REVIEW

DOI: 10.4274/ijca.2024.85057
Int J Cardiovasc Acad 2024;10(2):22-30

Antiarrhythmic Properties of Beta Blockers: Focus on Nebivolol

Bülent Görenek[1], Ali Nazmi Çalık[2], Alper Kepez[3], Ahmet Öz[4], Çağlar Özmen[5], Ümit Yaşar Sinan[6], Osman Can Yontar[7], Çağan Yıldırım[3]

[1]Department of Cardiology, Eskişehir Osmangazi University Faculty of Medicine, Eskişehir, Turkey
[2]Clinic of Cardiology, University of Health Sciences Turkey, Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital, İstanbul, Turkey
[3]Department of Cardiology, Marmara University Faculty of Medicine, İstanbul, Turkey
[4]Clinic of Cardiology, İstanbul Training and Research Hospital, İstanbul, Turkey
[5]Department of Cardiology, Çukurova University Faculty of Medicine, Adana, Turkey
[6]Department of Cardiology, İstanbul University-Cerrahpaşa Institute of Cardiology, İstanbul, Turkey
[7]Department of Cardiology, Samsun University Faculty of Medicine, Samsun, Turkey

Abstract

Beta-blockers are commonly used medications for cardiovascular diseases. Beta-blockers are effective antiarrhythmic agents, and they are class 2 agents in the Vaughan-Williams classification. In this review, we first attempt to mention the physiology of beta-adrenergic activation in the myocardium and the role of excessive beta-adrenergic activation in arrythmiagenesis. Then, we will summarize the pharmacological properties of beta blockers and their use in specific arrhythmias. Special emphasis will be given to nebivolol, a new generation cardioselective beta-blocker with vasodilator activity, given the limited data regarding its use in arrhythmias.

Keywords: Beta-blockers, arrhythmias, anti-arrhythmic medications, nebivolol

INTRODUCTION

Cardiac arrhythmia is a common problem in clinical practice. Although the annual incidence of ischemic stroke and myocardial infarction is reported to be similar, the frequency is higher in the elderly, those with chronic kidney disease, and those with heart failure.[1] The fact that the sympathetic nervous system (SNS) plays an important role in the neurohormonal activation of cardiovascular diseases makes beta-blockers indispensable in the treatment of coronary artery disease, heart failure, and arrhythmias. Antiarrhythmic medications are typically categorized according to the Vaughan-Williams (VW) classification system. Beta-blockers constitute class 2 agents in the VW classification.[2] Nebivolol is a cardio-selective beta-blocker with additional endothelium-dependent vasodilating activity that stimulates nitric oxide (NO) synthesis, resulting in NO-mediated vasodilation. Considering its positive effects on cardiac pathologies, nebivolol can be involved in both direct and indirect treatment of rhythm disorders.[3]

In this article, the role of autonomic nerve activity in arrhythmias, the molecular mechanisms of action, and the pharmacological properties of Beta-Adrenergic Blockers, as

To cite this article: Görenek B, Çalık AN, Kepez A, Öz A, Özmen Ç, Sinan ÜY, Yontar OC, Yıldırım Ç. Antiarrhythmic Properties of Beta Blockers: Focus on Nebivolol. Int J Cardiovasc Acad. 2024;10(2):22-30

Address for Correspondence: MD Çağan Yıldırım, Department of Cardiology, Marmara University Faculty of Medicine, İstanbul, Turkey
E-mail: caganyildirim94@hotmail.com
ORCID ID: orcid.org/0000-0002-8732-4555

Received: 31.03.2024
Revised: 23.06.2024
Accepted: 27.06.2024
Published Online: 02.07.2024

well as the evidence-based potential effects of Nebivolol as an anti-arrhythmic drug in different cardiac pathologies, are discussed.

1. Overview: Role of β-adrenergic Activation in Heart

The SNS is responsible for organisms' "fight or flight" response to constant changes in the surrounding environment. It is crucial for maintaining life in a stable position. Activation of the SNS triggers a series of physiological and metabolic events that ultimately result in an interaction between catecholamines and adrenoreceptor. In brief, catecholamines increase heart's rate and contractility, at the same time regulate blood pressure, airway reactivity, and metabolism.[4,5]

Normal heart function depends on the organized and coherent working of two types of cells: conduction system cells and cardiomyocytes. These two types of cells work together, and only if they are in harmony would cardiac muscles work as desired. The relationship between these two cells' functions is complex and nave; however, it is crucial to maintain coherence otherwise rhythm problems may occur. The heart contains pacemaker cells throughout the conduction system, whereas pacemaker cells in the sinoatrial node function as primary pacemakers in sinus rhythm. Any dysfunction in these pacemaker cells may result in the activation of other pacemaker cells that are localized in other parts of the conduction system, such as the atrioventricular node and bundle of His, thus generating escape beats. Rhythm disturbances have many reasons, primarily problems with signal production and vicious cycles in signal propagation (reentry). It is possible to suggest that the overexcitation of the SNS is responsible for most of these phenomena.[4]

There are five adrenoreceptor, namely α1, α2, β1, β2 and β3. We will focus on β1, β2 and β3 due to their cardiac effects.

β1 adrenoreceptor constitute nearly 80% of all β receptors in the human heart. β1 stimulation generally starts with bonding between norepinephrine and G-stimulator protein and continues with activation of adenylyl-cyclase, which transforms adenosine triphosphate to cyclic adenosine monophosphate (cAMP). Increased cAMP levels activate protein kinase A (PKA), which phosphorylates several proteins involved in cardiac function, such as L-type calcium channels, phospholamban, troponin I, and ryanodine receptors. Calcium transition into cytoplasm and increase in contractility take place. In specialized conduction cells (pacemaker cells), PKA phosphorylates ion channels in the cell membrane, leading to calcium inflow and increased signal frequency. Moreover, the conduction velocity of atrioventricular node cells increases.[6] All these modulations lead to increased heart rate (chronotropy), contraction force (inotropy), relaxation speed (lusitropy), and conduction (dromotropy).

β2 adrenoreceptor are mostly found in the smooth muscle cells of bronchioles. In the human heart, β2 adrenoreceptor are nearly 20% of whole β receptors and they are mostly capable of bonding with epinephrine. Just like β1 adrenoreceptor, they act over the adenylyl cyclase-cAMP-PKA axis. However, in this scenario, increased intracellular cAMP inhibits the release of stored calcium, which facilitates muscle relaxation. In addition, this process increases contractility and heart rate. Distinctively from β1 effect, β2 stimulation augments coronary vasodilatation during stressful events.[7] Although both β1 and β2 receptors use the adenylate cyclase pathway β1 receptors express higher functional effects in cardiomyocytes.

The cardiac effect of β3 adrenoreceptor are supposed to be a mechanism by which its NO increases in situations of overstimulation in β1 and β2 receptors.[8] As a result of NO generation, β3 adrenoreceptor pathway in the ventricular myocardium is accompanied by decreased contractility.[8] Catecholamines directly stimulate β adrenergic receptors, and chronic catecholamine exposure leads to desensitization and downregulation of β1 and β2 receptors via G-protein coupled kinases (GRK). β3 adrenoreceptor differ from β1 and β2 receptors by not having GRK recognition sites, so their levels remain unchanged or upregulated and act as a protective mechanism against chronic catecholamine exposure.[9]

2. Role of the Autonomic Nervous System in Arrhythmia

The autonomic nervous system (ANS), which consists of the sympathetic (SNS) and parasympathetic nervous systems (PNS), plays a major role in the regulation of cardiac electrophysiological activity and triggers cardiac arrhythmia. Sympathetic efferent fibers reach the heart through the paravertebral stellate ganglion (inferior - middle cervical).[10] Vagal preganglionic fibers reach the heart via the superior cervical, inferior cervical, and thoracic rami, which anastomose cardiac sympathetic nerves to form the cardiac plexus. Cardiac ganglia are distributed along the plexus and become more abundant near the heart, particularly subepicardially.[11] Both SNS and PNS can act as pro- and anti-arrhythmic.[12] The SNS and PNS provide autonomic control by interacting with the intrinsic and extrinsic cardiac nervous systems. This interaction is complex and differs for all specific arrhythmias. For instance, an increase in both sympathetic and PNS activity may be the trigger for AF occurrence.[13] On the other hand, sympathetic activity is proarrhythmic, whereas parasympathetic activation is antiarrhythmic, especially in ventricular arrhythmia associated with myocardial ischemia.[14] Similarly, SNS triggers ventricular arrhythmia and sudden cardiac death (SCD) in some hereditary cardiac channelopathies [long QT syndrome type 1, catecholaminergic polymorphic ventricular tachycardias (VT)]. In Brugada syndrome, SNS activation suppresses arrhythmia, whereas PNS activation may be arrhythmogenic.

Hence, decreased and/or increased vagal tonus can cause arrhythmia through complex electrophysiological mechanisms, similar to sympathetic overactivation. Therefore, an appropriate balance between sympathetic and PNS activity is essential for maintaining normal sinus rhythm.[12,14]

SNS activation and increased catecholamine release are important triggers of arrhythmias via various effects on electrophysiological system. Sympathetic overactivation is associated with atrial fibrillation (AF) and ventricular arrhythmias [ventricular premature complex, VT and ventricular fibrillation (VF)]. Catecholamines activate cardiac beta receptors via the cAMP/protein kinase cascade. Exposure of cardiomyocytes to endogenous and exogenous catecholamines causes autonomic tachyarrhythmias by increasing the rate of spontaneous depolarization. In addition, since sympathetic nerve endings are not uniformly distributed in the heart, a shortening of the refractory period occurs at varying degrees in different parts of the heart during increased sympathetic activation. This process may end with re-entry circuits. The presence of coexisting facilitating factors as ischemia and/or electrolyte imbalance might increase the susceptibility of myocardium to arrythmia generation in a hyperadrenergic state. Sympathetic activation may also increase ventricular arrhythmia generation by inducing ischemia. Norepinephrine secreted locally by the ischemic region accelerates ischemic cell damage, which might end in VF. Therefore, beta blockers that prevent sympathetic activation and, in resistant cases, sympathetic denervation are effective treatment methods for the prevention and treatment of various arrhythmias.[15] Physical and emotional stress, sleep disorders, metabolic disorders, and medical conditions, surgery, and drugs might trigger arrhythmia by increasing SNS activity. Moderate exercise is beneficial in both healthy individuals and patients with CVD; intense and strenuous exercise can trigger arrhythmia via sympathetic hyperactivation in patients with CVD. Physical and emotional stress can cause cardiac arrhythmia in patients with CVD. An optimal sleep pattern (average of 7 hours a day) is necessary to maintain the ANS. Short sleep duration, ineffective sleep, insomnia, and sleep breathing disorders have pro-arrhythmic effects. Sleep disorders cause both AF and ventricular arrhythmias.

Overactivation of PNS is also responsible for maladaptive change and arrhythmia occurrence. It has long been established that vagal stimulation is associated with AF.[15] The underlying mechanism is a shortened atrial refractory period. However, vagal stimulation decreases the risk of VT/VF occurrence under ischemic conditions. Increased PNS activity compared with SNS activity is referred to as vagotonia. Vagotonia is pro-arrhythmic in Brugada syndrome. Disturbances of rapid inactivation at slow cardiac rates induce a persistent sodium current that lengthens repolarization. Variable action potential durations due to repolarization differences were proposed to cause reentry.[16] Vagal activation and increased inflammatory response secondary to atrial stretch are responsible for AF in elite athletes.

2a. Supraventricular Tachyarrhythmias

There are different types of SVTs that occur with abnormal automaticity or triggered activity due to increased SNS activity. On the other hand, SVTs due to reentry may also be induced by increased sympathetic activity. In patients with atrioventricular nodal re-entering tachycardia (AVNRT), the tachycardia circuit may be sensitive to catecholamines. Increased SNS activity can trigger potential malignant arrhythmias in Wolf-Parkinson-White syndrome. Increased sympathetic activity might accelerate AV conduction in the accessory pathway, resulting in the conversion of atrial tachyarrhythmias (AF, atrial flutter) to VF and SCD in these patients. Atrial tachycardia may develop due to imbalance between SNS and PNS. Adrenergic sensitivity characterizes atrial tachycardia associated with increased automaticity and/or triggered activity rather than re-entry. Inappropriate sinus tachycardia is used to describe sinus tachycardia with a heart rate >100 bpm in sinus rhythm without an underlying primary cause. It has been suggested that an increased sympathetic tone is the main cause of this arrhythmia.

There is evidence that abnormal ANS activation is closely related to AF development. The atria are the innermost chambers of the heart. They are innervated with fibers originating from both intra-cardiac and extra-cardiac autonomic nerves and ganglia. Autonomic imbalance not only acts as a trigger for AF occurrence but also may create a substrate for arrythmia development. AF itself might also induce autonomic imbalance. The imbalance between SNS and PNS activation has been suggested to be the main contributing factor to the development and maintenance of AF. Although PNS is the main mechanism underlying spontaneous AF, adrenergic stimulation is also a co-regulatory mechanism in the initiation and maintenance of cholinergic-mediated AF.[12] Strenuous exercise can create an appropriate arrhythmogenic atrial substrate by affecting autonomic tone in elite athletes.[17]

2b. Ventricular Tachyarrhythmias

The ANS is the main contributor to VT/VF occurrence. In the presence of facilitating factors, such as channelopathy, ARVC, acquired structural heart disease, MI, and heart failure, sympathetic and parasympathetic imbalance can trigger ventricular arrhythmia and SCD. Sympathetic system activation can act as both a trigger (increased automaticity/triggered activity and extrasystole) and a substrate (shortened action potential duration, heterogeneity in repolarization). Sympathetic system activation has also been suggested to be involved in the

pathogenesis of idiopathic VTs, especially those originating from the outflow tracts. The intense sympathetic innervation of the right ventricular outflow tract (RVOT) might increase the susceptibility of RVOT to VT development in the presence of increased sympathetic activation.

3. Pharmacological Properties of Beta-adrenergic Blockers

Beta-blockers are antagonists of β-adrenergic receptors that play a significant role in controlling physiological processes, such as blood pressure, heart rate, airway reactivity, and the central nervous system. They bind to β-adrenergic receptors, blocking the binding of norepinephrine and epinephrine to these receptors and exerting sympatholytic effects.[18-21] β1 adrenergic receptors are dominant in the heart, while β2 adrenergic receptors are dominant in the peripheral vascular bed, bronchi, and pancreas. On the other hand, β3 adrenergic receptors are mainly found in the urinary bladder, gall bladder, adipose tissue, and small and large intestines.

Beta-blockers are generally divided into three groups:

- First-generation beta-blockers (propranolol, sotalol) are non-selective agents and inhibit both β1 and β2 adrenergic receptors.

- Second-generation beta-blockers (atenolol, bisoprolol, metoprolol) are cardioselective drugs that bind to β1 adrenergic receptors with higher affinity.

- Third-generation non-selective beta-blockers (carvedilol, labetalol, carteolol) are drugs that additionally exhibit alpha-adrenergic receptor blockade, resulting in vasodilatory effects. Due to this characteristic, they are referred to as "vasodilatory beta-blockers". This vasodilatory activity reduces peripheral vascular resistance while positively contributing to the hemodynamic profile by preserving or improving cardiac output, stroke volume, and left ventricular function.[22]

Beta-blockers bind to β1 adrenergic receptors located in the heart's conduction system and myocyte, preventing the release of norepinephrine from sympathetic adrenergic nerve terminals and the binding of circulating norepinephrine and epinephrine to these receptors. Therefore, they reduce the heart rate (chronotropy), cardiac contractility (inotropy), the conduction velocity of impulses in the heart (dromotropy), and the rate of cardiac relaxation (lusitropy) (Figure 1).

3a. Pharmacological Properties of Beta-blockers

1. Selectivity: Non-selective beta-blockers have equal affinity for β1 and β2 adrenergic receptors, and they block both receptors. Cardiac-selective beta-blockers have a higher affinity for β1 adrenergic receptors.[23]

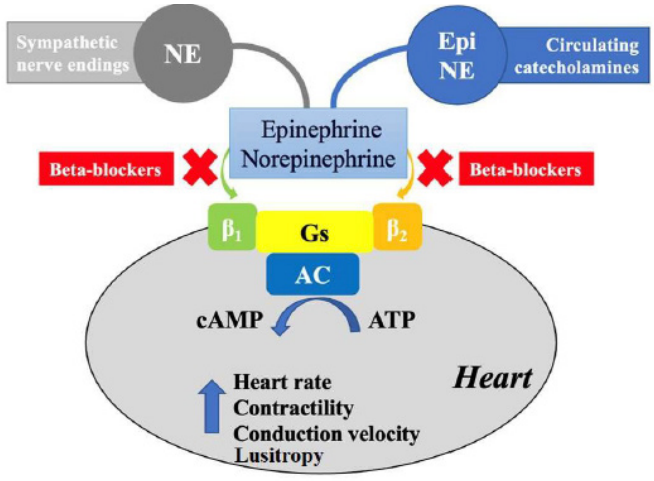

Figure 1: Mechanism of action of beta-blockers in the heart

Epi: Epinephrine, NE: Norepinephrine, AC: Adenylyl cyclase, Gs: Gs-protein

2. Intrinsic sympathomimetic activity: Some beta-blockers, when bound to β-adrenergic receptors, can exhibit partial agonist effects by partially activating the receptor while blocking the binding of norepinephrine. Beta-blockers with intrinsic sympathomimetic activity (ISA) have fewer myocardial depressant, conduction slowing, and bronchoconstrictive effects than other beta-blockers.[23] In addition, ISA may induce arterial vasodilation and increase arterial compliance in the long term, which may lead to additional beneficial effects regarding hypertension treatment.

3. Membrane stabilizing activity: Some beta-blockers exhibit membrane stabilizing activity (MSA) similar to sodium channel blockers (Class I antiarrhythmics). MSA is believed to be more effective against arrhythmias.[23]

4. Lipophilic properties: Lipophilic beta-blockers (acebutolol, carvedilol, labetalol, metoprolol, nebivolol, propranolol) are well absorbed by the gastrointestinal system when consumed orally. These drugs undergo significant first-pass elimination in the liver, resulting in systemic bioavailability ranging from 10% to 75%.[23]

5. Hydrophilic properties: Hydrophilic beta-blockers (atenolol, betaxolol, bisoprolol, carteolol, celiprolol, nadolol, pindolol, sotalol, tertatolol) are minimally metabolized in the liver and primarily eliminated by the kidneys during first-pass metabolism. These agents have weak blood-brain barrier penetration, and their dosages generally do not vary between individuals.

6. Inverse agonism: A beta-blocker that reduces the basal activity of beta receptors to a greater extent than the basal state in the absence of agonists and antagonist agents is defined

as inverse agonism. Some beta-blockers block β-adrenergic receptor activity based on the degree of inverse agonist activity rather than simple receptor blockade. The significance of this pharmacological property in the efficacy of these agents is not yet clear.[23]

The clinical indications and pharmacological properties of commonly used beta-blockers in daily practice are summarized in Table 1.

3b. Side Effects and Contraindications of Beta-blockers

Most of the side effects of beta-blockers are related to their cardiac effects. Bradycardia, hypotension, decreased exercise capacity, and atrioventricular (AV) conduction block are the most common side effects. Beta-blockers are contraindicated in patients with sinus bradycardia or partial AV block. When used together, beta-blockers and cardiac-selective calcium channel blockers (verapamil, diltiazem) should be used with caution because they can cause additive electrical and mechanical depression in the heart.

Non-selective beta-blockers significantly increase the risk of bronchospasm by blocking β2 adrenergic receptor activity in patients with asthma. Therefore, it is advisable to avoid the use of these agents in patients with chronic obstructive pulmonary disease or asthma who present with severe bronchospasm. In patients with diabetes, beta-blockers can mask tachycardia, which is a warning sign of insulin-induced hypoglycemia and should be used with caution in such patients.

4. Beta Blockers as Antiarrhythmic Agents for Nebivolol

Beta-blockers are group 2 antiarrhythmic agents based on the VW classification. Previous studies have confirmed the effectiveness of beta blockers in the treatment of arrythmia.[24] The observations from the Randomized AFFIRM Trial suggested that beta-blockers are the most effective agents for rhythm control in patients with AF.[25] The VALIANT trial showed that beta blockers applied within the first 24 hours decreased early mortality in patients who sustained VT/VF after myocardial infarction.[26] The MADIT-II trial has shown that among patients with intracardiac defibrillators (ICD), those treated with the highest dose of beta-blockers had a decreased incidence of ventricular arrhythmias that ended up with ICD shock compared with patients who did not receive beta-blockers.[27] Recent guidelines recommend beta-blockers for the treatment of supraventricular and ventricular arrhythmias.[28,29]

Nebivolol is a third-generation beta-blocker that exerts NO-mediated vasodilatory and antioxidative actions through β3 receptor agonism.[30] Nebivolol is most beta-1 selective with a long action duration.[31] It does not possess any intrinsic sympathomimetic or membrane-stabilizing activity exists. High beta-selectivity is an advantage of nebivolol in the treatment of advanced chronic obstructive pulmonary disease or asthma compared with the nonselective beta-blockers propranolol, sotalol, and nadolol. Its absorption is not affected by foods, and 98% of it is bound to proteins in the circulation. Hepatic metabolism occurs, and its half-life is approximately 10 hours.[23] Nebivolol and carvedilol do not decrease cardiac output

Table 1: Clinical indications and pharmacological properties of beta-blockers.

Drug/Agent	ISA	MSA	Lipophilic	Hydrophilic	Comment
β1-selective					
Acebutolol	+	+	+		
Atenolol				+	
Bisoprolol					
Esmolol					Short acting Intra/postop HT treatment
Metoprolol			+		
Nebivolol			+		NO release Vasodilator activity
Non-selective (β1/β2)					
Carvedilol		+	+		NO release and α1 blocker
Labetalol	+	+	+		α1 blocker
Nadolol				+	
Penbutolol	+				
Pindolol	+	+		+	
Propranolol		+	+		Beta blocker prototype
Sotalol				+	K+ channel antagonist

HT: Hypertension, ISA: Intrinsic sympathomimetic activity, K+: Potassium, MSA: Membrane stabilizing activity, NO: Nitric oxide

unlike other beta-blockers.[23] There are some data in the literature related to the use of nebivolol for the treatment of arrhythmias. These studies are presented in Table 2.

4a. Beta-blockers for the Treatment of Supraventricular Tachycardias

The use of parenteral beta-blockers is recommended in the treatment of regular narrow-complex supraventricular tachycardias (SVT) if vagal maneuvers and adenosine fail to terminate the arrhythmia. Beta-blockers should not be used in patients with decompensated heart failure. Beta-blockers can also be used to treat wide QRS complex tachycardias if the hemodynamic status is stable.[23]

Beta-blockers may be used to treat inappropriate sinus tachycardia. Combination with ivabradine may be a more effective strategy.[43] Non-selective beta-blockers might be an option for the treatment of postural orthostatic tachycardia syndrome if non-pharmacological therapy fails.[44] Beta-blockers are an option in the long-term treatment of SVT if catheter ablation is not available. Beta-blockers can be used in the treatment of focal atrial tachycardia in hemodynamically stable patients if adenosine fails to control arrhythmia. Both beta-blockers and non-dihydropyridine calcium channel blockers have been recommended for the acute treatment of multifocal atrial tachycardia; however, there is evidence that metoprolol is more effective than verapamil in the treatment of multifocal atrial tachycardia.[45] Selective beta-blockers

Table 2: Data related to the antiarrhythmic effects of nebivolol in the literature.

Reference	Type of study	Subject (number)	Type of arrhythmia	Conclusion	Positive/Negative
Erdil et al.[32]	Human	200	POAF	Nebivolol was found to be as effective as metoporolol.	Positive
Shubik et al.[33]	Human	20	AF	Shown to effectively control heart rate	Positive
Gasser et al.[34]	Human	62	AF	Decrease in the frequency of atrial fibrillation and arrhythmia symptoms in moderate and severe hypertension	Positive
Mulder et al.[35]	Human	2128	AF	Nebivolol had no effect on endpoints in elderly patients with heart failure and atrial fibrillation.	Negative
Hopton et al.[36]	Human	1	CPVT	For patients with gain of function variants in RyR2, carvedilol and nebivolol may be effective treatments.	Positive
Tan et al.[37]	Basic science-animal	-	CPVT	Nebivolol has a RyR2-targeted effect that suppresses VTs induced by Ca2+ release.	Positive
Lu et al.[38]	Animal	Rats and guinea-pigs	VT/VF	It has been shown to significantly reduce reperfusion-induced arrhythmias (VT and VF) in those receiving nebivolol as pretreatment.	Positive
Lu et al.[38]	Animal	Guinea pig	VT/VF	Nebivolol has been found to significantly reduce ischemia-induced ventricular fibrillation (VF). It was determined that it increased the VF threshold depending on the dose of nebivolol.	Positive
Lu et al.[39]	Animal	Guinea pig	VF	Nebivolol increases VF threshold	Positive
Simsek et al.[40]	Human	105	VT	Significant reduction from baseline in QTc dispersion after treatment with Nebivolol in patients with coronary slow flow	Positive
Galetta et al.[41]	Human	25	VT	In hypertensive patients with left ventricular hypertrophy, treatment with nebivolol significantly decreased QT dispersion.	Positive
Nazeri et al.[42]	Animal	Yucatan pigs	Tachycardia induced cardiomyopathy	Both nebivolol and metoprolol failed to prevent cardiomyopathy	Negative

AF: Atrial fibrillation, Ca: Calcium, CPVT: Catecholaminergic polymorphic ventricular tachycardia, POAF: Prevention of atrial fibrillation, RyR: Ryanodin receptor, QTc: Corrected QT, VF: Ventricular fibrillation, VT: Ventricular tachycardia

should be used in the long-term treatment of recurrent and symptomatic multifocal atrial tachycardia. Beta-blockers are recommended for ventricular rate control in patients with macro-reentrant-type atrial tachycardia.[23]

Beta-blockers and cardio-selective calcium channel blockers are recommended for the acute treatment of AVNRT. Beta-blockers can also be used for long-term treatment of AVNRT if catheter ablation is not available.[23] Beta-blockers are also advised in the acute treatment of AV reentrant tachycardia (AVRT) if vagal maneuvers and/or adenosine have failed to terminate the arrhythmia. Beta-blockers should be used with caution in the long-term treatment of AVRT if there is evidence of preexcitation.[23] Beta-blockers are contraindicated in patients with preexcited AF.

4b. Beta-blockers in Patients with Atrial Fibrillation

AF is one of the most common arrhythmias in clinical practice. Beta-blockers are the main agents used for ventricular rate control in patients with AF. Beta-blockers depress conduction in the AV node, and they can also be used in patients with compensated heart failure, unlike verapamil and diltiazem. Beta-blockers are more effective for rate control in patients with AF during exercise than cardiac glycosides.[46] The prophylactic use of beta-blockers is recommended for the prevention of postoperative AF development following cardiac surgery.[47] Nebivolol was found to be as effective as metoprolol in preventing postoperative AF in patients who underwent coronary artery bypass surgery.[32] Shubik et al.[33] reported that nebivolol effectively controlled the ventricular rate in patients with ischemic heart disease and chronic AF. They observed that a 5 mg daily dose was sufficient for most patients to achieve the desired ventricular rate.

The SENIORS trial demonstrated the effectiveness of nebivolol in decreasing the rates of mortality and hospital admissions compared with placebo among patients aged ≥70 years with a history of heart failure.[48] However, nebivolol treatment failed to reduce the rate of primary endpoints in elderly patients with stable heart failure and AF during a follow-up period of 21 months.[35] Nebivolol therapy also failed to reduce the incidence of AF during follow-up, raising questions related to the antiarrhythmic effects of the drug. A meta-analysis evaluated the effectiveness of beta-blockers in reducing the incidence of AF in patients with heart failure. Previous studies have evaluated the effects of beta-blockers that have proven efficiency in the treatment of HF and reported that beta-blockers significantly reduced the incidence of new-onset AF by 27%.[49] The cause of the discrepancy between the results of the SENIORS trial and this meta-analysis might be related to the older age of the study population in the SENIORS trial, who had a higher prevalence of AF (35%).

4c. Beta-blockers for Ventricular Arrhythmias

Effective treatment of underlying cardiac diseases and comorbidities is the mainstay of prevention of ventricular arrythmia and SCD. Beta-blockers are the only agents consistently proven to reduce the incidence of life-threatening arrhythmias and SCD.[29] Hence, they are considered the first-line agents to be used in the management of ventricular arrhythmias and prevention of SCD.[29] However, sotalol should be used with caution in patients with heart failure because of the risk of QT prolongation and potential proarrhythmic effects.[23]

The antiarrhythmic effects of nebivolol on ventricular arrhythmias developed during ischemia and reperfusion have been investigated in a few *in vivo* models. An experimental study on rats and guinea pigs has evaluated the effects of nebivolol on reperfusion and ischemia-induced arrhythmias.[38] Nebivolol significantly reduced the incidence of VT/VF and increased the VF threshold in various *in vivo* experimental models.[39] However, there is no solid evidence in humans regarding the beneficial role of nebivolol in the treatment of ventricular arrhythmias. The two studies that investigated this topic showed that nebivolol reduced QT dispersion in either patients with coronary slow flow after 3 months of treatment[40] or in hypertensive patients after 4 weeks of treatment.[41] Since QT dispersion is a marker of ventricular arrhythmia tendency, the authors concluded that nebivolol could contribute to arrhythmia risk reduction as well as SCD risk reduction.[40,41]

Nebivolol reduced the incidence of SCD compared with placebo in the SENIORS trial.[48] Since most SCDs are related to malignant arrhythmias, it might be suggested that nebivolol may have a beneficial effect on the incidence of ventricular arrhythmias. However, this hypothesis remains hypothesized and should be verified in large-scale randomized clinical trials with adequate statistical power that have ventricular arrhythmia burden reduction as the primary outcome.[30]

4d. Beta Blockers in Hereditary Arrhythmia Syndromes

Beta-blockers are the first-line agents used in the treatment of congenital long QT syndromes, except for LQT3.[50] Mexiletine is the preferred first-line treatment for LQT3 patients with mexiletine-responsive genetic mutations, and whether mexiletine should be administered as a standalone therapy or in combination with beta-blockers is uncertain.[50] Beta-blockers should also be used in patients with genetic mutations that cause a long QT interval, even if the baseline QT interval is within the normal range.[29]

Beta-blockers are effective in preventing ventricular arrhythmias in patients with catecholaminergic polymorphic VT. Beta-blockers without ISA should be used in these patients.[51]

Non-selective beta-blockers are preferred over selective beta-blockers in the treatment of CPVT.[52] Nebivolol has been shown to reduce ryanodine receptor-mediated calcium release, which plays an important role in arrhythmogenesis.[37] This action has been reported to be independent of NOS stimulation. Among the beta-blocker agents, only carvedilol and nebivolol decrease ryanodine receptor-mediated calcium release.[37] Nebivolol has a long elimination half-time and is a promising agent for Ca^{2+}-triggered arrhythmias. Results of clinical studies are needed to evaluate the clinical importance of the abovementioned pharmacological effects.

CONCLUSION

Beta-blockers are commonly used to treat arrhythmias. The antiarrhythmic effects of beta-blockers are related not only to beta adrenergic blockade but also to specific pharmacological actions associated with individual beta-blocker agents. Nebivolol has unique NO-mediated vasodilatory and antioxidative actions. Nebivolol has also been shown to reduce ryanodine receptor-mediated calcium release, which is known to play an important role in arrhythmogenesis. Although clinical data are limited, we believe that nebivolol might be a promising agent for the treatment of arrhythmias because of its unique pharmacological actions in addition to its effective and specific beta-1 adrenoreceptor-blocking action. Results of large-scale clinical studies with appropriate designs are needed to evaluate the clinical antiarrhythmic effects of nebivolol.

Ethics

Authorship Contributions

Surgical and Medical Practices: B.G., A.N.Ç., A.K., A.Ö., Ç.Ö., Ü.Y.S., O.C.Y., Ç.Y., Concept: B.G., A.N.Ç., A.K., A.Ö., Ç.Ö., Ü.Y.S., O.C.Y., Ç.Y., Design: B.G., A.N.Ç., A.K., A.Ö., Ç.Ö., Ü.Y.S., O.C.Y., Ç.Y., Data Collection or Processing: B.G., A.N.Ç., A.K., A.Ö., Ç.Ö., Ü.Y.S., O.C.Y., Ç.Y., Analysis or Interpretation: B.G., A.N.Ç., A.K., A.Ö., Ç.Ö., Ü.Y.S., O.C.Y., Ç.Y., Literature Search: B.G., A.N.Ç., A.K., A.Ö., Ç.Ö., Ü.Y.S., O.C.Y., Ç.Y., Writing: B.G., A.N.Ç., A.K., A.Ö., Ç.Ö., Ü.Y.S., O.C.Y., Ç.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Khurshid S, Choi SH, Weng LC, Wang EY, Trinquart L, Benjamin EJ, *et al.* Frequency of Cardiac Rhythm Abnormalities in a Half Million Adults. Circ Arrhythm Electrophysiol. 2018;11:e006273.
2. Lei M, Wu L, Terrar DA, Huang CL. Modernized Classification of Cardiac Antiarrhythmic Drugs. Circulation. 2018;138:1879-96.
3. Fongemie J, Felix-Getzik E. A Review of Nebivolol Pharmacology and Clinical Evidence. Drugs. 2015;75:1349-71.
4. Brodde OE. Beta-adrenoceptors in cardiac disease. Pharmacol Ther. 1993;60:405-30.
5. Brodde OE, Michel MC. Adrenergic and muscarinic receptors in the human heart. Pharmacol Rev. 1999;51:651-90.
6. Lefkowitz RJ, Rockman HA, Koch WJ. Catecholamines, cardiac beta-adrenergic receptors, and heart failure. Circulation. 2000;101:1634-7.
7. Barki-Harrington L, Perrino C, Rockman HA. Network integration of the adrenergic system in cardiac hypertrophy. Cardiovasc Res. 2004;63:391-402.
8. Moens AL, Yang R, Watts VL, Barouch LA. Beta 3-adrenoreceptor regulation of nitric oxide in the cardiovascular system. J Mol Cell Cardiol. 2010;48:1088-95.
9. Cannavo A, Koch WJ. Targeting β3-Adrenergic Receptors in the Heart: Selective Agonism and β-Blockade. J Cardiovasc Pharmacol. 2017;69:71-8.
10. Hasan W. Autonomic cardiac innervation: development and adult plasticity. Organogenesis. 2013;9:176-93.
11. Benarroch EE, Parasympathetic System; Overview, in Encyclopedia of the Neurological Sciences (Second Edition), Aminoff MJ, RB. Daroff Eds. Oxford: Academic Press, 2014, pp. 805-8.
12. Shen MJ, Zipes DP. Role of the autonomic nervous system in modulating cardiac arrhythmias. Circ Res. 2014;114:1004-21.
13. Sharifov OF, Fedorov VV, Beloshapko GG, Glukhov AV, Yushmanova AV, Rosenshtraukh LV. Roles of adrenergic and cholinergic stimulation in spontaneous atrial fibrillation in dogs. J Am Coll Cardiol. 2004;43:483-90.
14. Manolis AA, Manolis TA, Apostolopoulos EJ, Apostolaki NE, Melita H, Manolis AS. The role of the autonomic nervous system in cardiac arrhythmias: The neuro-cardiac axis, more foe than friend? Trends Cardiovasc Med. 2021;31:290-302.
15. Zhu C, Hanna P, Rajendran PS, Shivkumar K. Neuromodulation for Ventricular Tachycardia and Atrial Fibrillation: A Clinical Scenario-Based Review. JACC Clin Electrophysiol. 2019;5:881-96.
16. Popa IP, Șerban DN, Mărănducă MA, Șerban IL, Tamba BI, Tudorancea I. Brugada Syndrome: From Molecular Mechanisms and Genetics to Risk Stratification. Int J Mol Sci. 2023;24:3328.
17. Manolis AS, Manolis AA. Exercise and Arrhythmias: A Double-Edged Sword. Pacing Clin Electrophysiol. 2016;39:748-62.
18. Guimarães S, Moura D. Vascular adrenoceptors: an update. Pharmacol Rev. 2001;53:319-56.
19. de Lucia C, Eguchi A, Koch WJ. New Insights in Cardiac β-Adrenergic Signaling During Heart Failure and Aging. Front Pharmacol. 2018;9:904.
20. Wang J, Gareri C, Rockman HA. G-Protein-Coupled Receptors in Heart Disease. Circ Res. 2018;123:716-35.
21. Rockman HA, Koch WJ, Lefkowitz RJ. Seven-transmembrane-spanning receptors and heart function. Nature. 2002;415:206-12.
22. Frishman WH. Beta-Adrenergic Receptor Blockers in Hypertension: Alive and Well. Prog Cardiovasc Dis. 2016;59:247-52.
23. Wołowiec Ł, Grześk G, Osiak J, Wijata A, Mędlewska M, Gaborek P, *et al.* Beta-blockers in cardiac arrhythmias-Clinical pharmacologist's point of view. Front Pharmacol. 2023;13:1043714.
24. Grandi E, Ripplinger CM. Antiarrhythmic mechanisms of beta blocker therapy. Pharmacol Res. 2019;146:104274.

25. Olshansky B, Rosenfeld LE, Warner AL, Solomon AJ, O'Neill G, Sharma A, *et al.* The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study: approaches to control rate in atrial fibrillation. J Am Coll Cardiol. 2004;43:1201-8.

26. Piccini JP, Hranitzky PM, Kilaru R, Rouleau JL, White HD, Aylward PE, *et al.* Relation of mortality to failure to prescribe beta blockers acutely in patients with sustained ventricular tachycardia and ventricular fibrillation following acute myocardial infarction (from the VALsartan In Acute myocardial iNfarcTion trial [VALIANT] Registry). Am J Cardiol. 2008;102:1427-32.

27. Brodine WN, Tung RT, Lee JK, Hockstad ES, Moss AJ, Zareba W, *et al.* Effects of beta-blockers on implantable cardioverter defibrillator therapy and survival in the patients with ischemic cardiomyopathy (from the Multicenter Automatic Defibrillator Implantation Trial-II). Am J Cardiol. 2005;96:691-5.

28. Brugada J, Katritsis DG, Arbelo E, Arribas F, Bax JJ, Blomström-Lundqvist C, *et al.* 2019 ESC Guidelines for the management of patients with supraventricular tachycardiaThe Task Force for the management of patients with supraventricular tachycardia of the European Society of Cardiology (ESC). Eur Heart J. 2020;41:655-720.

29. Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, *et al.* 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Eur Heart J. 2015;36:2793-867.

30. Muresan L, Cismaru G, Muresan C, Rosu R, Gusetu G, Puiu M, *et al.* Beta-blockers for the treatment of arrhythmias: Bisoprolol - a systematic review. Ann Pharm Fr. 2022;80:617-34.

31. Gupta S, Wright HM. Nebivolol: a highly selective beta1-adrenergic receptor blocker that causes vasodilation by increasing nitric oxide. Cardiovasc Ther. 2008;26:189-202.

32. Erdil N, Kaynak M, Dönmez K, Disli OM, Battaloglu B. Nebivolol in preventing atrial fibrillation following coronary surgery in patients over 60 years of age. Rev Bras Cir Cardiovasc. 2014;29:581-7.

33. Shubik IuV, Medvedev MM, Kriatova TV. Kontrol' chastoty serdechnykh sokrashcheniĭ u bol'nykh s takhisistolicheskoĭ fibrilliatsieĭ predserdiĭ s pomoshch'iu nebivolola [Heart rate control with nebivolol in patients with tachysystolic atrial fibrillation]. Kardiologiia. 2003;43:52-5.

34. Gasser S, Gaugl K, Kraigher-Krainer E, Zunko S, Gasser R. Nebivolol Reduces Symptoms of Cardiac Arrhythmias in Patients with Arterial Hypertension: An Observational Pilot Study. Journal of Clinical and Basic Cardiology. 2007;9.

35. Mulder BA, van Veldhuisen DJ, Crijns HJ, Böhm M, Cohen-Solal A, Babalis D, *et al.* Effect of nebivolol on outcome in elderly patients with heart failure and atrial fibrillation: insights from SENIORS. Eur J Heart Fail. 2012;14:1171-8.

36. Hopton C, Tijsen AJ, Maizels L, Arbel G, Gepstein A, Bates N, *et al.* Characterization of the mechanism by which a nonsense variant in RYR2 leads to disordered calcium handling. Physiol Rep. 2022;10:e15265.

37. Tan Z, Xiao Z, Wei J, Zhang J, Zhou Q, Smith CD, *et al.* Nebivolol suppresses cardiac ryanodine receptor-mediated spontaneous Ca2+ release and catecholaminergic polymorphic ventricular tachycardia. Biochem J. 2016;473:4159-72.

38. Lu HR, Remeysen P, De Clerck F. Antiarrhythmic effects of nebivolol in experimental models in vivo. J Cardiovasc Pharmacol. 1994;24:986-93.

39. Lu HR, Remeysen P, De Clerck F. Antifibrillary action of class I-IV antiarrhythmic agents in the model of ventricular fibrillation threshold of anesthetized guinea pigs. J Cardiovasc Pharmacol. 1995;26:132-6.

40. Simsek H, Yaman M, Babat N, Akdag S, Akyol A, Demirel KC, *et al.* Decreased risk of ventricular arrhythmias with treatment of nebivolol in patients with coronary slow flow. Kardiol Pol. 2016;74:1174-9.

41. Galetta F, Franzoni F, Magagna A, Femia FR, Pentimone F, Santoro G, *et al.* Effect of nebivolol on QT dispersion in hypertensive patients with left ventricular hypertrophy. Biomed Pharmacother. 2005;59:15-9.

42. Nazeri A, Elayda MA, Segura AM, Stainback RF, Nathan J, Lee VV, *et al.* Comparative Efficacy of Nebivolol and Metoprolol to Prevent Tachycardia-Induced Cardiomyopathy in a Porcine Model. Tex Heart Inst J. 2016;43:477-81.

43. Ptaszynski P, Kaczmarek K, Ruta J, Klingenheben T, Cygankiewicz I, Wranicz JK. Ivabradine in combination with metoprolol succinate in the treatment of inappropriate sinus tachycardia. J Cardiovasc Pharmacol Ther. 2013;18:338-44.

44. Fu Q, Vangundy TB, Shibata S, Auchus RJ, Williams GH, Levine BD. Exercise training versus propranolol in the treatment of the postural orthostatic tachycardia syndrome. Hypertension. 2011;58:167-75.

45. Arsura E, Lefkin AS, Scher DL, Solar M, Tessler S. A randomized, double-blind, placebo-controlled study of verapamil and metoprolol in treatment of multifocal atrial tachycardia. Am J Med. 1988;85:519-24.

46. IC Van Gelder, M Rienstra, HJ Crijns, B Olshansky. Rate control in atrial fibrillation. Lancet. 2016;388:818-28.

47. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, *et al.* 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J. 2021;42:373-498.

48. Flather MD, Shibata MC, Coats AJ, Van Veldhuisen DJ, Parkhomenko A, Borbola J, *et al.* Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J. 2005;26:215-25.

49. Nasr IA, Bouzamondo A, Hulot JS, Dubourg O, Le Heuzey JY, Lechat P. Prevention of atrial fibrillation onset by beta-blocker treatment in heart failure: a meta-analysis. Eur Heart J. 2007;28:457-62.

50. Zeppenfeld K, Tfelt-Hansen J, de Riva M, Winkel BG, Behr ER, Blom NA, *et al.* 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Eur Heart J. 2022;43:3997-4126.

51. Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, *et al.* Executive summary: HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. Heart Rhythm. 2013;10:e85-e108.

52. Peltenburg PJ, Kallas D, Bos JM, Lieve KVV, Franciosi S, Roston TM, *et al.* An International Multicenter Cohort Study on β-Blockers for the Treatment of Symptomatic Children With Catecholaminergic Polymorphic Ventricular Tachycardia. Circulation. 2022;145:333-44.