Expert Opinion

Nebivolol, a third generation beta-blocker

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Abstract

Nebivolol is a third generation beta-blocker, which is a cardiac beta-1 receptor antagonist and an endothelial beta-3 receptor agonist (beta-3 intrinsic sympathomimetic activity, or ISA). It is highly liphophilic and is metabolised in the liver. Like other beta-blockers with beta-2 or beta-3 ISA, nebivolol is a vasodilator and antioxidant as a result of endothelial nitric oxide (NO) release. Peripheral and aortic central pressures are reduced via a fall in total peripheral resistance. Hard end-point data exist only for heart failure. Unlike beta-blockers without ISA (bisoprolol, metoprolol, carvedilol), which reduce resting heart rate by about 14 beats per minute (bpm) and all-cause death by about 35% in patients with systolic heart failure (reduced ejection fraction), nebivolol (in common with other beta-blockers with ISA eg bucindolol and xamoterol) reduces resting heart rate by about 8–9 bpm and all cause mortality by about 17%. Nebivolol also reduces all-cause mortality in diastolic heart failure (normal ejection fraction) by about 17%. Thus, nebivolol behaves like a typical beta-blocker with beta-2 or beta-3 ISA.

Keywords: beta-3 intrinsic sympathomimetic activity; nitric oxide; anti-oxidant activity; systolic heart failure; diastolic heart failure.

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Introduction

A whole 50 years has passed since the first beta-blocker, propranolol, appeared on the market [1]. Propranolol, a so-called first generation beta-blocker (BB) which blocks both beta-1 and beta-2 receptors (non-selective), was followed by second-generation BBs such as atenolol and metoprolol which preferentially block beta-1 (over beta-2 receptors), i.e. so-called cardioselective or beta-1 selective BBs. Then came the third-generation BBs, with additional vasodilatory effects i.e. carvedilol, labetalol, celiprolol, bucindolol, and nebivolol. Nebivolol's particular claim was to be highly beta-1 selective, with vasodilatory and antioxidant properties, involving nitric oxide (NO) release i.e. it was unique[2].

The purpose of this review is to examine the clinical pharmacology of nebivolol, and to assess its role in cardiovascular medicine.

Clinical Pharmacology

Pharmacokinetics

The pharmacokinetic properties of nebivolol have been described by Prisant [3] and Cruickshank [4].

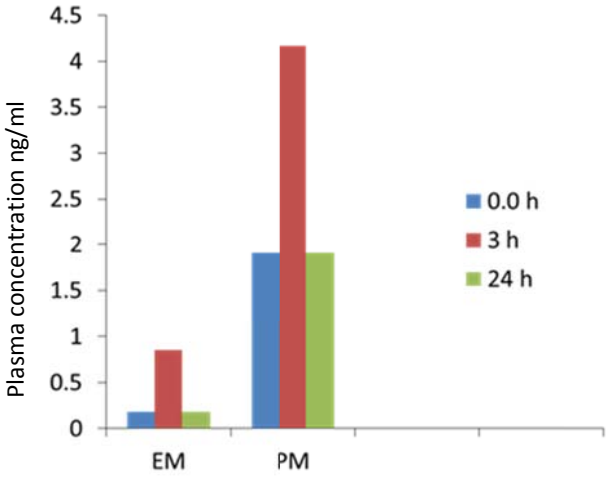

Figure 1. Plasma levels of D-nebivolol (beta-1 blockade) in extensive (EM) and poor (PM) metabolisers, after 3 months therapy. Lefebvre J, *et al.* 2006.

Metabolism

Nebivolol is highly lipophilic and, like metoprolol and timolol, is heavily metabolised in the liver via the cytochrome P4502D6 enzyme system. This enzyme system is vulnerable to genetic polymorphism, involving poor (PM) and extensive (EM) metabolisers, resulting in high variation in plasma concentrations of nebivolol [5]. Thus, mean steady state plasma concentrations of D- and L-nebivolol are 10- and 12-fold greater in PMs than EMs (**Figure 1**).

This highly significant difference ($P < 0.0001$) in plasma levels was, surprisingly, not associated with differences in blood pressure control or adverse reactions (though beta-1 selectivity, vs the beta-2 receptor, will be markedly diminished at the high plasma levels observed in PMs).

Poor metabolisers (PM) account for about 8–10% of the UK white population [6], and possibly 30% of Chinese [7]. Nebivolol is rapidly absorbed, and food does not modify this process [3]. Peak plasma concentrations occur at about 2 hours, with a half-life of 11 hours. Thus once daily dosing is appropriate.

Modifying Factors

The volume of distribution of lipid-soluble BBs is significantly decreased in obese patients [3], indicating that such agents diffuse less extensively into fatty, rather than lean, tissue. However, obesity does not result in significant differences in the pharmacokinetic profileof nebivolol [3].

In patients with severe hepatic impairment, e.g. cirrhosis, metabolism of nebivolol is diminished, so that blood levels of the drug are markedly increased (with subsequent loss of beta-1 selectivity and the potential for increased adverse reactions [3]).

In patients with renal dysfunction, dosage reduction with nebivolol is generally not necessary [3].

Drug Interactions

There is the potential for drug-interaction with agents that are metabolised via the same liver cytochrome P4502D6 system as nebivolol. Thus, the anti-ulcer drug cimetidine, when co-administered with nebivolol, induces a significant increase in plasma levels of unchanged nebivolol, but no change in heart rate or blood pressure [3]. Other drugs which are metabolised in a similar fashion to nebivolol, e.g. the ARB losartan, the ACE-I ramapril and furosemide, did not significantly modify plasma levels of nebivolol [3]. Likewise there are no kinetic interactions between nebivolol and digoxin, spironolactone and warfarin [3].

Pharmacodynamics

Nebivolol's d- and l- enantiomers

Nebivolol is a racemic mixture of 2 enantiomers, d- and l-nebivolol, each associated with distinct pharmacological properties [8–10]. The d-enantiomer occupies the cardiac beta-1 receptor in a highly selective manner, while the l-enantiomer occupies sites(s) in the vascular endothelium, resulting in nitric oxide (NO) release, anti-oxidant effects, and vasodilation [8–9], and a fall in blood pressure via a reduction in total peripheral resistance (TPR) [10].

Is Intrinsic Sympathomimetic Activity (ISA) involved in the Vasodilatory Action of Nebivolol?

Early studies in animals [11] and human cardiac tissue [12–13] indicated that nebivolol possessed no ISA. Others suggested that nebivolol possessed beta-2 ISA, involving NO production [14].

However, later studies involving modern technology [15–18] indicated that vasodilatation induced by nebivolol was via beta-3 agonism i.e. beta-3 ISA.

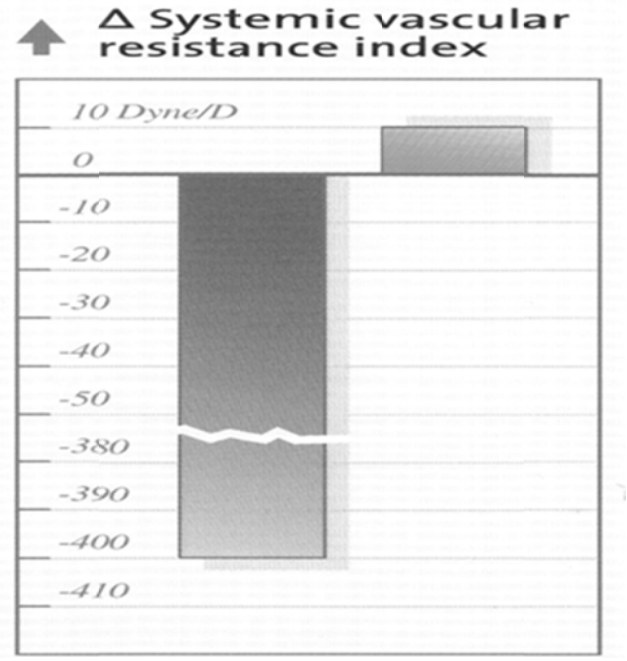

Figure 2. Effect of nebivolol (on left) and atenolol on systemic vascular resistance in hypertension [23].

Beta-3 ISA and Nitric Oxide Release

The beta-3 receptor is widespread throughout the body [19], occurring in the brain, adipose tissue, gut, liver and partial circulation, urinary bladder, blood vessels (endothelium), myocardium and myometrium. Stimulation of the cardiac beta-3 receptor has negative inotropic effects, and stimulation of endothelial beta-3 receptors induces vasorelaxation [19]. Vasodilation (in humans) via beta-3 stimulation is associated with endothelial NO release [20]. Nebivolol induces vasodilatation in this fashion [3, 21], resulting in a fall in forearm vascular resistance [22] (**Figure 2).** In hypertensive patients, compared to atenolol which tends to increase total peripheral resistance, nebivolol effects a significant 13% reduction in peripheral resistance [23].

Beta-3 Stimulant Effects upon the Myocardium

In hypertensive patients [23], compared to atenolol which causes a significant 24% reduction in cardiac output, nebivolol causes a significant 8% increase in ejection fraction and significant 21% increase in stroke volume. However, in both the non-failing [17] and failing [24] human heart, beta-3 stimulation induces an NO-dependent negative inotropic effect.

Nebivolol and Antioxidant Effects

Oxidative stress is a process whereby NO synthase (NOS) is uncoupled, so that instead of NO production there is production of peroxynitrite, a reactive oxygen species (ROS) which is toxic to the vasculature [25].

In vitro and *in vivo* studies have indicated that nebivolol scavenges ROS, resulting in improved endothelial function [26–27]. In hypertensive patients, in contrast to atenolol, nebivolol significantly lowered levels of ROS and superoxide concentration in the plasma and endothelial cells [28].

It has been suggested that the above action of nebivolol could lead to cardioprotective effects [3].

How beta-1 Selective is Nebivolol?

Literally speaking nebivolol is not beta-1 selective, as it occupies both the beta-1 and beta-3 receptors. However, beta-1 selectivity normally relates to the beta-1 and beta-2 occupancy. On that basis, nebivolol is highly beta-1 selective. In one study [13] nebivolol was somewhat less beta-1 selective than bisoprolol, but in 3 others was somewhat more selective than bisoprolol and other beta-blockers [12, 29–30]. The reason for these disparities could be explained by the use of different radioligands, or by experimental fluctuations.

So how "unique" is the Pharmacological Profile of Nebivolol?

Haemodynamics

There are BBs, other than nebivolol, that exert beta-blockade plus vasodilation.

Carvedilol exerts both beta- and alpha blockade. However, on chronic therapy there is evidence suggesting that alpha-blockade-induced vasodilatation is no longer present, due to tachyphylaxis [31–32].

Pindolol exerts both beta-1 and beta-2 blockade, and beta-2 ISA. Thus, on chronic therapy pindolol induces a significant increase in cardiac output and a significant fall in vascular resistance [33] i.e. a similar haemodynamic profile to nebivolol.

Beta-3 ISA

Pindolol has been reported to possess no beta-3 ISA in studies involving rat ileum [34] and human atrium [35]. However, others have demonstrated beta-3 agonism in human fat cells [36] and hamster ovaries [37].

Bucindolol has been shown to stimulate beta-3 receptors in hamster ovaries [37].

Oxprenolol has been shown to be an agonist of beta-3 receptors in human fat cells [36].

Alprenolol, at higher doses, possesses beta-3 agonist properties hamster ovarian cells [38].

Labetaolol acts as a partial agonist on beta-3 adrenoceptors in the guinea-pig stomach [39].

Endothethelial Nitric Oxide (NO) Release and beta-adrenoceptor Stimulation

As already indicated [21], the vasodilatory effect of nebivolol is associated with NO release. However, nebivolol is not the only vasodilatory beta-blocker that is associated with this phenomenon.

Thus, pindolol (beta-2 and beta-3 ISA) [40], bopindolol (beta-2 ISA) [41], oxprenolol (beta-2 ISA) [42] and celiprolol (beta-2 ISA) [41, 43–45], are all beta-blockers with NO-dependent vasodilatory properties.

It is thus apparent that stimulation of beta-1, beta-2 and beta-3 receptors results in NO-release [40]. Hence, beta-stimulants such as isoprenaline [40], salbutamol [40, 46–48], clenbuterol [47] and albuterol [49], induced vasodilation involving NO-release. With salbutamol, tracheal relaxation is also associated with release of NO [50].

Reduction in Oxidative Stress

As already noted [28], in hypertensive subjects nebivolol displays antioxidant properties. Such properties are not possessed by BBs without ISA, e.g. metoprolol [28] or atenolol [51].

However, nebivolol is not unique as a BB which displays anti-oxidant properties. Celiprolol, with beta-2 ISA, stimulates nitric oxide release and exhibits anti-oxidant properties [52]. Carvedilol, a non-selective beta-blocker with alpha-1 blocking vasodilating properties, also displays anti-oxidant properties in both animals [53–54] and man [55–56].

Is the possession of anti-oxidant properties, in addition to beta-blockade, useful clinically? There are suggestions that the answer may be yes [57–58]. However, this topic will be discussed later in the clinical section.

Table 1. Acute post-myocardial patients, randomised to placebo vs L-arginine; trial stopped due to excess deaths in L-arginine group.

	Placebo	L-Arginine (%)	*P* value
Mortality	0.0	8.6	0.01

From Schulman SP, Becker LC, Kass DA. L-Arginine therapy in acute myocardial infarction. JAMA. 2006; 295: 58-64.

Certainly, on the general (non-BB) front, there are concerns about nitric oxide and anti-oxidants. While the dangers of oxidative stress are well recognised in diabetes [59], cancer progression [60], and post coronary artery interventions [61], there is recognition of an anti-oxidant paradox [62–63]. Thus, there are scenarios when an excess of NO aggravates the atheromataous process [64–65]; a worrying thought in view of the high level of antioxidant supplement intake in countries like the USA [66]. Likewise, the fact that in the post-myocardial infarction period, L-arginine (substrate for NO synthase) significantly increased mortality vs randomised placebo [67] (**Table 1**), is of concern.

The results of large randomised trials involving anti-oxidants give little reason for optimism. Meta-analyses of placebo-controlled trials involving antioxidants concluded that beta-carotene, vitamin A, and vitamin E, were all associated with significant increases in mortality [68]! In the randomised, double-blind, placebo-controlled Physicians' Health Study [69], vitamin E was associated with a significant increased risk of haemorrhagic stroke. Thus, while anti-oxidant vitamins do not decrease [70], and may increase [71], cardiovascular events and mortality, a further concern is the possibility that cancer-risk may be increased [72].

So is the Pharmacological Profile of Nebivolol Unique?

The simple answer is no. Other vasodilating BBs, such as pindolol, increase cardiac output and lower peripheral resistance, as does nebivolol. Other vasodilating BBs, such as pindolol, bucindolol, oxprenolol, alprenolol and labetalol, have some beta-3 stimulatory properties associated with release of NO. Vasodilatory BBs like carvedilol and celiprolol, possess anti-oxidant properties.

Table 2. Morphological changes in heart failure with normal ejection fraction (HFNEF) and reduced ejection fraction (HFREF).

Parameters	HFNEF	HFREF
Microscopic and Neuroendocrine Features		
Cardiac cell hypertrophy	Increased	Minimal
Resting tension of cardiomyocytes	Increased	Decreased
Myofilament density	Preserved	Decreased
Titin N28/N28A ratio	Increased	Decreased
Insterstitial collagen	Increased	Decreased
MMP-1/TIMP-1 ratio	Little changed	Decreased
Patterns of peptide growth factor induction	Different	Different
ß-Receptor down-regulation and/or myocardial ß-adrenergic receptor desensitization (postsynaptic)	Present	Present
Norepinephrine	Increased	Increased
B-type natriuretic peptide	Increased	More increased
Resting Echocardiographic Parameters		
LV cavity size	Normal or decreased	Increased
LV shape and geometry	Little changed	Spherical
LV mass index	Increased	Increased
LV mass to cavity ratio	Increased	Normal or decreased
Relative wall thickness	Increased	Normal
End-diastolic volume/wall stress	Normal or decreased	Increased
End-systolic volume/wall stress	Normal	Increased
LV ejection fraction	Normal	Decreased
Longitudinal velocity/strain	Decreased	More increased
Radial strain	Decreased	More increased
LV twist (torsion)	Normal or decreased	Decreased
LV twisting rate	Normal or decreased	Decreased
LV untwisting rate	Normal or decreased with/without delayed onset	Decreased

HFNEF, heart failure with normal ejection fraction; HF, heart failure with reduced ejection fraction; LV, left ventricular; MMP-1, matrix metalloproteinase-1; TIMP-1, tissue inhibitor of metalloproteinases-1. From *Yip GW-K, Frenneaux M, Sanderson JE. Heart failure with a normal ejection fraction: new developments. Heart. 2009; 95: 1549-1552.*

Clinical Aspects

Heart Failure

Types of Heart Failure

There are 2 basic types of heart failure, one termed systolic heart failure, with a reduced ejection fraction (HFREF), and diastolic heart failure, with a normal ejection fraction (HFNEF). **Table 2** shows the characteristics of patients with either type of heart failure [73]. HFREF comprises about 50% of all heart failure, and 65% of HFREF is associated with coronary artery disease [74]. In contrast, a typical case of HFNEF would be an elderly female, with a history of systolic hypertension, concentric left ventricular hypertrophy – LVH (as opposed to eccentric LVH in HFREF), with a small left ventricular cavity [75].

Beta-blockers and Mortality in Heart Failure with Reduced Ejection Fraction (HFREF)

Not all BBs are equal in their ability to reduce all-cause mortality in patients with HFREF [4, 76] (**Figure 3).** It is apparent that the 3 BBs without ISA, i.e. bisoprolol [77], metoprolol slow release [78] and carvedilol [79], reduced all-cause mortality significantly by about 35%, accompanied by significant reductions of heart rate of 13–14 bpm. By contrast, the 3 BBs with ISA had no

significant benefit concerning reduction of all-cause death. Xamoterol, with a high level of beta-1 ISA, actually increased all-cause death vs placebo [80]. Bucindolol, with beta-2 ISA [81] and nebivolol, with beta-3 ISA [82], lowered heart rate by 8–9 bpm, and reduced all-cause death by a non-significant 10–12%.

The SENIORS trial has been heavily criticised [83–84]. After exclusion of patients with HFNEF (diastolic heart failure), it was concluded that compared to placebo nebivolol reduced the primary end-point by only 16–17%, being about half the efficacy of bisoprolol [77], metoprolol [78] and carvedilol [79] in HFREF.

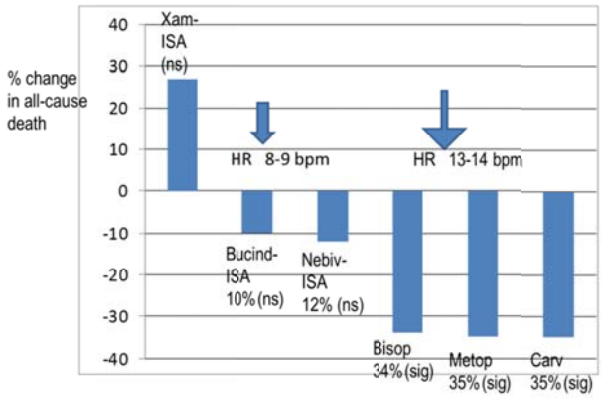

Figure 3. Beta-blockers and hard end-point placebo-controlled trials in heart failure (on ACEIs); ISA (xamoterol, bucindolol, and nebivolol) reduces fall in heart rate (HR) and efficacy (all-cause death) compared to beta-blockers with no ISA.

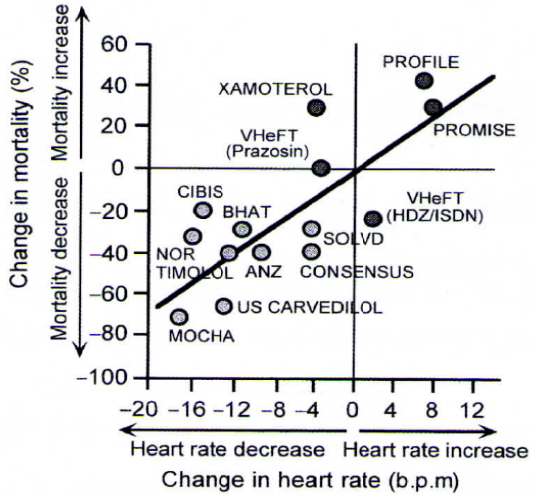

Figure 4. Cardiovascular mortality in relation to changes in heart rate in chronic systolic heart failure.
Cook S, *et al.* 2006.

However, it has been pointed out that a) about one third of patients in SENIORS had HFNEF, and that higher doses of nebivolol resulted in a 25% reduction in all cause death or cardiovascular hospitilization [85], and b) in patients with an ischaemic aetiology of their heart failure, ischaemic events were reduced by about one third, with no benefit to non-ischaemic patients [86].

Heart Failure and the Heart-rate Factor

In HFREF studies, there is a clear relationship between change in heart rate and all-cause mortality [87] (**Figure 4**), with best results arising at heart rates less than 71 bpm [88]. Such issues are relevant when considering the benefits of adding the sino-atrial blocker ivabradine to beta-blocker therapy in heart failure [89].

Beta-blockers and Heart Failure with Normal Ejection Fraction (HFNEF)

It has been stated that no treatments benefit patient with HFNHF [90, 91]. However, nebivolol makes a claim to be the only beta-blocker to benefit patients with HFNHF [92], as does carvedilol at higher dosage [93]. Retrospective [94] and observational studies claim that BBs are effective in reducing death or hospitalization in HFNHF. Certainly in post myocardial infarction cases of HFNEF, BBs were protective [95, 96].

Hypertension

There have been no "hard end-point" studies with nebivolol, in patients with essential hypertension.

Effect of Nebivolol upon Peripheral Blood Pressure, and Side Effects

Age and race are important regarding antihypertensive efficacy of BBs. When plasma renin is low, as in elderly and Black subjects, traditional BBs are less effective in lowering blood pressure [96, 97]. While it has been stated that BBs like bisoprolol [98] and nebivolol [99] are equally effective in lowering blood pressure in elderly and Black subjects, others [100] state that nebivolol is less effective at lowering blood pressure in the elderly.

In younger/middle-aged hypertensive subjects, nebivolol is superior to randomised placebo in lowering blood pressure [101–102]. Nebivolol displayed an anti-

hypertensive action similar to atenolol [103], metoprolol [104], bisoprolol [105] and carvedilol [106].

In the elderly nebivolol lowered blood pressure to a similar degree as amlodipine [107].

Side Effects – The side effect profiles of highly beta-1 selective nebivolol and bisoprolol are similar [105]. However, compared to only moderately beta-1 selective atenolol [103, 108] and metoprolol [109], there is no metabolic disturbance involving lipids, blood glucose and insulin-sensitivity, with nebivolol. Compared to amlodipine [107] nebivolol is better tolerated. Sexual dysfunction is more likely with metoprolol than nebivolol [110]; in this respect nebivolol is similar to bisoprolol [111]. Occasional cases of skin lichenoid eruption occur with nebivolol [112]. Walking distance in hypertensive patients with peripheral arterial disease is not altered by nebivolol, and in this respect does not differ from metoprolol [113] or thiazide diuretics [114].

Nebivolol and Central Blood Pressure

Central pressures are important, as they are possibly the best predictors of future cardiovascular events [115–117].

Not all BBs decrease central pressure. Only vasodilatory BBs, that decrease pressure wave reflection from the periphery, lead to a decrease in central aortic blood pressure [118]. This point was well illustrated in double-blind, randomised, crossover study in middle-aged hypertensive subjects where the BB dilevalol (with beta-2 ISA) was compared to atenolol [119]. While both BBs lowered brachial blood pressure to a similar degree, dilevalol was significantly more effective than atenolol in lowering central SBP and augmentation index. Likewise in elderly hypertensive subjects, atenolol has proved to be ineffective in lowering central aortic pressures, compared to ACE-inhibitors, diuretics and calcium blockers [120].

Nebivolol is relatively effective in reducing central aortic pressure. Under both open [121] and randomised, placebo-controlled conditions [122], nebivolol has been shown to be effective in lowering central systolic, diastolic, and pulse-pressures. Compared to atenolol [123, 124] and metoprolol [125–127], nebivolol has more favourable effects on central pressures. However, once diuretics are added to BB therapy, the advantage of nebivolol over metoprolol in reducing central aortic pressure disappears [128].

Is Nebivolol Unique, as a Beta-blocker in Lowering Central Aortic Pressures?

The simple answer is no. As indicated above, dilevolol, a BB with beta-2 ISA, was effective in lowering central aortic pressures [119]. Also celiprolol, a BB with beta-2 ISA, had favourable effects upon central pressures [129]. Carvedilol, a vasodilating BB with alpha-blocking properties, is superior to atenolol in reducing central aortic pressure [130]. Indeed, inhalation of the beta-2 stimulant salbutamol, results in fall in central systolic pressure [131].

Interestingly, in young/middle-aged hypertensive subjects, even a highly beta-1 selective BB with no ISA or alpha-blocking properties i.e. bisoprolol, was, unlike atenolol, found to possess positive arterial distensibility/compliance properties leading to a significant fall in central arterial systolic pressure [132].

Heart Rate

Nebivolol reduces resting heart less than BBs without ISA. For example, in middle-aged hypertensive subjects, nebivolol was similar to atenolol in lowering blood pressure, but reduced heart rate significantly less [108]. This may have prognostic implications, as the Framingham Group have shown that in untreated male hypertensive subjects followed-up for 36 years, the best results in terms of all-cause death, coronary heart disease and cardiovascular events were at lower heart rates [133] (**Figure 5**).

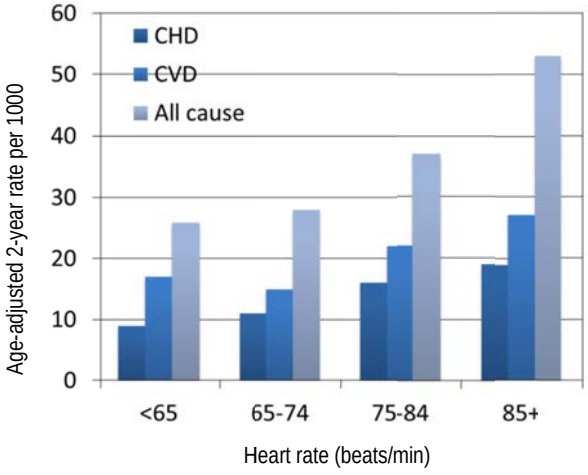

Figure 5. Framingham: Effect of resting heart rate on all-cause death, CHD and CVD events in untreated male hypertensives, followed-up for 36 years. Gillman MW, *et al.* 1993.

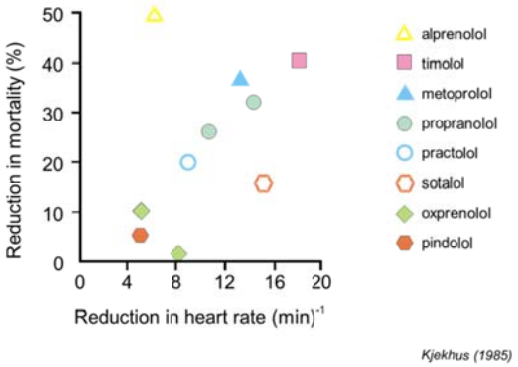

Figure 6. Beta- blockers, oral 4 days post MI – best mortality reduction with low heart rates.

Ischaemic Heart Disease

There are no hard endpoint data in this area regarding nebivolol.

Nebivolol may not be the ideal BB to prescribe in the post myocardial infarction period. As indicated earlier, in the post-infarction period, L-arginine (substrate for NO synthase) significantly increased mortality vs randomised placebo [67] (**Table 1**). Also, nebivolol lowers resting heart rate less than a classic BB like atenolol [134]. This may be important, as reduction in mortality post myocardial infarction relates to reduction in heart rate, with BBs possessing ISA i.e. pindolol and oxprenolol being the least effective [135] (**Figure 6**)**.** A similar story holds for non-fatal re-infarction [136].

Summary and Conclusions

Nebivolol is a third-generation beta-blocker (BB) with beta-3 intrinsic sympathomimetic activity (ISA). Its d-isomer occupies the cardiac beta-1 receptor, effecting beta-1 blockade, while the l-isomer occupies cardiac and vascular beta-3 receptors, the latter effecting vasodilatation. Nebivolol is metabolised via the hepatic P4502D6 enzymatic system, so that in slow-metabolisers (comprising about 10% of the UK population) blood levels are increased 10–20 fold (with loss of beta-1 selectivity vs the beta-2 receptor).

Resting heart rate is lowered to a lesser degree with nebivolol than with BBs without ISA e.g. atenolol, metoprolol, bisoprolol (this may have prognostic implications). Blood pressure decreases via a fall in total peripheral resistance (as with other vasodilating BBs with ISA, like pindolol and celiprolol). In common with other BBs with ISA, nebivolol decreases central aortic pressure, is associated with nitric oxide (NO) release, and possesses anti-oxidant properties. Thus, as is sometimes claimed, nebivolol does not possess a unique pharmacological profile.

Hard endpoint data with nebivolol exist only for heart failure. For patients with systolic heart failure (low ejection fraction) nebivolol, like other BBs with ISA (i.e. xamoterol and bucindolol) was associated with a non-significant reduction in all-cause death. These results compare poorly with the results of BBs without ISA, i.e. carvedilol, metoprolol, and bisoprolol, that reduce the risk of all-cause death by a significant 34-35%. Patients with diastolic heart failure (normal ejection fraction) benefited to a degree from nebivolol, with a fall in all-cause death of 17–18%.

Thus, nebivolol is similar to other BBs with ISA in terms of its pharmodynamic profile, its effect on central blood pressure, and in its relatively poor results (vs BBs without ISA) in reducing all-cause death in patients with systolic heart failure.

Disclosure

There are no conflicts of interest.

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