

Beta Blockers in the Management of Hypertension

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ABSTRACT

Hypertension, a prevalent condition increases the risk of stroke and coronary heart diseases. Rising rates and associated complications makes treatment of hypertension very important. Evidence clearly shows that effective reduction of blood pressure decreases the incidence of cardiovascular morbidity and mortality. Beta blockers have been used in the management of hypertension for several years, but with increasing options and accumulating evidence, their use as initial treatment is questioned. However, beta blockers play an important role in select patient population. In this article, overview of beta blockers in the treatment of hypertension is discussed.

Introduction :

Non-communicable diseases, majorly contributed by cardiovascular diseases are significant global concern worldwide. Hypertension is one of the most prevalent cardiovascular conditions across the world including in India. Literature review of studies from India suggests significant increase in prevalence of hypertension over last few years. The current prevalence of hypertension is about 25% and 10-15% among adults from urban and rural population respectively¹. High blood pressure increases the risk of life-threatening events such as stroke and coronary heart disease². Compared with normal people, patients with uncontrolled hypertension have higher prevalence of atrial fibrillation³. In addition to the risk of complication, the rates of hypertension and associated burden are expected to rise in coming years⁴. Considering the high prevalence of hypertension and risk of complications, effective management of hypertension is very important. Effective reduction of blood pressure helps to decrease cardiovascular morbidity and mortality⁴. Different interventions including lifestyle, pharmacotherapy with antihypertensive agents and, and lipid lowering agents are useful in reducing blood pressure and

cardiovascular risk⁵. Several classes of drugs including diuretics, calcium channel blockers (CCBs), rennin angiotensin aldosterone system (RAAS) blockers i.e. angiotensin converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor blockers (ARBs) and beta-blockers are available for the management of hypertension. The older approach of step-up care in which diuretics and beta-blockers were recommended as first line agents has changed today touse of combination therapy in low doses. This approach is mainly adapted because of the better efficacy and tolerability. Use of high dose of single agent is thus usually avoided. Several such combination products are available in India⁵.

In this article we discuss the overview of beta blockers including their benefits and limitations in the treatment of hypertension and the patient profile which benefits from beta blockers.

Beta blockers in the management of hypertension :

Beta blockers are one of the oldest antihypertensive medicines available for the treatment of hypertension. These agents have better tolerability compared to previous options such as centrally acting drugs and ganglion blockers. The better safety profile favored use of beta blockers over older agents. Moreover, beta blockers also offer an advantage in other cardiovascular diseases⁶.

Classification of beta-blockers :

Beta blockers differ in their pharmacological properties such as lipophilicity, receptor specificity

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and elimination half-life⁷. Overall, beta blockers can be broadly divided into three classes; first generation, second generation and third generation agents (**Table 1**). Similarly, these agents can also be classified as non-selective and selective beta blockers. The first generation agents are non-selective and lack vasodilatory property.⁸ The examples of selective agents are atenolol, acebutolol, betaxolol, bisoprolol, celiprolol, esmolol, metoprolol and nebivolol^{9,10}. Nebivolol, carvedilol and acebutolol also have vasodilatory property⁸.

Table 1 : Classification of beta blockers

First generation	Second generation	Third generation
Nadolol	Acebutolol	Carteolol
Penbutolol	Atenolol	Carvedilol
Pindolol	Betaxolol	Celiprolol
Propranolol	Bisoprolol	Labetalol
Timolol	Esmolol	Nebivolol
	Metoprolol	

Nebivolol is a third generation agent with vasodilatory properties. Compared to the older beta blockers, nebivolol has better pharmacological profile including metabolic, hemodynamic and tolerability effects. Due to vasodilatory effect, it may have beneficial effects in many hypertensive patients⁴.

Mechanism of action of beta blockers in hypertension :

Beta-blockers are effective agents for the treatment of primary hypertension as well as isolated systolic hypertension. Several mechanisms of antihypertensive actions have been postulated including reduction in the heart rate, decreased myocardial contraction and reduced cardiac output, inhibition of rennin release, inhibition of sympathetic outflow resulting in decreased release and pressor effects of catecholamines¹⁰.

Efficacy of beta-blockers in hypertension :

Beta-blockers have been extensively studied in the management of hypertension. Some of the major clinical trials with beta blockers are discussed in this section. The MRC trial¹¹ evaluated effect of propranolol, diuretic (bendrofluazide) and placebo

in adult patients between the age group of 35-64 years with mild hypertension. The treatment with both active agents reduced incidence of stroke, but not the coronary event rate. Reduction in stroke rate was significantly better with bendrofluazide compared to propranolol. Reduction in stroke rate was seen in only among non-smokers receiving propranolol. The second landmark study i.e. Heart Attack Primary Prevention in Hypertension (HAPPHY) trial¹² compared effects of diuretics versus beta blockers. In this study, there was no difference in the blood pressure reduction, incidence of coronary heart disease or incidence of diabetes between two groups. The incidence of fatal stroke was slightly lower with beta-blockers. Another study i.e. MAPHY study compared metoprolol versus thiazide diuretics as initial treatment in patients between 40-64 years of age. Reduction in blood pressure was similar in both groups. However, total mortality rate in patients receiving metoprolol was significantly lower primarily because of lower mortality due to coronary heart disease and stroke¹³.

The Medical Research Council trial¹⁴ conducted to examine whether diuretic or atenolol reduced risk of stroke, coronary heart disease, and mortality among hypertensive older adults. Atenolol and diuretic both reduced blood pressure better than placebo group. Similarly, reduction in stroke, coronary events and all cardiovascular events with active treatment was 25%, 19% and 17% respectively. Diuretic group performed better in reducing risk of these events compared with the placebo whereas beta blocker had no significant effects.

The Swedish Trial in Old Patients with Hypertension (STOP-Hypertension)¹⁵ compared effects beta-blockers and diuretic versus placebo. This trial demonstrated benefits of antihypertensive treatment in elderly population in terms of significant reductions in cardiovascular morbidity and mortality and total mortality. The UK Prospective Diabetes Study (UKPDS)¹⁶ showed equally effective blood pressure reduction with captopril and atenolol. Both agents were also similar in reducing the risk of macrovascular end points. The results highlight the fact that control of blood

pressure may be more important than the class of antihypertensive medicine prescribed.

The International Verapamil-Trandolapril Study (INVEST)¹⁷ comparing outcomes of calcium channel blocker versus non-calcium antagonist strategy in patients with hypertension and coronary artery disease showed similar results with both therapies.

Overall, beta blockers show better effects compared to placebo. The above studies also demonstrate effectiveness and safety of beta blockers versus other therapies such as diuretics and calcium channel blockers in the treatment of hypertension. A meta-analysis showed 19% reduction in the risk of stroke for all beta blockers¹⁸.

With accumulating evidence and clinical experience, use of beta blockers especially the older agents as initial treatment of hypertension is questioned. Nevertheless, beta blockers still have an important role in the treatment of hypertension in selected patient population.

Studies casting doubt on the use of beta-blockers in hypertension :

Several comparative studies versus other antihypertensive agents and meta-analyses conducted over the years cast doubts about the use of first line agents in the treatment of hypertension. A meta-analysis assessing comparative efficacy of beta-blockers versus diuretics in elderly hypertensives showed better efficacy of diuretics in preventing cerebrovascular events, fetal strokes, coronary heart disease and cardiovascular as well as all-cause mortality. This meta-analysis suggested that beta blockers should not be considered as first-line therapy for the treatment of uncomplicated hypertension in the elderly patients.¹⁹

Later in 2002, the LIFE study (Losartan Intervention For Endpoint reduction in hypertension study),²⁰ a large randomized trial among patients with essential hypertension between 55 to 80 years of compared once daily losartan-based therapy versus atenolol-based therapy. The results of this study showed that losartan is better in preventing cardiovascular morbidity and mortality compared to atenolol.

Losartan also was found to be better tolerated.

A comprehensive review and meta-analysis conducted by Carlberg B and colleagues²¹ showed that there was no major difference in blood pressure lowering between atenolol and other active treatments. The findings suggested higher mortality with atenolol compared to other active treatment²¹. Another meta-analysis demonstrated better effects of beta blockers compared to placebo or no treatment. However, when compared to other drugs, the relative risk of stroke was more with beta blockers¹⁸. A Cochrane review performed to evaluate overall benefits of beta-blockers on morbidity and mortality in adults with hypertension demonstrated that starting treatment with beta-blockers results in modest benefits in terms of reduced cardiovascular disease but without significant benefits on mortality. Beta-blockers are found to be inferior other antihypertensive agents in these regards²². These data negatively highlights beta blockers in the management of hypertension. However, some points are worth mentioning before making conclusive statements about beta blockers in the management of hypertension. It must be remembered that heterogeneity i.e. individual differences within different beta blockers is well known.

Trials comparing active treatment versus either placebo or no treatment show almost similar benefits of blood pressure reduction with different drugs such as diuretics, beta-blockers, angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers².

The data which mainly raised the doubts on the efficacy of beta blockers in the management of hypertension is derived mainly from older agents such as atenolol propranolol and metoprolol⁷.

These older agents are devoid of vasodilatory properties. Moreover, atenolol was used as once daily instead of multiple dose administration required considering its pharmacokinetic and pharmacodynamic profile. Atenolol taken once daily may not provide protection against raised blood pressure for 24 hours^{10,23}.

A large study in treatment naïve hypertensive patients without hypertension-related complication treated with beta blocker monotherapy showed better treatment persistence in non-atenolol group compared to atenolol. The patients treated with atenolol had earlier treatment discontinuation whereas new - beta blockers had lower risk of treatment discontinuation as compared with atenolol. Betaxolol performed poorer compared to atenolol in terms of risk of discontinuation²⁴.

A recent meta-analysis has shown that beta-blockers significantly reduce arterial stiffness, peripheral blood pressure and heart rate compared to placebo. Comparison with ACE inhibitors or angiotensin receptor blockers show less favorable impact of beta blockers on blood pressure and arterial stiffness but better effect on the heart rate²⁵.

Currently outcome data from large studies on newer agents like carvedilol and nebivolol is lacking. Studies evaluating effects of these agents with vasodilatory properties and better metabolic profile on cardiovascular events are required in order to make definite conclusive statements on the complete class of beta-blockers²⁶.

Beta blockers in renal diseases :

Beta blockers can reduce cardiovascular mortality in patients with renal disease. Moreover, they also have renal benefits which could be important in patients with chronic renal disease. Recently it has been shown that beta blockers may reduce or prevent progression of renal impairment in people having hypertension, diabetes, and renovascular disease possibly because of reduced renal oxygen consumption.²⁷ In patients with chronic kidney disease beta blockers can be used as second line therapy after agents acting on rennin-angiotensin system²⁸.

In another study, use of beta-blocker for the treatment of hypertension in surgically managed patient did not show association with the risk of progression or death from renal cell carcinoma²⁹.

Safety and tolerability of beta blockers :

Choice of antihypertensive drugs depends on

several factors. One of the important factors is risk of adverse events resulting in discontinuation of adverse events. Every class of antihypertensive medicine is associated with treatment discontinuation; however the risk differs between different classes.

Beta blockers may be associated with adverse events such as lethargy / fatigue, depression, sleep disturbances, aggravation of asthma and side effects related to peripheral blood vessels²⁶. Tolerability of beta blockers in elderly people is generally poor compared to other antihypertensive agents²⁶. Hyperglycemia and increased risk of diabetes is another concern with use of beta blockers in patients with hypertension. Beta blockers can also adversely affect blood glucose and mask the episode of hypoglycemia, requiring careful use in patients with diabetes³⁰. A meta-analysis of data involving 94,492 hypertensive patients receiving treatment with beta blockers showed higher risk of new-onset diabetes mellitus compared to other non-diuretic antihypertensive drugs³¹. Several mechanisms including increase in body weight, reduced blood flow to skeletal-muscle tissue resulting in impaired glucose uptake and dyslipidemia have been suggested to play a role in the development of diabetes. Beta blockers may increase insulin resistance and increase the risk of diabetes.²⁶ A meta-analysis showed higher risk of discontinuation with beta blockers compared to other classes such as diuretics, calcium channel blockers, drugs acting on renin angiotensin aldosterone system. Angiotensin receptor blockers are favored drugs because of the lesser risk of adverse events³².

Like diuretics, beta-blockers may raise serum uric acid levels; hence they should be cautiously used in patients with gout or those with increased risk of gout³³.

Current place of beta blockers in the management of hypertension :

According to the current literature review and guidelines beta-blockers are not the first line agents for the treatment of hypertension. As per the Joint National Committee (JNC) 8 report, they are the

reserve drugs for the management of hypertension post-myocardial infarction and congestive heart failure³⁰.

Despite controversy, beta-blockers still has an important place in the management of hypertension³⁴ for certain patient populations especially those with comorbid conditions such as coronary heart disease, recent history of myocardial infarction, arrhythmia, atrial fibrillation, chronic stable heart failure, resistant hypertension, thyrotoxicosis, migraine, essential tremors^{6,35,36}. Beta blockers may be a valuable option for treatment of hypertension in patients with these comorbidities.

In general population of hypertensive patients, lower blood pressure is associated with the lower risk of coronary events. Beta blockers are the best antihypertensives for use in patients with history of recent myocardial infarction.³⁷ Similarly, during last few years there has been increase in use of beta blockers in treatment resistant hypertension³⁵.

Beta-blockers are useful antihypertensive agents for patients with resting tachycardia. The benefits offers by beta-blockers in these patients include reduction in pulse rate, reduced myocardial contraction, oxygen consumption and prevention of arrhythmias. They also reduce exercise induced hypertension²³.

In patients under age of 60 years, beta blockers may provide similar benefits like other agents in terms of reduction in mortality, stroke or myocardial infarction. The risk of beta blockers is more in elderly population. Younger population does not have excess risk with beta-blockers⁷. So, beta-blockers may be preferred in younger population compared to elderly.

Patients undergoing non-cardiac vascular surgery are another important population who can get benefits with the use of beta-1 selective blockers. These agents have potential to decrease peri-operative mortality and non-fatal heart attacks³⁶. Considering these benefits patients receiving beta blockers for conditions such as coronary artery disease or tachyarrhythmias should continue using them because stopping beta-blockers before surgery could be harmful³⁸.

Considering the differences in the pharmacological profile of different beta-blockers, highly beta1 selective blockers would be better for hypertension management because of their lower propensity to cause adverse events on pulmonary system³⁶.

Conclusion :

Despite controversy, beta blockers hold an important place in the management of hypertension. Though they are not recommended as first line agent in patients with uncomplicated hypertension, their role in specific patient populations (e.g. those with pre-existing heart disease) and drug resistant hypertension is important. Considering potential heterogeneity in the members, complete class of beta-blockers should not be neglected in the management of hypertension. It is difficult at the moment to generalize effects of older agents to the complete class of beta blockers and dismiss of them in the treatment of hypertension. Newer agent may show promise for early use in the management of hypertension because of its different pharmacodynamics and tolerability profile. Larger outcomes with newer beta-blockers are required to confirm the benefits.

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