Effects of a Perindopril-Based Blood Pressure–Lowering Regimen on the Risk of Recurrent Stroke According to Stroke Subtype and Medical History

The PROGRESS Trial

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Background and Purpose—The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) showed that blood pressure lowering reduced stroke risk in patients with a history of cerebrovascular events. Here, we report the consistency of treatment effects across different stroke subtypes and among major clinical subgroups.

Methods—PROGRESS was a randomized, double-blind trial among 6105 people with a prior history of cerebrovascular events. Participants were assigned to active treatment (perindopril for all participants and indapamide for those with neither an indication for nor a contraindication to a diuretic) or matching placebo(s).

Results—During a mean of 3.9 years of follow-up, active treatment reduced the absolute rates of ischemic stroke from 10% to 8% (relative risk reduction [RRR], 24%; 95% confidence interval [CI], 10 to 35) and the absolute rates of intracerebral hemorrhage from 2% to 1% (RRR, 50%; 95% CI, 26 to 67). The relative risk of any stroke during follow-up was reduced by 26% (95% CI, 12 to 38) among patients whose baseline cerebrovascular event was an ischemic stroke and by 49% (95% CI, 18 to 68) among those whose baseline event was an intracerebral hemorrhage. There was no evidence that treatment effects were modified by other drug therapies (antiplatelet or other antihypertensive agents), residual neurological signs, atrial fibrillation, or the time since the last cerebrovascular event.

Conclusions—Beneficial effects of a perindopril-based treatment regimen were observed for all stroke types and all major clinical subgroups studied. These data suggest that effective blood pressure–lowering therapy should be routinely considered for all patients with a history of cerebrovascular events. (Stroke. 2004;35:116-121.)

Key Words: angiotensin converting enzyme inhibitors ■ blood pressure ■ intracerebral hemorrhage ■ randomized controlled trials ■ stroke, ischemic

The principal clinical presentations of cerebrovascular events are ischemic stroke (IS), intracerebral hemorrhage (ICH), and transient ischemic attack (TIA). Although there appears to be overlap in the determinants of each of these clinical presentations, different pathophysiological processes have been implicated, and clinical uncertainty remains about the effectiveness of prevention strategies across the different clinical presentations and between different population groups.1,2

Blood pressure (BP) levels are strongly predictive of the risks of both first and recurrent cerebrovascular events.3–6 BP lowering has long been established as an effective treatment for the prevention of first stroke among individuals with hypertension.7 In the last decade, it has also been shown to be protective among other high-risk patient groups both with and without elevated BP levels.8–10 Most recently, the Perindopril Protection Against Recurrent Stroke Study (PROGRESS)11 extended the evidence about the beneficial effects of BP lowering on the risk of stroke to include individuals with a history of prior cerebrovascular events, regardless of the baseline level of BP.12 We report here the generalizability of the effects of BP lowering in PROGRESS on the different types of outcome strokes and the effects of study treatment in subgroups of participants defined by type of prior cerebrovascular event and related aspects of medical history.
Materials and Methods

Study Design and Participants

The design of PROGRESS has been described in detail elsewhere. Briefly, 6105 participants were recruited between May 1995 and November 1997. Participants were eligible if they had a history of cerebrovascular events (stroke or TIA but not subarachnoid hemorrhage) within the previous 5 years. In addition, participants were required to have no clear indication for or contraindication to treatment with an angiotensin-converting enzyme inhibitor. There were no BP criteria for entry. The institutional ethics committee of each collaborating center approved the trial, and all participants provided written, informed consent.

Participants who tolerated at least 4 weeks of run-in therapy with perindopril were randomly assigned in a double-blind manner to continued active treatment or placebo. Active treatment comprised a flexible regimen based on perindopril (4 mg/d), with indapamide (2.5 mg/d; 2 mg/d in Japan) in those participants for whom the responsible study physician felt that there was no specific indication for or contraindication to the use of a diuretic. Those participants assigned placebo received tablets identical in appearance to the active agent(s). The rationale for using combination therapy (perindopril and indapamide or double placebo) rather than single-drug therapy (perindopril or single placebo) whenever possible was to maximize the fall in BP.

Definitions and Classification

For the purposes of both eligibility and outcome assessment, stroke was defined as “evidence of an acute disturbance of focal neurological function with symptoms lasting more than 24 hours and thought to be due to ICH or ischemia” (International Classification of Diseases, ninth revision [ICD-9], code 431, 433, 434, 436, or 437). TIA was defined using the same World Health Organization criteria as “an acute disturbance of focal neurological or monocular function with symptoms lasting less than 24 hours and thought to be due to arterioembolic or thrombotic vascular disease” (ICD-9 code 435). All baseline and follow-up strokes were subclassified whenever possible as IS (ICD-9 code 433 or 434), ICH (ICD-9 code 431), or unknown type (ICD-9 436, 437). The Trial of 10I72 in Acute Stroke Treatment [TOAST] criteria12 were used to further subclassify IS recorded during follow-up as lacunar stroke, cardioembolic stroke, large-artery stroke, or unknown ischemic type.

Baseline cerebrovascular event was defined as the most recent cerebrovascular event by local study investigators using evidence from the medical history and physical examination supplemented by clinical records and/or radiological findings if available (CT and/or MRI). All suspected stroke outcome events recorded during follow-up were first reviewed and reported by the relevant local study investigator and then evaluated by a neurologist on the central collaborating center. Participants were first reviewed and reported by the relevant local study investigator and then evaluated by a neurologist on the central collaborating center. The study investigator and then evaluated by a neurologist on the central collaborating center, and all participants provided written, informed consent.

Major Clinical Subgroups

The effects of treatment were estimated for mutually exclusive subgroups at baseline defined by the type of the most recent cerebrovascular event (IS, ICH, stroke of unknown type, or TIA) and for other participant subgroups defined on the basis of the presence or absence of each of the following baseline characteristics: (1) aspirin or other antiplatelet therapy, (2) nontrial antihypertensive medication, (3) current smoking, (4) residual neurological signs, (5) atrial fibrillation, and (6) qualifying cerebrovascular event within the last 6 months.

The effects of treatment were also compared between participants for whom combination therapy was planned at randomization and participants for whom single-drug therapy was planned.

Statistical Analysis

Analyses were conducted according to the intention-to-treat principle. Differences in BP between randomized groups during follow-up were estimated with linear mixed models, and Cox’s proportional-hazards models were used to estimate hazard ratios for the effects of study treatment on risk of stroke.12 Percentage risk reductions were calculated as [(1 – hazard ratio) × 100]. Among participants who had >1 outcome event during follow-up, survival time to the first relevant event was used in each analysis. For example, a participant who suffered an IS and an ICH during follow-up contributed to each of the relevant cause-specific outcome analyses, but only the first event contributed to the analysis of total stroke. Because the overall effect of treatment on stroke was greater among participants treated with combination therapy than among those treated with single-drug therapy, treatment effects in subgroups were standardized for the proportions of the study population for whom combination (58%) or single-drug (42%) therapy was planned by taking weighted averages of the estimates obtained for the 2 therapies.13 Tests of the homogeneity of the effects of treatment between subgroups were performed by adding an interaction term to the appropriate statistical model.

Results

Baseline Characteristics

The characteristics of randomized participants are described in detail elsewhere11,12 and are summarized in Table 1 by randomized group and in Table 2 by subgroups defined on the basis of the most recent cerebrovascular event. The diagnosis of baseline cerebrovascular event was based on radiographic imaging in 4586 participants (90%) with a history of stroke. Within each of these subgroups (and indeed all other subgroups investigated), there was good balance of baseline participant characteristics between the randomized groups (data not shown). However, those participants who received combination therapy tended to be younger, have higher BPs at entry, and have more coronary heart disease.12

Occurrence of Stroke and Stroke Subtypes During Follow-Up

Over a mean follow-up duration of 3.9 years, 727 participants experienced a total of 886 strokes: 656 ischemic (158 lacunar, 88 large artery, 46 cardioembolic, and 364 of unknown ischemic type), 123 hemorrhagic, and 107 of unknown type (Figure 1). Classification of outcome stroke subtype was based on radiographic evidence and/or autopsy reports for 694 events (89%). The End Point Adjudication Committee reviewed a further 76 possible stroke events that were not confirmed as strokes. The committee also made a number of reclassifications between stroke subtypes, principally the reclassification of strokes reported as lacunar to unknown ischemic type.

Effects of BP Lowering on Outcome Strokes of Different Types

During follow-up, the overall mean difference in BP between participants assigned active treatment and those assigned placebo was 9/4 mm Hg (SE, 0.3/0.2 mm Hg), and there was a corresponding 28% (95% confidence interval [CI], 17 to 38) overall reduction in risk of stroke among actively treated participants compared with untreated participants (Figure 2). The risk of IS was reduced by 24% (95% CI, 10 to 35), with separately significant effects of treatment on large-artery IS (relative risk reduction [RRR], 39%; 95% CI, 5 to 61) and unclassified IS (RRR, 19%; 95% CI, 0 to 35). The estimated effects of study treatment on lacunar (RRR, 23%; 95% CI,
TABLE 1. Baseline Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Active (n=3051)</th>
<th>Placebo (n=3054)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age, y (SD)</td>
<td>64 (10)</td>
<td>64 (10)</td>
</tr>
<tr>
<td>Female, %</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Asian,* %</td>
<td>39</td>
<td>39</td>
</tr>
<tr>
<td>Most recent cerebrovascular event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Unknown stroke</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>TIA, %</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Median time since qualifying event, mo</td>
<td>8 (2–21)</td>
<td>8 (2–22)</td>
</tr>
<tr>
<td>(interquartile interval)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other medical history, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Diabetes</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>CHD†</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Carotid disease‡</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Blood pressure and hypertension status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean SBP, mm Hg (SD)</td>
<td>147 (19)</td>
<td>147 (19)</td>
</tr>
<tr>
<td>Mean DBP, mm Hg (SD)</td>
<td>86 (11)</td>
<td>86 (11)</td>
</tr>
<tr>
<td>Hypertension,§ %</td>
<td>48</td>
<td>48</td>
</tr>
<tr>
<td>Medication, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplatelet therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypertensive therapy¶</td>
<td>50</td>
<td>51</td>
</tr>
<tr>
<td>Oral anticoagulants</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Lipid-lowering therapy#</td>
<td>13</td>
<td>15</td>
</tr>
</tbody>
</table>

*Participants recruited from People’s Republic of China or Japan
†History of myocardial infarction or coronary revascularization, or angina (supported by documented electrocardiographic or angiographic evidence).
‡Carotid disease=previous carotid endarterectomy, previous carotid angioplasty, or carotid stenosis >50% (confirmed by angiogram or Doppler).
§Systolic blood pressure ≥160 mm Hg and/or diastolic blood pressure ≥90 mm Hg.
||Use of aspirin or other antiplatelet agent.
¶ Currently treated hypertension.
#Use of HMG-CoA reductase inhibitor or other cholesterol-lowering agent.

−7 to 44) and cardioembolic (RRR, 23%; 95% CI, −38 to 57) strokes were similar in magnitude but not separately statistically significant. Active treatment also produced a large and definitive reduction in the risk of ICH (RRR, 50%; 95% CI, 26 to 67), but the effect of treatment on strokes of unknown type (of which there were few) was less certain (RRR, 18%; 95% CI, −24 to 45).

For the participants (58%) who received combination therapy, the mean BP difference between the active and placebo groups was 12/5 mm Hg compared with 5/3 mm Hg among those who received single-drug therapy (42%). There were correspondingly greater effects of active treatment compared with placebo on the risk of stroke among the participants treated with combination therapy (RRR, 43%; 95% CI, 30 to 54) compared with those treated with single-drug therapy (RRR, 5%; 95% CI, −19 to 23) (P<0.001 for homogeneity). A similar pattern was observed for each of the major stroke subtypes. The relative risk of IS was reduced by 36% (95% CI, 19 to 49) among those who received combination therapy compared with 6% (95% CI, −21 to 26) among those who received single-drug therapy (P=0.02 for homogeneity). For ICH, the RRRs were 76% (95% CI, 55 to 87) and −1% (95% CI, −75 to 42) (P<0.001 for homogeneity). A parallel but nonsignificant trend was seen for strokes of unknown type, with estimates of effect of 29% (95% CI, −22 to 58) for combination therapy and 0% (95% CI, −90 to 47) for single-drug therapy (P=0.4 for homogeneity).

Effects of BP Lowering on Stroke Risk Among Patients With Different Types of Cerebrovascular Events

There were differences in the baseline characteristics of subgroups defined on the basis of the most recent cerebrovascular event at baseline in terms of demographics, disease history, and treatment patterns (Table 2). The mean follow-up BP differences between active and placebo-treated partici-
pants, however, were broadly comparable in the 3 principal subgroups for which the baseline cerebrovascular diagnosis was established (IS, 9/4 mm Hg; ICH, 11/4 mm Hg; TIA, 8/3 mm Hg) but slightly smaller for those with a stroke of unknown type (5/4 mm Hg). The RRRs for stroke were 26% (95% CI, 12 to 38) among patients with a baseline IS, 49% (95% CI, 18 to 68) among patients with a baseline ICH, 23% (95% CI, −23 to 52) among patients with a baseline TIA, and 33% (95% CI, −36 to 67) among patients with a baseline stroke of unknown type (Figure 3), with no evidence of differences between these subgroups (P=0.65 for homogeneity). Among subjects with an IS or a TIA at entry, 80% of recurrent strokes were ischemic and 9% were hemorrhagic, whereas among study participants whose qualifying event was an ICH, 50% of recurrent strokes were hemorrhagic and 35% were ischemic in origin.

**Effects of BP Lowering on Stroke Risk According to Medical History**

Active treatment produced separately significant reductions in the relative risk of stroke among all but 2 of the participant subgroups studied. The analyses provided no evidence of differences in the size of the treatment effect between any of the subgroups (P>0.1 for homogeneity for all comparisons) (Figure 4), with treatment benefits independent of concomitant use of antiplatelet or antihypertensive therapy, current smoking, residual neurological signs, atrial fibrillation, and time since the last cerebrovascular event.

**Discussion**

This large-scale randomized trial clearly demonstrates that, among patients with a history of cerebrovascular events, the beneficial effects of BP-lowering treatment are generalizable across different stroke outcomes and different clinical groups. These findings provide the strongest rationale yet for considering the use of effective BP-lowering therapy among all patients with a history of cerebrovascular events. On the basis of these data, it would be anticipated that, with the combination therapy used in PROGRESS, an RRR of approximately similar magnitude as that achieved overall would be observed in most of these patients.12

Patients with a history of ICH for whom there was no previously established secondary preventive therapy may gain particular benefit from effective BP-lowering therapy. Among such individuals in PROGRESS, the rate of stroke recurrence was higher than among those with prior IS, partly as a consequence of the “tracking” of stroke types.15,16 Because the observed effect of study treatment on ICH was about twice as great as that for IS, the overall benefits of treatment were particularly large. The greater proportional effect of treatment may be due to a stronger association of BP with ICH5 and the younger mean age of this patient group (the association of BP with stroke risk appears to attenuate with increasing age).4

The effects of treatment on subtypes of IS outcomes were broadly similar, although the CIs for each were wide, and it remains possible that moderate differences may exist. The
results of similar analyses from 2 previous large-scale trials\textsuperscript{10,16} were inconclusive, in part because of the much smaller number of events, but overall the estimates of the effects of treatment on each stroke subtype were comparable across all 3 studies.

In addition to the consistent benefits observed for different stroke outcomes, there was also consistency in the benefits observed among participant subgroups. Beneficial effects of treatment were observed regardless of baseline cerebrovascular event history and were independent of the time since the preceding cerebrovascular event, use of concomitant antiplatelet or antihypertensive therapy, current smoking, atrial fibrillation, or residual neurological signs. Of the 16 participant subgroups studied, separately significant beneficial effects of treatment were not observed in only 4 groups (current smokers, patients with atrial fibrillation, and patients with either TIA or stroke of unknown type recorded as the most recent cerebrovascular event), and in each case, this was most likely a consequence of inadequate statistical power rather than a true absence of effect in the subgroup. Hence, it would be prudent to consider all patients with cerebrovascular events for BP-lowering therapy.

Findings from observational studies have previously raised concerns about possible harmful effects of BP lowering among patients with ischemic cerebrovascular disease.\textsuperscript{17,18} However, this study provides clear evidence not only that BP lowering is an effective preventive therapy in such individuals but also that greater benefits accrue with more intensive BP lowering. Trends toward greater effects of combination therapy compared with single-drug therapy were present for all outcomes and in all subgroups included in these analyses. This finding suggests that BP reduction rather than BP-independent effects of the study treatments is the principal mechanism of stroke avoidance for both ischemic and hemorrhagic events.

### Table: Risk Reduction by Stroke Subtype

<table>
<thead>
<tr>
<th>Qualifying event</th>
<th>Number of events/ total participants</th>
<th>Favours</th>
<th>Favours</th>
<th>Risk Reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Ischemic</td>
<td>229/2135 302/2127</td>
<td></td>
<td></td>
<td>28% (12 to 38%)</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>32/305 54/305</td>
<td></td>
<td></td>
<td>49% (18 to 68%)</td>
</tr>
<tr>
<td>Stroke of Unknown Type</td>
<td>13/119 21/132</td>
<td></td>
<td></td>
<td>33% (-36 to 67%)</td>
</tr>
<tr>
<td>TIA</td>
<td>33/491 43/490</td>
<td></td>
<td></td>
<td>23% (-23 to 52%)</td>
</tr>
<tr>
<td><strong>OVERALL</strong></td>
<td>307/3051 420/3054</td>
<td></td>
<td></td>
<td>28% (17 to 38%)</td>
</tr>
</tbody>
</table>

### Figure 3. Effects of BP lowering on stroke risk among patients with different types of qualifying cerebrovascular event. Hazard ratios and 95% CI for risk of stroke during follow-up in subgroups defined by type of most recent cerebrovascular event. Symbols as in Figure 2.

### Figure 4. Effects of BP lowering on stroke risk among major clinical subgroups. Hazard ratios and 95% CI for risk of stroke during follow-up in subgroups defined by previous medical history. Unfilled boxes represent estimates for individual subgroups; solid box, overall estimate of effect in whole study population. Other symbols as in Figure 2. Antiplatelet therapy means the use of aspirin or other antiplatelet agent; antihypertensive therapy, currently treated hypertension; and residual neurological signs, signs identified by the investigator at baseline assessment. Atrial fibrillation included current disease based on examination or a positive history.
In summary, the large size, randomized design, and central adjudication of outcome events by an independent committee in PROGRESS make it unlikely that the observed effects on stroke outcomes, obtained by treatment with a perindopril-based regimen, were a consequence of either chance or bias. Of particular note, the substantial benefits reported here for patients with a history of hemorrhagic events provide the first proven preventive therapy for this patient group. However, it is clear that effective BP lowering should be considered for every patient presenting with a history of cerebrovascular disease, regardless of disease type.

Acknowledgments

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References

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