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Review

Beta-blockers in Cardiovascular Therapy: A Review

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Abstract

The role of beta-adrenergic receptor antagonists in cardiovascular therapy has been the subject of various studies over time, these agents representing one of the oldest class of drugs used for the treatment of cardiovascular diseases. Although beta-blockers have been excluded from guidelines as the first-line therapy in essential hypertension, they remain the first choice in patients with heart failure, coronary artery disease, and atrial fibrillation. In this article, we review the major clinical evidence for the use of beta-blockers in cardiovascular diseases.

Several trials have demonstrated that beta-blockers reduce mortality in patients with heart failure with a reduced ejection fraction. Also, beta-blockers have beneficial properties in patients with heart failure with preserved ejection fraction. Guidelines recommend beta-blockers for the relief of symptoms in cases of angina pectoris and for the control of the ventricular rate in cases of atrial fibrillation. Also, beta-blockers have numerous benefits in hypertensive patients with diabetes mellitus. In conclusion, beta-blockers are an important class of cardiovascular drugs, reducing the mortality and morbidity rates in patients with cardiovascular diseases.

Keywords

: beta-blockers, cardiovascular disease, hypertension, coronary artery disease

Highlights

- ✓ Beta-adrenoreceptor antagonists (beta-blockers) are an important class of cardiovascular medications, used for decades in patients with arterial hypertension, chronic heart failure, and coronary artery disease, representing the cornerstone therapy.
- ✓ Guidelines recommend beta-blockers for the relief of symptoms in cases of angina pectoris and in the control of the ventricular rate in cases of atrial fibrillation.

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Introduction

Beta-adrenoreceptor antagonists (beta-blockers) are an important class of cardiovascular medication, used for decades in patients with arterial hypertension, chronic heart failure, and coronary artery disease, representing the cornerstone therapy in these cases (1). Studies have consistently demonstrated that agents such as bisoprolol, carvedilol, and metoprolol reduce hospitalizations in patients diagnosed with heart failure NYHA functional class II to IV (2). Beta-blockers also represent the first-line therapy in patients with hypertension associated with heart failure and/or coronary artery disease (3).

Discussions

Mechanisms of action

Beta-adrenoreceptor antagonists reduce the activity of the sympathetic nervous system through the blockade of beta-receptors, such as beta1-, beta2- and beta3 receptors (1) (Table 1).

Beta1-adrenergic receptors are found preferentially in the heart and the renal juxtaglomerular apparatus. Beta1-receptors have less influence on vascular muscles (4). The blockade of this subtype of beta-receptors results in bradycardia and increased diastolic coronary filling time, with reduced heart oxygen requirement. These effects are beneficial in cases of heart failure and myocardial ischemia (5). Bisoprolol and nebivolol are the agents with the highest beta1 selectivity effect (3).

Beta2-adrenergic receptors are found in the smooth muscles of the blood vessels, their stimulation resulting in vasodilation (6).

Beta3-adrenergic receptors are localized in the heart and adipocytes, their blockade with nonselective beta-receptor antagonists result in weight gain and other metabolic effects, such as hyperglycemia (5).

Cardioselectivity, or beta1- and beta2- receptor selectivity, is the characteristic of beta-receptor antagonists to block beta1 or beta 2 adrenergic receptors preferentially. Atenolol and bisoprolol are cardioselective beta-blockers, having an affinity for beta1-adrenergic receptors (7). These subtypes of beta1-receptors are associated with reduced cardiac output and also with reduced heart rate and contractility (6). The Medical Research Council for the treatment of hypertension in the elderly conducted a randomized trial which enrolled 4,396 hypertensive patients treated with atenolol. In this trial, atenolol was associated with a significant reduction in cardiovascular events over a period of 5 years (8).

The Metoprolol Atherosclerosis Prevention in Hypertensives (MAPHY) study was a trial on 3,234 hypertensive patients investigating the effects of metoprolol in reducing cardiovascular complications of hypertension compared to thiazide diuretics. Patients who received metoprolol had a lower risk of experiencing cardiovascular events, compared to patients treated with a thiazide diuretic (9).

Table 1. Classification of beta-blockers (2)

Non-selective beta-blockers (both beta1- and beta 2- receptor antagonism)	Propranolol Carvedilol (with additional alfa1-receptor blocking activity) Labetalol (with additional alfa1-receptor blocking activity) Nadolol Pindolol Sotalol Timolol
Beta1-selective beta-blockers	Bisoprolol Metoprolol Nebivolol Esmolol Acebutolol Atenolol

The third generation of beta-receptor antagonists, such as carvedilol, labetalol, and nebivolol, have vasodilating effects (10). Carvedilol and labetalol have vasodilating effects through the association of alpha-receptor blockade and the result is represented by a decreased peripheral vascular resistance (3). These vasodilating properties are associated with other effects such as decreased ventricular preload and afterload (6).

Messerli et al. noticed that beta-blockers are associated with metabolic disorders, such as weight gain and an increased incidence of new-onset diabetes (11). In 2007, in a meta-analysis which included 94,492 patients treated with beta-blockers, Bangalore et al demonstrated that beta-receptor antagonists are associated with low insulin sensitivity, 22% of patients treated with beta-blockers being diagnosed with new-onset diabetes (12).

In 2009, Manrique et al. also reported that beta-blockers are associated with erectile dysfunctions in up to 20% of the patients treated with beta-blockers (13).

Beta-blockers in heart failure

The administration of beta-blockers is recommended in patients with heart failure, these agents being associated with lower mortality and morbidity rates (7). Trials and

major studies with bisoprolol, carvedilol, and metoprolol, administered to patients diagnosed with heart failure, have revealed a decreasing incidence of mortality and morbidity (14).

Heart failure is associated with arterial hypertension. Bui et al. concluded that 75% of heart failure cases are preceded by hypertension (15). In a 2011 article on this topic, Gheorghiade et al. highlighted the importance of the use of beta-blockers in heart failure (16). The authors confirmed that beta-blockers reduce the heart rate, have anti-ischemic effects, and inhibit the release of angiotensin-converting enzymes (ACE) (14). Also, by blocking the sympathetic activity, beta-blockers are associated with the improvement of the ventricular function and of the hemodynamic parameters (7).

In 2003, a randomized trial by Nodari et al. noted that beta-blockers are associated with a decreased pressure in the pulmonary artery and improvement of the left ventricular ejection fraction in patients with diastolic heart failure (17). Moreover, the administration of beta-blockers to patients with heart failure for a long period of time has been associated with the improvement of hemodynamic parameters (16).

Guidelines of the European Society of Cardiology (ESC) and the American Heart Association (AHA) recommend the administration of beta-blockers associated with ACE inhibitors to reduce hospitalizations in patients with heart failure (18). Also, in cases of patients with heart failure and atrial fibrillation, beta-blockers are the first-line treatment to control the heart rate (10). Guidelines recommend the use of beta-blockers to reduce mortality in hypertensive patients who associate myocardial infarction in their history (11). The ESC guidelines on peripheral artery disease recommend beta-blockers for patients diagnosed with heart failure who associate peripheral artery disease, because symptoms of intermittent claudication are not affected by beta-blockers (19). However, in patients with peripheral arterial disease, the administration of selective beta-blockers with peripheral vasodilator action, such as nebivolol, is preferred. Also, nebivolol stimulates nitric oxide synthase, resulting in increased levels of nitric oxide, with vasodilating effects (16).

Randomized trials that investigated the effects of beta-blockers in heart failure demonstrated that these agents are associated with a decreased risk of mortality and hospitalizations (20).

The Cardiac Insufficiency Bisoprolol Study (CIBIS-II) was a randomized trial conducted in 1999 in Europe (21). This study enrolled 2,647 patients with heart failure

NYHA functional class III or IV with reduced ejection fraction, who were treated with bisoprolol. The trial was interrupted early because bisoprolol demonstrated a significant reduction in mortality, compared to placebo. This trial confirmed that in patients with heart failure, beta-blockers improve the left-ventricular function (20).

The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) was a trial performed on 2,289 patients diagnosed with heart failure and reduced ejection fraction (22). This study investigated the role of carvedilol in patients with systolic heart failure for a period of 10 months and observed that the use of carvedilol is associated with a relief of heart failure symptoms and decreased hospitalizations. The mortality rate in this study was reduced by 35% for patients treated with carvedilol (20).

Also, the Metoprolol Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF) was conducted between 1997-1998 and enrolled 3,991 patients diagnosed with heart failure NYHA functional class III-IV (23). This study investigated the role of metoprolol in addition to standard therapy in cases of heart failure. The results showed that metoprolol significantly reduced the mortality rate (24).

The Study on the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart failure (SENIORS) enrolled 2,128 patients over 70 years old, diagnosed with heart failure. This trial showed that nebivolol is associated with reduced mortality and morbidity and reduced hospitalization in 14% of the cases, compared to placebo (25).

The Carvedilol or Metoprolol European Trial (COMET) was a randomized controlled trial on 3,029 patients that compared the benefits of carvedilol or metoprolol in patients with chronic heart failure. The investigators observed that carvedilol reduces mortality of cardiovascular causes, the risk of sudden cardiac death, and the incidence of stroke and myocardial infarction, compared to metoprolol (26).

In a study by Bohm et al. in 2011, which enrolled patients with heart failure, it was noted that the administration of beta-blockers before admission to the hospital and after discharge was associated with lower mortality in patients with acute decompensation of heart failure (27).

Also, in cases of patients with heart failure with preserved ejection fraction, the ESC and AHA guidelines recommend the administration of beta-blockers (28). Studies on this topic have demonstrated that beta-blockers are associated with reduced mortality in these cases (25).

Moreover, a meta-analysis on this topic conducted by Bavishi et al. in 2015 noted that beta-blockers are associated with reduced mortality in patients with heart failure (29).

Beta-blockers in arterial hypertension and diabetes

It is well known that hypertension is associated with an increased risk of heart failure, stroke, and renal disease, and thus, a good therapeutic control of blood pressure is essential (30).

The Medical Research Council for the treatment of hypertension in the elderly conducted a trial on 4,396 hypertensive patients treated with hydrochlorothiazide or atenolol (31). This trial found that hydrochlorothiazide is associated with a lower risk of cardiovascular events than atenolol (20). On the other hand, the Heart Attack Primary Prevention in Hypertension (HAPPHY) trial, performed on 6,569 patients, compared the benefits of the use of diuretics versus beta-blockers in hypertensive patients. This study showed no additional benefits between beta-blockers versus thiazide diuretics in cardiovascular prognosis (32).

Also, atenolol was compared to losartan in the Losartan Intervention for Endpoint Reduction (LIFE) trial, performed on 9,193 hypertensive patients. In this trial, the beneficial effects of atenolol compared to losartan in hypertensive patients with left ventricular hypertrophy were investigated, with results showing no differences between the two groups (33).

Studies demonstrated that metoprolol has more benefits in hypertensive patients (34). The Metoprolol Atherosclerosis Prevention in Hypertensives (MAPHY) trial, which investigated the benefits of metoprolol versus thiazide diuretics in hypertensive patients with risk factors for coronary disease discovered that the treatment with metoprolol in these cases reduces the risk of coronary events. The results showed that treatment with metoprolol is associated with a lower incidence of cardiovascular events (35).

Diabetes mellitus is associated with an increased risk of developing cardiovascular diseases and the association with hypertension doubles the risk. In patients with diabetes mellitus, the risk of heart diseases is two times higher compared to patients without diabetes (36).

The ESC and AHA guidelines recommend all classes of antihypertensive therapy in hypertensive patients who associate diabetes mellitus. Also, beta-blockers are recommended in diabetic patients with acute myocardial infarction (29). In diabetic patients with prior myocardial infarction, beta-blockers reduce the incidence of arrhythmias, sudden cardiac death, and the recurrence of cardiac ischemic events (37). Kjekshus et al. discovered

that diabetic patients treated with beta-blockers have a 10% mortality rate compared to 23% in patients who are not receiving beta-blockers (38). Guidelines recommend the use of beta-blockers in patients with diabetes and heart failure to reduce hospitalization and mortality (36).

Although beta-blockers have negative metabolic effects, with increased insulin resistance, guidelines recommend the administration of beta-blockers in diabetic patients because the adverse metabolic effects are fewer than the benefits in these cases (39). Trials on this issue found that a good control of hypertension is more important in these patients, having macrovascular and microvascular benefits (40). The UK Prospective Diabetes Study investigated the effects of blood pressure control in hypertensive patients who associate diabetes, after 9 years of follow-up. In this study, the administration of atenolol was associated with a lower risk of microvascular and macrovascular complications in 32% of the cases (41).

Beta-blockers and coronary artery disease

Beta-blockers represent the main class of drugs in patients with coronary artery disease, having multiple benefits. The effects of beta-blockers in these cases are based on their negative inotropic and chronotropic properties. Beta-blockers reduce heart rate, contractility, and systolic blood pressure, resulting in reduced myocardial oxygen requirements. Also, beta-blockers prolong the diastolic filling time, with improved coronary perfusion (42). Beta-blockers increase the perfusion of the hibernating ischemic myocardial areas and reduce the myocardial wall stress, with a low risk of myocardial rupture after acute myocardial infarction (38, 43).

In patients diagnosed with angina pectoris, beta-blockers are the essential treatment, reducing the symptoms and preventing cardiovascular events. Beta-blockers are recommended for the control of angina symptoms in patients with coronary artery disease (44, 45).

Beta-receptor antagonists are recommended in patients with silent ischemia and with a large area of ischemic myocardial tissue (42). Also, beta-blockers are used in cases of microvascular angina. Cardioselective beta₁-receptor antagonists are used most frequently in patients diagnosed with coronary artery disease (37).

A study performed in 2001 by Gotlieb et al., which enrolled 69,000 patients with prior myocardial infarction treated with beta-blockers, demonstrated that the use of beta-receptor antagonists was associated with increased survival rates in 40% of the patients (46). It was noticed that in cases of stable angina pectoris, the use of beta-blockers is associated with symptom relief.

A meta-analysis conducted by Huang et al. in 2012 assessed the impact of beta-blockers on the mortality rate in cases of stable angina pectoris and concluded that cardioselective beta-blockers improve survival rates (47).

Data from the literature state that beta-blockers have a protective role regarding the recurrence of cardiovascular ischemic events (48). In an analysis performed by Bangalore et al. in 2014, patients with prior myocardial infarction treated with beta-blockers were at lower risk of recurrent myocardial infarction, although the mortality rates were not improved (49).

The COMMIT trial (CIOpidogrel and Metoprolol in Myocardial Infarction Trial) was a randomized trial which investigated the role of intravenous and oral administration of metoprolol in 45,852 patients with acute myocardial infarction from 1,250 hospitals in China, between 1999-2005 (50). This trial showed that the early use of beta-blockers in acute myocardial infarction reduces the rates of re-infarction and ventricular arrhythmia, but the risk of cardiogenic shock remains high (49), especially in patients above 70 years old, with a systolic blood pressure <120 mmHg and in patients with myocardial infarction Killip class III (31).

Also, beta-blockers have beneficial effects in patients with acute myocardial infarction and heart failure with a reduced ejection fraction. CAPRICORN (CARvedilol Post-Infarct SurvIval COntRolled evaluationN) was a 2001 trial enrolling 1,959 patients from 17 countries, with a follow-up of 1.3 years (50). This trial investigated the effect of carvedilol after myocardial infarction in patients with left ventricular dysfunction, demonstrating that the treatment with carvedilol was associated with decreased mortality in these cases (51).

Beta-blockers and heart rate control

Atrial fibrillation is the most common arrhythmia in clinical practice and it is associated with increased risks of morbidity and mortality. Hypertension, ischemic cardiomyopathy, valvular disease, and thyroid diseases are risk factors for the development of atrial fibrillation (27, 52, 53).

Beta-adrenergic receptor antagonists are included in class II antiarrhythmic agents. Their benefit in atrial fibrillation is the ventricular rate control. They act by blocking the effects of catecholamine hormones on beta1-adrenergic receptors, resulting in a decreased sympathetic activity of the heart. Also, beta-blockers decrease the atrioventricular conduction through the atrioventricular node (33).

The ESC guidelines recommend that patients with atrial fibrillation be treated with beta-blockers in order to

achieve ventricular rate control and to regulate the irregular heart rhythm (50). The oral administration of beta-blockers is recommended to control the ventricular rate in patients with persistent or permanent atrial fibrillation (54).

Also, beta-blockers are recommended for the prevention of atrial fibrillation in patients with hypertrophic cardiomyopathy. The AHA guidelines recommend the use of beta-blockers to control the ventricular rate in patients with heart failure and acute coronary syndrome, without high risks of cardiogenic shock (55).

The AFFIRM trial (the Atrial Fibrillation Follow-up Investigation of Rhythm Management) was a multicenter trial, which enrolled 4,060 patients diagnosed with non-valvular atrial fibrillation (56). This trial compared rate-control and rhythm-control strategies for the treatment of atrial fibrillation. The results showed that beta-blockers have beneficial effects for the ventricular rate control in 70% of patients with atrial fibrillation (57).

Conclusions

The benefit of the use of beta-blockers in cardiovascular diseases has been confirmed in numerous trials. These trials have demonstrated that beta-blockers reduce mortality in patients with heart failure with a reduced ejection fraction. Also, beta-blockers have beneficial properties in patients with heart failure with preserved ejection fraction. Guidelines recommend beta-blockers for the relief of symptoms in cases of angina pectoris and for the control of the ventricular rate in cases of atrial fibrillation. Also, beta-blockers have numerous benefits in hypertensive patients with diabetes mellitus. In conclusion, beta-blockers are an important class of cardiovascular drugs, reducing the mortality and morbidity rates in patients with cardiovascular diseases.

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Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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