

Beta Blockers are Good Choice as First line Antihypertensive Agents

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ABSTRACT

Beta blockers are in use for more than 3 decades in the treatment of hypertension and are still recommended as first line agents by some of the national and international guidelines. Since beta blockers are heterogenous class of agents with diverse pharmacologic properties, the unfavorable data revealed in the recent meta-analysis is from studies involving the traditional beta blockers (propranolol, atenolol) which are non vasodilating. The vasodilating beta blockers (carvedilol, nebivolol, bisoprolol) reduce blood pressure through reduction of systemic vascular resistance rather than decreasing cardiac output as is seen with traditional beta blockers.

Traditional beta blockers have adverse effects on metabolic and lipid parameters whereas vasodilating beta blockers have neutral or beneficial effects on metabolic and lipid parameters. Vasodilator beta blockers lower BP to a similar degree as other antihypertensive drugs. They also provide better central aortic pressure reduction than traditional beta blockers.

It is unlikely that there will be a single first line drug for hypertensives as most patients will eventually require multiple drugs to control their blood pressure. The choice of treatment will be influenced by associated co-morbidities, underlying cardiovascular risk factors, age of the patient and potential adverse effects. (J Clin Prev Cardiol. 2013;2(2):101-5)

Keywords: Beta blockers, Hypertension

Introduction

For more than 3 decades beta blockers have been widely used in the treatment of hypertension and are still recommended as first line agents (1,2). Beta blockers have been in use not only in hypertension but in other cardiovascular conditions. Since long period, beta blockers have assumed a guideline-recommended treatment option for hypertension. However, recent meta-analyses have questioned whether beta blockers are an appropriate therapy given outcomes data for other antihypertensive drug classes. Much of the unfavorable reports were from studies involving non vasodilating, traditional beta blockers such as atenolol. Vasodilatory beta blockers (carvedilol, nebivolol, bisoprolol) reduce blood pressure (BP) by reducing systemic vascular resistance while maintaining cardiac output rather than reducing cardiac output as is observed in atenolol, propranolol. Vasodilatation may also ameliorate adverse effects on metabolic and lipid parameters including an increased risk for new onset diabetes. In patients with

hypertension and diabetes or coronary artery disease, vasodilating beta blockers cause effective BP control with neutral or beneficial effects on important parameters for the comorbid disease (3).

Although traditional beta blockers effectively lower brachial (arm) BP, recent clinical data suggests that they are less effective in reducing central aortic pressure compared with other antihypertensive drugs (4). Increased central aortic pressure has been associated with an increased risk for vascular events, especially stroke. Traditional beta blockers have associated side effects in particular fatigue and sexual dysfunction. However, vasodilator beta blockers have very few side effects comparable to placebo.

Pseudo-antihypertensive Efficacy

Traditional beta blockers are not only less efficacious at reducing arm blood pressure but also have a lesser effect on important central aortic pressure when compared with RAAS blockers, diuretics and calcium antagonists.

In the CAFÉ (Conduit Artery Functional End Point) study (5) for the same peripheral blood pressure, a 4.3 mmHg greater central aortic systolic pressure and 3.0 mmHg greater central aortic pulse pressure was noted with atenolol based treatment compared with the amlodopine-based treatment. The study results

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also strongly suggest that central aortic systolic blood pressure may be more predictive of cardiovascular events like myocardial infarction and stroke, than the brachial blood pressure measurements. Considering this discrepancy between arm and central blood pressure, the antihypertensive effect of beta-blockers can be best described as a ‘pseudo antihypertensive’ efficacy.

Beta Blockers in Hypertension and Other Cardiovascular Indications

Bangalore *et al.* (6) in their review critically analyzed the evidence supporting the use of beta blockers with hypertension and evaluate the evidence for its role in other indications. Given the increased risk of stroke, their “pseudo antihypertensive” efficacy (failure to lower critical aortic pressure), lack of effect on regression of target end organ effects like left ventricular hypertrophy and endothelial dysfunction, the risk benefit ratio for beta blockers is not desirable. However, beta blockers remain very efficacious agents for the treatment of heart failure, certain types of arrhythmias, hypertrophic obstructive cardiomyopathy and in patients with prior myocardial infarction.

Giles *et al.* (7) in their correspondence article, “beta blockers therapy in hypertension - A need to pause and reflect”, have emphasized that most of the evidence summarized by Bangalore *et al.* (6) concerns studies of atenolol. However, the authors did not stress the point that less favorable clinical outcomes seen with atenolol versus other therapies might be due to an absence of 24 hours efficacy as atenolol was used 50 mg once daily. In fact, the INVEST (International Verapamil-Trandolapril Study) (8) showed no difference in outcomes between a beta blocker and calcium antagonist, because in this trial atenolol was given twice daily. Similarly, data from UKPDS (United Kingdom Prospective Study) (9) also showed atenolol given twice daily to have efficacy similar to an ACE-inhibitor in preventing cardiovascular complications in hypertensive diabetic patients.

Drugs for First line Treatment in Hypertension

National and International guidelines recognize five classes of drugs for the first-line treatment of hypertension – beta blockers, diuretics, angiotension converting enzyme inhibitors, angiotension receptor blockers and calcium channel blockers. However, achieving a lower BP is more important than a choice of drugs used in

the treatment. Many patients will need more than one drug to achieve the desired level. Beta blockers remain important and effective drugs but age and co-morbidities need to be considered when selecting a first line of drug. In younger patients, beta blockers should remain the first line anti-hypertensive drug. There are different types of beta blockers. (Table 1).

Table 1.

Classes of beta blockers

Action	Adrenergic Selectivity	Examples
Non-selective	beta1 and beta2	propranolol Sotalol*
Selective	beta1 >beta2	atenolol Metoprolol, Succinate Metoprolol Tartrate (sustained release) bisoprolol
Non-selective and vasodilating	beta1, beta2 and alpha1	labetalol carvedilol
Non-selective and vasodilating (nitric oxide pathway)	beta1 and beta2	nebivolol

*used primarily as a class III antiarrhythmic drug

Joint National Committee (JNC)

Beta blockers along with diuretics were regarded as the preferred first line treatment from 1984-1997 (JNC III to VI). The JNC VII recommends beta blockers as first line treatment for ‘compelling’ indications on an equal basis with calcium antagonists, RAAS blockers (2).

European society for hypertension/European society of cardiology

European society for hypertension/European society of cardiology (ESH/ESC) guidelines published in 2008 maintain beta blockers as first line therapy for hypertension. They also recommend beta blockers as suitable drugs for initiation and maintenance of blood pressure treatment. Furthermore, ESH/ESC and the American College of Clinical Endocrinologists recognize the difference between vasodilatory beta blockers and traditional beta blockers in patients with metabolic risk factors. Beta blockers, particularly vasodilating beta blockers, will continue to play a critical role in treatment of hypertension hence it will be a mistake to dismiss the entire class (7).

Khan and McAlister (10) in their meta-analyses of beta blockers as first line therapy for hypertension, confirm that they should not be used in older patients (age >60

years) if they do not have another indication for those agents such as heart failure, post myocardial infarction (MI) or symptomatic coronary artery disease. They recommend use of beta blockers as first line therapy in younger patients without contraindications or prior intolerance to thiazide diuretics. In younger patients, beta blockers are associated with a significant reduction in cardiovascular morbidity and mortality.

Khan and McAlister¹⁰ organized their meta-analysis according to different age groups. The primary outcome was a composite of stroke, MI and death. They identified 32 randomized controlled trials that evaluated the efficacy of beta blockers as first line therapy for hypertension in preventing major cardiovascular outcomes. Trials on older (>60 years) patients were separated from those younger (mean age >60 years) patients. On analysis they found in placebo controlled trials, beta blockers reduced major cardiovascular events in younger patients by 14% but not in older patients. In active comparative trials, beta blockers showed efficacy similar to that of other antihypertensive drugs in younger patients. Hence they recommend that beta blockers should be used as first line drug of choice in younger patients but not in elderly.

Vasodilatory Beta Blockers

The peripheral vasodilation reduces cardiac after load and preload and reverses adverse arterial remodeling (stiffness) (11).

Carvedilol

Carvedilol is a vasodilating third generation beta blocker without the negative hemodynamic and metabolic effects of traditional beta blockers, which can be used as cardioprotective agent. Compared with traditional beta blockers, carvedilol maintains cardiac output, has a reduced prolonged effect on heart rate and lowers BP by decreasing vascular resistance. It also has favored effects on metabolic and lipid metabolism suggesting that it could be considered for treatment of hypertensive patients with metabolic syndrome or diabetes mellitus (12).

Nebivolol

Nebivolol reduces systemic vascular resistance through stimulation of nitric oxide release (13). It is safe and well tolerated. In an open 6 week trial in 6,356 cases of mild hypertension (DBP-90-115 mmHg), and mean SBP of 162 mmHg, nebivolol (5-10 mg daily) significantly reduced mean SBP and DBP from baseline (-24 and

-13 mmHg respectively, $p < 0.001$ for both) (3). In a meta-analysis of 12 randomized clinical trials in hypertension, achievement of BP target reduction with nebivolol was higher than that of ACE inhibitors and similar to that of other beta blockers, CCBs and losartan (14). Nebivolol is an alternative to other beta blockers used in heart failure but has less robust evidence of survival benefit. It is contraindicated in patients with hepatic impairment and should be avoided in severe renal failure. Stopping nebivolol abruptly can worsen heart failure or precipitate angina, MI or ventricular arrhythmias in patients with ischemic heart disease.

Bisoprolol

It is a selective type B1 adrenergic receptor blocker and is beneficial in the treatment of hypertension, ischemic heart disease, congestive heart failure, preventive treatment before and primary treatment after heart attack, decreasing the chance of recurrence (15).

Mechanism of action: It is cardioprotective because it selectively blocks catecholamine (adrenalin) stimulation of beta1 adrenergic receptors which are mainly found in heart muscle cells and heart conduction tissue but also found in juxtaglomerular cells in the kidney.

Bisoprolol decreases the adrenergic stimulation of heart muscle and pace maker cells (16). Betablockers can precipitate bronchial asthma. However, bisoprolol, metoprolol, nebivolol have less effect on the beta2 (bronchial) receptors and therefore relatively cardio selective. They have lesser effect on airways resistance but are not free of this side effect. Bisoprolol is used to treat cardiovascular diseases such as hypertension, coronary artery disease, arrhythmias and treatment of MI after the acute event. Bisoprolol should be started with low doses as it reduces also the muscular power of the heart (17). Bisoprolol has a higher degree of beta1 selectivity compared to other beta1 selective beta blockers however nebivolol is 3.5 times more beta-selective (18).

Labetalol

Labetalol is a nonselective beta blocker with alpha receptor-blocking activity and minimal intrinsic sympathomimetic activity. Therefore, it has been useful in hypertensive emergencies. Because of its safety, it is mainly used in hypertension during pregnancy. Labetalol is generally well tolerated in these clinical studies. On the basis of data from small clinical trials, labetalol is equally effective in lowering SBP and more effective in lowering 24-hour DBP compared to a CCB or ACE inhibitors (18).

Beta Blockers in Hypertension with Associated Co-morbidities

Beta blockers are used in patients of hypertension associated with diabetes mellitus, coronary artery disease and heart failure or in patients who have had MI (19). In these particular conditions, the effects of beta blockers on the myocardium itself may provide benefits beyond lowering BP (20).

Diabetes Mellitus

With traditional beta blockers, there is risk of new onset diabetes mellitus (DM). A meta analysis by Bangalore *et al.* (21) of 12 trials involving 94,492 hypertensive patients reported a 44% increased new onset DM risk with pooled data of atenolol and propranolol compared with placebo. However, vasodilatory beta blockers (carvedilol and nebivolol) have shown neutral or beneficial effects on metabolic parameters in patients with diabetes and hypertension (22,23). Additionally, carvedilol and nebivolol had no adverse effect on glycosylated hemoglobin.

However, the GEMINI (Glycemic effects in Diabetes Mellitus Carvedilol-Metoprolol comparison in hypertensives) trial (24), treatment of diabetics with metoprolol resulted in the increase in HbA1c, whereas treatment with carvedilol did not increase and carvedilol improved insulin resistance. Similarly nebivolol improved insulin resistance, proving the fact that not all beta blockers have same effect. In another GEMINI trial (25), patients on metoprolol had significant weight gain but patients on carvedilol did not, stressing the point that all beta blockers are not the same.

Coronary artery disease

American Heart Association (AHA) recommends a BP of <130/80 mm Hg for patients associated with coronary artery disease. Treatment of coronary artery disease is recommended because beta blockers not only reduce BP but also decrease myocardial oxygen demand (25). Because of amelioration of rest and hyperemic coronary blood flow, vasodilatory beta blockers are a better option than traditional beta blockers in patients with high coronary risk.

Post myocardial infarction

AHA guidelines recommend beta blockers in hemodynamically hypertensive patients after MI (19).

Among the vasodilatory beta blockers, only carvedilol is indicated for patients with post MI left ventricular dysfunction (26).

Effects on left ventricular hypertrophy (LVH) regression

Left ventricular hypertrophy is a strong predictor of cardiovascular mortality and morbidity and its regression lowers the risk, independent of blood pressure lowering effect (27). In a meta-analysis of 104 studies comparing the various anti-hypertension treatments on LVH regression, beta blockers caused the least LVH regression compared with RAAS blockers, calcium antagonists and diuretics. Beta blockers unlike RAAS blockers, do not decrease collagen content in the myocardium and hence are not that effective in LVH regression (28).

Heart failure

Beta blockers specifically bisoprolol, metoprolol succinate and carvedilol improve systolic heart failure by inhibiting the negative stress associated with sympathetic nervous system activation. Fonarow *et al.* (29) have shown that risk for mortality and rehospitalization are significantly lower in patients with LVF who continue beta blockers after discharge compared to patients not continuing beta blockers treatment.

Chronic heart failure

Many studies have shown a substantial reduction in the mortality rate (-30%) and morbidity with beta blockers as well as improvement in symptoms and the patient's well being (30). Particularly, bisoprolol, metoprolol and nebivolol have shown good results. Multiple meta-analysis have echoed this observation, showing mortality benefit in the overall cohort (31).

Conclusion

There are intrinsic differences among members of beta blockers. Actually, vasodilatory beta blockers lower BP to a similar degree as other antihypertensive drugs. They also provide better control on aortic pressure reduction than traditional beta blockers and have favorable or neutral metabolic effects. Actually as per recent recommendations, most patients will require multiple drugs to achieve BP goals. In patients with co-morbidities, combination therapy will be essential to achieve lower goals. Hence while addressing the question of beta blockers' effectiveness, the answer lies

not in global generalizations but in assessing individual patients and specific beta blocking agents (3).

It is unlikely that there will be a single first line drug for hypertensives as most patients will eventually need multiple drugs to control their blood pressure. Treatment has to be individualized for all patients. The choice of treatment should be influenced by underlying cardiovascular risk factors, co-morbidities and potential adverse effects but also by the age of patient.

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