clearly superior trough-to-peak ratio for its antihypertensive effect.[41,42] Furthermore, nebivolol has been associated with a lower reduction in cardiac index, a significant increase in stroke volume index and a decline in mean pulmonary artery pressure and pulmonary wedge pressure, both at rest and peak exercise, compared with atenolol.[43] Similar results were obtained in studies comparing the haemodynamic effects of nebivolol with those of metoprolol[13,32,44] or bisoprolol.[45] In contrast with other β-blockers, nebivolol does not reduce exercise tolerance,[46] possibly because it does not inhibit the formation of free fatty acids, which are a substrate for energy expenditure, to the same extent as other β-blockers.

4. Nebivolol in Patients with Heart Failure

Nebivolol has been extensively investigated in hypertension and has received approval in many jurisdictions for this indication. While β-blockers have historically been avoided in patients with heart failure, nebivolol plays an important role in the management of hypertension in patients with heart failure and coronary artery disease. β-blockers can slow or even reverse the progression of heart failure and improve left ventricular function via antagonism of sympathetic nervous system effects.[47] In patients with a low ejection fraction, β-blockers reduce hospital admissions for worsening heart failure and the risk of death by 30%.[48] The aforementioned SENIORS trial[11] showed that the β_1-selective vasodilating β-blocker nebivolol was well tolerated and effective in reducing mortality and morbidity in patients of age >70 years with heart failure regardless of the initial ejection fraction.[49] Furthermore, it has recently been shown that

Table IV. Summary of metabolic effects of nebivolol treatment in several different studies[21,24,26,28-35]

Study	Type and number of patients	Type and duration of drug treatment	Impact on metabolic parameters
Dedov et al.[8]	35 hypertensive and diabetic	Nebivolol vs placebo; 8 weeks	Significant reduction in triglycerides with nebivolol
Predel et al.[9]	18 hypertensive	Nebivolol; 6 weeks	No change in lipid or carbohydrate metabolism
Flather et al.[11]	2128 with congestive heart failure	Nebivolol vs placebo; mean follow-up 21 months	Incidence of new-onset diabetes mellitus similar with nebivolol and placebo
Poirier et al.[30]	25 hypertensive with glucose intolerance	Nebivolol vs atenolol; 16 weeks (crossover design)	No change in insulin sensitivity with nebivolol, significant reduction (20%) with atenolol
Fogari et al.[31]	30 hypertensive and diabetic	Nebivolol vs atenolol; 6 months	Both drugs neutral on lipid profile and insulin sensitivity
Makolkin et al.[32]	35 hypertensive and diabetic with ischaemic heart disease	Nebivolol vs metoprolol; 8 weeks	Reduction in serum triglycerides with nebivolol; no change with metoprolol
Rizos et al.[33]	30 hypertensive and dyslipidaemic	Nebivolol + pravastatin vs atenolol + pravastatin; 24 weeks	No change in triglycerides and reduction of HOMA index (20%) with nebivolol; no change in HOMA index and increase in triglycerides (19%) with atenolol
Celik at al.[13]	80 hypertensive	Nebivolol vs metoprolol; 6 months	Reduction in HOMA index and insulin levels with nebivolol
Agabiti Rosei et al.[38]	68 hypertensive	Nebivolol vs lisinopril; 3 months	No adverse effect on carbohydrate and lipid metabolism with either drug
Lacourciere et al.[39]	51 hypertensive	Nebivolol vs nifedipine sustained-release; 12 weeks	Reduction in total and LDL cholesterol with both drugs
Lacourciere and Arnott[40]	240 hypertensive	Nebivolol vs HCTZ vs nebivolol + HCTZ (factorial design); 12 weeks	No change in serum lipids, lipoproteins or apolipoproteins with any treatment. Small increase in triglycerides with HCTZ

HCTZ = hydrochlorothiazide; **HOMA** = Homeostasis Model Assessment; **LDL** = low-density lipoprotein.

nebivolol improves coronary microvascular function,[50] which is associated with increased morbidity and mortality, in patients with idiopathic dilated cardiomyopathy.

5. Tolerability and Compliance

Nebivolol 5 mg/day is generally well tolerated in patients with hypertension and has a tolerability profile similar to or more favourable than that of other β-blockers.[51] Tolerability issues associated with nebivolol in hypertensive patients have been covered in depth in previous publications.[44,49] The fact that heart rate and cardiac contractility reductions are less pronounced with nebivolol than with other β-blockers[44] may partly explain its better safety profile. For example, the incidence of fatigue during nebivolol treatment in hypertensive patients is about 50% less than that with atenolol,[44] mainly because of the lesser effect of nebivolol on exercise capacity. In addition, the incidence of some adverse events typical of β-adrenoceptor antagonism, such as bradycardia, other bradyarrhythmias, depression, impotence, worsening of cardiac contractility and bronchospasm, is very low (around 1%) during treatment with nebivolol.[10]

Compliance with therapy represents an important issue that should be taken into account when choosing an antihypertensive drug.[52] Unfortunately, the discontinuation rate with β-blockers and diuretics is particularly high compared with newer classes of antihypertensive drugs.[53] Therefore, poor compliance with therapy seems to be a major point of weakness of β-blocker-based treatment. However, selective β-blockers have been shown to be associated with similar improvements in quality of life to ACE inhibitors and much greater improvements than are seen with nonselective β-blockers.[54] Reasons for the observed unsatisfactory drug compliance may include a relatively high incidence of adverse effects and relatively poor blood pressure responses. However, as evident from previously discussed data, nebivolol has a good safety profile and

does not appear to be associated with most of the adverse events reported with other β-blockers. Therefore, it is likely that patients treated with nebivolol may have better adherence to therapy with this agent than to other β-blockers, although this aspect should be addressed in further, specific, long-term studies.

6. Conclusion

New evidence from recently completed clinical studies of nebivolol, a highly selective β_1-blocker with additional vasodilating activity mediated by endothelial NO release, confirms previous findings that nebivolol differs from other β-blockers. The combination of β-adrenoceptor antagonism and NO-mediated vasodilation not only potentiates the blood pressure-lowering activity of nebivolol but also confers a broader favourable metabolic profile, which is clinically relevant in the treatment of hypertensive patients.[22] In particular, the antioxidant properties of nebivolol and its neutral or favourable effects on both carbohydrate and lipid metabolism are well documented. The neutral effects on lipids and insulin resistance are also seen with highly selective β-blockers such as low-dose bisoprolol. However, nebivolol is the most selective β-blocker and is the only agent of its class to show an ancillary vasodilating property. These properties help to differentiate nebivolol from nonvasodilating β-blockers, such as atenolol, metoprolol or bisoprolol.

The observation that nebivolol enhances or restores NO-mediated vasodilation in hypertensive patients has important therapeutic implications in view of the well established protective role of NO against cardiovascular risk factors, particularly with regard to the development of atherosclerosis. Similarly, the favourable metabolic profile of nebivolol, as demonstrated by recent investigations showing that use of nebivolol is associated with a decrease in serum lipids, increased insulin sensitivity and no increase in the incidence of new-onset diabetes, appears to have clinically relevant benefits. These benefits are also observed in the presence of the metabolic syndrome, a condition often present in hypertensive patients.

On the basis of this evidence, it may prove to be unreasonable to associate third-generation agents, such as nebivolol, that have a different and distinct metabolic profile from that of older agents, with the suggestion that β-blockers are not suitable for first-line hypertension therapy. Current European[1] and US guidelines[55] state that β-blockers are useful and important therapeutic tools for the clinician and β-blockers are used in a wide range of hypertensive patients, including those with ischaemic heart disease, tachyarrhythmias and heart failure. It will be interesting to see if the new updates of the European and US guidelines concur with the NICE-BHS recommendations[2] or whether they separate β-blockers into subgroups based on their impact on metabolic outcomes.

Clinical studies to date suggest that nebivolol may be s suitable therapeutic option for patients requiring β-blocker therapy. Because of its multiple mechanisms of action, nebivolol may offer potential safety and tolerability advantages over conventional β-blockers and possibly also over other classes of antihypertensive agents.[5,44]

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