Combined therapy with indapamide and perindopril but not perindopril alone reduced the risk for recurrent stroke

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 Sep 29;358:1033-41.

QUESTION

In patients with a history of stroke or transient ischemic attack (TIA), is perindopril alone or combined with indapamide more effective than placebo for reducing fatal or nonfatal stroke?

DESIGN

Two* randomized (allocation concealed†), blinded {patients, clinicians, data collectors, outcome assessors, data analysts, and manuscript writers}‡,† placebo-controlled trials with mean follow-up of 3.9 years (Perindopril Protection against Recurrent Stroke Study [PROGRESS]).

SETTING

172 centers from 10 countries.

PATIENTS

6105 patients (mean age 64 y, 70% men) who had a history of stroke or TIA in the previous 5 years, had no definite indication for or contraindication to an angiotensin-converting enzyme (ACE) inhibitor, and were clinically stable for ≥ 2 weeks after their most recent vascular event. 6102 patients (> 99%) completed follow-up for fatal events.

INTERVENTION

Some patients were allocated to perindopril, 4 mg daily (n = 1281), or to single placebo (n = 1280). Other patients, for whom the responsible physician found no specific indication for or contraindication to a diuretic, were allocated to perindopril plus indapamide (indapamide dose 2.0 or 2.5 mg daily) (n = 1770) or to double placebo (n = 1774).

MAIN OUTCOME MEASURES

Fatal or nonfatal stroke. Secondary outcomes included fatal or disabling stroke with the disability defined at the first scheduled follow-up visit after the event and a composite vascular end point of nonfatal stroke, nonfatal myocardial infarction, or death from any vascular cause.

MAIN RESULTS

Analysis was by intention to treat. Patients who received perindopril and indapamide had greater reductions in blood pressure and in stroke, stroke subtypes, and vascular events than did patients who received double placebo ($P < 0.001$) (Table). Perindopril alone showed no more reduction in stroke or major vascular events than did single placebo (Table). The relative effects of combination therapy did not differ in patients with and without a pre-existing diagnosis of hypertension.

CONCLUSIONS

In patients with a history of stroke or transient ischemic attack, treatment with indapamide and perindopril was more effective than treatment with placebo for reducing fatal or nonfatal stroke. Treatment with perindopril alone was not effective.

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For correspondence: Not available.

*The authors disagree with our reporting of their study as 2 separate trials.

†See Glossary.

‡Information provided by author.

Antihypertensive therapy vs placebo for stroke at a mean of 3.9 years§

Outcomes	Perindopril + indapamide	Double placebo	RRR (95% CI)	NNT (CI)
Stroke	8.5%	14%	43% (30 to 54)	17 (13 to 27)
Major vascular events	13%	21%	40% (29 to 49)	14 (10 to 20)
Outcomes	**Perindopril alone**	**Single placebo**	**RRR (CI)**	**NNT**
Stroke	12.3%	12.9%	5% (–19 to 23)	Not significant
Major vascular events	17.7%	18.5%	4% (–15 to 20)	Not significant

§Abbreviations defined in Glossary; NNT and CI calculated from data in article.

COMMENTARY

PROGRESS contains 2 distinct trials. The combination of perindopril and indapamide showed large and consistent benefits; perindopril alone did not. The results of the 2 trials should not be combined or even compared: The patients differed in age, blood pressure, and other features, and the results were heterogeneous.

The results of PROGRESS cannot tell us whether the benefits of combination therapy were from indapamide alone or from the combination of indapamide and perindopril. Support for a diuretic monotherapy effect comes from other studies, including the Post-stroke Antihypertensive Treatment Study (1), in which indapamide alone (vs placebo) showed a 29% relative reduction (P = 0.0013) in stroke recurrence. No single diuretic has been shown to be superior to any other diuretic. Stroke results for other ACE inhibitors are mixed and include the Heart Outcomes Prevention Evaluation (HOPE) trial (2), in which ramipril showed greater reductions than placebo, and the Captopril Prevention Project trial (3), in which captopril showed an increased risk for stroke over that with diuretics or β-blockers, or both.

PROGRESS suggests that all stroke patients, regardless of hypertensive status, should be treated with a diuretic. Adding an ACE inhibitor can be considered on the basis of the large effect of combination therapy in PROGRESS or in the HOPE trial, but it has not been proved to give additional protection; direct comparisons of diuretics and diuretics plus ACE inhibitors are lacking. Furthermore, evidence continues to grow that patients with ischemic stroke should be treated with some form of antithrombotic therapy and a coenzyme A reductase inhibitor (statin).

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References

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