

RAPID APPRAISAL

Name of Trial: Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial – Blood Pressure Lowering Arm (**ASCOT – BPLA**): a multicentre randomised controlled trial

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Question: What is the difference in effect on non-fatal myocardial infarction and fatal coronary heart disease of treatment regimens based on atenolol and bendroflumethiazide versus those based on amlodipine and perindopril?

Summary: Compared with atenolol and bendroflumethiazide, treatments based on amlodipine and perindopril resulted in larger reductions in blood pressure and were associated with reduced cardiovascular morbidity, non fatal MI and fatal CHD, total coronary events, total cardiovascular events and procedures, all-cause mortality and fatal and non-fatal stroke. Reductions in the primary endpoint of non-fatal MI and fatal CHD were not significant. It remains unclear if these benefits result from improved blood pressure lowering alone or if other drug-related factors are involved. Absolute differences between treatment regimens are small and the cost-effectiveness of initiating treatment with the amlodipine-perindopril regimen has not been assessed.

Did the study ask a clearly focussed question?

Yes This trial¹ compared blood pressure regimens based on atenolol and bendroflumethiazide with those based on amlodipine and perindopril.

The primary endpoint was the effect on non-fatal myocardial infarction (MI) and fatal coronary heart disease (CHD). Secondary endpoints included all-cause mortality, total stroke, primary endpoint minus silent MI, all coronary events, total cardiovascular events and procedures, cardiovascular mortality, and non-fatal and fatal heart failure.

Atenolol and bendroflumethiazide (plus potassium if necessary) were chosen as this was felt to be the most frequently used combination. Amlodipine and perindopril were chosen as they were considered to potentially have a more favourable metabolic profile.

19,342 patients aged 40-79 years with either untreated hypertension (systolic blood pressure (SBP) ≥ 160 mmHg, diastolic blood pressure (DBP) ≥ 100 mmHg, or both) or treated hypertension with a SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, or both were recruited. (85 patients were excluded after randomisation due to BP measurement irregularities). Additionally, patients had at least 3 of the following cardiovascular risk factors: left ventricular

hypertrophy, type 2 diabetes, peripheral arterial disease, previous stroke or transient ischaemic attack, male sex, 55 years or older, microalbuminuria or proteinuria, smoking, TC:HDL-C ≥ 6 or a family history of premature CHD.

Exclusion criteria included previous MI, currently treated angina, fasting triglycerides >4.5 mmol/L, cerebrovascular event within previous 3 months, heart failure or uncontrolled arrhythmias.

Was the study design appropriate?

Yes This was a multicentre, prospective, investigator-initiated and investigator-led randomised controlled trial, conducted in the UK and Ireland, and the Nordic countries. The trial was supported mainly by Pfizer, but also by Servier.

Were participants appropriately allocated to intervention and control groups?

Yes Participants were allocated to the two intervention groups according to a pre-specified algorithm. Randomisation was a computer generated optimum allocation blinded for any person involved in undertaking the study. In the Nordic countries, family practices randomised

patients, and in the UK and Ireland, regional centres, to which patients were referred by their family doctors, recruited patients. Participants in the two groups were well matched.

Were participants, staff and study personnel ‘blind’ to participants study group?

A PROBE (open treatment and blinded endpoint evaluation) design was used; participants and investigators were not blinded but those evaluating end points were unaware of treatment allocation.

Were all the participants who entered the trial accounted for at its conclusion?

At conclusion, all participants were accounted for; however, information was incomplete for 121 (1.3%) and 171 (1.8%) participants in the amlodipine and atenolol arms, respectively. Of these patients – 81 and 102, respectively, were alive at last visit, 24 and 36, respectively, had withdrawn consent and 16 and 33, respectively, had been lost to follow up. The time to first event was compared using an intention to treat analysis.

Were the participants in all groups followed up and data collected in the same way?

Participants were monitored and followed up in the same way. Follow up visits for both groups were at 6 weeks, 3 months, 6 months and then 6-monthly. Antihypertensive therapy was titrated at every follow-up visit to achieve target BPs. There were pre-specified algorithms for both arms to reach BP targets. 16% of the amlodipine group and 26% of the atenolol group crossed over to a drug included in the group to which they were not allocated.

Was the study large enough?

The study was designed to have 80% power at a two-sided significance level of 5% for the primary endpoint. To achieve this, at least 18,000 patients needed to be followed up for an average of 5 years. The trial was stopped early in October 2004, due to the fact that those allocated the amlodipine-based regimen had significantly lower all-cause mortality as well as better outcomes on several other secondary outcomes than those on the atenolol regimen. The study was powered for 1150 individuals to reach the primary endpoint, but due to the early termination, only 903 endpoints arose. The study was therefore underpowered for the primary endpoint.

How are the results presented and what is the main result?

After a median follow up of 5.5 years, the mean BP in the overall study population dropped from 164.0/94.7 to 136.9/78.3 mmHg. At the close of the trial, 53% of patients had achieved both the SBP and DBP targets. BP values were an average of 2.7/1.9 mmHg lower in the amlodipine arm than the atenolol arm over the course of the trial (p<0.0001). By the end of the trial, 78% of patients were taking at least 2 antihypertensive drugs, with only 15% and 9% taking amlodipine and atenolol monotherapy, respectively. The respective average numbers of antihypertensive drugs were 2.2 and 2.3; 8% of patients required 4 or more drugs. 40% were using antihypertensives other than those prespecified by the protocol.

The primary endpoint of non-fatal MI and fatal CHD was not significantly affected by treatment allocation, even though fewer individuals in the amlodipine arm reached the primary endpoint (429 vs 474; unadjusted HR 0.90, 95%CI 0.79-1.02, p<0.1052) compared with the atenolol arm. However, the amlodipine regimen was associated with significant reductions in all of the secondary endpoints, with the exception of fatal and non-fatal heart failure. Fatal and non-fatal stroke (327 vs 422; HR 0.77, 95%CI 0.66-0.89, p=0.0003), total cardiovascular events and procedures (1,362 vs 1,602; HR 0.84, 95%CI 0.78-0.90, p<0.0001), and all-cause mortality (738 vs 820; HR 0.89, 95%CI 0.81-0.99, p=0.025) were all significantly less common in the amlodipine arm.

Absolute risk reductions (ARRs) and numbers needed to treat (NNTs) for the amlodipine regimen compared to the atenolol regimen are calculated below. These assume treatment for 5.5 years:

	Primary Endpoint (Not statistically significant)	Stroke	Total CV events & procedures	All-cause mortality
ARR	0.48%	1.00%	2.53%	0.86%
NNT	209	101	40	116

Trial investigators used a post-hoc analysis involving a combination of the primary endpoint plus coronary revascularisations. This did show a significant difference in favour of the amlodipine arm (596 vs 688; HR 0.86, 95%CI 0.77-0.96, p=0.0058). This decision was based on the increased use of interventional procedures to prevent MI over the course of the study. This was not a pre-specified endpoint.

How safe were the regimens?

25% of patients stopped therapy due to an adverse effect, with no significant difference between the two groups. The proportions of patients stopping therapy due to serious adverse effects did differ significantly: 2% (162/9639) vs

3% (254/9618) for the amlodipine and atenolol groups, respectively. A small but statistically significant reduction in the development of diabetes, a pre-specified tertiary endpoint was associated with the amlodipine-based regimen ($p < 0.0001$), (ARR=2.43%).

Patients in the atenolol arm were titrated up to 100mg atenolol before bendroflumethiazide was added. This is higher than the dose of 50mg recommended for the control of hypertension in the UK.² The resultant increase in dose-related side effects may have contributed to the higher drop-out rate and the increased rate of diabetes in this group.

How precise are the results?

The 95% confidence interval of the hazard ratio for the primary endpoint crosses the line of no effect (0.79 to 1.02) indicating no statistically significant difference in the prespecified primary endpoint. However, secondary endpoints, with the exception of fatal and non-fatal heart failure, were significantly less common in the amlodipine arm and 95% confidence intervals are provided.

The ASCOT trial included a cholesterol-lowering arm, in which, out of the trial total, 10,305 patients with low cholesterol were also randomised to receive either placebo or atorvastatin.³ ASCOT-LLA confirmed that statin therapy reduced the risk of CHD and stroke in people with treated hypertension, even when BP was optimally controlled.⁴

Can the results be applied to the local population?

Randomised patients consisted of a very high percentage of mainly white (95%) males (77%). The mean age was 63 years with a mean BMI of 28.7, and they had at least 3 other cardiovascular risk factors. It is unclear how well the results can be extrapolated to lower risk patients commonly seen in general practice. However, the benefits of the amlodipine arm appeared consistent irrespective of age, gender and other patient factors.

Conclusions

This trial's results reinforce the need for close titration of treatment, and for multi-drug therapy to control BP when needed. It is not clear if the benefits of the amlodipine arm were due to better BP control or other factors.

Close adherence to treatment protocols involving titration of antihypertensives results in more patients reaching target BP.

Current national guidelines do not agree on choice of antihypertensive therapy.^{4,5} A meta-analysis showed that the main driver of benefit from BP lowering therapy is the actual BP lowering, and there is little evidence of additional

drug class-specific benefits with regard to major cardiovascular outcomes overall.⁴ ASCOT-BPLA has demonstrated more rapid BP control and improved cardiovascular outcomes with a regimen based on amlodipine and perindopril compared with one based on atenolol and bendroflumethiazide. The result should be seen in the context of other research. The earlier ALLHAT study⁶ did not show benefits of calcium channel blockade or ACEI vs diuretic therapy using chlorthalidone. A recent meta-analysis⁷ has suggested reduced cardiovascular benefit from use of atenolol compared to other drugs, and the combination of a beta blocker with a thiazide consistently increases the risk of diabetes.⁸

Interpretation of these results is complex and advice on how they should affect prescribing in primary care will be provided in due course by the following collaborative National Institute for Health and Clinical Excellence (NICE)/British Hypertension Society (BHS) review. This is likely to discourage the early use of beta blockers in hypertension. In the meantime;

- a) There is inadequate evidence to switch well controlled patients at low risk of diabetes who are taking thiazide/beta blocker combinations.
- b) Patients should be provided with combination treatment as needed to achieve target blood pressure. The actual BP remains more important than the choice of drug.
- c) There is evidence of the safety and efficacy of diuretics in the management of hypertension and their early use in therapy should not be discouraged.

Overall, most classes of drugs have been shown to be similarly safe and effective, but the control of hypertension remains suboptimal for the majority of patients. It is important not to treat BP in isolation without taking other risk factors into account as this will leave the patient at an unacceptably high risk of cardiovascular complications and death, particularly from CHD and stroke.⁴

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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, G – guidelines

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