Summary points

For most clinical trials it is impossible to identify which patients will usually respond to treatment

It is often assumed without proof that such individual response is important

The difficulties of interpretation are exacerbated if continuous measurements are dichotomised

Since individuals differ by more than their genes, genetic variability cannot exceed individual variability

Carefully designed repeated period crossover trials have a useful role in identifying individual, and by extension genetic, response

interactions, and patient by treatment interaction can be examined only by repeated crossover trials.⁸ Such trials can then be analysed using random effect models in a way that will permit the resolution of variability into various sources: the overall effect of treatment, variability between patients, variability within patients, and patient by treatment interaction.⁹

The pharmaceutical industry has rarely, if ever, carried out the sort of trial that would permit identifica-

tion of patient by treatment interaction. Thus statements that the drugs don't work on most people are based on mere supposition; the drugs may work moderately well for all people. To identify those drug and disease combinations for which individual response is important and hence for which genetic factors may be, it will be important to plan and analyse carefully.

Contributors and sources: SS used to work in the pharmaceutical industry and his research interests include design and analysis of clinical trials, in particular crossover trials.

Competing interest: SS is a consultant to the pharmaceutical industry.

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The PROGRESS trial three years later: time for a balanced report of effectiveness

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Has the use of the phrase "perindopril based blood pressure lowering regimen" resulted in an oversimplistic and hence inaccurate interpretation of the results of the PROGRESS trial creeping into the literature and clinical practice?

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Any doctor who keeps up to date with the stroke literature will be familiar with PROGRESS—the perindopril protection against recurrent stroke study,¹ a clinical trial which had resulted, by February 2004, in more than 35 ancillary publications. The aim of the study was to "resolve clinical uncertainty about the efficacy and safety of routine blood-pressure-lowering therapy for individuals with a history of stroke or transient ischemic attack."¹ The trial found that blood pressure lowering was safe and effective, but three years after its publication, the optimal antihypertensive regimen for secondary stroke prevention remains unclear. The title of the study, together with its results as reported, may lead the unwary reader to conclude that perindopril used alone protects against recurrence of stroke. Although this was actually not a finding of PROGRESS, the study design and data presentation obfuscate this fact rather than making it clear.

Design of the trial

The PROGRESS trial had a "flexible" design, which meant that not all patients received the same antihypertensive regimen. Patients who had had a stroke or transient ischaemic attack in the previous five years were

eligible. They were also required to have "no definite indication (such as heart failure) for treatment with an ACE inhibitor and no definite contraindication (such as previous intolerance) to such treatment." The entry criteria did not include blood pressure, but treatment with agents other than angiotensin converting enzyme inhibitors was recommended to patients with uncontrolled hypertension before they entered the trial. Patients were then randomised, on a double blind basis, to either active treatment or placebo. All active treatment patients received treatment with perindopril. Indapamide was added "at the discretion of the individual physician" if a patient had "no specific indication for or contraindication to treatment with a diuretic."¹

After a mean follow up of 3.9 years, the active treatment group as a whole had significantly fewer strokes and major vascular events. However, a prespecified subgroup analysis showed that although participants treated with the combination of perindopril plus indapamide had a significantly lower stroke risk than patients who received double placebo (43% risk reduction; 95% confidence interval 30% to 45%), patients treated with perindopril alone had a stroke risk that was not discernibly different from placebo (5% risk reduction, -19% to 23%). Even though there was

Figure 3: Cumulative Incidence of stroke among participants assigned active treatment and those assigned placebo

In the PROGRESS trial, the phrases "active treatment" or "perindopril-based blood-pressure-lowering regimen" refer to amalgamated data from the perindopril alone and perindopril plus indapamide treatment arms. Perindopril alone provided no detectable benefits. Reproduced with permission from Elsevier¹

significant heterogeneity in the sizes of these treatment effects ($P < 0.001$), the PROGRESS results are repeatedly presented as amalgamated data. For example, "a flexible blood-pressure-lowering regimen, which included perindopril for all patients and indapamide for 58%, reduced blood pressure by an average of 9/4 mm Hg and the risk of stroke by more than a quarter" distinctly de-emphasises the fact that the regimen of perindopril alone had no measurable effect on outcome.

Reaction to results

Shortly after the study was published, an editorial (in line with a small number of earlier critical letters and commentaries²⁻⁴) in the *American Journal of Hypertension* stated explicitly the two major problems with PROGRESS. Firstly, it is illogical and misleading to combine two treatment arms that have significantly heterogeneous results—if the findings from two trial arms differ substantially "then the findings need to be presented separately and interpreted separately"; secondly, "the major limitation of the PROGRESS trial was the failure to include a group randomized to indapamide alone."⁵ These editorialists speculated that indapamide alone may have reduced stroke by as much as 38% (43% for the combined therapy minus 5% for perindopril alone), which would be consistent with the 34% risk reduction seen with low dose diuretics in the primary prevention setting⁶ and the 29% risk reduction seen with indapamide alone in the post-stroke antihypertensive treatment study (PATS).⁷ However, from the design of PROGRESS, one cannot know whether the benefit seen with combination therapy is due to indapamide alone or to an additive or synergistic effect of indapamide with perindopril. What is clear is that the benefit is not attributable to perindopril alone.

The same editorial also argues that the blood pressure differences between the two arms (5/3 mm Hg for perindopril alone *v* 12/5 mm Hg for the combined therapy) are unlikely to explain the large difference in stroke reduction.⁵ For example, the blood pressure reduction with indapamide alone in the PATS trial was

only 5/2 mm Hg, less than the reduction seen with perindopril alone in PROGRESS. Yet indapamide alone in PATS was associated with significant stroke reduction, while perindopril alone in PROGRESS was not. Several other large studies, however, have provided evidence that for most cardiovascular outcomes it is the amount of blood pressure reduction, rather than the particular regimen used, that determines the benefits of treatment.⁸⁻¹⁰ Although this is acknowledged in the PROGRESS paper, it is not expressed in the conclusion, which says of perindopril and indapamide that "treatment with these two agents should now be considered routinely for patients with a history of stroke or transient ischemic attack."¹

Further publications of PROGRESS data

Since the publication of the *American Journal of Hypertension* editorial, several other publications of the PROGRESS data have appeared, describing the results of various outcome measures, all of which continue to report the results in the same manner, combining the treatment arms and calling them the "perindopril-based blood pressure-lowering regimen."¹¹⁻¹⁴ That the study's results as presented are misleading is shown by the fact that at least three review articles have misinterpreted the findings. An article in the "EBM: trials on trial" section of the *Medical Journal of Australia* which put the PROGRESS trial "on trial" concludes that "in most patients [who have had a stroke], ACE inhibitor therapy could be started initially at the time of discharge or at post discharge follow-up. However, to maximize the blood-pressure-lowering effect, most patients should receive combination therapy."¹⁵ A Russian language review of hypertension control in stroke prevention concluded, on the basis of PROGRESS, that "antihypertensive therapy of patients with the history of acute cerebral circulation disorder with ACE inhibitor perindopril is effective in secondary prophylaxis in such patients."¹⁶ A recent review of PROGRESS in the *International Journal of Clinical Practice* concluded that "treatment based on perindopril significantly reduces stroke (28%)" and advised clinicians, with respect to choice of treatment, that "stable patients post stroke should be considered for perindopril, and indapamide if possible."¹⁷

Authors' and readers' responsibilities

Evidence from major clinical trials such as the PROGRESS study is used by clinicians to make important treatment decisions for their patients. It is the responsibility of discerning readers and clinicians to interpret data carefully; however, it is also the responsibility of the authors of a paper to present results with the least possible bias. Although PROGRESS was set up to test perindopril, the trial provided no evidence of its benefit as single drug therapy for preventing recurrent strokes. Moreover, there is no evidence to date that using perindopril in combination with indapamide is more beneficial than using indapamide alone. A trial explicitly comparing the combination with indapamide alone would be needed to resolve this issue. In the meantime, a more cautious and balanced presentation of the results of the PROGRESS trial is warranted.

Summary points

The PROGRESS trial reports that a “perindopril-based blood-pressure-lowering regimen” provided significant protection against recurrent stroke

Only the subgroup receiving both perindopril and indapamide had reduced stroke recurrence; the study design did not include a subgroup randomised to indapamide alone (previously shown to reduce stroke recurrence)

Some reviews of the PROGRESS trial have advocated using perindopril alone for prevention of stroke recurrence, which does not follow from the findings

Results from major drug trials must be clearly presented to avoid misinterpretation by busy clinicians

Contributors and sources: The authors are both academic physicians with an interest in language and how it is used in scientific discourse. RW is a neurologist working mainly in the fields of epilepsy and electroencephalography; CZ is an internist working mainly in the fields of palliative care and social science in medicine. This article was written after the PROGRESS trial was brought to the authors' attention by events surrounding the management of a patient in their teaching hospital.

Competing interests: None declared.

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Commentary: The PROGRESS trial three years later: time for more action, less distraction

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Since the publication of the results of the PROGRESS trial, there has been much comment in the *BMJ* and elsewhere.^{1 2} Most of this acknowledges the importance of the findings for the care of patients with cerebrovascular disease. These patients are at high risk of stroke recurrence, and before the trial was completed few interventions had been proved to reduce this risk. Aspirin was known to modestly reduce the risk of recurrence of ischaemic stroke, but no treatment had been shown to reduce the frequently catastrophic recurrence of cerebral haemorrhage. This situation was changed profoundly by the results of PROGRESS, which showed that a simple blood pressure lowering regimen substantially reduced the risks of recurrent stroke,³ disability,⁴ and cardiac events⁵ across a broad range of blood pressure levels in patients with either ischaemic or haemorrhagic cerebrovascular disease.

PROGRESS was conceived during an era in which many stroke specialists were concerned about possible risks of blood pressure lowering in patients with compromised cerebral circulation. While epidemiological evidence indicated that the lowest blood pressure levels were associated with the lowest risks of stroke

recurrence,⁶ prevailing clinical opinion required us to allow individual doctors the discretion to determine the intensity of the blood pressure lowering regimen they provided to individual patients. The treatment regimen in the study comprised the angiotensin converting enzyme inhibitor perindopril and the diuretic indapamide. Our objective was to have as many patients as possible treated with both drugs; however, the treating doctors decided whether to introduce indapamide after patients had been stabilised on perindopril.

Although PROGRESS was not designed to determine the separate effects of perindopril and indapamide, the benefits of combination treatment with these agents proved to be particularly large, with stroke risks cut by almost a half and reductions in most other cardiovascular outcomes, including death. Conversely, treatment with perindopril alone provided no detectable benefits, although the 95% confidence intervals were wide and modest benefits could not be excluded. Not surprisingly, therefore, the principal conclusion was that patients with cerebrovascular disease should be considered routinely for combination treatment with perindopril and indapamide.³ This regimen