

Atenolol in Hypertension

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Introduction

World over hypertension remains one of the major risk factors for cardiovascular & cerebrovascular diseases. Its prevalence is increasing due to increasing longevity, obesity, changes in diet and a sedentary lifestyle coupled with stress. The WHO hypertension guidelines clearly point out that treatment of hypertension prevents cardiovascular diseases and extends life but hypertension remains poorly detected and even worse, poorly managed.

Beta blockers are among one of the safest and most effective antihypertensive drugs available. So impressive have been their utility in hypertension that all Joint National Committees (JNCs) from JNC 1 to the latest JNC7 have recommended betablockers as first line of therapy in hypertension. The discovery of betablockers in particular propranolol by Sir James Black in 1962 was described by the Nobel committee as the "greatest breakthrough in pharmaceuticals against heart illness since the discovery of Digitalis 2000 years ago".¹

Ever since the antiischemic, antihypertensive and antifailure properties of betablockers were discovered (in that order) there have been notable changes in our perspective and use of these agents. The anti-ischemic role is well accepted, the anti-failure properties are increasingly recognized but the antihypertensive role is being questioned.² The controversy over the use of betablockers as first line therapy in hypertension was fuelled by the new recommendations of the National Institute for Health and Clinical Excellence (NICE) in collaboration with the British Hypertension Society. They suggested that betablockers should not be preferred as first line of therapy, a combination of betablockers and diuretic puts the patient at an increased risk of diabetes, and in patients aged less than 55 years an ACE inhibitor or angiotensin receptor blocker is preferred.

Atenolol was first introduced in 1976 and has been approved by the US FDA from August 1981 as a therapeutic agent for both hypertension and coronary artery disease. Atenolol is one of the most commonly prescribed betablockers all over the world with more than 40 million prescriptions per year in the US alone.³

This article aims to address these controversies, in particular the effectiveness of atenolol in hypertension

Pharmacokinetics of Atenolol

Atenolol is a β_1 selective antagonist with lowest lipid solubility among all betablockers. It differs from Pindolol and Propranolol in that it does not have an intrinsic sympathomimetic action or membrane stabilising activity. It acts by competing with catecholamines for binding at β_1 adrenergic receptors in the heart and vascular smooth muscle, thus inhibiting sympathetic stimulation. This results in reduction in heart rate, cardiac output, systolic and diastolic blood pressure. Reduction in peripheral resistance is gradually seen with chronic therapy. Endocrine and metabolic actions of Atenolol include lowering of plasma renin activity and free fatty acid levels. Although Atenolol may prolong insulin-induced hypoglycemia, this is less than that of nonselective beta-blockers. Atenolol has a complex

effect on lipid metabolism; however, it's less than that of other nonselective betablockers. Betablockers have a little effect on LDL but do increase plasma VLDL and triglyceride levels and lower plasma HDL levels.⁴

Atenolol is hydrophilic, hence, relatively lower concentrations are found in brain tissue. Absorption after an oral dose is often incomplete and peak plasma levels are obtained 2 – 4 hours later. Although plasma, half life is 6 – 8 hours, it is increased in renal failure as the major route of excretion is through the kidneys.

Antihypertensive Effects

Atenolol lowers both systolic and diastolic blood pressures but postural hypotension is uncommon. The reduction in lying, standing and exercise BP is 15 – 20%. Most patients respond to a single oral dose of 50 mg daily. Higher doses of 100 and 200 mg do not significantly alter blood pressure levels. All beta blockers are not equally effective in lowering blood pressure. Beta 2 blockade by preventing beta 2 vasodilatory response may increase resting blood pressure. Thus non-selective agents like Propranolol and Nadolol are less effective than Atenolol in lowering BP. Atenolol is only moderately beta 1 selective, and at 100 mg it blocks 80% of β_1 receptors and 20% of β_2 receptors. On the other hand highly selective β_1 blockers like Bisoprolol are more effective in controlling BP, since they do not block beta 2 receptors.

As renin secretion is mediated via β_1 receptors, beta blockers reduce plasma renin in both normals and hypertensives.⁵ Atenolol and other beta blockers increase beta receptor sensitivity and triggers inhibitory responses at a lower BP. This results in a fall in mean blood pressure.

A 24 hour control of blood pressure is important particularly during the early morning times when BP peaks. The peak to trough BP control ratio over 24 hours of Atenolol is only 31% as compared to a 78% ratio of Bisoprolol, so patients are vulnerable in the early morning peak to adverse cardiovascular events.⁶

Review of Atenolol Trials

This is broadly divided into trials, which compared Atenolol to other antihypertensives and atenolol used in observational trial or vs placebo.

Atenolol vs Placebo Trials

The Medical Research Council trial for treatment of hypertension in older adults was a UK based randomized placebo controlled trial.⁷ Patients were randomized to atenolol 50 mg daily or hydrochlorothiazide plus amiloride and compared to a placebo. Results of this trial showed that compared to the placebo group the diuretic treated group significantly reduced stroke, coronary and all cardiovascular events. There was no significant reduction in these end points in the atenolol treated group. Hence atenolol was not effective in the older hypertensive age group. Subgroup analysis showed that control of blood pressure was poorer in smokers, especially in those randomized to atenolol, and active treatment with a drug reduced events only in nonsmokers. However, the percentage of smokers was similar in the diuretic and atenolol treated groups.

The Dutch TIA trial study group was a double-blind placebo controlled-randomized trial in which 1473 patients being treated for TIA with aspirin were given 50mg of atenolol or a placebo and followed up for 2.6 years.⁸ The objective was to find out whether 50 mg of atenolol/day reduced death from vascular events like stroke or myocardial infarction when compared to a placebo. Analysis of the results showed that atenolol did not have any favorable effect on the primary or secondary outcome events. There was trend towards a lower incidence of fatal or nonfatal stroke and a higher incidence of adverse cardiac events in the atenolol treated group. The authors concluded that in patients with TIA / nondisabling stroke, atenolol did not prevent important vascular events.

David Blackburn and associates conducted a retrospective cohort study in Saskatchewan Canada on the use of atenolol as the initial antihypertensive agent.⁹ This was an observational trial and 3 other cohorts included were thiazide diuretics, a calcium blocker and an ACE inhibitor. The study was done to see whether Atenolol was associated with an increased risk for cardiovascular morbidity and mortality. Authors found that compared with the other 3 drugs, Atenolol treated patients had a similar clinical outcome, with no increase in adverse events.

The HEP trial was a randomized controlled study in which elderly hypertensives in the age group 60-79 years were treated with Atenolol and compared to placebo.¹⁰ The mean follow up was for 4.4 years and thiazide diuretics were added to 60% of patients in the Atenolol group. There was a 30% reduction in stroke in the Atenolol treated group.

The TEST trial was a Swedish multicentre study in patients who had a recent TIA / stroke.¹¹ The effect of Atenolol and placebo in reducing death, MI and stroke was analyzed. 10% of patients who were on Atenolol therapy withdraw due to side effects of atenolol. This study failed to show any statistical significant reduction in death or a repeat stroke. There was a favorable trend in the atenolol treated group in reducing MI and overall mortality (statistically nonsignificant).

Trials Comparing Atenolol with Other Antihypertensives

These include the UKPDS, ELSA, HAPPHY, LIFE, STOP, CONVINCENCE and INVEST trials. The study by Savoia et al used Atenolol as add on therapy to other antihypertensives. Other trials of relevance being discussed are post hoc analysis of Life trial by Fyhrquist et al and Cruickshank et al's study with Atenolol in moderate to severe hypertensive patients.

UKPDS – a prospective randomized trial included 1148 mild to moderate hypertensive patients with Type II diabetes and a mean age of 56 years.¹² 2 groups of patients with tight and less tight control of blood pressure were analyzed at the end of 8 years. In the "tight" BP control group, patients were assigned to either Captopril or Atenolol. Results of the study showed that there was a trend to superiority of Atenolol over Captopril in reducing both primary and secondary end points including all cause mortality, cardiovascular mortality, peripheral vascular disease and microvascular disease.

The ELSA trial was a fairly large European trial which was conducted over a 4 year period and hypertensive patients were treated either with Lacidipine or Atenolol.¹³ The carotid internal medial thickness and plaques in the carotid arteries were analyzed. There was no significant difference in cardiovascular events in both treatment arms though plaque regression and

reduction in intimal medial thickness, was more in the Lacidipine treated group.

The HAPPHY trial compared Beta blockers Atenolol and Metoprolol to a diuretic in patients with mild to moderate hypertension. The incidence of fatal stroke was slightly lower in the beta blocker treated arm. Total mortality and cardiovascular events were same in both groups. The incidence of fatal and non-fatal coronary artery disease was slightly higher in the Atenolol treated group (statistically insignificant)

In the LIFE trial patients with hypertension and ECG signs of left ventricular hypertrophy (LVH) were treated with Atenolol or Losartan with an option of add-on therapy with a diuretic.¹⁵ Patients were followed up for a mean of 4.7 years. The study showed clearly Losartan was superior to Atenolol in reducing all cause and cardiovascular mortality and new onset diabetes. This is despite similar BP lowering effects of both drugs. Importantly the benefit of Losartan was more in the elderly hypertensives.

The STOP hypertension trial was a prospective randomized multicentre trial conducted in Sweden in 1627 elderly patients with hypertension.¹⁶ Metoprolol controlled release, Atenolol, Pindolol and a diuretic were compared. All drugs were equally effective in lowering Diastolic BP. However the diuretics were more effective in lowering systolic BP. Among the beta blockers, Pindolol was more potent in lowering systolic BP, but Atenolol was more effective in reducing HR.

Cruickshank et al, studied 939 patients with moderate to severe hypertension who were followed upto 10 years and treated with Atenolol with add-on therapy of diuretics, with or without vasodilators.¹⁷ Stroke mortality was reduced by 50%, LVH was reversed and all-cause and MI related mortality reduced.

The INVEST study was a large trial involving 22576 patients with hypertension and coronary artery disease (CAD) treated with Verapamil sustained-release or Atenolol.¹⁸ If required, add-on therapy with Trandolapril or diuretic was allowed. Both groups were equally effective in lowering blood pressure, and clinical outcomes including death, non-fatal MI and stroke were similar in all group at end of two years.

The CONVINCENCE trial compared Verapamil to Atenolol or diuretic in hypertensive patients.¹⁹ It was a multicentre trial involving 15 countries involving 16,602 participants. Reduction in systolic and diastolic BP was similar in all groups. The primary outcome including stroke, MI and cardiovascular death were similar in both groups. They proved that Atenolol was as effective as Verapamil. However, there was statistically insignificant trend of 18% lower incidence of acute MI and 15% higher incidence of stroke in the Verapamil treated group.

The ASCOT – BPLA trial again was a large trial involving 19,257 hypertensive patients in the 4th – 7th decade.²⁰ Patients either received Amlodipine or Atenolol. Option of add-on therapy with Doxazocine was available. There was no difference between the two groups in primary end-point, non-fatal and fatal MI. Both systolic and diastolic BP was better lowered with Amlodipine. With regard to the secondary and tertiary end points Amlodipine was superior in reducing cardiovascular events, cardiac mortality and new onset diabetes.

Discussion

Meta-analysis of the studies, which compared Atenolol to placebo revealed there was no differences in outcome between Atenolol and placebo with respect to all-cause mortality,

cardiovascular mortality or myocardial infarction.²¹ This is despite significant differences in BP lowering in favor of Atenolol. The stroke risk was lower in the Atenolol group compared to the non-treated groups. In fact in the HEP trial there was a 43% reduction in stroke in the Atenolol group compared to placebo.¹⁰ But 60% of the patients in the Atenolol treated arm had added on treatments with other antihypertensives and only 20% of patients had Atenolol as monotherapy.

The MRC trial of treatment in older hypertensives showed active therapy with diuretics or Atenolol would significantly reduce cardiovascular events compared to a placebo.⁷ However, the diuretic was more effective than Atenolol in spite of the adverse lipid effects like elevation of LDL cholesterol. They may have been due to a better BP lowering effect of the diuretics. Interestingly, the lack of a cardio-protective effect of Atenolol was also seen in the HAPPHY study.¹⁴ On subgroup analysis it was evident that lowering of BP was important in reducing adverse events. In the MRC trial, control of BP in smokers assigned to the Atenolol arm was definitely poor. This may have affected the final result of the study. The stroke risk in the Atenolol group was 2 – 4 times that of the diuretic group but a small reduction in stroke was seen in nonsmokers.

Blackburn et al in their study compared Atenolol to diuretic, ACE inhibitor and calcium blockers. The mean age of the patients in their study was 60 years. They found that Atenolol was equally effective as the other drugs and not associated with any adverse cardiovascular events. The HEP trial in elderly hypertensives showed that treatment with Atenolol resulted in a 30% reduction in stroke. Needless to say 60% of patients treated with atenolol had a diuretic added subsequently.

In the Dutch TIA trial again Atenolol had no clear benefit in reducing adverse events like stroke and cardiac events. But the number of patients enrolled in the Atenolol arm was only 732 and it is difficult to draw conclusions from such a small study group. Secondly, the patients enrolled in the Atenolol arm were at lower risks for vascular events as patients with diabetes and heart failure were excluded. Only 25% of patients in Atenolol group had history of hypertension vs 50% in the placebo group. So annual risk for a combined adverse effect was more in the latter group. Finally, at end of 3 years only 64% in the surviving group were taking Atenolol. Twice as many patients in the atenolol group stopped medication compared to placebo due to side effects. This would have definitely affected the results.

The ASCOT BPL trial, which compared Amlodipine to Atenolol found with regard to the primary end point of all cause mortality, non-fatal MI and fatal coronary artery disease both the drugs were equally effective.²⁰ Secondary and tertiary end-points for cardiovascular outcomes were in favour of Amlodipine. The drawbacks of the trial were that it had an open label therapy that would have influenced treatment of patients and documentation of events. Next, the test was prematurely terminated without prospectively publishing the criteria for termination of the study. This would make the results non-interpretable.

Among the comparative trials of Atenolol, the UKPDS and CONVINC trials were favourable and INVEST trial did not show a clear advantage of Atenolol over Verapamil. The LIFE, ASCOT BPL & STOP hypertension trials showed a less favourable outcome in atenolol treated patients. The TEST and the HEP trial were the only observational trials of Atenolol, which showed a favourable outcome.

In diabetic patients with hypertension, 2 studies compared atenolol to an ACE inhibitor / ARB. In LIFE trial Atenolol was

compared to losartan and in UKPDS Atenolol was compared to Captopril. Divergent results came out. UKPDS had a comparatively younger age group (mean age 56 years) vs the LIFE in which the mean age was 67 years. In the LIFE trial both drugs were equally effective in lowering BP but all cause mortality and primary end points were less in Losartan group. Losartan had lesser side effects than Atenolol and ECG evidence of LVH regressed with Losartan. In contrast, the UKPDS showed a trend towards less primary outcomes in the atenolol group. This included diabetes-related total mortality, stroke, MI and both macro and micro vascular disease. Tight control of BP with either Captopril or Atenolol reduced both macrovascular and microvascular complications. Both drugs are equally effective in reducing fatal and nonfatal complications of diabetes and heart failure. There were no additional renoprotective effects of Captopril compared to Atenolol. All though HbA1C increased initially in Atenolol group, at end of 9 years levels were near similar in both groups.

Conclusion

Young hypertensive patients have a relatively compliant peripheral vasculature. They have high plasma renin activity and increased sympathetic tone. Atenolol effectively reduces plasma renin activity and, by its betablocking effect reduces the effect of circulating catecholamines on target organs. This could explain the efficacy of atenolol in the UKPDS trial and lack of benefit in the LIFE trial (older hypertensives). As young hypertensives have a relatively compliant vasculature the blockade of beta 2 receptors on the blood vessels and increase in tone would be less harmful than in older patients with a non-compliant rigid vasculature. Although diuretics are as effective as Atenolol in reducing BP the cardiovascular protective effects could be more due to its blockade of sympathetic activity.

Reduction in central aortic pressure plays an important role in reducing cardiovascular complications. The CAFÉ trial clearly showed Atenolol was less effective than calcium blockers in reducing aortic pressures.²² Calcium blockers reduce peripheral resistance and slow reflection waves from peripheral to central. The decrease in peripheral compliance causes an increased amplitude of the reflection wave from the periphery. If the reflected wave arrives back at the aortic root in systole, it augments the peak aortic pressure. Betablockers with vasodilator properties like Nebivolol was superior to Atenolol in reducing aortic pulse pressure.²³

In the elderly hypertensive patients the peripheral vasculature becomes less compliant and there is a rise in diastolic BP. Importantly, with aging there is a reduction in plasma renin activity and decrease in sensitivity of beta receptors. Atenolol will thus be less effective. The increasing peripheral resistance causes an augmented reflected wave and rise in aortic systolic pressure. As the reflected wave does not appear in diastole the coronary filling is reduced. Hence, an ACE inhibitor or ARB would be more effective, thus explaining the results of the MRC⁷ and LIFE¹⁵ studies.

Hypertensive patients with LVH (left ventricular hypertrophy) invariably have a high peripheral resistance. In the elderly hypertensive the increasing systolic load faced by the heart will result in more hypertrophy of the cardiomyocytes. Atenolol, as it does not reduce central aortic pressure, will not cause significant regression in LVH. This could explain superiority of Losartan to Atenolol in regression of LVH.

Atenolol with a plasma half-life of 6-7 hours does not

control 24 hour BP as effectively especially in the early morning vulnerable period. This may explain the trend towards higher fatal and nonfatal cardiovascular events in the HAPPHY¹⁴ trial

In hypertensive patients with coronary artery disease Atenolol could still have a benefit viz-a-viz its action in reducing cardiac work (HR, stroke volume), improving diastolic filling of heart and the coronaries, and reduction in the threshold for ventricular fibrillation.

Finally, in diabetic hypertensive patients, the UKPDS trial showed that the tight control of BP was responsible for the potential benefits of Atenolol, despite its adverse metabolic effects like increase in insulin resistance, transient elevation in HbA1C, increase in weight and adverse lipid profile.

In middle-aged obese hypertensives who have a narrow pulse pressure the MRC, UKPDS and IPPPSH studies shows betablockers like Atenolol are more effective than placebo or diuretics in reducing cardiovascular events.

The overwhelming pool of evidence suggests that older antihypertensives like Atenolol will have a lesser role to play in the future. Newer betablockers and the ACE inhibitor / ARB's are more effective in lowering blood pressure and adverse events. But, in special subgroups as mentioned earlier, Atenolol still has a role to play if not as primary therapy as a second line therapy. In developing countries like India with cost considerations playing an important role in patient compliance, atenolol need not be relegated to the background.

References

1. Chrysant SG, Chrysant GS, Dumas B current and future study of Betablockers in treatment of Hypertension, *Clin Cardiol* 2008;31: 6:249-252
2. Cruickshank JM. Are we misunderstanding Betablockers. *International journal of Cardiology* 2007; 120: 10 –27
3. Bangalore S, Messerli FH, Kostis JB etal Cardiovascular protection using betablockers: *J Am Coll Cardiol* 2007; 50: 563-572
4. Day JL, Metcalf J, Simpson CN. Adrenergic mechanisms in control of plasma lipid concentrations. *BMJ* 1982; 284 : 1145 – 8
5. Buhler PR, Laragh Jh, Vaughen ED etal Propranolol inhibition of renin secretion. A specific approach to diagnosis and treatment of renin dependent hypertensive diseases. *N Engl J Med* 1972; 287: 1209 – 1214
6. Black HR, Elliot WT, Grandits G, etal CONVINCENCE research group. Principal results of the Controlled Investigation of Cardiovascular End points (CONVINCE) trial. *JAMA* 2003; 289 : 2073 – 82
7. MRC working party. Medical Research Council trial of treatment of hypertension in older adults: principal results. *BMJ* 1992; 304: 405-12
8. The Dutch TIA trial study group. Trial of secondary prevention with Atenolol after transient ischaemic attack on nondisabling ischaemic stroke. *Stroke* 1993; 24: 543 – 48
9. Blackburn DF, Lamb DA, Eurich DT etal. Atenolol as initial antihypertensive therapy, an observational study comparing first line agents *J Hypertens* 2007; 25: 1499 – 1505
10. Coope J, Warrender T5. Randomised trial of treatment of hypertension in elderly patients in primary care. *BMJ* 1986; 293: 1145-51
11. Eriksson S, Olofsson BO, Wester PO. Atenolol in the secondary prevention after stroke. *Cerebro Vasc Dis* 1995; 5; 21-25
12. UK prospective Diabetes study group. Efficacy of Atenolol and Captopril in reducing risk of macrovascular and microvascular complications in Type II Diabetes UKPDS 39. *BMJ* 1998; 317: 713 –20
13. Zanchetti A, Bond G, Hennig M etal Calcium antagonist Lacidipine slows down progression of Asymptomatic Carotid atherosclerosis. *Circulation* 2002; 106: 2422-27
14. Wilhelmssen L, Berglund G, Elmfeldt D etal. Betablockers vs Diuretics in Hypertensive men. Main results from the HAPPHY trial. *J hypertens* 1987; 5: 561-72
15. Kjeldsen SE, Dahloff B, Devereux RB etal, Effects of Losartan on Cardiovascular morbidity and mortality in patients with isolated systolic hypertension and left ventricular hypertrophy. LIFE sub study. *JAMA* 2002; 288: 1491-8.
16. Ekbom T, Dahlöf B, Hansson*L etal. Anti Hypertensive efficacy and side effects of 3 Betablockers and a diuretic in elderly hypertensives. A report from the STOP- Hypertension study. *J Hypertens* 1992; 10: 1525 – 1530.
17. Cruickshank JM. Reduced total mortality from myocardial infarction and stroke in moderate /severe Hypertensives treated with Tenormin (Atenolol) *Drugs Exptl. Clin. Res.*1990 XV1(3)133-136
18. Pepine EJ, Handberg EM, Cooper- Detloff R etal A Calcium antagonist vs a Non calcium antagonist. Hypertension treatment strategy for patients with Coronary Artery disease. INVEST trial *JAMA* 2003; 290: 2805-2816
19. Black HR, Elliot JW, Grandits G etal Principal results of the Controlled Onset Verapamil Investigation of Cardiovascular End points (CONVINCE TRIAL) *JAMA* 2003; 289: 2073-2082
20. Sever PS, Dahlof B, Poulter NR etal Rationale design, methods and baseline demography and participants of the Angloscandinavian Cardiac outcomes trial. ASCOT investigators. *J Hypertens* 2001; 19: 1139-1147
21. Sawicki PT, Mc Gauran N. Have ALLAHAT, ANBP₂, ASCOT-BPLA and so forth improved our knowledge about better hypertension care ? *Hypertension* 2006; 48: 1-7
22. Williams B, Lacy PS, Thorn SM etal Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. *Circulation* 2006 Mar 7; 113(9): 1213-25.
23. Dhakam Z, Yasmin, Mc Eniery CM etal. A comparison of atenolol and nebulolol in isolated systolic hypertension. *Jr of Hypertens* 2008; 26: 351 - 56.