

The Current Status of Atenolol in Ischemic Heart Disease



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Introduction

Beta adrenergic receptor blocking agents (commonly referred to as beta blockers) are amongst the most versatile drugs used in cardiovascular therapeutics. Although no longer recommended as first-line therapy in hypertension, they are effective in several other cardiovascular conditions including coronary artery disease, heart failure, hypertrophic cardiomyopathy, congenital cyanotic heart disease, tachyarrhythmias, and channelopathies. Here, we briefly review the status of the commonly-used beta blocker atenolol across the varied spectrum of coronary artery disease.

Pharmacology and Mechanisms of Action

Atenolol is a cardioselective (β_1 -selective) beta blocker without membrane stabilizing or partial agonist activity.¹ Unlike propranolol and metoprolol which are lipophilic, atenolol is hydrophilic. Therefore, it has a longer elimination half life (6-7 hours) and does not significantly cross the blood brain barrier. It is excreted largely unchanged in the urine, and dose reduction is advised if the creatinine clearance is below 35 ml/min.²

In general, beta blockers are effective in coronary artery disease by virtue of the following effects-

1. Reduction in heart rate, myocardial contractility, and systolic blood pressure leads to decreased myocardial oxygen demand. Beta blockers attenuate the rise in heart rate in response to exercise.
2. Prolongation of diastole due to a reduction in the heart rate improves the coronary perfusion
3. Anti-arrhythmic effect
4. Improve myocardial energetics by inhibiting catecholamine-induced release of free fatty acids from adipose tissue.^{3,4}
5. Reduce myocardial oxidative stress^{3,4}
6. Vasodilatation - seen with some of the newer 'third generation' beta blockers like nebivolol (nitric oxide mediated) and carvedilol (alpha receptor blockade). Atenolol does not have vasodilatory properties.

By acting on (β_2 receptors on the coronaries, beta blockers can inhibit vasodilatation. However, this effect is usually offset by their effects on the heart rate and contractility. They can exacerbate coronary vasospasm in Prinzmetal angina⁵ and are therefore contraindicated in this condition.

Indications in Coronary Artery Disease

1. Acute Myocardial Infarction:

In the ISIS-1 study,⁶ 16,027 patients with suspected acute myocardial infarction were randomized to either a control

group or a group receiving IV atenolol. The atenolol group showed a significant reduction in vascular mortality, most of which occurred between days 0-1. However, most subsequent studies have involved IV metoprolol. Whether intravenous beta-blockers should be used routinely at all in STEMI is debatable, with studies revealing mixed results.⁷⁻¹¹ The use of IV beta blockers is considered a class IIb indication in the ESC guidelines¹² for the management of STEMI, and is considered a Class IIa indication in the ACC/AHA guidelines¹³- to be used in patients without contraindications and with hypertension or tachycardia at the time of the initial presentation.

2. Post Myocardial Infarction - Secondary Prevention

Beta blockers are recommended in all patients following myocardial infarction for secondary prevention since they reduce mortality,¹⁴⁻¹⁶ yet continue to be underused in this setting. There has been some debate over whether or not this benefit is a class effect of beta blockers. Rinfret et al¹⁷ studied 31,576 post MI patients over the age of 65 years who were started on metoprolol (67%), atenolol (24%), or acebutolol (9%) within 90 days of discharge. They observed that patients on atenolol or acebutolol had a significantly lower mortality as compared to the metoprolol group. However, in a study of 69,338 patients who were prescribed beta blockers following MI, Gottlieb et al¹⁸ found that the mortality was identical with metoprolol and atenolol, while it was higher with propranolol (non-cardioselective). Similarly, in a study¹⁹ of 32,259 post-MI patients, it was found that except for sotalol, different beta blockers had similar efficacy in reducing mortality and preventing recurrence of MI. On the other hand, in a metaanalysis²⁰ of 71 trials evaluating the effect of beta blockers on the mortality after myocardial infarction, metoprolol had a greater benefit when compared to atenolol and propranolol in reducing 1 week mortality, reinfarction, and SCD. It was suggested that ancillary properties like beta-1 selectivity, lack of intrinsic sympathomimetic activity (ISA) and lipophilicity were responsible for this benefit. A small study²¹ showed similar effects of atenolol and carvedilol on the surrogate marker of ejection fraction when used in post-MI patients.

3. Chronic Stable Angina

Beta blockers are commonly used in the pharmacological management of chronic stable angina. The ACC/AHA guidelines²² recommend that beta blockers be used as first line therapy in stable angina. There is a surprising lack of large long-term randomized studies comparing individual beta blockers in stable angina. Most trials including atenolol²³⁻²⁷ have involved only small numbers of patients. The studies comparing atenolol with other classes of anti-anginals are summarized below (Table 1).

The dosage of Atenolol in chronic stable angina is 50-200 mg/day given as a single oral dose. The dose is gradually stepped up, depending on symptom relief and tolerability.

In the light of this data, Atenolol appears to be a useful

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Table 1 : Trials Comparing Atenolol with Other Classes of Anti-Anginal Drugs

Study	Durn.	Medications	Results	Comments
Pehrsson et al ²⁸ (2000)	351	Amlodepin (N=116)vs Atenolol (N=116) vs Combination (N=119). All pts. received nitrates	Time to onset of ST ↓ time to onset of angina, total exercise time, maximum achieved workload, and peak intensity of angina	Individual drugs as effective as combination. Atenolol better than amlodepin and as effective as combination in reducing silent ischemia
TIBET (Fox et al ²⁹ , 1996)	608	Atenolol 50 mg bd vs Nifedipine SR 20 mg bd, vs their combination.	Significant improvements in exercise parameters and significant reductions in ischaemic activity during daily activities, when compared with placebo	No differences between the groups for the measured ischemic parameters. Greater reduction in BP with combination group.
Findlay et al ^w (1987)	15	Atenolol 100mg OD vs Verapamil 120 mg TDS vs Combination		Combination was most effective in reducing angina, nitrate consumption, but significantly reduced the EF
Hopkinson et al ³¹	30	Verapamil SR 320 mg OD vs Atenolol 100mgODin exercise induced angina		Equal antianginal efficacy. Lower heart rates with Atenolol

therapeutic option in patients with CSA.

4. Unstable Angina/Non-ST Elevation MI

Oral beta blocker therapy including atenolol is recommended³² in all patients with non ST elevation Acute Coronary Syndromes in the absence of contraindications. Since there are large no trials comparing individual agents in this setting, it is probably reasonable to use a cardioselective agent, with gradual uptitration of the dose.

5. Silent Ischemia

Beta blockers are beneficial in silent ischemia, probably by preventing accelerations in heart rate which can precipitate such episodes. In a small randomized trial³³ of 24 patients, both atenolol and nifedipine were effective in reducing silent ischemic events, but atenolol was more effective in reducing the number and duration of the episodes. The ASIST study³⁴ found atenolol to be superior over placebo in reducing ischemic events; however, this did not translate into a statistically significant improvement in outcome.

6. Sudden Cardiac Death

Beta blockers including atenolol have been shown to significantly reduce the incidence of Sudden Cardiac Death (SCD) in the post-MI patients.³⁵ Metoprolol^{36,37} proven efficacy in reducing SCD. It has been suggested³⁸ that rather than this being a class effect of beta blockers, it may be related to the degree of lipid-solubility - metoprolol being more lipophilic as compared to atenolol. An intriguing suggestion to explain this phenomenon is that lipophilic agents penetrate the CNS and help maintaining a high vagal tone during stress.^{39,40}

7. Post CABG Atrial Arrhythmias

Atrial fibrillation can occur in upto 30%⁴¹ of patients following CABG, especially on the 2nd or 3rd post-operative day. The routine use of prophylactic beta blockers have been shown to reduce the incidence of atrial fibrillation post-CABG and is currently recommended.⁴² There is evidence^{43,44} to show that atenolol, as expected, is effective in this setting. Lamb et al,⁴³ in a study of 60 patients, showed atenolol to be superior to placebo in preventing the occurrence of supraventricular arrhythmias in post-CABG patients.

In a study⁴⁵ of 254 patients scheduled to undergo CABG randomized to atenolol (50 mg/day) and sotalol (80 mg

twice daily), the incidence of AF was significantly higher in patients with atenolol as compared to sotalol (22% vs 10%, p = 0.013). Burgess et al,⁴⁶ in a meta analysis of 14 trials, found sotalol to be superior to other beta blockers

Tolerability

Although atenolol can potentially produce a number of cardiac as well as non-cardiovascular adverse effects, there is limited long-term data assessing its tolerability in coronary artery disease. In a study⁴⁷ of more than 55,000 patients post -MI, the continuation rates of beta blockers at 1, 3, and 5 years were 78, 64, and 58% respectively. This compared unfavourably with patients on ACE inhibitors and statins, in whom the continuation rates at 5 years were 74% and 82% respectively. As of now, however, there is a paucity of large randomized trials assessing the long-term continuation rates of atenolol in patients with stable angina and UA/NSTEMI.

Careful monitoring of the blood pressure and heart rate, as well as for symptoms and signs of heart failure is important. Sometimes, it may be helpful to stagger administration of beta blockers, ACE inhibitors and other vasodilators if the patient experiences significant dizziness or orthostatic hypotension.⁴⁸

Some of the important adverse effects with beta blockers are discussed below -

1. COPD

Beta blockers are contraindicated in patients with a history of asthma, and can exacerbate airway obstruction in patients with chronic obstructive pulmonary disease (COPD).

Cardioselective beta blockers (like atenolol and metoprolol) are less prone to exacerbate obstructive airway disease. In a Cochrane database review, Salpeter et al⁴⁹ identified 11 studies of single-dose treatment and 9 of treatment for longer durations, ranging from 2 days to 12 weeks, that met selection criteria. Cardioselective beta-blockers, given as a single dose or for longer duration, produced no change in FEV1 or respiratory symptoms compared to placebo, and did not affect the FEV1 treatment response to beta2-agonists. The ESC guidelines suggest that beta blockers can be used in patients with COPD, and that selective beta-blockers would be preferable. It is important to monitor lung function in patients with COPD on beta blockers.

2. Central Nervous System (CNS) side effects

The use of beta blockers has been associated with CNS side effects like unpleasant dreams, sleep disturbances, hallucinations, and depression. However, the incidence of such adverse effects is generally not high. J P van Melle et al,⁵¹ in a study of post-MI patients, found that the incidence of depression did not differ significantly in beta blocker users and non-beta blocker users. It has been suggested that hydrophilic beta blockers (like atenolol) may be less prone to cause neurological disturbances, since they don't cross the blood brain barrier. However, when Ko et al⁵² reviewed more than 35000 subjects in 15 trials, they found that beta blockers were not associated with a significant increase in the annual incidence of depressive symptoms, while there was a small increase in the incidence of fatigue. Significantly, there were no significant differences between hydrophilic and lipid-soluble agents.

3. Erectile dysfunction

Beta blockers have been incriminated in erectile dysfunction - an important quality of life consideration, especially in younger individuals. Nonetheless, it is important to realize that other co-morbid factors⁵³ may be responsible for this complication - these include age, diabetes, smoking, dyslipidemia, and high blood pressure itself. The assumption that beta blockers cause a significantly high incidence of sexual dysfunction (and fatigue) is being increasingly questioned. In their review, Ko et al⁵² found that beta blockers were associated with only a small (though significant) annual increase in the risk of reported sexual dysfunction (5 per 1000 patients). This increase was not affected by the lipid-solubility of the beta blocker or by whether early-generation or late-generation agents were used.

It has been suggested that there could be an important psychological element contributing to impotence caused by beta blockers - indeed, one study⁵⁴ involving metoprolol suggested that men were much more likely to experience erectile dysfunction with this drug if they were told before the study about this potential adverse effect. Similar results were found by Silvestri et al⁵⁵ in a study with atenolol.

Nebivolol by virtue of its nitric oxide mediated vasodilatory effect in the corpus cavernosum, may reduce the incidence of erectile dysfunction. Boydak et al⁵⁶ compared the effects of nebivolol and atenolol with and without chlorthalidone in 131 men with newly diagnosed hypertension. At the end of 12 weeks, they found that the mean number of episodes of satisfactory sexual intercourse per month was significantly decreased from the baseline in the groups receiving atenolol and atenolol with chlorthalidone.

There are few studies directly comparing the effect of atenolol with other classes of drugs on sexual dysfunction. Two small studies suggest that lisinopril⁵⁷ and valsartan⁵⁸ may have a lower incidence of this side effect as compared to atenolol when used in hypertensive patients.

Thus, it appears that although atenolol does cause a small increase in the incidence of sexual dysfunction, the problem is not as frequent as commonly believed. Nebivolol may have an advantage over older agents (including atenolol) by virtue of its nitric oxide - mediated vasodilatory effects in the corpus cavernosum.

4. Metabolic Effects

Beta blockers therapy can adversely affect the lipid profile by increasing levels of LDL-Cholesterol, VLDL, and Triglycerides. They can also reduce HDL-C levels.^{59,60} It has been suggested that these changes are maximum with non-selective agents, lesser with prominent with highly selective beta blockers without ISA (like atenolol and metoprolol), and least with agents possessing ISA.⁶¹

Two small studies^{62,63} found a significant lowering of HDL-C with atenolol as compared to pindolol when used in patients with hypertension. One of the studies⁶² also demonstrated an elevation in VLDL, while the other⁶³ found an increase in triglyceride levels with atenolol. A study⁶⁴ comparing the short-term effects of four beta blockers (propranolol, atenolol, nadolol, and pindolol) demonstrated falls in HDL-C levels with the first three, and a rise in TG and apolipoprotein B with propranolol.

Beta blockers are known to adversely influence glucose tolerance. However, there is a lack of data comparing atenolol with other beta blockers in the setting of IHD. In a small randomized study⁶⁵ comparing carvedilol and atenolol in 45 patients with type II diabetes and hypertension, Carvedilol was found to favourably influence insulin sensitivity and glycemic control, whereas atenolol increased fasting plasma glucose and insulin levels. Moreover, patients on carvedilol had significant falls in triglyceride levels and elevations in HDL while those on atenolol had the opposite findings. On the other hand, Foqari et al⁶⁶ found no significant adverse effect of either atenolol or nebivolol on the insulin sensitivity or lipid profile in 30 hypertensive patients with Type 2 Diabetes mellitus.

Summary and Conclusions

With the exception of carvedilol in post-MI patients with LV dysfunction and possibly sotalol in prevention of post-CABG AF, there is little evidence favouring any particular beta blocker in the other forms of coronary artery disease. Atenolol therefore remains a useful therapeutic option across the varying spectrum of CAD.

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