

## Evidence Based Medicine

# Effects of a perindopril-based blood-pressure-lowering regimen in patients with previous stroke or transient ischaemic attack (progress). How do the results affect practice in Pakistan?

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### Why is this study important?

Stroke is the leading cause of sustained disability worldwide. Contrary to popular belief, two thirds of stroke mortality will occur in the developing world in patients less than 70 years of age. Among those who survive a stroke or TIA, the risk of recurrent stroke is very high. Thus, broad interventions that decrease the risk of stroke are welcome in the developing world.

Blood pressure had been recognized as an important determinant of the risk of initial stroke in several studies which had included both hypertensive as well as normotensive patients.<sup>1,2</sup> However, the association between hypertension and stroke recurrence was not as clear from previous studies.

The aim of this particular study was to determine the effects of a flexible blood pressure lowering regimen on the risk of stroke recurrence and other major vascular events in patients who had a history of stroke or Transient ischaemic attack. The patients were recruited regardless of their entry blood pressure levels.

### Who were the participants?

The study was conducted in 172 centers from ten countries. Most of these countries were European except China and Japan (contributed a total of 2335 subjects) and Australia and New Zealand (contributed 1110 subjects). There were no South Asian patients.

Patients were eligible if they had a history of stroke or transient ischaemic attack within the previous 5 years and in the opinion of the responsible physician, no clear indication or contraindication to ACE inhibitor therapy. These patients were recruited at a median time of 8 months after their stroke regardless of their blood pressure level- such that the mean blood pressure amongst those classified as hypertensive was 159/94 and non hypertensive was 136/79. Hypertension was defined as a blood pressure of >160 systolic or >90 diastolic for this study.

A total of 7121 patients were entered into a four week pre-randomization run-in period during which they received open label perindopril. 1061 were ineligible or withdrew. Eventually 6105 were randomized, 3544 to combination

therapy or double placebo and 2561 to perindopril alone or placebo.

### What was the intervention?

Intervention arm comprised a flexible regimen based on perindopril 4 mg daily with or without Indapamide 2.5 mg daily. The decision to use a combination was left to the discretion of the treating physician. In the placebo arm the participants received either single placebo identical to perindopril or a double placebo similar to perindopril and Indapamide. A total of 3051 patients were randomized to active treatment, of these 1770 received combination therapy and 1281 got single agent. In the placebo arm, 1774 were randomized to double placebo, and 1280 to single placebo.

Patients were followed up for an average of four years after randomization. In the first year they were seen on five occasions, and then six monthly thereafter. At these visits, information was collected regarding adherence to treatment, Blood pressure, cognitive function, disability, occurrence of major clinical events and tolerability of the study treatment.

### What was the outcome?

Blood pressure was reduced by an overall average of 9.0/4.0 mm Hg in those who received active treatment compared to those assigned placebo and this difference was maintained throughout the follow-up period. Also those who received double therapy had a greater reduction compared to single agent (12.3/5.0 mm Hg vs. 4.9/2.8 mm Hg).

Ten percent of patients in the active group and 14% in the placebo group had a recurrent stroke during the follow-up period which translated into a relative risk reduction of 28% [95% CI 17-38%; p<0.0001]. This benefit was accrued over all stroke subtypes and was maximal in patients with haemorrhagic strokes.

The benefit extended to other major vascular events also, with fewer total major coronary events in the active arm [26% relative risk reduction; 95% CI 6-42], and fewer non fatal strokes and non fatal myocardial infarction in the active arm. However, there was no significant difference in the two arms with respect to all cause mortality and vascular mortality.

Among participants who received the combination therapy, the reduction in blood pressure was more (mean 12/5 mmHg), and the stroke risk was also significantly lower when compared to double placebo. This was observed for all stroke subtypes, and for total major coronary events, and for non fatal stroke, non fatal MI and vascular death. These differences were not as pronounced when single agent was compared to placebo.

Another important outcome of this study was that active treatment with either perindopril alone or its combination with Indapamide, conferred similar advantages in both hypertensive and non-hypertensive individuals. Hypertension was defined as systolic blood pressure >160 mm Hg or diastolic blood pressure >90 mm Hg at baseline).

### **What were the conclusions?**

The authors concluded that the study treatment was shown to be safe and effective across a broad range of patients, irrespective of their baseline blood pressures and the type of their initial stroke. The results suggest that 5 years' treatment with the combination of perindopril and Indapamide would have resulted in the avoidance of one fatal or major non-fatal vascular event among every 11 patients (95% CI 9-16).

### **Is this study relevant to clinical practitioners within Pakistan?**

A National Health Survey conducted during early 90s in Pakistan revealed that 33% of the population above age of 45 has hypertension. Hypertension is the single most important modifiable risk factors for both ischaemic and haemorrhagic

strokes and it would be much more prevalent in this group of individuals. In contrast to developed countries a greater proportion of patients in Pakistan has hypertensive ICH - where according to this study the benefit of treatment is maximal. It appears that the degree of reduction in blood pressure impacts a favourable outcome. Whether additional drug class specific pleiotropic effects also benefit the patient is unknown.

With the kind of impact reported with blood pressure lowering in this study, all patients with history of stroke or TIA should be put on anti-hypertensives. The amount of risk reduction is in fact more than what can be achieved with antiplatelets like aspirin. Also the benefit is seen across all stroke subtypes, which means that this is one treatment that can be instituted without the need for neuroimaging which in many parts of Pakistan is still not feasible. However, it should be made very clear that these are chronic stable stroke patients where there is no evidence to support risk of stroke progression by lowering blood pressure.

### **Recommended Reading**

1. Eastern Stroke and Coronary Heart Disease Collaborative Research Group. Blood Pressure, cholesterol and stroke in eastern Asia. *Lancet* 1998; 352: 1801-7.
2. Prospective Studies Collaboration. Cholesterol, diastolic blood pressure, and stroke: 13 000 strokes in 450 000 people in 45 prospective cohorts. *Lancet* 1995; 346: 1647-53.
3. PROGRESS. Weinberger J. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. *Curr Cardiol Rep* 2003; 5: 140.
4. Jafar TH, Rahbar MH, Khan AQ, Hattersley A, Schmid CH, Chaturvedi N. Ethnic subgroup differences in hypertension in Pakistan. *J Hypert* 2003; 21: 905-12.
5. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003; 42: 1206-52.