Beta Blockers in Hypertension: Taking the Back Seat?

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Introduction

It was in 1960s when Sir James W. Black, working with Imperial Chemical Industries (a British pharmaceutical company) developed Beta-Blockers. He was honored with Nobel Prize for his discoveries (1). Since that time Beta Blockers have benefited millions of patients with Ischemic heart disease. Beta blockers are used in myocardial infarction, chronic ischemic heart disease, hypertension, thyrotoxicosis and for somatic manifestation of anxiety disorders. Thus these are one of the most prescribed class of drugs in United States, with four different Beta blockers in top 50 prescribed drugs (2). Most of guidelines by Joint National Committee (JNC) have recommended beta blockers as first line therapy for hypertension and same is recommended in JNC-VII report of 2003 (3). Thus beta blockers have remained first line therapy for about 30 years.

Evidence against Beta Blockers in Hypertension

It was in 1998 that Messerli et al raised some controversies regarding use of beta-blockers as first line treatment of hypertension (4). They observed significantly less benefit with beta blocker therapy versus diuretic based therapy. They found beta blockers ineffective for preventing coronary heart disease, cardiovascular mortality and all cause mortality. This was not referred to in JNC VII report which recommended diuretics as first line therapy with beta blockers as suitable alternative especially in heart failure and ischemic heart disease and diabetes mellitus. Messerli et al again recommended in 2003 to drafters of guidelines to review the role of beta blockers in uncomplicated hypertension (5).
British society of Hypertension in 2004 recommended AB/CD algorithm for treatment of hypertension. They recommended ACE inhibitors or ARBs (A) or beta blockers (B) for patients below 55 years of age and calcium channel blockers (C) or diuretics (D) for patients above 55 year age (6). It was in 2006 that British Hypertension Society modified the recommendations stating that “beta blockers are no longer preferred as a routine initial therapy for hypertension” (7). Similarly European society of Cardiology in 2007 again stated that beta blockers could be used as first line therapy.

In the more recent trials like the ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm) study of 19,257 patients with hypertension and at least 3 other coronary risk factors but no clinically overt coronary artery disease, Atenolol-based treatment resulted in a 14% greater risk of coronary events and 23% greater risk of stroke when compared with an amlodipine-based regimen (8).

In the meta-analysis by Lindholm et al. (9), in the studies comparing beta-blockers to placebo, beta-blockers resulted in a 19% reduction in stroke. However, when a sensitivity analysis was performed using only mixed beta-blocker/diuretics studies versus placebo, the beta-blocker arm suddenly became more efficacious. Similarly, in the comparison of beta-blockers with other antihypertensive agents, a sensitivity analysis of only the mixed beta-blocker/diuretics studies failed to show the increased risk of stroke observed when all studies were included. It therefore appears that most of the beneficial effects of these trials may be the result of the diuretics and hence these studies do not provide evidence to suggest the beneficial effect of beta-blockers.

Again in 2007 Bangalore along with Messerli and others published a critical review of beta blockers and cardiovascular protection (10). They observed a long list of side effects and disadvantages of beta blockers including 1) weight gain; 2) decrease in exercise tolerance; 3) precipitation of diabetes; 4) little effect on regression of left ventricular hypertrophy; 5) failure to improve endothelial function.

Carlberg et al (11) did meta-analysis of about 9 studies. This included 4 studies which compared Atenolol with placebo or no treatment and 5 studies which compared Atenolol with other antihypertensive drugs. There was no difference in outcome with Atenolol as compared to placebo as far as all cause mortality and myocardial infarction is concerned. While comparing Atenolol with other antihypertensive drugs, though there was comparable decrease in blood pressure there was higher mortality and incidence of strokes with Atenolol.

A recent paper by Bangalore et al (12) in which they went through data base search from 1966 to 2008 about beta blockers in treatment of hypertension included studies with data on heart rate and found higher mortality with
slower heart rate associated with beta blockers. A meta analysis of more than 94 thousand patients by Bangalore et al revealed 22% increased risk of new onset diabetes and 15% increased risk of stroke in patients receiving beta blockers (13).

With this evidence available beta blockers have lost their position as first line therapy in uncomplicated hypertension without compelling indication and should be used in cases with heart failure, post myocardial infarction and tachyarrhythmias only.

**Possible Reasons**

What could be the reasons of lesser benefits with beta blockers though these drugs decrease the blood pressure? Various reasons are.

1) Large number of side effects which could lead to decrease in adherence to medication.
2) Increased risk of new onset diabetes.
3) Pseudo-antihypertensive effect. Here we record decrease in brachial blood pressure as is seen in clinic but central aortic pressure does not fall proportionately. This was shown in CAFE (Conduit Artery Function Evaluation) study. In this study differential impact of blood pressure lowering drugs on central aortic pressure and clinical outcome was studied. Beta blockers (Atenolol) did lower brachial blood pressure without much effect on aortic blood pressure. It is the central aortic pressure which determines the outcome of treatment (14).
4) Most of these studies were with Atenolol and Metoprolol. Could these results be due to shorter half life of these drugs which does not result in smooth 24 hr blood pressure control?
5) Also these beta blockers have no peripheral vasodilating effect as is is seen in newer generation beta blockers e.g. Carvidilol and Nebivolol. These newer beta blockers may not have pseudo-antihypertensive effect due to vasodilatory action, but needs evidence.

**Conclusion**

It is at present appropriate to desist from using beta blockers as first line treatment for uncomplicated hypertension and should not be used as reference drugs in future randomized controlled trials of hypertension, but they still can be used as add on therapy in hypertension.

This evidence against beta blockers can not be blindly extrapolated to newer generation beta blockers like Carvidilol and Nebivolol which have vasodilatory properties and are unlikely to have pseudo-antihypertensive effect. Also data regarding theses beta blockers is still insufficient to discard these as well.

**References:**

Conflict of Interest: None

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