Blood pressure and secondary prevention of strokes

How low should we go?

Parisa Rezaiefar, MD Kevin Pottie, MD, MCLSC, CCFP

PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure–lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet **2001;358:1033-41**.

Research question

Does treating mild hypertension help prevent secondary stroke?

Type of article and design

Prospective, multicentre, randomized, placebo-controlled, 4-year trial.

Relevance to family physicians

Cerebrovascular disease remains the second leading cause of death worldwide despite advances in treatment of hypertension and platelet aggregation.[1] The degree of disability caused by non-fatal strokes imposes a heavy burden on our aging population and our health care system.

One in six patients suffering a stroke or transient ischemic attack (TIA) will face a further cerebrovascular accident within 5 years.[2] Secondary prevention of stroke includes determining the mechanism or cause of the stroke. Is it ischemic or embolic? Are there modifiable risk factors, such as atrial fibrillation, hypertension, hyperlipidemia, and smoking? Routine lifelong acetylsalicylic acid therapy, unless clearly contraindicated, has become standard treatment for secondary stroke prevention.[3] Debate over the initial choice of antiplatelet agent has surfaced recently. The critical appraisal of Dalton et al[4] of a study comparing ASA plus dipyridamole with ASA alone[5] provides a useful update on new developments in the field of antiplatelet therapy.

Treatment guidelines for hypertension for primary prevention of stroke[6] are based on level I evidence and have been disseminated widely. Only limited and even contradictory evidence, however, is available for assessing the efficacy of reducing hypertension for secondary prevention of ischemic stroke and intracerebral hemorrhage.

An early observational study[7] showed a J-shaped relation between blood pressure (BP) levels and recurrence of stroke, and this suggested there was a risk in treating some stroke patients for hypertension. A larger clinical trial[8] demonstrated a more linear relationship, with a 28% reduction in stroke recurrence for each 10 mm Hg reduction in systolic BP. Results of a more recent meta-analysis of four randomized trials[9] supported this linear risk reduction, but unfortunately suffered from wide confidence intervals and failed to dispel doubts about the importance of the treatment effect. As a result, the efficacy of reducing BP for secondary prevention of ischemic stroke and intracerebral hemorrhage has remained controversial.

Overview of study and outcomes

The perindopril protection against recurrent stroke study (PROGRESS) set out to determine the effect of BP–lowering agents on secondary prevention of stroke and serious vascular events in patients who had had previous TIAs or strokes.

The study included patients who had a history of strokes (ischemic or intracerebral hemorrhagic) or TIAs within the previous 5 years and had no indications for, or major contraindications to, taking angiotensin-converting enzyme (ACE) inhibitors. There were no BP criteria on entry. Patients with very high BP levels, however, received antihypertensive therapy with medications other than ACE inhibitors before entering the study.

The study used a run-in phase before commencing the trial. All eligible patients (7121) entered a 4-week test phase dur-

Critical Appraisal reviews important articles in the literature relevant to family physicians. Reviews are by family physicians, not experts on the topics. They assess not only the strength of the studies but the "bottom line" clinical importance for family practice. We invite you to comment on the reviews, suggest articles for review, or become a reviewer. Contact Coordinator Michael Evans by e-mail **michael.evans@utoronto.ca** or by fax (416) 603-5821.

Dr Rezaiefar *is a family medicine resident and* **Dr Pottie** *is an Assistant Professor in the Department of Family Medicine at the University of Ottawa in Ontario.*

← FOR PRESCRIBING INFORMATION SEE PAGE 1688

ing which they received 2 mg of perindopril daily. Of the 7121 patients, 1016 (14%) were excluded during the run-in phase due to dizziness, hypotension, cough, or suspected intolerance, and one occurrence of non-fatal angioedema.

The 6105 patients who tolerated the run-in phase were entered in the prospective trial on a double-blind basis. Investigators used match-pair randomization to allocate patients to active treatment and placebo groups based on intention to use single or double therapy (determined before randomization by treating physicians), study centre, age, sex, BP levels, and qualifying event. Of the 3051 patients in the active treatment group, 1281 received single-drug therapy with 4 mg of perindopril daily, and the remaining 1770 received combination therapy that included 2.5 mg of indapamide daily. Combination therapy was used to maximize reduction in BP levels. In the placebo group, 1774 patients received a double placebo, and the remaining 1280 received a single placebo.

All groups had similar follow up during the next 4 years. Follow up included five visits during the first year after randomization and visits every 6 months during the following years. The primary study outcome was defined as fatal or non-fatal stroke. Stroke was defined as an acute disturbance of focal neurologic function with symptoms lasting more than 24 hours or resulting in an earlier death. Strokes were considered non-fatal if patients remained alive for 28 days after onset of the event. Secondary outcomes included non-fatal or disabling stroke, total major vascular events, total and cause-specific death, and hospital admission. An end point adjudication committee reviewed and coded outcomes according to the ninth revision of the International Classification of Diseases.

Results

Baseline characteristics of placebo and treatment groups were well balanced in terms of BP levels, sex, cerebrovascular history, smoking, diabetes, coronary artery disease, and antiplatelet therapy. In subgroup analysis, however, the combination therapy and double-placebo groups tended to have younger patients and a higher proportion of men. As would be expected, these groups also had higher BP levels.

Mean BP of all study participants was 147/86 mm Hg at the first visit. Almost half the patients (2916, 48%) were classified as hypertensive with a mean BP of 159/94 mm Hg. The remaining 52% were considered nonhypertensive, with a mean BP of 136/79 mm Hg.

Mean duration of follow up was 3.9 years. By the end of the scheduled follow-up period or at death during follow up, 714 (23%) of the active group and 636 (21%) of the control group had discontinued therapy due to cough (active 2.2%, placebo 0.4%); hypotension (active 2.1%, placebo 0.9%); and heart failure requiring treatment with ACE inhibitors (active 2.2%, placebo 2.3%). Three cases of non-fatal angioedema were documented in the group treated with perindopril.

Effect on stroke. Primary outcome measurement showed a 28% relative risk reduction (RRR) (95% confidence interval [CI] 17% to 38%) for all strokes. The annual rate of new strokes remained consistent throughout the 4-year follow-up period at 2.7% in the treatment group and 3.8% in the control group. The RRR for fatal or disabling stroke was 33% (95% CI 15% to 46%) and for non-fatal or disabling strokes was 24% (95% CI 9% to 37%).

Effect on major vascular events. The authors measured the effect of treatment on other major vascular events, such as fatal and major non-fatal strokes and myocardial infarction, and reported a RRR of 26% (95% CI 16% to 34%).

Effect on mortality and hospitalization. There was no significant difference in mortality rates between treatment and control groups. There was a significant median reduction of 2.5 days in duration of hospitalization, however, between treatment and control groups with an RRR of 9% (95% CI 1% to 15%).

Effect on hypertension. An average reduction of 9.0/4.0 mm Hg was noted in the active therapy group as compared with the placebo group. Combination therapy reduced BP by 12.3/5.0 mm Hg; single therapy reduced BP by 4.9/2.8 mm Hg relative to placebo. Blood pressure reduction was only slightly different between hypertensive (9.5/3.9 mm Hg) and nonhypertensive (8.8/4.2 mm Hg) patients.

Analysis of methodology

This study was well designed and executed. It successfully randomized a large group of patients to treatment and control groups, blinded both patients and treating physicians to treatment, and used an independent team to review and classify final outcomes. The run-in design enhanced compliance and limited the drop-out rate during the substantial 4-year follow-up period. Loss to follow up was impressively low: two in the treatment group, one in the control

← FOR PRESCRIBING INFORMATION SEE PAGE 1700

group, and the drop-out rate was similar in treatment (23%) and placebo (21%) groups.

A minor theoretical concern arises from the inequality in the subgroups: the combination-therapy and double-placebo groups tended to have patients with higher BP levels, younger patients, and a higher proportion of men. Before randomization, treating physicians selected patients for either combination therapy or monotherapy in order to mitigate concerns for patients' well-being during the trial. There were, however, no stated criteria for this selection process. These differences were not between treatment and control groups, but rather among subgroups. Therefore, the linear risk reduction relationship does not appear to be threatened, only the degree of treatment effect when data are applied to all patients.

The patients included in this international, multicentre trial, hypertensive patients with several other cardiovascular risk factors including diabetes, smoking, and coronary artery disease,[10] could reasonably reflect a Canadian primary care patient population. The only concern might be the socioeconomic diversity of the sample, which is not apparent from the report.

Application to clinical practice

This is an important study. It is the first randomized controlled trial using a large cohort and a substantial follow-up period to look at the efficacy of treating hypertension for secondary prevention of stroke. It clearly demonstrates the importance of lowering BP levels for secondary stroke prevention. It also challenges our current hypertensive target treatment guidelines for patients who have had strokes or TIAs.

At entry, BP levels averaged a modest 147/86 mm Hg. Nevertheless, this study was able to demonstrate a significant clinical benefit from lowering these patients' BP, a 28% reduction in strokes (adjusted relative risk [ARR] 3.7%, number needed to treat [NNT] 27 for 4 years), and a 33% reduction in incidence of fatal and disabling strokes (ARR 1.9%, NNT 53 for 4 years). These RRs are clinically significant considering the amount of disability and death related to strokes, and they resolve the ambiguities regarding the J-shaped relation between BP levels and stroke recurrence.

The study also showed a 26% reduction in major vascular events, fatal and non-fatal strokes, and myocardial infarction (ARR 4.7%, NNT 21 for 4 years). In practice, patients commonly have several cardiovascular risk factors, and thus it is reassuring to find that aggressive treatment of hypertension provides consistent benefits across major vascular disease categories. These results are comparable to outcomes recorded in the Heart Outcomes Prevention Evaluation (HOPE) study.[11]

The 28% reduction in secondary strokes is similar to findings in primary stroke prevention; the Systolic Hypertension in the Elderly Program (SHEP)[12] for example, showed that lowering BP by 11.4/3.0 mm Hg reduced incidence of stroke by 36%. In the PROGRESS, the clinical relevance becomes greater when we look at the combination therapy group (RRR 43%). This difference can be explained by combination therapy's greater effect on BP; combination therapy lowered BP by 12/5 mm Hg; single therapy lowered BP by only 5.0/3.0 mm Hg. This suggests that in clinical practice, patients who have higher BP levels would benefit more from antihypertensive treatment than patients who are not hypertensive.

Some patients cannot tolerate the side effects of an ACE inhibitor–based regimen. The run-in phase led to a 14% drop-out rate, and trial saw 2% more treated patients than placebo patients drop out. In clinical terms, however, these drop-out rates are low, and there was no evidence that patients who were unable to tolerate the medications differed significantly from the rest of the study population.

Evidence continues to accumulate on the benefits of treating even mildly hypertensive patients at risk of cardiovascular disease, particularly in light of likely end-organ damage: renal,[13] cardiac,[11] and now cerebrovascular.

Bottom line

- Treating mild hypertension in patients who had had previous strokes or TIAs reduced the risk of recurrent strokes by 28% (NNT 27 for 4 years); reduced the risk of major vascular events by 26% (NNT 21 for 4 years); and reduced the median duration of hospitalization for recurrent strokes by 2.5 days.
- Treatment did not affect overall mortality rates.
- A reduction of 12.0/5.0 mm Hg in BP decreased the incidence of recurrent stokes by 43% and major vascular events by 40%.
- Combination therapy might be more effective because it lowers BP to a greater extent than monotherapy does.

References

1. World Health Organization. *World Health Report 1999.* Geneva, Switz: WHO; 1999.
2. Hankey G, Warlow C. Treatment and secondary prevention of stroke: evidence, cost, and effects on individuals and populations. *Lancet* 1999;354:1457-63.
3. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994;308:81-106.

FOR PRESCRIBING INFORMATION SEE PAGE 1690 ➔

Points saillants

- Le traitement de l'hypertension légère chez les patients ayant déjà souffert d'un accident vasculaire cérébral ou d'une ischémie cérébrale transitoire réduisait le risque de récurrence d'un accident vasculaire cérébral de 28% (NNT 27 pendant 4 ans); réduisait le risque d'incidents vasculaires majeurs de 26% (NNT 21 pendant 4 ans); et réduisait de 2,5 jours la durée moyenne d'hospitalisation pour les accidents vasculaires cérébraux récurrents.
- Le traitement n'influait pas sur les taux de mortalité globaux.
- Une baisse de 12,0/5,00 mm Hg dans la pression artérielle réduisait de 43% l'incidence des accidents vasculaires cérébraux récurrents et de 40% l'incidence d'incidents vasculaires majeurs.
- Une polythérapie pourrait être plus efficace parce qu'elle réduit davantage la pression artérielle qu'une monothérapie.

4. Dalton B, Papoushek C, Evans MF. Is acetylsalicylic acid plus dipyridamole superior to ASA alone for secondary prevention of stroke? [Critical Appraisal]. *Can Fam Physician* 2001;47:2235-9.
5. Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci* 1996;143:1-13.
6. Feldman RD, Campbell N, Larichelle P, Boll P, Burgess ED, Carruthers G, et al. 1999 Canadian recommendation for the management of hypertension. *Can Med Assoc J* 1999;161(Suppl 12):S1-22.
7. Irie K, Yamaguchi T, Minematsu K, Omac T. The J-curve phenomenon in stroke recurrence. *Stroke* 1993;24:1844-9.
8. Rodgers A, MacMahon S, Gamble G, Slattery J, Sandercock P, Warlow C. Blood pressure and risk of stroke in cerebrovascular disease. United Kingdom Transient Ischaemic Attack Collaboration Group. *BMJ* 1996;313:147.
9. Rodgers A, Neal B, MacMahon S. The effects of blood pressure lowering in cerebrovascular disease. *Neurol Rev Int* 1997;2:12-5.
10. PROGRESS Management Committee. PROGRESS (Perindopil Potection Against Recurrent Stroke Study): characteristics of the study population at baseline. *J Hypertens* 1999;17:1647-55.
11. Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000;342:145-60.
12. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA* 1991;265:3255-65.
13. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. *BMJ* 1998;317:703-13.