Blood-pressure lowering for the secondary prevention of stroke

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In 1997, a quantitative overview of outcome trials of antihypertensive treatment among patients with stroke showed that among hypertensive stroke survivors, blood-pressure-lowering therapy decreased the recurrence of fatal and non-fatal stroke by 28% (95% CI 15–39). The primary aim of the PROGRESS trial, the protocol of which was published 5 years ago, was to find out the precise effects that a blood-pressure-lowering regimen based on an angiotensin-converting-enzyme inhibitor would have on stroke risk in patients with a history of transient ischaemic attacks or minor strokes. The results of this trial are published in today’s *Lancet*. Compared with placebo, perindopril (4·0 mg/day) with or without indapamide (2·0–2·5 mg/day) reduced systolic pressure by 9 mm Hg and diastolic pressure by 4 mm Hg, and the occurrence of stroke by 28% and that of major cardiovascular complications by 26%. These relative-risk reductions were similar in hypertensive and non-hypertensive patients, in participants with a history of ischaemic or haemorrhagic cerebrovascular disease, in patients recruited from eastern or western populations, and in patients enrolled early or late after their qualifying cerebrovascular event (IQR 2–22 months). These benefits were observed against a background of standard medical and surgical care, including other antihypertensive drugs for half the participants and antiplatelet therapy for most patients with a past ischaemic cerebrovascular event. PROGRESS thus reproduces the findings of the overview and extends them to normotensive people.

In view of the large number of patients who experience transient ischaemic attacks or minor strokes and the absolute benefit that can be achieved, the clinical implications are important. So how easy is it to translate the findings into guidelines for clinical practice? In PROGRESS hypertension was defined irrespective of treatment status. The blood-pressure cut-off points of 160 mm Hg systolic and 90 mm Hg diastolic were based on the lowest levels adopted in trials that showed that antihypertensive treatment regimens reduced the risk of stroke, but the threshold of systolic hypertension was 20 mm Hg higher than the definition of normotension in recent consensus documents. Furthermore, PROGRESS does not indicate the level to which blood pressure should be lowered or how blood pressure should be managed in patients with acute stroke. Also, the PROGRESS findings cannot be extrapolated to patients with occlusive or stenotic disease of the main cerebral arteries, in whom the cerebrovascular perfusion pressure is already decreased and whose risk of a first or recurrent brain infarct is substantially raised.

Pending consensus among expert committees, a reasonable approach is to start or intensify blood-pressure-lowering therapy in middle-aged or older patients who in the preceding 2 weeks to 5 years have had a cerebrovascular event, whose clinical condition is stable, and in whom there is no contraindication to blood-pressure-lowering therapy. The target blood pressure should be a normal pressure (<130/85 mm Hg) on conventional measurement by a doctor or nurse. In most hypertensive patients, combination therapy will be needed to attain this tightness of blood-pressure control. The blood pressure should be lowered gradually over several months to avoid side-effects and disruption of the autoregulation of cerebral blood flow. Unduly rapid or severe reduction of blood pressure can cause brain infarcts or transient ischaemic attacks. Orthostatic hypotension in older or frail patients should also be avoided. Patients with occlusive or severe stenotic disease of the carotid arteries should be identified before blood pressure is reduced, to prevent recurrence of stroke.

Advances in clinical medicine commonly raise new issues, and PROGRESS is no exception. Unexpectedly, a pre-specified subgroup analysis revealed striking heterogeneity of treatment-effect sizes for stroke risk between participants who received perindopril plus indapamide and those who received perindopril alone. Combination therapy reduced blood pressure by 12/5 mm Hg and stroke risk by 43%, with similar benefits in hypertensive and non-hypertensive patients. Treatment with perindopril alone lowered blood pressure by 5/3 mm Hg, but did not affect stroke recurrence. The 95% CI of the relative-risk reduction ranged from −19% to 23%. In a recent review of 27 outcome trials in which 136 124 patients participated, odds ratios to be expected for between-group differences of 5 or 12 mm Hg in systolic pressure were calculated by metaregression. The relative-risk reductions observed in PROGRESS for the perindopril-only group differed significantly from those predicted by the metaregression, but those for combination therapy did not (panel). Thus, the clinical outcome for the perindopril-only group is out of line not only within the context of PROGRESS itself but also with the evidence on the primary prevention of stroke in many previous outcome studies. A chance finding, as suggested by the PROGRESS investigators, cannot be ruled out, but is unlikely in the light of all available evidence.

If blood pressure and random variation do not explain the null results in the perindopril-only group in the PROGRESS trial, what could? Before randomisation, doctors had to opt whether any individual patient would receive single-drug or combination therapy. The patients selected for the latter strategy were younger, predominantly male, had higher blood pressure at entry, were more likely to be hypertensive or to have coronary heart disease, and were recruited sooner after their qualifying event. Statistical adjustment for the entry characteristics of the PROGRESS participants did
not remove the heterogeneity. In the Post-stroke Antihypertensive 'Treatment Study' indapamide (2.5 mg/day) decreased blood pressure by 5/2 mm Hg and, in accordance with other trials testing thiazide diuretics versus placebo, reduced the recurrence of fatal and non-fatal stroke by 29%. In the CAPPP trial, fatal and non-fatal stroke were 1.25 times (95% CI 1.01–1.25) more common in patients randomised to captopril than in those assigned conventional therapy with diuretics, \( \beta \)-blockers, or both. Because of the sheer number of patients who, on the basis of the results of PROGRESS, are becoming eligible for blood-pressure-lowering therapy, further research should be done to clarify whether drugs in classes more expensive than diuretics, in particular angiotensin-converting enzyme inhibitors, qualify as initial blood-pressure-lowering agents for the secondary prevention of stroke.

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2 PROGRESS Management Committee. Blood pressure lowering for the secondary prevention of stroke: rationale and design for PROGRESS. J Hypertens 1996; 14 (suppl 2); S41–S46.


**Trimethoprim-sulphamethoxazole prophylaxis in sub-Saharan Africa**

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The risk that large-scale distribution of trimethoprim-sulphamethoxazole (co-trimoxazole) might accelerate bacterial and parasitic resistance to antibiotics has been a concern since the recent WHO-UNAIDS recommendations that adults and children in Africa with HIV/AIDS be given co-trimoxazole prophylactically against opportunistic infections. The risk of co-trimoxazole-induced cross-resistance to sulfadoxine-pyrimethamine is an important aspect of this issue, because sulfadoxine-pyrimethamine is one of the most widely available and affordable antimalarial treatments, now recommended as the first-line drug in some African areas.

In today’s Lancet Jayasree Iyer and colleagues report that in *Plasmodium falciparum* there is complete cross-resistance between pyrimethamine and trimethoprim at the molecular level. These investigators advocate clinical studies to assess the effect of co-trimoxazole prophylaxis on the efficacy of sulfadoxine-pyrimethamine before co-trimoxazole prophylaxis is given routinely to patients with HIV/AIDS.

The debate about risks and benefits of co-trimoxazole prophylaxis in Africa is complex. That co-trimoxazole prophylaxis in Africa might accelerate the resistance of pathogens to antibiotics is indeed the leading concern. Factors to be considered in assessing the risk of accelerating resistance include the specific mechanisms underlying the resistance of bacterial and parasitic pathogens to trimethoprim and sulphamethoxazole, resistance to co-trimoxazole itself and induced cross-resistance to other drugs, and whether the potential mechanisms of cross-resistance may lead to multidrug resistance. In addition, these factors need to be considered at the level of the individual taking co-trimoxazole prophylactically as well as at the population level. For example, bacterial monoresistance to co-trimoxazole in an individual is unlikely to be the most worrying aspect of the problem if alternative drugs are available, and the rate of monoresistance to co-trimoxazole of bacteria cultured from people taking this drug prophylactically should not be viewed as a harmful consequence as long as these individuals continue to benefit from the prophylaxis. In adults participating in the ANRS 059 trial between 1996 and 1998 in Ivory Coast and who are still being followed up while they take co-trimoxazole, 75% of pathogens cultured from patients taking co-trimoxazole from 1996 to 2000 were resistant to co-trimoxazole, but the incidence of bacterial diseases during this period was half that among the placebo group during the trial. On the other hand, monoresistance to co-trimoxazole may lead in the long term to therapeutic problems at the individual level if it affects non-bacterial pathogens such as *Isospora belli* for which there is no alternative therapy. Monoresistance to co-trimoxazole also be a problem in the long term at the population level if it affects pathogens causing infections for which co-trimoxazole is still the recommended first-line drug (for example, pneumonia...