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Original Article

Effect of Beta-blockers on Hypertension and Heart Failure with Reduced Ejection Fraction: A Systematic Review of Randomized Controlled Trials

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Abstract

Background: Beta-blockers have long been used as the treatment for hypertension (HTN) with comorbidities such as heart failure (HF), angina, and myocardial infarction. Numerous clinical trials showed the effects of beta-blockers to prolong life and to relieve symptoms. In particular, four particular beta-blockers – namely metoprolol, carvedilol, bisoprolol, and nebivolol, have been shown to have salutary effects in HF patients. **Objectives:** We evaluated the effects of these four beta-blockers in patients with HTN and HF with reduced ejection fraction (HFrEF). **Methods:** We carried out a systematic literature search in PubMed and Cochrane for randomized controlled trials on the use of beta-blockers in HTN and HFrEF in reducing hospitalization, morbidity, and mortality. **Conclusion:** The beneficial effects of metoprolol, carvedilol, bisoprolol, and nebivolol primarily stem from their attenuation of sympathetic nervous system (SNS) activity that prevents further cardiac structural changes and dysfunction, as seen in relation to uncontrolled HTN. However, other effects such as antioxidant and anti-endothelin effects possessed by carvedilol and the enhanced secretion of nitric oxide with nebivolol are also being attributed to having protective and beneficial outcomes on HF patients.

Keywords: Adrenergic beta-blockers, beta-antagonists, beta-blockers, bisoprolol, carvedilol, congestive heart failure, hypertension, metoprolol, nebivolol

Research Question

Among adults with hypertension (HTN) and heart failure (HF) with reduced ejection fraction (HFrEF), how effective are beta-blockers in reducing the rates of hospitalization, morbidity, and mortality? [Figure 1].

Significance of the study

With the current guidelines in the management of HTN with HFrEF, there is no specific recommendation, on which particular beta-blocker is recommended. With this study, the researchers aimed to be able to recommend which specific beta-blockers can be recommended in HTN with HFrEF patients.

Objectives

General objective

The general objective of this study was to evaluate the effects of the different beta-blockers in patients with HTN and HFrEF.

Specific objectives

The specific objectives of this study were as follows:

- To discuss the pathophysiologic mechanisms behind the development of HTN and HF
- To determine which beta-blockers are effective in reducing rates of hospitalization, morbidity, and mortality among hypertensive patients with HFrEF.

Materials and Methods

Study selection

The authors searched for randomized control trials on PubMed Database and Cochrane central register of controlled trials. The following keywords were used: HTN, HF, congestive HF (CHF), beta-blockers, adrenergic beta-blockers, and beta-antagonists. Particular studies were selected according to the set inclusion criteria.

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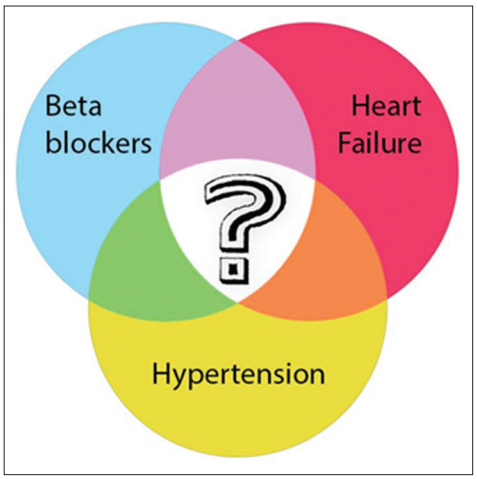

Figure 1: The research question probes the effectivity of beta-blockers in adults with hypertension with concomitant HF

Inclusion criteria

The researchers included studies fulfilling all of the following criteria:

- Randomized
- Controlled with placebo or active treatment agents
- Double or single blinding
- Diagnosis of HTN and HFrEF in the study group
- Published in PubMed or Cochrane within the past 50 years.

Background of the Study

Pathogenesis of HTN

The maintenance of a normal arterial blood pressure (BP) is essential for organ perfusion. This involves a number of physiological mechanisms primarily the plasma volume, autonomic nervous system, and renin-angiotensin-aldosterone system.[1] In cardiovascular physiology, BP is determined by the product of cardiac output (CO) and total peripheral resistance (TPR).

$$BP = CO \times TPR \qquad \text{Equation (1)}$$

Derangements in said mechanisms, along with genetic and environmental factors, result in HTN, which is characterized usually by a normal CO and an increased TPR.[2] In early HTN, however, TPR is not increased but due to the sympathomimetic overactivity, the BP goes up. There is an increased CO to which the rise in TPR acts as a response to prevent transmission of high pressure to the capillary bed that could cause cell apoptosis. If left untreated, TPR is further increased, resulting to increased pressure load and trophic effects such as volume load and growth factors such as catecholamines and angiotensin II.[2]

HTN and HF

HTN is considered the second most common risk factor in the development of HF, alongside myocardial infarction (MI).[3] The former is considered pertinent due to its worldwide prevalence and a three-fold increase in risk for the development of HF.[4] In the case of uncontrolled and long-standing HTN, the decrease in CO and thus development of HF is brought about by increase in afterload and a decrease in venous capacitance.[5-7] Chronic HTN then causes pressure-mediated cardiac remodeling with the left ventricular hypertrophy (LVH), left ventricular stiffness, and ultimately diastolic dysfunction.[8] Consequences of LVH can lead to cardiomyopathy with reduced myocardial contractility and impaired cardiac reserve and cardiac arrhythmias (single premature contractions and dysrhythmias),[9-11] all of which cause further decrease in CO and worsening of HF [Figure 2].

While MI and HTN are separate risk factors for HF, there is a link between the latter and MI, due to the high frequency (30–40%) of associated coronary risk factors such as dyslipidemia, diabetes, smoking, and obesity observed in hypertensive patients.[4]

History of beta-blockers

Beta-blockers remain to be the most widely used therapeutic drug in both non-cardiac and cardiac conditions. It was first introduced into clinical medicine in 1964 by Sir James Black and approved by the US Food and Drug Administration in 1973 for the treatment of angina.[12,13] Since then, a myriad of beta-blockers has been available in the market as part of a physician's armamentarium in treating cardiovascular diseases, particularly HTN and HF.

Types of beta-blockers

Beta-blockers are divided into two main categories: Beta-1 selective blockers and non-selective beta-blockers (with effects to beta-2 receptors). Two studies by Wong and Wright depicting efficacy of both beta-1 selective blockers and non-selective beta-blockers have shown to be able to reduce BP compared to placebo, but their results are not significant with each other.[14,15]

As deduced from Table 1, four of 20 beta-blockers seen in this study are mainly used in the management of HF.

Pharmacologic properties of beta-blockers

Blockade of beta-adrenergic receptors (AR) fundamentally interferes with the sympathetic regulation of the heart by mediating the effects of catecholamines (e.g., norepinephrine and epinephrine). At rest, beta-blocker administration minimally affects heart rate and contractility, but on exertion, it significantly suppresses the increase in heart rate and contractility induced by exertion [Figure 3].[17] There are at least three distinct types of beta receptors: beta-1, beta-2, and beta-3.[18,19] The stimulation of beta-1 receptors found in heart muscle, increases heart rate, contractility and atrioventricular conduction, and decreases AV node refractoriness. Stimulation of beta-2 receptors found in heart muscle but more prominent in bronchial and peripheral vascular smooth muscle, vasodilates the blood vessels, and bronchodilates the lungs. Beta-3, found in adipose tissue and heart muscle, may reduce cardiac contractility and mediate catecholamine-induced thermogenesis, i.e., by utilization of brown adipose tissue.[20,21]

Table 1: Types of beta-blockers[16,17]

Drug	Adrenergic receptor blocking activity	Intrinsic sympathomimetic activity (partial agonist)	Membrane stabilizing activity	Congestive heart failure (reduced ejection fraction)
Acebutolol	B1	+	+[2]	–
Alprenolol	B1 and B2	+	+	–
Atenolol	B1	–	–	–
Betaxolol	B1	–	+	–
Bisoprolol	B1	–	–	+
Bupranolol	B1 and B2	–	–	–
Carteolol	B1 and B2	++	–	–
Carvedilol	B1, B2, and A1	–	++	+
Celiprolol	B1	+	–	–
Esmolol	B1	–	–	–
Labetalol	B1, B2, and A1	+	±	–
Metoprolol	B1	–	±[2]	+
Nadolol	B1 and B2	–	–	–
Nebivolol	B1	–	–	+
Oxprenolol	B1 and B2	+	+	–
Penbutolol	B1 and B2	+	–	–
Pindolol	B1 and B2	+++	±	–
Propranolol	B1 and B2	–	++	–
Sotalol	B1 and B2	–	–	–
Timolol	B1 and B2	–	±	–

(-) No activity [1]Inhibits B2-receptors (bronchial and vascular) at higher doses. (+) Low Activity [2]Only detectable at higher doses than needed for Beta-blockade. ++ Moderate activity. +++ High activity. ± No/low activity

In a non-failing heart, 80% of the expressed adrenoreceptors are beta-1 and 20% are beta-2; the ratio becomes almost equal in a failing heart when beta-1 receptors are downregulated correlating with the severity of the heart disease.[21] On the other hand, myocardial beta-3 receptors, present both in the atria and ventricles, are overexpressed in HF and HTN [Figure 4].[22] Stimulation of beta-3 receptors may decrease cyclic adenosine monophosphate (cAMP) generation, thereby reducing cardiac contractility, which is in contrast to the stimulation of beta-1 and beta-2 receptors that increase cAMP levels. Despite the potential for beta-receptor exploitation for many heart disease, for all practical purposes, so far, beta-1 and beta-2 receptor blockers have been the only target for clinical application [Table 2].[23]

There have been recent studies that aim to prove the importance of beta-3 overstimulation in HF patients and its importance in providing a "break in inotropic stimulation."[24] This still newly studied mechanism of β3-AR stimulation involves the use of nitric oxide (NO) release through NO synthase activation, with its mechanism still unclear.[25] As discussed earlier, β3-AR is upregulated in failing hearts in both human and animal models. According to Cannavo and Koch, beta-blocker usage helps in blocking the effects of catecholamines and prevents further β1 and β2-ARs downregulation, while increasing the activity of β3-ARs.

Table 2: Novel mechanisms of selected beta-blockers that may have an effect in reducing the effects of heart failure with reduced ejection fraction in hypertensive patients[28-30]

Beta-blocker	Beta-3 adrenergic receptor action	Generation of NO
Metoprolol	Upregulation	Yes
Carvedilol	Downregulation	No
Nebivolol	Upregulation	Yes
Bisoprolol	No	No

NO: Nitric oxide

Further studies are being underway to determine the specific properties of currently used beta-blockers in the market and if there are any changes to β3-AR utilization.[26] A study by Zhao *et al.* showed that metoprolol (selective β1-blocker) showed no change in β3-AR yet small doses of the same drug are shown to improve long-term outcomes in patients with CHF, while carvedilol (non-selective β1-blocker) showed β3-AR downregulation.[27] A study by Sharma *et al.*, however, showed the use of metoprolol in improving cardiac function by enhancing the β3-AR upregulation and NO generation.[28] Nebivolol in recent years has also showed activated cardiac β3-ARs, leading to a significant reduction of infarct size and reduce cardiac fibrosis and apoptosis.[29,30]

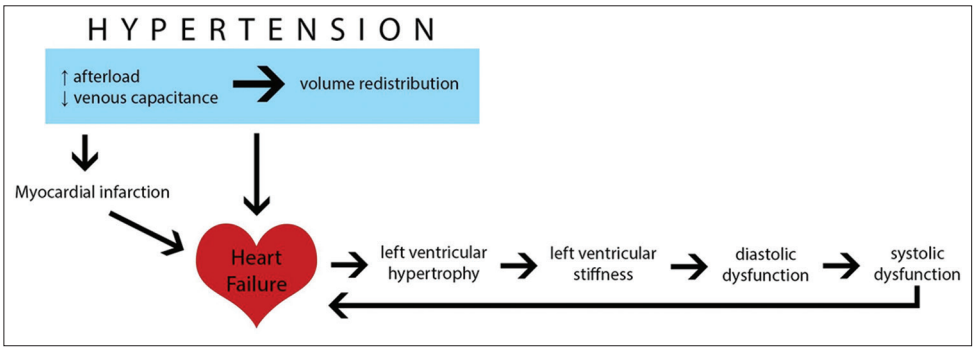

Figure 2: Graphic representation of how hypertension would lead to heart failure and subsequent negative effects

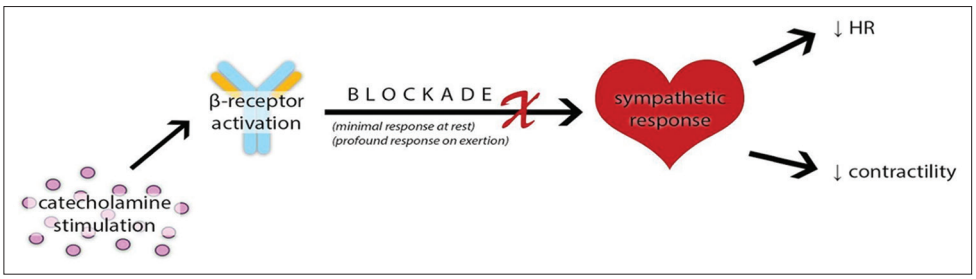

Figure 3: Manifestation on how catecholamine blockade though its receptor would lead to the blunting of sympathetic response of the heart

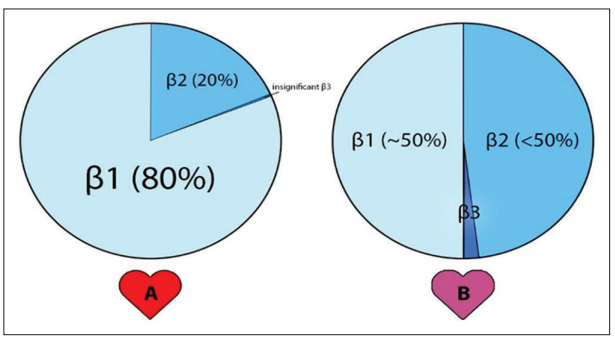

Figure 4: The pie graph represents the theoretical amount of beta-receptors in a normal heart (a) and a diseased heart (b) note that in a diseased heart, the number of beta-1 and beta-2 receptors are close to equal, with detectable values of beta-3 receptors[24]

In a study by Cleland *et al.*, wherein 11 randomized multinational clinical studies were evaluated for the treatment of HF, it was found out that beta-blockers improve left ventricular systolic function and reduce cardiovascular morbidity and mortality for patients with HF and left ventricular ejection fraction (LVEF) of < 40% in sinus rhythm; however, the said benefits are not seen for patients with LVEF of >/= 50%.[31]

Metoprolol

Metoprolol, initially marketed in 1967, is a beta-1 selective antagonist and is one of the known beta-blockers to have proven benefit when given in HF patients, along with bisoprolol and carvedilol. It was found to have a protective effect on sudden death in hypertensive patients as well as prevention of sudden death post-MI primarily through its antifibrillatory effect. This improved beta-blockade may confer some protection to the disappearance of vagal tone and sudden sympathetic nervous system (SNS) activity that causes ventricular fibrillation and therefore sudden death.[32] There are only two studies which have evaluated the efficacy of beta-blockade with survival being the predefined endpoint in HF. These are the Metoprolol CR/XL Randomized Intervention in CHF (MERIT-HF) study and the Cardiac Insufficiency Bisoprolol Study II (CIBIS II). The two beta-blockers in the said studies are both lipophilic and are highly beta-1 selective antagonist. Looking at the results of these two studies, death due to worsening of the HF was significantly decreased with beta-1 blockade.[33]

Bisoprolol

Similar salutary effects in HF were shown in the CIBIS II trial, wherein the positive effect of bisoprolol, initially marketed in 2000, was demonstrated on all-cause mortality. This was primarily attributed to its antiarrhythmic effect through prevention of alteration in cardiac structure and function, which is seen in hypertensive patients as indicated by having progressive increase in the left ventricular mass and decline in CO as the disease progresses. Theoretically speaking, blockade of both beta-1 and 2 adrenoreceptors should confer better cardiac protection and prevention of arrhythmia through inhibition of catecholaminergic effects. However, it was found that blocking beta-1 receptors are enough to prevent fatal arrhythmia and ultimately decrease the rate of sudden death.[34]

Carvedilol

Carvedilol, marketed in 1995, is unlike bisoprolol and metoprolol since it blocks both beta-1 and beta-2 receptors, as well as alpha-1 receptors. This added blockade can provide additional benefit in preventing adverse outcomes of the SNS through the noradrenergic mechanisms. This added blockade was shown to have favorable outcomes in patients who are classified to be in New York Heart Association Functional Class III or IV. A possible explanation is that carvedilol, aside from having additional adrenergic blocking activities, also has antioxidant activity and anti-endothelin effects which can attenuate the SNS effects on the circulatory system. In a study evaluating the efficacy of carvedilol on survival in patients with severe chronic HF, the investigators have shown that previously reported salutary effects of carvedilol on morbidity and mortality in patients with mild-to-moderate HF were again noted in patients with severe HF enrolled in this trial.[35]

Nebivolol

Nebivolol, marketed in 2008, has peripheral vasodilating properties mediated by the modulation of the endogenous production of NO, thereby causing endothelium-dependent relaxation. It acutely lowers BP and reduces peripheral vascular resistance with an increase in stroke volume but without compromising left ventricular function. HTN is characterized by progressive stiffening of the ventricle that leads to diastolic dysfunction or HF, and nebivolol plays a central role by causing higher diastolic peak filling rates which means that there is more ventricular distensibility and relaxation that causes improved CO.[36]

Particularly in HF secondary to coronary artery disease, nebivolol decreases BP and heart rate through beta-1 blockade that is then compensated by an increase in stroke volume. Another novel characteristic of nebivolol is that it protects blood vessels from atherosclerosis by significantly increasing wall distensibility and compliance. In the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with HF (SENIORS), wherein patients of age >70 years with HF were enrolled, regardless of the initial ejection fraction, a decreased rates of mortality and morbidity were demonstrated.[37]

Conclusion

The beneficial effects of metoprolol, carvedilol, bisoprolol, and nebivolol primarily stems from their attenuation of SNS activity that prevents further cardiac structural changes and dysfunction, as seen in relation to uncontrolled HTN that causes LVH and impaired CO. However, other effects such as antioxidant and anti-endothelin effects possessed by carvedilol, and the enhanced secretion of NO with nebivolol is also being attributed to having protective and beneficial outcomes on HF patients.

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