blood pressure is an unhealthy thing to have, to a large extent. Prospective population-based observational studies have shown a continuous, positive relationship between blood pressure and the risk of stroke or other major vascular events. There is no “safe” level of blood pressure below which the risk ceases to diminish. The association is even stronger than one might surmise from casual measurements, because of regression to the mean on subsequent readings. After appropriate correction, prolonged differences in usual diastolic blood pressure of 5, 7.5, and 10 mm Hg are respectively associated with at least 34%, 46%, and 56% relative risk reduction of stroke.1,2 The effectiveness of antihypertensive treatment in the primary prevention of stroke leaves no doubt about the causality of the relationship: systematic reviews show that a diastolic blood pressure reduction of 5 to 6 mm Hg results in a large decrease in stroke rate, in the order of 35% to 50%.3,4

Until now, the question remained whether blood pressure reduction was equally beneficial in patients after a transient ischemic attack (TIA) or a stroke. Theoretically, irreparable damage might already have occurred at the time of the first manifestation of cerebrovascular disease. A slightly crude analogy is that abstaining from cigarettes greatly improves prognosis in the general population but not much in patients with bronchial asthma. Systematic reviews showed equivocal benefit of blood pressure reduction in 4 clinical trials in which an episode of brain ischemia was the qualifying event.5 In subsets of patients with previous stroke from trials of antihypertensive treatment in general, the evidence was somewhat more robust, but not for normotensive patients.6

Therefore the recently published PROGRESS trial can be regarded as an impressive undertaking.7 The target population consisted mostly of patients with ischemic stroke, brain TIA, or transient monocular blindness, in whom the presumed cause was arterial. Patients with intracerebral hemorrhage were also included; they formed 11% of the trial population, while 4% had a stroke of unknown type. After a 4-week run-in period on active trial medication, 6105 patients were randomized between antihypertensive treatment and placebo; this number far exceeds those of the 4 previous trials combined (2742). The active treatment consisted of 1 or 2 drugs: always the angiotensin-converting enzyme (ACE) inhibitor perindopril (4 mg per day), in 58% of cases also the diuretic agent indapamide (mostly 2.5 mg per day). The choice between combined treatment (or double placebo) and perindopril alone (or single placebo) was left to the discretion of the physician. Importantly, existing antihypertensive treatment was continued in an unchanged fashion (50% of patients in the 2-drug group, 51% in the perindopril-only group); the same applied to other drugs such as antiplatelet agents.

After an average follow-up period of almost 4 years in the PROGRESS trial, the rate of major vascular events (vascular death, nonfatal stroke, or vascular death) was 5.5% per annum in the placebo group. This hazard was reduced to an annual rate of 4.1%, ie, by 26% (95% CI 16% to 34%) in all patients on active drug treatment (combined or single). This result was driven mainly by the patients on combined treatment (40% reduction of major vascular events, 95% CI 29% to 49%), in whom blood pressure was lowered by a mean of 12/5 mm Hg. There was a nonsignificant hazard reduction of 4% (95% CI 15% to 20%) by perindopril alone, associated with a mean blood pressure reduction of 5/3 mm Hg. The difference between the effects of combined and single drug treatment remained the same after correction for baseline imbalances. Patients with a baseline blood pressure above 160/90 mm Hg benefited somewhat more (29% reduction of major vascular events, 95% CI 16% to 40%) than nonhypertensive participants (24%, 95% CI 9% to 37%); this difference was attributable almost exclusively to the perindopril-only group. Strokes were prevented to the same degree as other vascular events, and equally in different stroke types: fatal or disabling versus moderately disabling, and ischemic versus hemorrhagic stroke.

The internal validity of the PROGRESS study seems unquestionable. The choice of outcome events is realistic in that they reflect the patient’s point of view that it is important not only to avoid strokes, but also to avoid sudden death or myocardial infarction. A plea to restrict analysis to vascular events in the brain can still be heard,8 but fortunately this “iatrocentric” perspective is on the decline. The results of the PROGRESS study are robust and important. Nevertheless, as so often happens in science, every answer raises new questions. Can the beneficial effects be generalized to everyday neurological practice? Is it only the blood pressure reduction that counts, independent of the drugs used? And should we now really start lowering blood pressure in “normotensive” patients with cerebral ischemia, even in the elderly?

The first question in the assessment of the external validity of trial results should always be: “Do I recognize my patients?”
Most patients in the PROGRESS study came from industrialized areas. Since the trial was on an outpatient basis, most participants were probably able to lead an independent life, although the final report does not specify this. The mean age (64 years) is what one might expect, as is the proportion of women (30%) and that of patients with TIsAs (22%). The main problem with generalizability is the extended time window for inclusion after the qualifying event. Few neurologists will continue to care for patients who had a TIA or nondisabling stroke for as long as 5 years. The median interval from qualifying event to inclusion was 8 months, the interquartile range 2 to 22 months. A sizable proportion of the trial patients therefore consists of “diehards,” resistant to the cumulative annual toll of around 3% deaths and disabling strokes to be expected in a population cohort of patients with cerebrovascular disease.9 Would the study drugs prevent strokes and heart attacks to the same degree in the first few months after the initial events, when the risk of stroke recurrence is highest? The deleterious effects of high blood pressure occur in the long term, so the answer might well be negative—despite the lack of a significant difference within the study.

The run-in period of 4 weeks on active drugs is another factor that somewhat limits the generalizability of the trial results. Of the 7121 patients who entered the preliminary phase of the trial, 1016 (14%) withdrew before actual randomization—mostly because of side effects from perindopril or sometimes indapamide. This means that physicians should keep in mind that the patient in front of them may well be the 1 out of 7 who is unable to tolerate the study drugs. In the “intention-to-treat situation,” the point estimate of the reduction of major vascular events therefore drops from 26% to 22%.

Is it indeed the blood pressure reduction per se that confers the protective effects against stroke and other cardiovascular events, and not special properties of a particular drug? Several arguments support this point of view. Firstly, the combined treatment in the PROGRESS trial (4 mg perindopril plus 2.5 mg indapamide per day) lowered the blood pressure to a greater extent in the PROGRESS trial (4 mg perindopril plus 2.5 mg indapamide) than perindopril alone.6 mm Hg.11 This means that physicians should keep in mind that the patient in front of them may well be the 1 out of 7 who is unable to tolerate the study drugs. In the “intention-to-treat situation,” the point estimate of the reduction of major vascular events therefore drops from 26% to 22%.

Should neurologists now start advising patients with cerebrovascular disease and (nearly) normal blood pressures to use antihypertensive drugs? Active drugs are rarely innocuous; such a course of action seems at odds with the fundamental tenet of medicine: “First do no harm.” Yet the incontrovertible fact remains that specifically for patients with blood pressures below 160/90 mm Hg, the combined treatment in the PROGRESS trial reduced the absolute rate of major vascular events from 4.4% to 3.5% per annum. In other words, one major vascular event can be prevented by treating 22 “normotensive” patients for 5 years with the combination of perindopril and indapamide, or with any other drug or combination of drugs that lowers blood pressure by 12/5 mm Hg—regardless of existing antihypertensive treatment. This “number needed to treat” is in the same order of magnitude as that of antiplatelet agents in patients with cerebral ischemia. Perhaps neurologists need to overcome a natural timidity and unfamiliarity vis-à-vis a category of drugs that is commonly attributed to the realm of internal medicine. On the other hand, the results of clinical trials are just averages; they do not apply to every patient in the same way.12 In elderly patients with a nondisabling stroke or TIA, life expectancy and comorbidity should be weighed against possible side effects of antihypertensive drugs—especially orthostatic hypotension with its attendant risk of falls and fractures. And in patients with “misery perfusion” in the presence of arterial occlusions, the blood pressure should probably be raised rather than lowered.13 Medicine remains an art. Thanks to the PROGRESS trial, our art can be applied against the background of considerably more knowledge than we had before.

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References


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The PROGRESS Trial: Preventing Strokes by Lowering Blood Pressure in Patients With Cerebral Ischemia: Emerging Therapies: Critique of an Important Advance

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