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Scientific Update™

The PROGRESS Trial and the Prevention of Recurrent Stroke: Applying Results to Clinical Practice

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Blood pressure is a key determinant for the risk of initial stroke in both hypertensive and non-hypertensive individuals. Until recently, there have been little data regarding the association between blood pressure and recurrent stroke. The recently published Perindopril pROtection aGainst REcurrent Stroke Study (PROGRESS) demonstrates that a blood pressure lowering regimen consisting of the angiotensin-converting enzyme (ACE) inhibitor, perindopril, and the diuretic, indapamide, reduces the incidence of recurrent stroke among hypertensive and non-hypertension subjects with a history of stroke. In this issue of *Cardiology Scientific Update*, new data from the PROGRESS study regarding coronary events, cognitive function, new subgroup analyses, as well as the clinical applications of the study, will be reviewed.

Stroke is the second leading cause of death worldwide and of disability in developed countries.[1,2] In North America, approximately 5 million people have had a stroke and 550,000 new cases occur each year.[3] Among those who survive a stroke or transient ischemic attack (TIA), close to 20% will suffer another stroke within 5 years.[4] Blood pressure is a key determinant for the risk of initial stroke in both hypertensive and non-hypertensive individuals.[5] The risk of primary stroke can be reduced by lowering blood pressure in patients with hypertension and by the use of antiplatelet agents in patients with vascular disease.[6-8] To date, however, little is known about the relationship between blood pressure and recurrent stroke, and importantly, whether lowering blood pressure in hypertensive or non-hypertensive patients will reduce the risk of recurrent stroke. An illustration of this uncertainty was the proposed J-shaped relation between blood pressure and recurrent stroke in patients with a recent history of ischemic stroke.[9] Furthermore, studies that have demonstrated reduction of strokes with blood pressure lowering have not distinguished the treatment effect on ischemic and hemorrhagic stroke, the latter being particularly devastating.

The PROGRESS Study

The PROGRESS study was a large-scale, international, investigator-initiated study designed to examine the effects of a flexible blood pressure-lowering regimen, consisting of the ACE inhibitor, perindopril, and the diuretic, indapamide, on the risk of stroke and other major vascular events in hypertensive and non-hypertensive patients with a history of stroke or TIA. The design and principal results of the study have been published recently.[10]

In brief, 6105 subjects from 172 centres in Europe, Australasia, and Asia participated in the study. Patients were eligible if they had a history of stroke or TIA within the previous 5 years. Importantly, there were no blood pressure entry criteria; however, individuals with uncontrolled hypertension were recommended for treatment with an antihypertensive regimen other than ACE inhibition prior to entry. Likewise, it was recommended that participants should be clinically stable for at least 2 weeks after their most recent vascular event, including

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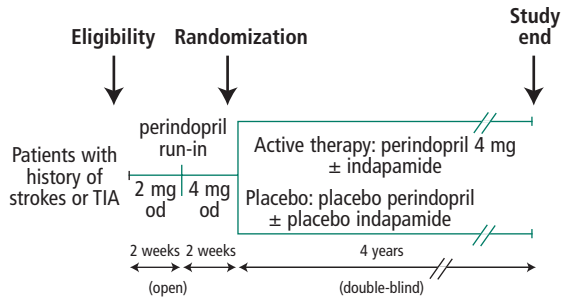
Figure 1: PROGRESS Study design



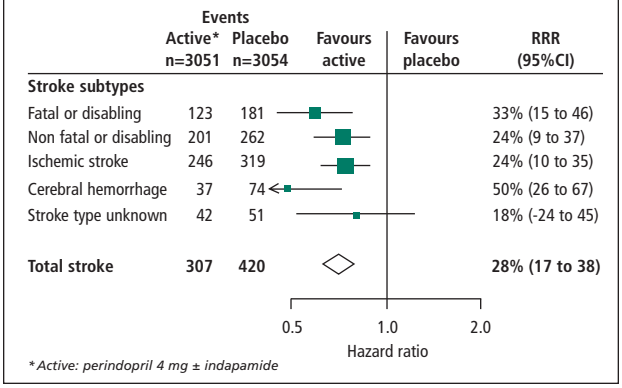
TIA = transient ischemic attack

stroke, before study entry. The study design is summarized in Figure 1.

Randomization was preceded by a 4-week run-in period during which tolerability to open-label perindopril had to be demonstrated. Active treatment comprised a regimen based on perindopril 4 mg once a day with the addition of indapamide 2.5 mg daily (2.0 mg daily in Japan) if the attending physician judged that there would be no specific indication or contraindication to the use of a diuretic. The rationale for allowing the use of combination therapy was to maximize the level of blood pressure lowering using the study regimen. However, the PROGRESS study design was unique in that the investigators were asked *before* randomization to decide, based on clinical judgment, on the choice of monotherapy with perindopril or combination therapy with perindopril and indapamide. Accordingly, the randomized treatment allocation could be stratified according to intention to use perindopril alone (or placebo) or the combination (or double placebo). The other pre-specified subgroups included centre, age, gender, entry blood pressure, and qualifying event.

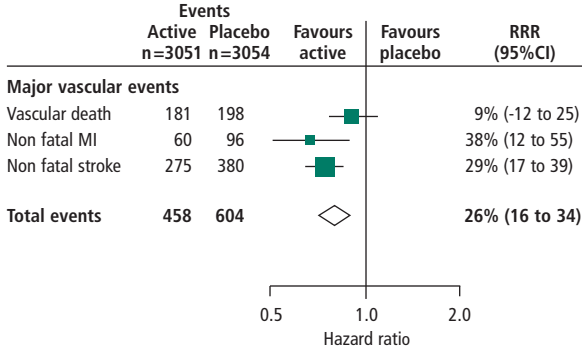
The primary study outcome was fatal or non-fatal stroke. Secondary outcomes included fatal or disabling stroke, total

Figure 2: PRIMARY outcome: Recurrent stroke



RRR = relative risk reduction

Figure 3: Major vascular events



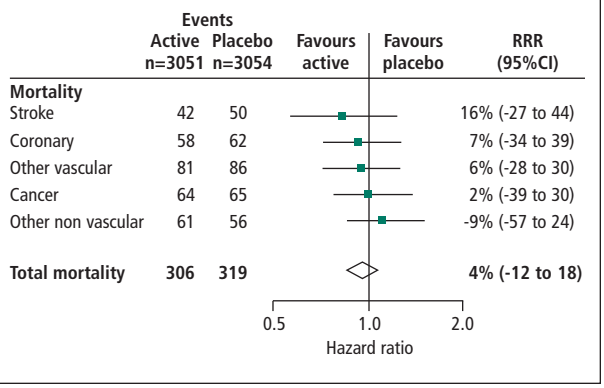
RRR = relative risk reduction

major vascular events (non-fatal stroke, non-fatal myocardial infarction [MI], or death due to any vascular cause), total and cause-specific deaths, and hospital admissions. The calculation of sample size (6000 participants and follow-up of 4 years) assumed an annual stroke rate of between 1.5%-2.0% in the placebo group, an average difference of 4 mm Hg diastolic blood pressure (DBP) between the active treatment and placebo groups, and a reduction of 30% in total stroke risk with active treatment.

Primary results

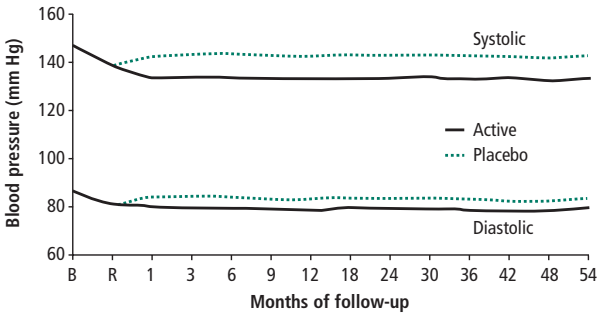
The primary results of the PROGRESS study have been published recently.[10] Briefly, 7121 patients entered the run-in phase, of which 1016 patients withdrew or were ineligible. The remaining 6105 patients were then randomized to combination active therapy or double placebo (n=3544), single active therapy or placebo (n=2561). 3051 patients were randomized to active therapy (1770 combination, 1281 single) and 3054 patients were randomized to placebo therapy (1774 double placebo, 1280 single). In the active therapy group, 2 patients were lost to follow-up, whereas in the placebo group, one patient was lost to follow up. The mean duration of follow up was 3.9 years.

Figure 4: Mortality



RRR = relative risk reduction

Figure 5: Blood pressure differences



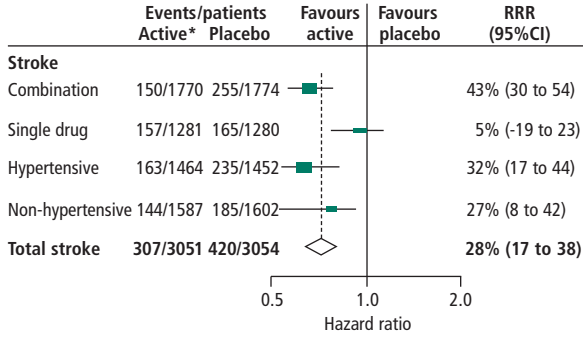
R = Randomization

The active and placebo treatment groups were comparable in baseline demographics. The mean age was 64 years, 30% were women, and 39% were Asians (China or Japan). Seventy-one per cent had stroke as the qualifying event (71% ischemic stroke, 11% cerebral hemorrhage, 5% stroke of unknown etiology), 22% had TIA or amaurosis fugax as the qualifying event. The median time between qualifying event and randomization was 8 months. Randomized therapy was continued in 86% of patients on active therapy and 87% of patients on placebo.

Results of the primary outcome, stroke, are shown in Figure 2. The overall risk of recurrent stroke was reduced by 28%. This risk reduction was significant regardless of whether the stroke was fatal/disabling or neither, or whether it was due to ischemic or hemorrhagic etiology. Results of the major secondary outcomes, namely major vascular events and mortality, are shown in Figure 3 and 4, respectively. Major vascular events were reduced by active treatment by 26%, driven by reductions in both non-fatal MI and non-fatal stroke. Mortality, on the other hand, was not significantly reduced (4%).

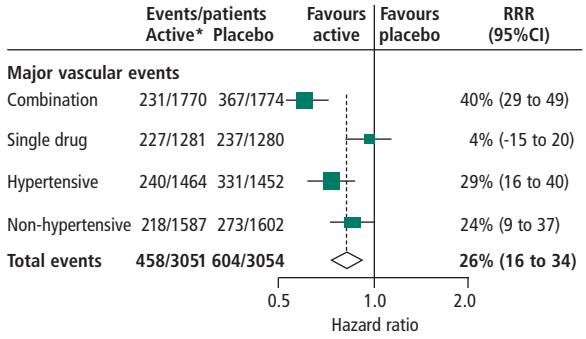
The effect of treatment on systolic blood pressure (SBP) and DBP are shown in Figure 5. SBP and DBP were reduced by an overall average of 9.0 ± 0.3 (mean ± SE) and 4.0 ± 0.2 mm Hg,

Figure 6: Effects of study treatment regimen and history of hypertension on stroke



RRR = relative risk reduction

Figure 7: Effects of study treatment regimen and history of hypertension on vascular events



RRR = relative risk reduction

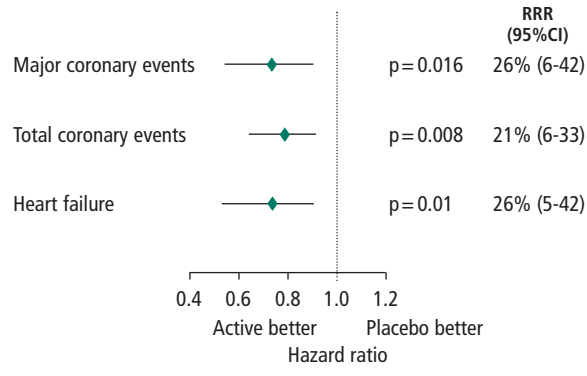
respectively. These differences were maintained throughout the study. The differences in blood pressures were greater in patients who received combination therapy (SBP 12.3 ± 0.5 mm Hg, DBP 5.0 ± 0.3 mm Hg) than in those who received single therapy (SBP 4.9 ± 0.6 mm Hg, DBP 2.8 ± 0.3 mm Hg).

The effects of the study treatment on stroke and major vascular events in two pre-specified subgroups are shown in Figure 6 and 7, respectively. Among patients who received combination therapy, the risk of stroke and major vascular events were reduced significantly by 43% and 40%, respectively. These benefits, however, were not observed in patients who received single drug therapy. On the other hand, with respect to history of hypertension (>160/90 mm Hg), reduced risk of stroke and vascular events were significant in both the hypertensive, as well as the non-hypertensive patients.

New data

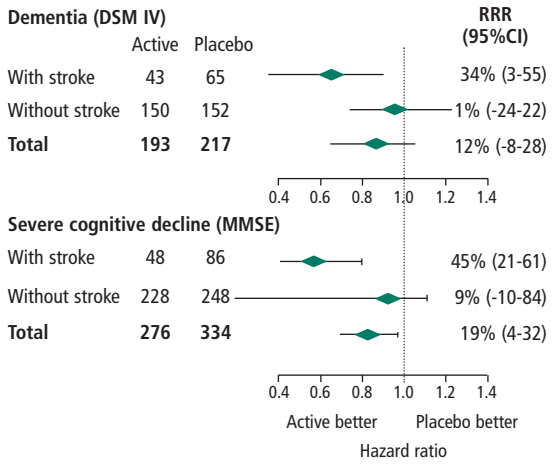
New data on cardiac events, dementia, and cognitive function, as well as other subgroup analyses, were presented recently at the late-breaking sessions of the American Society of Hypertension meeting. These data are not yet published and may

Figure 8: Cardiac events



RRR = relative risk reduction

Figure 9: Dementia and cognitive function



RRR = relative risk reduction

Table 1: Relative risk reductions of recurrent stroke by active treatment: subgroup analyses

	Risk reductions	95% CI
Hypertensive	32%	17-44
Non-hypertensive	27%	8-48
Cerebral infarction	23%	11-37
Cerebral hemorrhage	50%	25-71
Qualifying event <6 months	24%	4-39
Qualifying event >6 months	32%	12-40
Diabetic	38%	5-58
Non-diabetic	28%	6-39
Asian	39%	22-50
Non-Asian	22%	15-35

therefore be subject to modification. Data for cardiac events are shown in Figure 8. Major coronary events included non-fatal MI and death due to coronary heart disease (CHD). Total coronary events comprised non-fatal MI, death due to CHD, and need for revascularization. Heart failure events were defined as heart failure death, hospitalization, or discontinuation of study medications due to heart failure. As shown in Figure 8, the risk of these three cardiac events was reduced by 26%, 21%, and 26% respectively.

Data on dementia and severe decline in cognitive function as measured by the Mini-Mental Status Evaluation in patients with or without recurrent stroke are shown in Figure 9. In patients who developed recurrent stroke (the primary outcome), the risk of dementia was reduced by 34% and the risk of severe decline in cognitive function was reduced by 45%. These benefits of active therapy were not observed in patients who did not experience recurrent stroke. In patients who were screened negative for dementia at baseline, the risk of incident dementia in those with recurrent stroke (21 cases of new dementia in active group, 42 cases in placebo) was reduced by 50%; 95% confidence interval (CI), 15 - 70. The 16% reduction in those without recurrent stroke was not significant. When patients with or without recurrent stroke were combined (71 cases of new dementia in active group, 102 in placebo group), there was still a significant 31% reduction; 95% CI, 6 to 49. Overall, the number of patients considered disabled according to Barthel activities of daily living index[11] was smaller in the active group (160 cases) than in the placebo group (209 cases). This was driven by the significantly fewer cases of disability in the active group (58 cases) than in placebo group (102 cases) in those patients who had recurrent stroke.

In addition to the initial subgroup analyses based on treatment regimen (combination versus single drug) and history of hypertension at baseline, additional subgroup analyses have been conducted since publication of the main results. The relative risk reductions of recurrent stroke with active treatment and the primary outcome, according to medical history and demographics, are shown in Table 1. The benefit of active treatment on recurrent stroke is evident across a broad spectrum of underlying medical conditions and baseline demographics. Similar beneficial effects were observed on the secondary outcome, major vascular events, across similar subgroups, including the use of aspirin at baseline.

Finally, to further assess if the benefits of active treatment on recurrent stroke are applicable to patients with wide range of blood pressures, the effects on the risk of recurrent stroke according baseline SBP and DBP are shown in Table 2. Significant reductions in the risk of recurrent stroke were observed across three categories of baseline SBP and DBP, thereby supporting the observations from the primary subgroup analysis on baseline history of hypertension.

Discussion and clinical application

The principal finding of the PROGRESS trial is that in patients with a history of stroke and TIA within the previous 5 years, a blood pressure-lowering regimen that comprises the ACE inhibitor, perindopril, and the diuretic, indapamide, significantly reduces the risk of recurrent stroke and major vascular events. In those patients who have suffered recurrent stroke despite therapy, the risk of dementia and severe decline in cognitive function is still significantly reduced by the therapy.

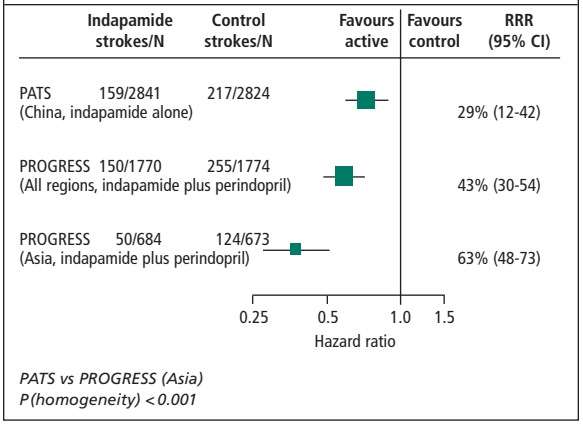
The observations from the two initial planned subgroup analyses – namely the treatment effect of combination versus single drug therapy and in the presence versus the absence of hypertension – provide insights regarding the relationship between blood pressure and recurrent stroke that may have important clinical implications. Combination therapy reduced SBP/DBP by 12/5 mm Hg and reduced stroke risk by 43%. On the other hand, single drug therapy reduced SBP/DBP only by 5/3 mm Hg and had no discernible effect (5% reduction, not significant) on the risk of recurrent stroke. The greater benefit of combination therapy can be explained by a better control of blood pressure in the combination group.

The apparent lack of benefit of single drug therapy on recurrent stroke and vascular events warrant further discussion. In doing so, one needs to address the following questions.

• First, are the baseline characteristics of the two groups similar? Analysis of the baseline demographics of patients who received combination (3544 patients) and single drug therapy (2561 patients) reveals that the two subgroups were comparable at baseline with regard to gender, age, and race. However, as per the design of the study, baseline SBP was slightly higher in the combination compared to the single drug group (149 and 144 mm Hg, respectively) and the proportion of patients with hypertension at baseline was also higher in the combination compared to the single drug group (54% and 40%, respectively). Furthermore, the annualized incidence of stroke in the placebo arms of the two groups was very similar. Therefore, minute differences of the two subgroups would unlikely explain the heterogeneity of treatment effects.

• Secondly, was the PROGRESS study sufficiently powered to detect differences in outcomes from single drug therapy? Several earlier trials using other antihypertensive regimens that failed to demonstrate an effect on stroke, characteristically had small reductions in blood pressure and involved smaller number of patients.[12] In this regard, it is useful to explore the relationship between the relative risk of stroke and blood pressure from the data of the United Kingdom Transient Ischemic Attack (UKTIA) trial.[13] UKTIA involved 2435 patients with blood pressure measurements also taken during a 4-year follow-up following the qualifying event (ie, TIA or minor stroke).[14] Based on the UKTIA study analysis, a decline of 3 mm Hg would be associated with a 3% reduction in recurrent stroke, comparable to the 5% (albeit insignificant) reduction reported in the single drug treatment group in PROGRESS. Given the relatively wide confidence intervals of the relative risks in the single drug treatment subgroup in PROGRESS, a treatment effect can neither be proven nor refuted.

Figure 10: Blood pressure lowering and recurrent stroke: Comparison of PATS and PROGRESS



RRR = relative risk reduction; N = total number of patients

• Thirdly, another explanation may be a selection bias introduced by the open-label run-in of perindopril, that excluded 1016 of the 7121 patients screened.

The second planned subgroup analysis demonstrated that both patients with, and without, hypertension benefited almost equally from active therapy. This observation was supported by the aforementioned subgroup analyses based on baseline SBP and DBP. These data therefore refute the proposed hypothesis of the "J-shape" relationship between blood pressure and risk of stroke,[9] including recurrent stroke. They therefore suggest that patients who have suffered a cerebral vascular event will benefit from a blood

Table 2: Risks of recurrent stroke according to baseline blood pressure (combination therapy sub-group)

Blood pressure		Placebo group	Active group	RRR (95% CI)
SBP	>160 mm Hg	19.5%	10.9%	47% (13-65)
	140-159 mm Hg	12.6%	7.8%	41% (26-75)
	<140 mm Hg	11.4%	7.1%	39% (15-66)
DBP	>95 mm Hg	16.5%	6.8%	62% (41-76)
	85-94 mm Hg	15.2%	10.2%	36% (12-53)
	<85 mm Hg	12.3%	7.8%	37% (12-55)
Total		**14.4%**	**8.5%**	**43%**

RRR = relative risk reduction

pressure lowering regimen even though they may be considered normotensive by current hypertension guidelines.

The patient population in the PROGRESS study is very similar to that of the Post-stroke Antihypertensive Treatment Study (PATS) conducted in China that has been reported only in preliminary form.[15] In this study, 5665 patients with a history of stroke and TIA were randomized to indapamide 2.5 mg (n=2841) or placebo (n=2824). With the exception that all of the patients were Chinese, the baseline demographics of PATS (including mean age, gender, baseline blood pressure, and etiologies of stroke) were otherwise very similar to those of the PROGRESS study. Follow-up was for 3 years and blood pressure reduction by indapamide was 5/2 mm Hg, which is similar to the single drug treatment group of PROGRESS. To explore the incremental effect of combination therapy, the treatment effects on recurrent stroke for the PATS study (indapamide versus placebo), for the combined drug therapy arm of the entire PROGRESS study and for the combined therapy arm of Asians (mostly from China) in the PROGRESS study are shown in Figure 10. In PATS, treatment with the diuretic indapamide alone reduced the risk of recurrent stroke by 29% (*P*=0.0009) in the Chinese patients. In PROGRESS (Asian patients), combined therapy with perindopril and indapamide reduced the risk of recurrent stroke by 63% (*P*=0.0007). This comparison once again underscores the importance of blood pressure lowering in patients with stroke and TIA. It demonstrates that optimal blood pressure reduction, and therefore reduction of the risk of recurrent stroke, can only be accomplished by combined therapy, ie, with a combination of an ACE inhibitor and a diuretic.

Conclusion

The main results and preliminary data from the PROGRESS study discussed in this *Cardiology Scientific Update* indicate that patients who have suffered a stroke or TIA should be treated with a blood pressure-lowering regimen, regardless of blood pressure levels and the etiology of the stroke, as long as they are clinically stable. Based on the design of PROGRESS, it can be recommended that therapy for patients with acute stroke be initiated as soon as they become stabilized (eg, prior to discharge). In patients with a remote history of stroke, therapy should be initiated at the next office visit. Blood pressure lowering should be initiated with a single agent, but quickly titrated to combined drug therapy which, based on current evidence, should comprise an ACE inhibitor such as perindopril and a diuretic such as indapamide. Such an approach will likely greatly reduce the incidence of recurrent stroke of all types and major cardiovascular events in the vast number of patients inflicted with stroke worldwide.

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