

Does lowering blood pressure prevent recurrent stroke?

Trial: PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001; 358: 1033-1041.



Question

In patients with a history of stroke or transient ischaemic attack, can further stroke be prevented by lowering blood pressure, even when it is not elevated?



Trial details

Design: Multicentre, randomised, double-blind, placebo-controlled trial with a mean 3.9-year follow-up.

Setting: 172 centres in 10 countries including Asia, Australasia and Europe.

Patients: 6105 patients, mean age 64 years, in stable condition after a stroke or transient ischaemic attack within the previous five years and with no definite indication or contraindication to an angiotensin-converting-enzyme (ACE) inhibitor.

Intervention: In 3051 patients, a flexible blood-pressure-lowering regimen based on the ACE inhibitor perindopril (4 mg daily), with the addition (in 58% of actively treated patients) of the diuretic indapamide (2.5 mg daily, or 2 mg daily in Japan), at the discretion of the treating physicians. Matching placebo in 3054 patients.

Main outcome measures: All strokes (fatal or non-fatal); secondary measures included fatal or disabling stroke, total major vascular events (non-fatal stroke, non-fatal myocardial infarction, vascular death), total and cause-specific deaths, hospital admissions, and (not reported yet) dementia and cognitive function.

Main results: Active treatment reduced blood pressure by a mean of 9/4 mmHg. Against a background of standard treatment, over four years active therapy reduced strokes from 14% in those assigned placebo to 10% (relative risk reduction, 28%; 95% CI, 17%–38%, $P < 0.0001$). Risk reduction was similar in those who were normotensive or with baseline systolic and diastolic blood pressures ≥ 160 or ≥ 90 mmHg, respectively, irrespective of any treatment. Active therapy also reduced the risk of total major vascular events by 26% (95% CI, 16%–34%; $P < 0.0001$) and major coronary events by 26% (95% CI, 6%–42%). After initial screening for tolerance during a four-week run-in, only 1% more patients stopped active therapy than those stopping placebo because of hypotension. In a subgroup analysis, combination therapy, but not monotherapy, had a significant benefit. In absolute terms, one in every 11 patients given combination therapy avoided death, myocardial infarction or stroke over five years of treatment.

Conclusion: Blood pressure lowering was beneficial; in the trial context, perindopril plus indapamide (but not perindopril alone) prevented stroke and major vascular events in patients whose condition was stable after a previous stroke or transient ischaemic attack.



Commentary

Rationale for the trial

About one in five stroke survivors suffer another stroke in the five years after the initial incident.¹ Blood pressure is related in a continuous manner to the risk of an initial stroke, but many strokes occur in individuals with normal blood pressure. However, there are fewer data on the

relationship between blood pressure and recurrent stroke. Systematic reviews of randomised trials of blood-pressure-lowering drugs in patients with hypertension who do not have clinical evidence of cerebrovascular disease show that sustained lowering of blood pressure reduces risk for stroke by about a third.² Fewer data are available on the effect of lowering blood pressure in individuals with a history of cerebrovascular disease.

Trial methods

Importantly, the trial tested the effect of treatment in patients with a wide range of entry blood pressures, including those who were normotensive, defined as systolic blood pressure less than 160 mmHg and diastolic blood pressure less than 90 mmHg. Because of this, the results of the trial are more generalisable than if it only included patients with hypertension. The design also allowed for clinician choice for single or combination therapy. The predefined outcomes were adjudicated by an expert committee and were deemed to be clinically relevant. Randomisation was appropriate with stratification for known prognostic factors. The sample-size estimates were robust and based on worthwhile and plausible differences in stroke rates. Analysis was on an intention-to-treat basis and subgroup analyses were pre-specified. Both absolute benefits as well as relative-risk reductions were reported.

New information

The study establishes the value of blood pressure lowering to prevent recurrent stroke (both ischaemic and haemorrhagic). In particular, it demonstrates the role of blood pressure lowering for secondary prevention of stroke in normotensive patients. PROGRESS is the first study to show benefit for Asian as well as white populations. The trial also showed that blood pressure lowering can prevent coronary events in patients with previous stroke, and that blood pressure lowering was safe at least two weeks after a stroke or transient ischaemic attack.



Implications for clinical practice

In patients who have just had a stroke (irrespective of their age, whether they are hypertensive or normotensive and whether they have sustained ischaemic or haemorrhagic stroke), after two weeks, or when their condition is judged to be clinically stable, blood-pressure-lowering intervention should be considered. In those who have had a stroke at some time in the past, treatment should similarly be considered. In some patients, such as those with bilateral carotid occlusive disease, there may be some risks, and the trial does not provide information relating to these. How-

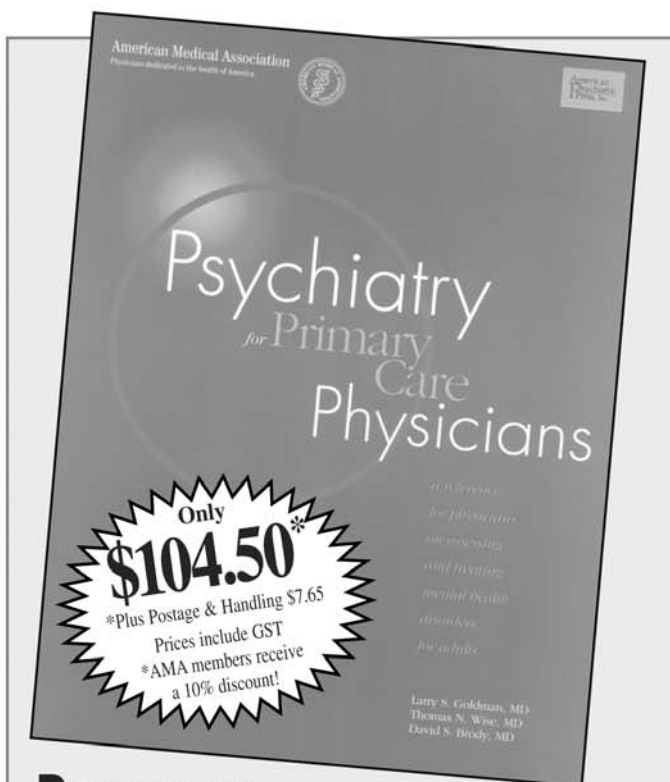
ever, in most patients, ACE inhibitor therapy could be started initially at the time of discharge or at postdischarge follow-up. However, to maximise the blood-pressure-lowering effect, most patients should receive combination therapy. The trial provides data to support use of a combination of perindopril and indapamide. PROGRESS does not provide data to show that other ACE inhibitors, other diuretics or other classes of antihypertensives would have the same demonstrable quantitative effects, nor was it designed to provide information on specific target blood pressure levels.

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2. Collins R, MacMahon S. Blood pressure, antihypertensive drug treatment and the risks of stroke and of coronary heart disease. *Br Med Bull* 1994; 50: 272-298. □



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