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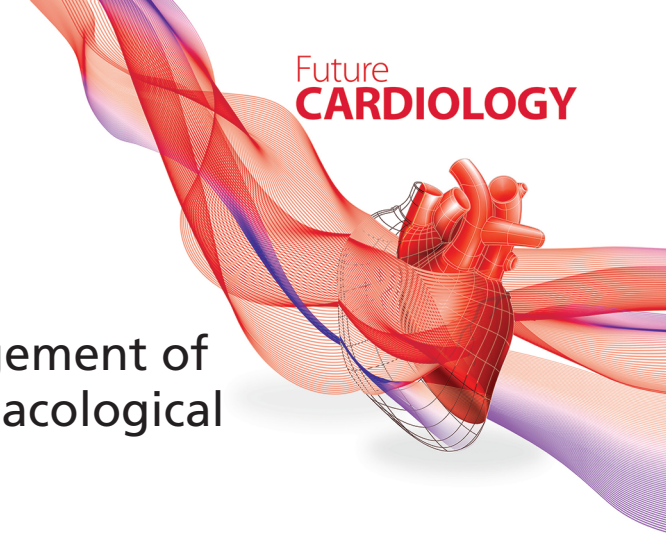

The role of nebivolol in the management of hypertensive patients: from pharmacological profile to treatment guidelines

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According to the most recent international guidelines, β-blockers maintain a central role in the management of hypertension, being recommended at any treatment step when there is a specific indication, such as heart failure, angina, postacute myocardial infarction, atrial fibrillation or pregnancy. However, β-blockers are not a homogeneous class: individual molecules differ in terms of pharmacological and clinical profile and are therefore suitable for different patient subtypes. In particular nebivolol, a third generation β_1-selective β-blocker with vasodilating properties, neutral metabolic effects and good tolerability, proved to have advantages over other β-blockers, which makes the drug suitable in a wide variety of hypertensive patients with or without comorbidities.

Lay abstract: β-blockers are the main class of antihypertensive agents currently available. Nebivolol is one of the most recent β-blocking agents and it has vasodilating effects which may be useful in hypertensive patients with heart disease of ischemic (restriction in blood supply) origin or with erectile dysfunction. It has a good tolerability profile which makes it safe to use in patients with metabolic abnormalities (such as diabetes or dyslipidemia) or chronic obstructive pulmonary diseases.

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Despite the substantial progress made in understanding the complex pathophysiologic mechanisms of hypertension, the best strategy to reduce the cardiovascular (CV) risk associated with hypertension remains blood pressure (BP) lowering, through the use of all major antihypertensive drug classes (angiotensin converting enzyme [ACE]-inhibitors, angiotensin receptor blockers [ARBs], β-blockers, calcium channel blockers [CCBs] and diuretics) [1]. However, BP control rates remain poor worldwide and across Europe [2], one of the main contributing factors being poor adherence to treatment [3]. Simplifying treatment algorithms and favoring single pills combinations to quickly achieve BP targets may help in improving adherence to treatment and optimizing its efficacy [4]. For this reason, the latest update of the European Society of Cardiology/European Society of Hypertension (ESC/ESH) guidelines for the diagnosis and treatment of hypertension proposed simplified drug treatment algorithms with the preferred use of an ACE inhibitor or ARB, combined with a CCB and/or a thiazide/thiazide-like diuretic, as the core treatment strategy for most patients, based on evidences on the ability of these classes to reduce CV events and improve patients' prognosis [1]. In addition, recognizing the potential advantages of β-blockers in hypertensive patients with concomitant CV pathologies (such as heart failure [HF], coronary artery disease (CAD), atrial fibrillation [AF]), current guidelines recommend their preferential use in these patients, in order to maximize treatment efficacy and tolerability [1]. Among β-blockers, third generation cardio-selective drugs with vasodilating and anti-oxidant properties, such as nebivolol, may show particular benefits, thanks to ancillary actions that go beyond the blockade of adrenergic receptors, to provide a better CV protection associated with a positive metabolic profile [1]. The efficacy and tolerability of third generation β-blockers have been demonstrated also in hypertensive patients with specific non-CV comorbidities (such as diabetes, respiratory obstructive diseases or erectile dysfunction [ED]) [5–7], in which conventional anti-adrenergic agents are usually contraindicated or not recommended as first choice

Table 1. Role of β-blockers in the management of hypertension according to current ESC/ESH guidelines.

Recommendation	ESC class of recommendation	ESC level of evidence
Drug treatment strategy for uncomplicated hypertension		
Among all antihypertensive drugs, ACE inhibitors, ARBs, β-blockers, CCBs and diuretics (thiazides and thiazide-like drugs such as chlorthalidone and indapamide) have demonstrated effective reduction of BP and CV events in RCTs, and thus are indicated as the basis of antihypertensive treatment strategies	I	A
It is recommended that β-blockers are combined with any of the other major drug classes when there are specific clinical situations, for example, angina, postmyocardial infarction, heart failure or heart rate control	I	A
Drug treatment strategy for hypertension and coronary artery disease		
In hypertensive patients with a history of myocardial infarction, β-blockers and RAS blockers are recommended as part of treatment	I	A
Drug treatment strategy for hypertension and heart failure with reduced ejection fraction		
In patients with HFrEF, it is recommended that BP-lowering treatment comprises an ACE inhibitor or ARB, and a β-blocker and diuretic and/or MRA if required	I	A
Drug treatment strategy for hypertension and atrial fibrillation		
A β-blocker or nondihydropyridine CCB should be considered as part of the treatment of hypertension if rate control is needed	IIa	B

ESC Classes of recommendations: Class I = evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective; Class IIa = weight of evidence/opinion is in favor of usefulness/efficacy.
ESC Levels of evidence: Level A = data derived from multiple randomized clinical trials or meta-analysis; Level B = data derived from a single randomized clinical trial or large nonrandomized studies.
ACE: Angiotensin-converting enzyme; ARB: Angiotensin receptor blocker; BP: Blood pressure; CCB: Calcium channel blocker; CV: Cardiovascular; ESC: European Society of Cardiology; HFrEF: Heart failure with reduced ejection fraction; MRA: Mineralocorticoid receptor antagonist; RAS: Renin–angiotensin system; RCT: Randomized controlled trial.
Adapted from [1].

drugs [1]. The aim of the present review was to elucidate the heterogeneity of the β-blockers class, by analyzing the pharmacological profiles of third generation agents, such as nebivolol, and the associated benefits in terms of efficacy and tolerability, which support guidelines' recommendations.

β-Blockers' role in the management of hypertension according to current guidelines

According to ESC/ESH guidelines, all five major antihypertensive classes (ACE-inhibitors, ARBs, β-blockers, CCBs and diuretics) are equally recommended for the treatment of hypertension: all of them effectively reduce BP and prevent CV events, with a similar efficacy in terms of overall CV morbidity and mortality [1]. ESC/ESH 2018 guidelines therefore recommend these drugs as the basis of antihypertensive therapy, defining some compelling/possible contraindications or preferential indications for each class [1].

In particular, β-blockers should be preferred for the treatment of hypertension in patients with symptomatic angina, postmyocardial infarction, HF with reduced ejection fraction (HFrEF), and in younger hypertensive women of child-bearing potential [1]. Evidences from randomized controlled trials (RCTs) and meta-analyses versus placebo have shown that β-blockers significantly reduce the risk of stroke, HF and major CV events in hypertensive patients; moreover, results from comparative studies showed that they are equivalent to other BP-lowering drugs in preventing major CV events, with the only exception of stroke, which however may originate from small differences in achieved central systolic BP (SBP) [1].

Treatment algorithms

Patients with uncomplicated hypertension

The treatment algorithm proposed by ESC/ESH guidelines for treatment of uncomplicated hypertension recommends initial therapy for most patients with a two drug-combination, ideally as a single pills combinations (SPCs). β-blockers can be used at any stage of the treatment algorithm, when there is a specific indication, for example, in HF, angina, post-AMI, AF or in younger women during pregnancy or planning it (recommendation IA) (Table 1) [1].

In addition, ESC/ESH guidelines provide a series of specific algorithms, indicating in which step to use β-blockers in the treatment of hypertension in the presence of comorbidities (e.g., HF, AF or CAD) [1].

Hypertensive patients with coronary artery disease

There are strong epidemiological relationships between CAD and hypertension. The INTERHEART study showed that 25% of the risk of a myocardial infarction can be attributed to hypertension [8]. Reducing BP has beneficial effects on the risk of myocardial infarction: a recent meta-analysis of randomized controlled trials (RCTs) of antihypertensive therapy showed that for every 10 mmHg reduction in SBP, CAD was reduced by 17% [9]. In hypertensive patients with CAD, β-blockers are the preferred components of the antihypertensive drug treatment strategy, in combination with blockers of the renin–angiotensin system (RAS) or CCBs (recommendation IA) (Table 1) [1].

Hypertensive patients with heart failure

Hypertension is the leading risk factor for the development of HF and most patients with HF have an antecedent history of hypertension [10]. In patients with hypertension, HF may develop as a consequence of CAD, which generally results in reduced ejection fraction (HFrEF), or as a consequence of left ventricular hypertrophy (LVH), which impairs left ventricular (LV) relaxation causing diastolic dysfunction with preserved ejection fraction (HFpEF) [1].

Treating hypertension with diuretics, β-blockers, ACE inhibitors or ARBs has been demonstrated to have a major impact on reducing the risk of incident HF and related hospitalization [11]. Similarly, ACE inhibitors, ARBs, β-blockers and mineralocorticoid receptor antagonists (MRAs) such as spironolactone and eplerenone are all effective in improving clinical outcome in patients with established HFrEF [12], and are therefore recommended for the treatment of hypertension in these patients (recommendation IA) (Table 1) [1].

The optimal treatment strategy for hypertensive patients with HFpEF is not known, but the strategy outlined above for HFrEF patients might also be the one to adopt in HFpEF patients [1].

Hypertensive patients with atrial fibrillation

Hypertension predisposes to cardiac arrhythmias, most commonly AF, which should be considered a manifestation of hypertensive heart disease [13]. In AF patients with high ventricular rate, β-blockers or nondihydropyridine calcium antagonists (e.g., diltiazem and verapamil) are recommended as antihypertensive agents (recommendation IIaB) (Table 1) [1]. In patients with reduced LV systolic function, β-blockers are often indicated and may need to be combined with digoxin to gain rate control [1]. In patients with HF, β-blockers may also prevent AF [1].

According to ESC/ESH recommendations, β-blockers as a class maintain a central role in the treatment of hypertension, also confirmed by AHA/AAC 2017 guidelines on hypertension management [14]. However, given the class heterogeneity of β-blockers, specific molecules might be preferred in specific conditions [1].

β-blockers are not a homogeneous class: clinical profiles & pharmacological properties of individual agents

ESC/ESH Guidelines point out that β-blockers seem to be less effective in the prevention or regression of target organ damage (LVH/carotid intima-media-thickness/aortic stiffness/small artery remodeling), to have a less favorable side effect profile (vs RAS blockers) and higher treatment discontinuation rate, and to be associated with an increased risk of new onset diabetes in predisposed subjects [1].

However, as stated by ESC/ESH Guidelines, β-blockers are not a homogeneous class [1]: among β-blockers, vasodilating agents such as nebivolol have favorable effects on central BP, aortic stiffness and endothelial dysfunction, no adverse effect on the risk of new-onset diabetes, and a more favorable side effect profile than previous generation molecules [1].

In this respect, a recent study showed that vasodilating β-blockers (nebivolol or carvedilol) induced a greater reduction of carotid BP, short-term BP variability and echocardiography parameters than atenolol in spontaneous hypertensive rats (SHR) [15]. In addition, chronic treatment with carvedilol or nebivolol compared with treatment with atenolol was more effective in the prevention of organ damage, expressed in terms of cardiac hypertrophy, cardiac and aortic collagen deposit, and local expression of fibrotic and inflammatory biomarkers (TGF-β, TNF-α and IL-6) [15]. The results of this study, besides confirming more favorable hemodynamic effects of nebivolol or carvedilol compared with the nonvasodilating β-blocker atenolol in SHR, provides further evidence of the protective CV effects of vasodilating β-blockers in uncomplicated hypertension [15]. These findings therefore suggest that some of the adverse hemodynamic changes and lower CV protection associated with nonvasodilating β-blockers in hypertensive patients might not apply to vasodilating β-adrenergic blocking agents [16].

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Table 2. Actions of different generation β-blockers on adrenergic receptors.

Generation	Molecules	β_1-antagonism	β_2-antagonism	β_3-agonism	α-antagonism
I	Propranolol	✓	✓	-	-
	Sotalol	✓	✓	-	-
	Nadolol	✓	✓	-	-
II	Atenolol	✓	-	-	-
	Metoprolol	✓	-	-	-
	Bisoprolol	✓	-	-	-
III	Carvedilol	✓	✓	-	✓
	Labetalol	✓	✓	-	✓
	Nebivolol	✓	-	✓	-

Adapted from [16–18].

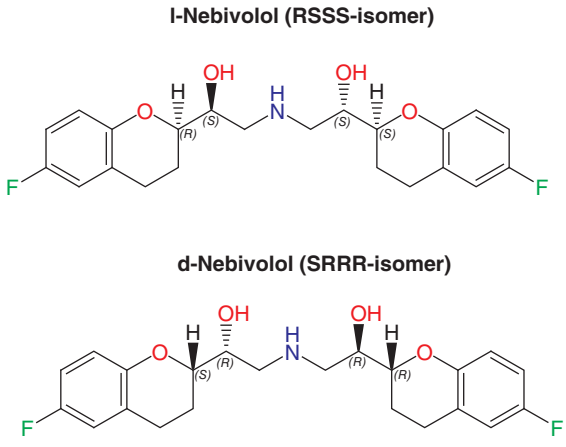

Figure 1. Chemical structure of the two isomers of nebivolol. Nebivolol has four asymmetric centers; the D-isomer refers to (S,R,R,R)-nebivolol and the L-isomer to (R,S,S,S)-nebivolol.

Pharmacological properties

The differences between nebivolol and other β-blockers demonstrated in experimental and clinical studies depend on the specific pharmacological properties of individual agents. β-blockers are divided into three generations with different biochemical and pharmacological properties, mainly deriving from their selectivity for β-adrenoceptors (β-AR) (Table 2) [16]. There are three main subtypes of β-ARs (β_1, β_2 and β_3), which are differentially distributed in the body: β_1 in cardiac tissue, β_2 in the lungs and β_3 in both adipose tissue and the heart. Their activation leads to diverse effects in different tissues: in particular, in the heart, β-ARs stimulation results in elevated heart rate (chronotropy) improved contractility (inotropy) and diastolic relaxation (lusitropy) (Figure 2) [17].

Non selectivity of first-generation drugs (propranolol, sotalol, etc.), targeting both β_1- and β_2-receptors, is responsible for the occurrence of bronchoconstriction and metabolic disruptions during antihypertensive therapy. The higher selectivity of second-generation drugs (atenolol, metoprolol, bisoprolol, etc.), mainly targeting β_1-receptors, associates with a more favorable side effect profile [17]. The additional vasodilatory properties of third-generation drugs (nebivolol, carvedilol, labetalol) warrant a better hemodynamic and tolerability profile (Table 2) [18]. In addition, individual molecules show peculiar features in terms of pharmacokinetics, intrinsic sympathetic activity (ISA), membrane stabilizing activity (MSA) as well as vasodilation, alpha-blockade, nitric oxide (NO) release and anti-oxidant properties [16].

So far, the mechanism behind the BP lowering effect of β-blockers is not completely understood, although several contributing mechanisms have been proposed. By antagonising β-ARs, β-blockers interfere with the over-activation of sympathetic nervous system (SNS) and RAS, which are known to contribute to hypertension (Figure 2) [17].

Nebivolol

Nebivolol belongs to the third-generation β-blockers exhibiting highly selective β_1-AR blockade and NO-mediated vasodilatation [17]. Nebivolol is the β-blocker with the highest selectivity for β_1-receptors compared with former generations, and with no ISA or MSA [17]. The drug exists as both L- and D-enantiomers (Figure 1). D-nebivolol has a 175-times higher affinity for β_1-receptors than L-nebivolol and is therefore mainly responsible for the cardiac effects [17]. On the other hand, L-nebivolol primarily mediates the endothelium-derived release of NO [17].

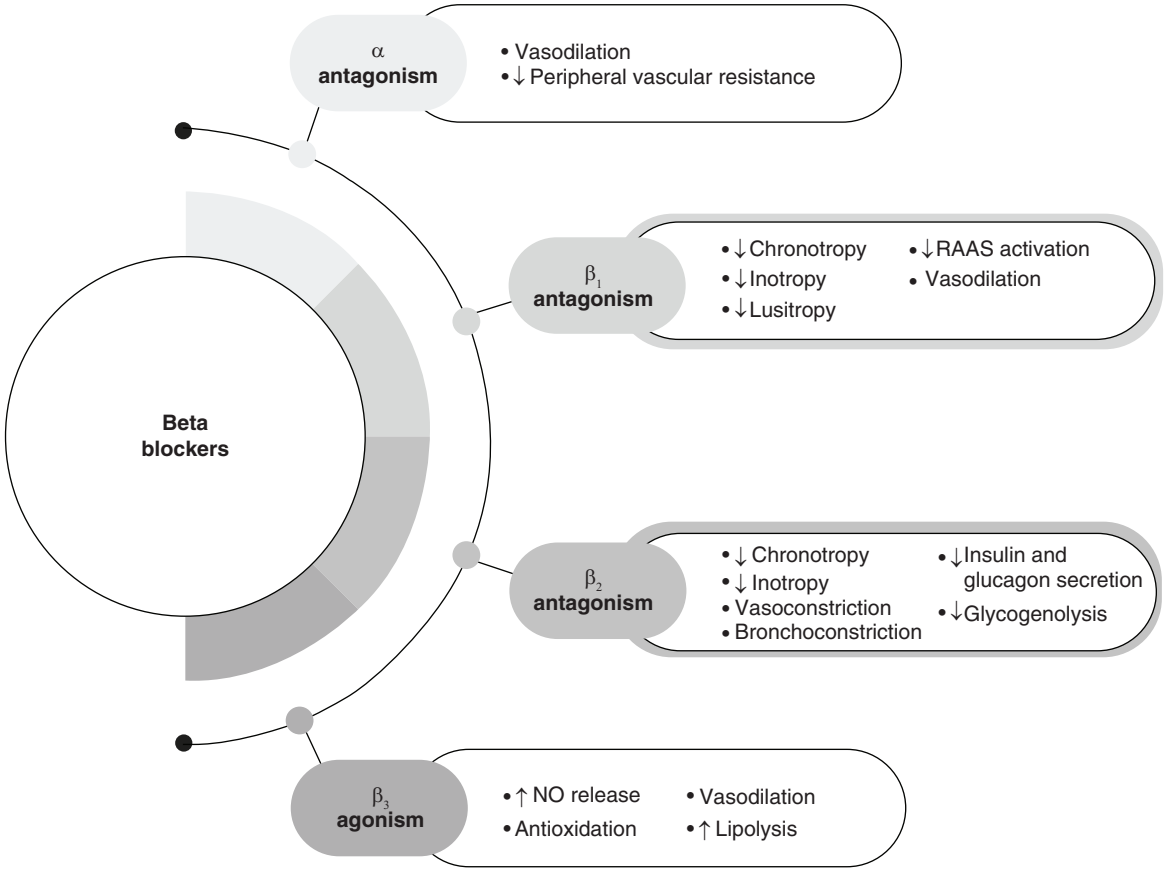

Figure 2. Mechanism of action of β-blockers.
NO: Nitric oxide; RAAS: Renin-angiotensin-aldosteron system.
Adapted from [16–18].

Specific pharmacological properties of nebivolol

D-nebivolol antagonises the β_1-ARs in the conductive tissue of the heart and in the myocytes, whereas L-nebivolol mediates the increase in NO-availability through enhanced activity of endothelial NO synthase and thereby increased NO release, whose main effects are vasodilation via stimulation of soluble guanylyl cyclase in the vascular smooth muscle cells [19], and reduction in reactive oxygen species (ROS) [20], which in the long term may improve endothelial dysfunction [18]. In addition, nebivolol was shown to induce lipolysis and promote thermogenic and mitochondrial genes through β_3-AR, which seem to be involved in heart protection [21].

Nebivolol in the treatment of hypertension

Nebivolol has shown good results in controlling hypertension in several studies, with few adverse events compared with placebo [22]. A very recent systematic review with subsequent meta-analysis on the use of nebivolol for hypertensive disease treatment, including a total of 12,465 patients with hypertension from 34 randomized clinical trials comparing it with drugs of the main antihypertensive classes, showed that in SBP management, nebivolol was superior to other β-blockers and diuretics and showed no difference in efficacy when compared with ARBs or CCBs. For diastolic BP control, nebivolol was more efficient than other β-blockers, ARBs, diuretics and CCBs [22].

These results were achieved with excellent tolerability: for all doses studied, from 1.25 to 40 mg daily, there was no statistically significant difference in the incidence of adverse events compared with placebo, or other antihypertensive medications such as ACE inhibitors, ARBs or diuretics, confirming the high tolerability of nebivolol. The comparison with other β-blockers demonstrated a better tolerability of nebivolol than atenolol or metoprolol ($p = 0.0001$) [22].

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Table 3. Main results of the SENIORS and SENIORS CAD trials.

Trial	Patient population	Primary end point (all-cause mortality or CV hospital admission), HR, 95% CI
SENIORS	Patients ≥70 years with HF (>60% hypertensive)	0.86, 0.74–0.99 p = 0.039
SENIORS CAD	Patients ≥70 years with HF of ischemic origin (>65% hypertensive)	0.68, 0.51–0.9 p = 0.008

CV: Cardiovascular; HF: Heart failure; HR: Hazard ratio.
Adapted from [24,27].

Nebivolol in hypertensive patients with cardiovascular comorbidities

Heart failure

HF is characterized by activation of both sympathetic nervous system and RAS, and inhibition of these two systems is the mainstay of current treatment [12]. β-blockers have been shown to reduce mortality and hospital admissions in patients with HF through reduction of adrenergic drive, improvement of autonomic balance, and reduction of ventricular wall stress [23], and are recommended by current ESC/ESH guidelines in patients with hypertension and concomitant HF [1]. In the SENIORS study, performed to assess the effects of nebivolol in patients ≥70 years (60% with concomitant hypertension), treatment with the third-generation β-blocker reduced the composite risk of all-cause mortality or CV hospital admission compared with placebo (hazard ratio [HR] 0.86, 95% CI 0.74–0.99; p = 0.039) (Table 3) [24]. The beneficial effects appeared after 6 months of treatment and the risk reduction continued to increase with longer treatment, without significant influence of age, gender or ejection fraction [24]. Death (all causes) occurred in 169 (15.8%) subjects on nebivolol and 192 (18.1%) on placebo (HR 0.88, 95% CI 0.71–1.08; p = 0.21) [24]. Study medication was well tolerated, and the majority of patients (68%) were able to reach a maintenance dose of 10 mg once daily after careful titration [24].

A sub-analysis of data stratified by baseline SBP and left ventricular ejection fraction (LVEF) showed that nebivolol appears to be safe and well tolerated, with similar benefits on the composite outcome of death or CV hospital admission irrespective of baseline SBP and LVEF [25].

A prespecified sub-analysis of the SENIORS trial, evaluating the effects of impaired (<35%) or preserved (>35%) LVEF on outcomes, confirmed that the effect of nebivolol in elderly patients with HF is similar in those with preserved or reduced EF in terms of all-cause mortality or CV hospitalizations (primary end point) (HR 0.86 vs 0.81; p = 0.720 for subgroup interaction). Effects on all secondary end points were similar between groups (HR for all-cause mortality 0.84 and 0.91, respectively) [26].

These results are of particular relevance, considering the growing prevalence of HF patients with a preserved EF in the last decades, also as a consequence of population aging in western countries, and the fact that no treatment able to reduce morbidity and mortality is currently available for this patient category [26].

The results of the SENIORS study extend the evidence of benefit of β-blockade in HF to patients ≥75 years, with mild LV dysfunction or preserved ventricular function, and those with concomitant hypertension, more closely resembling the general population of patients with HF [24].

The exact mechanisms underlying the benefits of nebivolol in patients with HF are not known, but may be related to the ability of the drug to modulate NO release, thus lowering peripheral resistance, and thereby reducing LV wall stress, adverse neurohormonal stimulation, and incidence of acute coronary events [24]. The good tolerability observed in the trial may also, in part, be related to the vasodilating properties of nebivolol, so that results may not be generalizable to other β-blockers when used in elderly HF patients [24].

Coronary artery disease

ESC/ESH Guidelines emphasize the role of β-blockers in HF, recommending bisoprolol, carvedilol, metoprolol succinate and nebivolol for treatment of all hypertensive patients with stable mild, moderate and severe HF from ischemic and nonischemic origin (recommendation IA) [1]. In the setting of HF, β-blockers blunt the activation of the adrenergic system and indirectly also of the RAS, which are known to play a key role in the progression of HF and adverse cardiac remodeling [27]. However, in addition to these effects, β-blockers have specific properties that may be useful in the management of patients with CAD [27]. Since ischemic heart disease is the primary cause of HF and β-blockers have proven favorable effects in CAD, β-blockers may be beneficial in the setting of HF of ischemic aetiology, not just by contrasting the neural hyper-activation, or by preventing remodeling, but for their specific

Table 4. Possible mechanisms underlying the beneficial effects of nebivolol in cardiovascular and noncardiovascular diseases.

Cardiovascular diseases	Mechanisms involved in nebivolol beneficial effects
Hypertension	β1-adrenergic blockade NO-mediated vasodilation Reduction of ROS
Heart failure	β1-adrenergic blockade NO-mediated vasodilation → reduced peripheral resistance and LV wall stress Reduction of RAAS activation
Coronary artery disease	Stimulation of NO production (through increased activity of NO synthase by activation of β_3-AR) → pharmacological preconditioning Prolongation of NO half-life by an antioxidant effect Coronary vasodilation Decreased platelet and leukocyte activation
Atrial fibrillation	Improved P-wave dispersion
Noncardiovascular diseases	
Diabetes and metabolic abnormalities	Improvement of insulin sensitivity and oxidative stress Neutral or beneficial effects on lipids and glucose Improvement of endothelial dysfunction (decrease of P-selectin and increase of adiponectin levels) → prevention of insulin resistance
Chronic obstructive pulmonary disease	β1-selectivity (lack of β2-adrenergic blockade) → no aggravation of bronchial obstruction
Erectile dysfunction	Vasodilation

β-AR: β-Adrenoceptors; LV: Left ventricular; NO: Nitric oxide; RAAS: Renin-angiotensin-aldosteron system; ROS: Reactive oxygen species.

effects on ischemic events [27]. Among β-blockers, nebivolol is known to possess additional properties beyond its action as an antagonist of β-AR, that may be relevant in terms of anti-ischemic action [27]. These ancillary beneficial properties derive from the capability of nebivolol to stimulate NO production secondary to increased activity of NO synthase by activation of β_3-AR, and to prolong NO half-life by an antioxidant effect. The consequent coronary dilation with increased coronary blood flow, as well as decreased platelet and leucocyte activation, may contribute to the improved anti-ischemic profile of nebivolol, not shared by other β-blockers [27].

An additional mechanism by which NO, and NO-potentiating agents (such as nebivolol), may induce cardiac protection against ischemic events, is pharmacological preconditioning, in other words, the occurrence of brief ischemic episodes which make heart more tolerant to subsequent major ischemic insults, through the activation of NO synthase, and subsequent increased production of NO. This effect can be mimicked by drugs that increase NO availability, such as nebivolol [27].

Unfortunately, previous clinical trials with β-blockers in HF have not reported their effect on ischemic events or have not examined the specific population of HF patients with ischemic aetiology. A sub analysis of the SENIORS trial focusing on patients with HF of ischemic aetiology (68.2% of the total study population), including 1452 patients (>65% with hypertension), showed a very significant effect (32% overall reduction) on the composite end point of ischemic (fatal and nonfatal) events and sudden death in the cohort treated with nebivolol (Table 3). These findings suggest that vasodilating β-blockers such as nebivolol may be effective in hypertensive HF patients with previous coronary disease through anti-ischemic mechanisms [27].

Atrial fibrillation

LVH was shown to be associated with increased prevalence of ventricular arrhythmias in hypertensive patients; accordingly, antihypertensive therapy targeted at regression or prevention of electrocardiographic LVH may reduce the incidence of arrhythmias, as demonstrated by clinical trials showing that antihypertensive therapy may delay or prevent the occurrence of cardiac arrhythmias and sudden cardiac death in patients with hypertension [28]. In particular, a study investigating the short-term electrophysiological effects of common antihypertensive drugs in hypertensive men showed that losartan and bisoprolol exert beneficial effects on ECG parameters of ventricular repolarization duration and heterogeneity, whereas hydrochlorothiazide significantly increased repolarization heterogeneity, and amlodipine did not affect ECG repolarization measures [29]. These findings suggest a possible role of antihypertensive therapy in favouring or preventing cardiac arrhythmias [28]. In particular, drugs targeting P-wave dispersion (an electrocardiographic predictor for development of AF), may be beneficial in this respect. Nebivolol was shown to be as effective as atenolol in improving P-wave dispersion in patients with mild-to-moderate hy-

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pertension, suggesting a possible preventive effect on AF [30]. These and other evidences suggest a possible benefit of nebivolol in preventing AF development, supporting the inclusion of β-blockers as a class among the drugs recommended by current ESC/ESH guidelines for treatment of hypertensive patients with AF [1].

Nebivolol in hypertensive patient with noncardiovascular comorbidities

Nebivolol possesses advantages over previous β-blockers, which makes the drug suitable in specific patient groups, including hypertensives with comorbidities such as obstructive airway diseases, Type II diabetes or metabolic syndrome, and sexually active men.

Obstructive airway diseases

Hypertension is the most frequent comorbidity in patients with chronic obstructive pulmonary disease (COPD): coincidence of the two diseases, which may affect 2.5% of the adult population, is associated with particularly high CV risk [31]. In the presence of COPD, the selection of antihypertensive drugs should consider their effects on pulmonary function. Among antihypertensives, β-blockers may negatively affect the reduced basal lung function in patients with COPD, diminish the effectiveness of emergency β-agonist administration, limit the benefit of long-acting β-agonist treatment, and make the discrimination of asthma and COPD more difficult [1].

However, among β-blockers, third generation agents are characterized by a much greater selectivity and affinity for β_1-adrenergic receptors than previous generations drugs, and are therefore more likely to preserve respiratory function [32].

In patients with COPD and concomitant conditions requiring the use of a β-AR blocker (e.g., myocardial infarction, congestive HF, cardiac arrhythmia and thyrotoxicosis), β_1AR-selective blockers can be used in combination with bronchodilator agents, with no risk of significant short-term reduction in airway function or of increase in the occurrence of COPD exacerbations [6]. The use of nebivolol in hypertensive patients with stable mild to moderate COPD was safe during a 2-week trial, showing that it is possible to suggest the use of nebivolol in hypertensive patients with COPD when a β-AR blocker is needed [6].

It should be noted that the efficacy and safety of β-blockers in patients with respiratory obstructive diseases also depends on the type of bronchial obstruction. In fact, the bronchoconstrictor response to a given β-AR blocking agent (and the consequent development of relevant symptoms) occurs mainly in patients with reversible bronchial obstruction (e.g., in patients with bronchial asthma), whereas it is much less pronounced in those with irreversible, or partially reversible bronchial obstruction (e.g., patients with COPD) [6]. Nevertheless, in patients with hypertension and stable mild to moderate asthma, nebivolol did not appear to affect airway patency even during peak antihypertensive efficacy, thus suggesting a favorable tolerability profile also in the presence of reversible airway obstruction [32]. Similarly, in patients with COPD and arterial hypertension, 5-week treatment with nebivolol caused no aggravation of bronchial obstruction and no significant changes of bronchial permeability, while producing a considerable improvement of endothelial dysfunction [33].

Diabetes & metabolic abnormalities

High BP is a common feature of Type 1 and particularly, Type 2 diabetes. BP reduction in people with diabetes has been shown to reduce major macrovascular and microvascular complications of diabetes, end-stage renal disease, as well as mortality [34]. According to ESC/ESH Guidelines, treatment should usually be initiated with a two-drug combination of an ACE inhibitor or ARB with a CCB or thiazide/thiazide-like diuretic, and treatment escalated according to the recommended treatment algorithm [1].

Also β-blockers may provide an effective CV protection in patients with Type 2 diabetes as a result of BP lowering. However, older β-blockers may have detrimental effects on glucose control, insulin sensitivity and lipid profile [5]. On the contrary, third-generation β-blockers with vasodilatatory effects have been shown to produce greater improvements in CV outcomes in patients with diabetes than in nondiabetics without influencing glycemic control and lipid levels, and may therefore offer therapeutic benefits not provided by traditional β-blockers in this population [5]. Nebivolol, unlike other β-blockers, has been found to improve insulin sensitivity and oxidative stress and have neutral or beneficial effects on metabolic parameters, such as lipids and glucose [5]. These benefits have been confirmed in real world clinical practice, as demonstrated by a postmarketing surveillance study: in hypertensive patients with concomitant diabetes, including patients intolerant or not responding to previous therapy, nebivolol was associated with a significant reduction in BP, as well as to improvements in blood glucose and LDL cholesterol

levels, while showing a positive tolerability profile. As a result, the majority of patients rated their overall experience as good to very good, which is likely to result in improved adherence with therapy [5].

Another advantage of nebivolol in patients with hypertension and Type 2 diabetes derives from its ability to improve endothelial dysfunction, which is considered an intrinsic component in the development of insulin resistance, and can lead to an activated state, characterized by increased platelet adhesion, aggregation and increased expression of P-selectin on platelet membranes. Nebivolol, in contrast to metoprolol, was shown to improve oxidative stress and insulin sensitivity, to decrease plasma soluble P-selectin and to increase adiponectin levels in hypertensive patients. These beneficial effects of nebivolol may contribute to a reduction in CV risk in hypertensive patients [35].

In addition to exert deleterious effects on glucose levels, nonselective β-receptor antagonists were shown to consistently reduce HDL cholesterol, and increase LDL cholesterol, and triglycerides. In contrast, β_1-selective antagonists, including nebivolol, were shown to improve serum lipid profile of hypertensive patients: mean blood sugar and lipid profile were found to be significantly elevated after 24 weeks of treatment with atenolol but not with nebivolol [36]. Antioxidant property of nebivolol and its ability to increase NO by reducing its oxidative inactivation may be responsible for its beneficial lipid and carbohydrate metabolic profile [36].

The absence of detrimental metabolic effects associated with nebivolol has been confirmed by the results of the SENIORS study, in which treatment with nebivolol did not affect serum glucose in either diabetic or nondiabetic patients [24]. Most interestingly, there were slightly fewer new cases of diabetes during treatment with nebivolol than with placebo (1.8 vs 2.1%) [37].

In summary, available evidence emphasizes how nebivolol exerts neutral or beneficial effects on insulin sensitivity and lipid metabolism in hypertensive patients, owing to its NO-mediated vasodilatory and antioxidative properties. Thus, nebivolol could be a favorable therapeutic option for the treatment of hypertension in patients with impaired glucose and lipid metabolism [38].

Erectile dysfunction

Sexual dysfunction is more prevalent in hypertensive individuals compared with the normotensive population, and often causes low adherence to or discontinuation of antihypertensive treatment [39]. In contrast to thiazide or thiazide-like diuretics, conventional β-blockers, or centrally acting agents (e.g., clonidine), which may induce or worsen sexual dysfunction in treated patients, ACE inhibitors, ARBs, CCBs or vasodilating β-blockers potentially exert neutral or beneficial effects [39].

For example, thanks to its vasodilating properties mediated through endothelial release of NO, nebivolol may facilitate penile erection and thereby be more appropriate than other β-blockers in patients with hypertension and ED, as documented by both observational and randomized studies [40]. In a large observational study including more than 1000 high-risk hypertensive patients, nebivolol was associated with a lower prevalence of ED (odds ratio: 0.27) and higher International Index of Erectile Function (IIEF) scores than other β-blockers [41]. In contrast with atenolol, which was shown in a randomized study to be associated with a decrease of the mean number of satisfactory sexual intercourses per month in treated hypertensive patients, nebivolol had no negative effects on sexual function [42]. In a double-blind, randomized, crossover trial, nebivolol had no detrimental effects on the IIEF erectile function sub-score (which instead decreased with metoprolol), whereas it increased other secondary sexual activity scores, such as orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction (which remained unchanged with metoprolol) [43]. In patients with coronary artery bypass surgery, nebivolol was associated with a significantly lower incidence of any grade ED compared with metoprolol [44]. Moreover, an improvement of erectile function score was shown in an open study in 69% of patients with ED while on β-blockers who switched to nebivolol therapy [45]. Finally, a review of four study on hypertensive patients comparing nebivolol with others β-blockers showed a lower or similar incidence of ED with nebivolol compared with other β-blockers [7]. Based on these results, nebivolol may be of use in the patient with or at risk of developing ED, when the use of a β-blocker is indicated as add-on antihypertensive treatment [7].

Based on the above evidences, the lack of detrimental effects of nebivolol on sexual function has been recognized by the EMA in the summary of the product characteristics of the drug [46] and by European Scientific Societies, in the recent ESC/ESH guidelines for the management of arterial hypertension [1], and in the recently published update of the ESH Working Group on sexual dysfunction [47]. Both documents highlight the within-class differences regarding the effects of β-blockers on erectile function, focusing on the divergent effects of nebivolol, which make it a valuable option in the management of hypertension [40].

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Limitations

Although the unique pharmacological profile of nebivolol coupled with clinical evidence supports its utility in the treatment of hypertension in patients with both CV (HF with reduced ejection fraction, CAD; AF) and non-CV comorbidities (diabetes, COPD, ED), the largest limitation in interpreting nebivolol trial data comes from the absence of long term outcome trials in patients with hypertension, as well as of direct comparative trials assessing its effect on CV morbidity and mortality versus other β-blockers [48].

Conclusion

Current hypertension guidelines recommend the preferential use of β-blockers for hypertensive patients with CV comorbidities such as HF, CAD, and AF. Within the heterogenous β-blockers class, nebivolol stands out for its beneficial effects on central pressure, endothelial function and aortic stiffness, as well as for its favorable tolerability profile, which makes it appropriate also for patients with specific non-CV comorbidities (such as diabetes, respiratory obstructive diseases or ED), in which conventional anti-adrenergic agents are usually contraindicated or not recommended as first choice drugs (Table 4).

Future perspective

Among β-blockers, nebivolol presents several advantages deriving from its peculiar pharmacologic properties, which make its use to be preferred in specific conditions, in which its vasodilating, anti-oxidant and anti-ischemic effects are of particular interest, and its good tolerability profile warrants patient's adherence to treatment (Table 4).

Executive summary

β-blockers' role in the management of hypertension according to current guidelines

- Current guidelines recognize the potential advantages of β-blockers in hypertensive patients with concomitant cardiovascular (CV) pathologies (such as heart failure, coronary artery disease, atrial fibrillation), recommending their preferential use in these patients.

β-blockers are not a homogeneous class

- Among β-blockers, third generation cardio-selective drugs with vasodilating and anti-oxidant properties, such as nebivolol, may show particular benefits, thanks to ancillary actions that may provide a better CV protection.

Nebivolol

- Nebivolol exhibits highly selective β1-adrenoceptors (AR) blockade and stimulation of nitic oxide production secondary to increased activity of NO synthase by activation of β3-AR.

Nebivolol in in hypertensive patients with CV comorbidities

- In hypertensive patients with coronary artery disease or heart failure of ischemic origin, β1-AR blockade and stimulation of NO production induce coronary dilation with increased coronary blood flow, as well as decreased platelet and leucocyte activation, and may contribute to the improved anti-ischemic profile of nebivolol, not shared by other β-blockers.
- Nebivolol was shown to be as effective as atenolol in improving P-wave dispersion in patients with mild-to-moderate hypertension, suggesting a possible preventive effect on atrial fibrillation.

Nebivolol in hypertensive patient with non-CV comorbidities

- Thanks to its tolerability profile, nebivolol can be used also in patients with specific non-CV comorbidities (such as diabetes, respiratory obstructive diseases or erectile dysfunction), in which conventional anti-adrenergic agents are usually contraindicated or not recommended as first choice drugs.
  - In patients with hypertension and respiratory obstructive diseases, nebivolol caused no aggravation of bronchial obstruction and no significant changes of bronchial permeability, while producing a considerable improvement of endothelial dysfunction.
  - In hypertensive patients with diabetes, nebivolol, unlike other β-blockers, has been found to improve insulin sensitivity and oxidative stress, with neutral or beneficial effects on metabolic parameters.
  - Since the vasodilating properties of nebivolol mediated through endothelial release of NO may facilitate penile erection, nebivolol may offer an advantage over other β-blockers in patients with hypertension and erectile dysfunction.

Future perspective

- Among β-blockers, nebivolol presents peculiar pharmacologic properties producing vasodilating, anti-oxidant and anti-ischemic effects which are of particular interest in specific patient populations, in which its good tolerability profile may also improve adherence to treatment.

Financial & competing interests disclosure

C Ferri conducted studies and was conference speaker for Menarini International. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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