

RAPID APPRAISAL

Name of Trial: Atenolol in hypertension: is it a wise choice?

Reference: Lancet 2004;364:1684-9

Question: What effect does atenolol have on cardiovascular morbidity and mortality in hypertensive patients?

Summary: The results of the meta-analysis suggest that although atenolol reduces blood pressure, it is not as effective as other antihypertensive drugs for preventing the long term consequences of hypertension. Other published evidence suggests that reducing blood pressure reduces cardiovascular events, irrespective of regime used. This research provides no evidence to question the use of atenolol as an add-on therapy

Did the review ask a clearly focussed question?

The authors evaluated the effect of atenolol on the rate of cardiovascular morbidity and mortality in patients with hypertension in comparison to no treatment or other antihypertensive drugs.

Did the authors look for the appropriate sort of papers?

The research was a systematic review of randomised controlled trials. The eligibility criteria for studies were; (1) primary hypertension (2) randomised controlled trial (3) predefined criteria of myocardial infarction, stroke and cardiovascular death (4) atenolol used alone as the first line drug in one of the treatment arms. The effort made by the authors to find all the relevant trials appeared to be adequate.

The review found four trials that compared atenolol with placebo and five that compared atenolol with other drugs for the treatment of hypertension.

It is not clear why the authors selected atenolol without evidence that it is different to other beta-blockers in terms of clinical

benefits/risks. They did claim that it is one of the most widely used beta-blockers clinically, and it has often been used as a reference drug in clinical trials.

Were the important relevant studies included?

Studies were identified through searching *The Cochrane Library*, MEDLINE, textbooks and personal communication with established researchers in hypertension.

Many studies were excluded because atenolol was one of several comparators. The meta-analysis may have been weakened as individual patient data was not available for patients randomised to atenolol in these studies.

Were the quality of the studies assessed?

There was no evidence that the reviewers had drawn up any criteria to assess the quality of each trial.

Was it reasonable to combine the results of the review?

The heterogeneity between the studies was assessed with X^2 test. Both outcome data comparing atenolol with placebo and other antihypertensive treatments showed that there was no evidence of statistical heterogeneity.

There were however differences between the patient populations. The largest study (LOSARTAN Intervention for Endpoint Reduction in Hypertension study¹ (LIFE) (n=9193)) included roughly the same number of patients as the other studies listed together (n=8478). As well as hypertension, these patients also had left ventricular hypertrophy (LVH).

An analysis that takes into account the differences between the trials might have been more appropriate (a random effects model).

What is the overall result of the review?

Overall this research demonstrates that when atenolol was used as a single drug for the treatment of hypertension the long-term goals of treatment (cardiovascular morbidity and mortality) were not achieved as well as with other drug treatments. Many factors such as type of patient, level of blood pressure and dose of treatment need to be taken into account in order to fully interpret these findings.

How precise are the results?

In the four studies (n=6825) patients were followed up for a mean of 4.6 years, despite major differences in blood pressure lowering, there was no outcome differences between atenolol and placebo on:

- on all-cause mortality (relative risk 1.01 [95% CI 0.89-1.15])
- cardiovascular mortality (0.99 [0.83-1.18])
- myocardial infarction (0.99 [0.83-1.19]).

The risk of stroke tended to be lower in the atenolol than the placebo group (0.85 [0.72-1.01]).

When atenolol was compared with other antihypertensives, there were no major differences in blood pressure lowering between the treatment arms. The meta-analysis showed a significantly higher

mortality (1.13 [1.02-1.25]) with atenolol treatment than with other active treatment, in the five studies (n=17,671) in patients who were followed up for a mean of 4.6 years. Cardiovascular mortality tended to be higher with atenolol treatment than with other antihypertensive treatment. Stroke was also more frequent with atenolol treatment.

Although atenolol was compared with all other antihypertensive agents as a single group it was not compared with specific drug groups. Without this information the results are difficult to interpret. No evidence is presented that atenolol has a less favourable risk-benefit profile in comparison to other beta-blockers.

Can the results be applied to the local population?

The study with the most significant impact on the overall analysis, the LIFE study¹, included patients with hypertension and LVH. The usual incidence of LVH in hypertensive patients is 25-30%². Another study, the UKPDS (UK Prospective Diabetes Study) was in hypertensive patients with diabetes. As there were such differences between the populations in the nine trials it is difficult to apply the results to local practice.

More importantly the British Hypertensive Society (BHS) remains concerned that there is a substantial under-treatment and poor rates of BP control in the UK. In fact the management of hypertension in the UK remains suboptimal for the majority of patients.³

One of the most recently published overviews of blood pressure agents suggests that the greater the reduction in blood pressure the larger the reduction in total major cardiovascular events.⁴ There was no significant differences in total major cardiovascular events between regimens based on ACE inhibitors, calcium antagonists, diuretics or beta-blockers (atenolol was included).⁴

In studies aiming to reduce blood pressure to below 140/90 mmHg about one half of patients will need treatment with more than one drug.⁵ This meta-analysis does not address the effectiveness of different antihypertensive drugs as add on therapy.

Atenolol remains a reasonable choice as an add-on therapy.

Were all important outcomes considered?

Atenolol differs from the other beta-blockers in its low lipophilic profile. Much of the evidence supporting beta-blockers comes from other drugs in the class - metoprolol, timolol and propranolol.⁶

The evidence that atenolol improves clinical outcomes is weak.⁷ The major study showing an advantage for atenolol was the Coope study, in which one of the outcome variables - stroke - was reduced by 43% in comparison with no treatment.⁸

Are the benefits worth the harms and costs?

The results of the meta-analysis suggest that although atenolol reduces blood pressure, it is not as effective as other antihypertensive drugs for preventing the long term consequences of hypertension. Other published evidence suggests that reducing blood pressure reduces cardiovascular events, irrespective of regime used.³

The research provides no evidence to question the use of atenolol as an add-on therapy. No direct evidence is presented that atenolol is better or worse than other beta-blockers as first line therapy. Currently available evidence indicates that as a class, beta-blockers appear as effective as thiazide diuretics and beta-blockers or thiazides are at least as effective as calcium channel blockers or ACE inhibitors as first line therapy. The only trial to date where beta-blockers have been shown to have a less favourable outcome was the LIFE trial involving patients with LVH, where atenolol was less effective than losartan.¹

Further research comparing an atenolol/thiazide based antihypertensive regimen with a calcium channel blocker/ACE inhibitor regimen is expected to be published within a year (ASCOT). Pending this, the results of this meta-analysis should not change the current NICE guideline recommendation that in primary care, drug therapy for hypertension should usually start with a thiazide diuretic, adding a beta-blocker unless the patient is at raised risk of new onset diabetes.⁵

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KEY RCT - randomised controlled trial, CT-controlled trial, O-open study, MA-meta analysis, R-review, U-unpublished, Abs- abstract, E-editorial

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