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.

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Primary outcome measurement

An average reduction of 9.5/3.9 mm Hg was noted in the active therapy group versus 2.5/4.0 mm Hg in the placebo group. Combination therapy 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 classified final outcomes. Of the 3051 patients in the active treatment group, 1281 received single-drug therapy with 4 mg of indapamide 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 phase 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.
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, 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) 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,11 cardiac, and now cerebrovascular.

Bottom line
• Treating mild hypertension in patients who 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 strokes 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
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.