Effects of a Perindopril-Based Blood Pressure–Lowering Regimen on Disability and Dependency in 6105 Patients With Cerebrovascular Disease
A Randomized Controlled Trial

Perindopril Protection Against Recurrent Stroke Study (PROGRESS) Collaborative Group

Background and Purpose—We sought to quantify the effects of blood pressure lowering on long-term disability and dependency among patients with cerebrovascular disease.

Methods—We performed a randomized, double-blind, placebo-controlled trial. A total of 6105 participants with a history of stroke or transient ischemic attack in the past 5 years were recruited from 172 hospital outpatient clinics in 10 countries. Subjects were randomly assigned to the following groups: active treatment (angiotensin-converting enzyme inhibitor perindopril [4 mg/d] for all patients, with the diuretic indapamide added at the discretion of treating physicians) or matching placebo(s). Measurements were disability (defined as a Barthel Index score $\geq 99/100$) and dependency (a positive response to the following question: “In the last 2 weeks has the patient required regular help with everyday activities?”).

Results—The median duration of follow-up was 4 years. At the last available assessment, 19% of the active treatment group and 22% of the placebo group were disabled (adjusted odds ratio, 0.76; 95% CI, 0.65 to 0.89; $P<0.001$). Twelve percent of the active treatment group and 14% of the placebo group were dependent (adjusted odds ratio, 0.84; 95% CI, 0.71 to 0.99; $P=0.04$). The effects of treatment appeared to be mediated primarily through the prevention of disability and dependency associated with recurrent stroke. Four-year treatment with the study drug regimen would be expected to result in the avoidance of 1 case of long-term disability for every 30 (95% CI, 19 to 79) patients.

Conclusions—Among individuals with cerebrovascular disease, a perindopril-based blood pressure–lowering regimen not only reduced the risk of stroke and major vascular events but also substantially reduced the risks of associated long-term disability and dependency. (Stroke. 2003;34:2333-2338.)

Key Words: antihypertensive therapy ■ indapamide ■ perindopril ■ stroke, hemorrhagic ■ stroke, ischemic

In 2000, there were approximately 20 million strokes worldwide,1 making cerebrovascular disease the sixth leading cause of disability, a burden predicted to rise substantially by 2020.2 Approximately one quarter of all strokes are fatal,1 and at least one third of nonfatal strokes result in long-term disability or dependency.3–5

Blood pressure levels are strongly predictive of the risks of initial and recurrent stroke,6,7 and blood pressure–lowering therapy reduces the risks of both fatal and nonfatal stroke in a variety of different patient groups.8,9 Most recently, the Perindopril Protection Against Recurrent Stroke Study (PROGRESS)10 extended evidence about the beneficial effects of blood pressure–lowering therapy on the risk of stroke to include individuals with a history of cerebrovascular disease.11 While a reduction in nonfatal stroke would be expected to reduce functional impairment, clear evidence of such an effect is absent. In this report we quantify the effects of the study treatment regimen on the prespecified secondary outcomes of long-term disability and dependency.10

Subjects and Methods

Design and Participants

The design of PROGRESS has been described in detail elsewhere.10 Briefly, 6105 participants were recruited from 172 collaborating centers in 10 countries between May 1995 and November 1997. The trial protocol was approved by the institutional ethics committee of each collaborating center, and all participants provided written informed consent. Participants were eligible if they had a history of stroke or transient ischemic attack within the previous 5 years. Participants were ineligible if they had a clear indication for, or contraindication to, angiotensin-converting enzyme inhibitor treatment or major baseline disability likely to prevent regular attendance at study clinics. There were no blood pressure criteria for entry.

Participants who tolerated and adhered to 4 weeks of run-in therapy with perindopril were randomly assigned, in a double-blind manner, to continued active treatment or matching placebo. Active
treatment comprised a flexible regimen based on perindopril (4 mg/d) for all participants, with the addition of indapamide (2.5 mg/d or 2 mg/d in Japan) in those for whom the responsible study physician believed that diuretic use was neither specifically indicated nor contraindicated. Participants assigned placebo received tablets identical in appearance to the active agents. “Combination therapy” (perindopril and indapamide or double placebo) rather than “single-drug therapy” (perindopril or single placebo) was used, wherever possible, to maximize the fall in blood pressure.\textsuperscript{10,11}

**Outcomes**

The primary outcomes for these analyses were the last available clinical assessments of disability and dependency, irrespective of whether participants died during follow-up. Assessments were scheduled for all participants at baseline, at the 6- and 12-month visits, and annually thereafter until the end of follow-up or prior death. Assessments were made by trained study staff unaware of study treatment allocation and included, wherever possible, an interview with both the participant and a friend or relative. While disability and dependency are interrelated, for the purposes of these analyses they were defined and assessed separately by 2 validated methods.

Disability was evaluated with a modified version of the Barthel Index of Activities of Daily Living, which assesses the amount of assistance required in 10 domains of self-care (personal hygiene, bathing, feeding, toileting, dressing, bladder management, and bowel control) and mobility (stair climbing, ambulation/wheelchair management, and chair-to-bed transfers).\textsuperscript{12,13} For each domain, assessments range from “unable to perform task” to “fully independent,” and possible total scores range from 0 (indicating the person is bedridden) to 100 (fully independent in basic physical self-maintenance). Most stroke trials have used a dichotomized end point to distinguish favorable from adverse outcomes, although a variety of cut points have been used.\textsuperscript{14,15} In the present study disability was defined as any submaximal score; while this would represent a score of ≤95 on the original Barthel scale (in which scores increase or decrease in increments of 5), use of the more sensitive modified Barthel Index (in which scores change in increments of 1)\textsuperscript{16} resulted in disability being defined as a score of ≤99.\textsuperscript{4}

Dependency was assessed by a single question: “In the last 2 weeks has the patient required regular help with everyday activities?” This has been proposed as a simple pragmatic method of evaluating functional ability in large-scale clinical trials.\textsuperscript{16}

Since disability and dependency are strongly related to the occurrence of stroke,\textsuperscript{4} the effects of treatment were assessed separately for the composite outcomes of disability (or dependency) after recurrent stroke and disability (or dependency) in the absence of recurrent stroke. Recurrent stroke was defined as a nonfatal stroke occurring during follow-up.

**Statistical Analysis**

We conducted analyses of treatment effects using 2-sided hypothesis tests, according to the principle of intention-to-treat, using logistic regression models to estimate odds ratios (ORs). Overall estimates of treatment effects were adjusted for baseline disability or dependency status. Subgroup analyses of the effects of treatment were conducted according to the following: the presence or absence of disability (or dependency) at baseline; planned study drug regimen (combination or single drug); and the presence or absence of hypertension (systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥90 mm Hg) at baseline. Estimates of treatment effects in the subgroups defined by study drug regimen and baseline hypertension status were adjusted for baseline disability or dependency status. In addition, since earlier analyses showed a greater effect on stroke among participants treated with combination therapy than among those treated with single-drug therapy,\textsuperscript{11} effects in the subgroups defined by baseline disability or dependency status and hypertension status were adjusted for the proportions of the study population taking combination (58%) or single-drug therapy (42%).\textsuperscript{11} Tests of homogeneity of the effects of treatment in participant subgroups were performed by adding an interaction term to the appropriate logistic model.

**Baseline Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Active (n=3051)</th>
<th>Placebo (n=3054)</th>
</tr>
</thead>
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<td>64 (10)</td>
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<td>Type of qualifying event, %</td>
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<td>Ischemic stroke</td>
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<tr>
<td>Cerebral hemorrhage</td>
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<tr>
<td>Unknown stroke</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>TIA or amaurosis fugax</td>
<td>22</td>
<td>22</td>
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<tr>
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<td>8 (2–22)</td>
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<tr>
<td>Mean (SD) systolic blood pressure, mm Hg</td>
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<td>147 (19)</td>
</tr>
<tr>
<td>Mean (SD) diastolic blood pressure, mm Hg</td>
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<td>86 (11)</td>
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<td>Hypertension, %</td>
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<tr>
<td>Not fully recovered, %</td>
<td>61</td>
<td>61</td>
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</tbody>
</table>

*Participants recruited from People’s Republic of China or Japan.\textsuperscript{11}†Participants may have had more than one type of qualifying event.‡Systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥90 mm Hg.§Positive response to the question: “In the last 2 weeks has the patient required regular help with everyday activities?”\textsuperscript{16}||Negative response to the question: “Does the patient feel that he or she has fully recovered from previous cerebrovascular events?”\textsuperscript{16}|

SD, standard deviation.

**Results**

**Baseline Characteristics**

The characteristics of participants in the PROGRESS study are described in detail elsewhere\textsuperscript{11,18} and summarized in the Table. There was good balance between treatment groups for characteristics that might influence the risk of disability, such as age, sex, type of qualifying event, and time since qualifying event. Missing disability (n=6) or dependency evaluations (n=2) at baseline were imputed as the 6-month visit values where possible. Those participants for whom there was no baseline or 6-month disability (n=3) or dependency assessment (n=2) were assumed not to be disabled or dependent at baseline. At study entry, approximately one fifth of participants were disabled and approximately one eighth were dependent, although the majority (almost two thirds) did not consider themselves to have “fully recovered” from their qualifying cerebrovascular event.

**Follow-up**

During a median follow-up period of 4 years (interquartile interval, 3 to 4) in each treatment group, the mean difference in blood pressure between active treatment and placebo groups was 9/4 mm Hg (SE 0.3/0.2).\textsuperscript{11} Among participants treated with combination therapy (58%), the mean difference in blood pressure between groups was 12/5 mm Hg (SE 0.5/0.3), whereas among those treated with single-drug therapy it was 5/3 mm Hg (SE 0.6/0.3).\textsuperscript{11}
During the scheduled follow-up period, 625 participants died: 306 (10%) in the active treatment group and 319 (10%) in the placebo group. All 6105 participants had at least 1 assessment of both disability and dependency (either at baseline or subsequently). Assessments performed after baseline and before either the end of follow-up or prior death were available for disability in 98% and for dependency in 99% of each treatment group. For the remainder, baseline assessments were used in the analyses. In each group, the median time from randomization to the last available assessments of disability and dependency was 4 years (interquartile interval, 3 to 4).

**Effects of Treatment on Disability**
At the last available assessment, 571 (19%) of participants randomized to active treatment and 672 (22%) of those randomized to placebo were disabled (Barthel Index score ≤99/100) (Figure 1). Of the 1243 disabled subjects, 267 (21%) had experienced a prior recurrent stroke, and for these individuals the median time interval between recurrent stroke and disability assessment was 25 months (interquartile interval, 9 to 36 months) in the active treatment group and 23 months (interquartile interval, 14 to 36 months) in the placebo group.

Active treatment reduced the odds of disability by 24% (OR, 0.76; 95% CI, 0.65 to 0.89; P < 0.001) (Figure 2). In sensitivity analyses, alternative cutoff points for disability according to Barthel score were considered. For any cutoff points down to 90, the results were essentially the same: for example, the 95 cutoff point gave an OR of 0.81 (95% CI, 0.68 to 0.95), and the 90 cutoff point gave an OR of 0.79 (95% CI, 0.65 to 0.96). As a result of decreasing numbers of events, CIs inevitably increased as the cutoff points reduced. For cutoff points <90, the results were considered unreliable since the power to detect the observed OR, with the use of a 5% hypothesis test, dropped to unacceptable levels. While at 90 there was 80% power, at 85 there was only 49% power. With a cutoff point as low as 60, power was reduced to 8%. As shown in Figure 2, the odds of disability after recurrent stroke were reduced by 36% (OR, 0.64; 95% CI, 0.50 to 0.82), while there was no clear effect of treatment in the absence of recurrent stroke (OR, 0.89; 95% CI, 0.75 to 1.05).

Among participants treated with combination therapy, active treatment reduced the odds of disability by 30% (OR, 0.70; 95% CI, 0.57 to 0.86). Among those treated with single-drug therapy, there was no significant effect of treatment (OR, 0.86; 95% CI, 0.68 to 1.10), although this result did not differ significantly from that among those treated with combination therapy (P = 0.3) because both effects have wide confidence limits with considerable overlap. Likewise, there was no clear evidence of any differences between the effects of treatment on disability in the other subgroups studied (for homogeneity, both P > 0.2).

Of the 10 domains of the Barthel Index, active treatment was associated with separately significant benefits (fewer participants requiring assistance) in the domains of bathing, feeding, dressing, ambulation, and managing stairs (Figure 3).

**Effects of Treatment on Dependency**
At the last available assessment, 362 (12%) of participants in the active treatment group and 427 (14%) in the placebo group were dependent (“required regular help with everyday activities” (Figure 1). Of the 1243 disabled subjects, 267 (21%) had experienced a prior recurrent stroke, and for these individuals the median time interval between recurrent stroke and disability was 25 months (interquartile interval, 9 to 36 months) in the active treatment group and 23 months (interquartile interval, 14 to 36 months) in the placebo group.

Active treatment reduced the odds of disability by 24% (OR, 0.76; 95% CI, 0.65 to 0.89; P < 0.001) (Figure 2). In sensitivity analyses, alternative cutoff points for disability according to Barthel score were considered. For any cutoff points down to 90, the results were essentially the same: for example, the 95 cutoff point gave an OR of 0.81 (95% CI, 0.68 to 0.95), and the 90 cutoff point gave an OR of 0.79 (95% CI, 0.65 to 0.96). As a result of decreasing numbers of events, CIs inevitably increased as the cutoff points reduced. For cutoff points <90, the results were considered unreliable since the power to detect the observed OR, with the use of a 5% hypothesis test, dropped to unacceptable levels. While at 90 there was 80% power, at 85 there was only 49% power. With a cutoff point as low as 60, power was reduced to 8%. As shown in Figure 2, the odds of disability after recurrent stroke were reduced by 36% (OR, 0.64; 95% CI, 0.50 to 0.82), while there was no clear effect of treatment in the absence of recurrent stroke (OR, 0.89; 95% CI, 0.75 to 1.05).

Among participants treated with combination therapy, active treatment reduced the odds of disability by 30% (OR, 0.70; 95% CI, 0.57 to 0.86). Among those treated with single-drug therapy, there was no significant effect of treatment (OR, 0.86; 95% CI, 0.68 to 1.10), although this result did not differ significantly from that among those treated with combination therapy (P = 0.3) because both effects have wide confidence limits with considerable overlap. Likewise, there was no clear evidence of any differences between the effects of treatment on disability in the other subgroups studied (for homogeneity, both P > 0.2).

Of the 10 domains of the Barthel Index, active treatment was associated with separately significant benefits (fewer participants requiring assistance) in the domains of bathing, feeding, dressing, ambulation, and managing stairs (Figure 3).

**Figure 1.** Trial profile.

**Figure 2.** ORs and 95% CIs for disability, disability following recurrent stroke, disability in the absence of recurrent stroke, and disability in major subgroups of participants. Solid boxes represent estimates of effect for composite end points, and unfilled boxes represent estimates of effect for subgroups. The areas of the boxes are proportional to the number of events, and horizontal lines represent 95% CIs. The solid diamond represents the overall estimate of effect and its 95% CI.
activities”) (Figure 1). Of the 789 dependent participants, 217 (28%) had also had a prior recurrent stroke.

Active treatment reduced the odds of dependency by 16% (OR, 0.84; 95% CI, 0.71 to 0.99; \( P = 0.04 \)) (Figure 4). Active treatment reduced the odds of dependency after recurrent stroke by 27% (OR, 0.73; 95% CI, 0.55 to 0.96), but there was no clear effect in the absence of a recurrent stroke (OR, 0.92; 95% CI, 0.76 to 1.12). Among participants treated with combination therapy, active treatment reduced the odds of dependency by 22% (OR, 0.78; 95% CI, 0.63 to 0.97). As for disability, there was no significant effect among those treated with single-drug therapy (OR, 0.92; 95% CI, 0.71 to 1.18), although, once again, these results were not significantly different (\( P = 0.4 \)). There was no clear evidence of differences between the effects of treatment in the other subgroups studied (both \( P > 0.7 \)).

**Discussion**

This large-scale randomized trial conducted among individuals with previous stroke or transient ischemic attack has demonstrated that a perindopril-based blood pressure lowering–regimen reduces not only the risk of stroke and major vascular events\(^1\) but also the risks of long-term disability and dependency. Over a median follow-up period of 4 years, the absolute risk of disability was reduced from 22% in the placebo group to 19% in the active treatment group, representing 1 case of disability avoided among every 30 (95% CI, 19 to 79) people treated for 4 years. The absolute risk of dependency was reduced from 14% to 12% (1 case of dependency avoided for every 47 [95% CI, 26 to 231] people treated for 4 years). These benefits were independent of the effects of study treatment on death and were observed against a background of standard care that included antiplatelet agents and/or nonstudy blood pressure–lowering drugs for the majority of participants. Furthermore, the effects appeared to be similar in both hypertensive and nonhypertensive individuals and in those with and those without evidence of disability or dependency at baseline.

The effects of treatment on disability and dependency appear to be mediated primarily through the prevention of...
recurrent strokes. This is consistent both with the results of epidemiological studies showing that disability and dependency are strongly associated with stroke\textsuperscript{8,9} and with the results of randomized trials that have shown blood pressure lowering to reduce the risk of stroke.\textsuperscript{8,9} In PROGRESS, the reduction in stroke risk was significantly greater among those treated with combination therapy using perindopril and indapamide than among those treated with perindopril alone,\textsuperscript{11} probably as a result of the greater reduction in blood pressure achieved. While there were no similarly clear differences between the different drug regimens in their effects on disability and dependency, the results were consistent with moderately greater effects of combination therapy than single-drug therapy, as might be anticipated for a treatment effect mediated primarily through blood pressure–lowering and stroke prevention.

The large size and randomized design of the study make it unlikely that the observed treatment benefits are a consequence of either chance or bias, although these possibilities cannot be ruled out. In particular, it is unlikely that the results were importantly affected by differential rates of follow-up between the treatment groups, as may have been the case in some previous trials;\textsuperscript{20} in PROGRESS, at least 1 assessment of disability and dependency was available for all participants, and follow-up assessments were available in >98% of participants in each group, including the majority of those who subsequently died. Additionally, the results were not dependent on the chosen cutoff for the definition of disability, since the estimate of treatment effect was not materially altered when analyses were repeated with a lower cut point (Barthel Index \(\geq95/100\)), as used in some other studies.\textsuperscript{14,15}

Functional recovery from stroke-related disability and dependency usually plateaus approximately 6 months after stroke,\textsuperscript{13} and, in PROGRESS, the median time from randomization (or recurrent stroke) to final assessment substantially exceeded this period. The observed benefits are therefore likely to reflect the long-term effects of treatment. It is likely that the observed effects underestimate the true absolute and relative benefits of adherence to the study treatment regimen. First, approximately one fifth of study participants in each group discontinued randomized treatment prematurely.\textsuperscript{11} Second, the Barthel Index may not detect mild to moderate degrees of physical disability\textsuperscript{15,21,22} and does not assess other important areas of function such as speech or cognitive function.\textsuperscript{23} In PROGRESS, this is apparent from the observation that while only approximately 20% of participants were defined as disabled at baseline, 61% considered themselves "not fully recovered" from their qualifying cerebrovascular event.

Two separate assessments of functional ability were made in PROGRESS: the Barthel Index of Activities of Daily Living, which assesses performance in 10 domains of function, and a single, easily administered, “dependency” question. In PROGRESS, the largest clinical trial to have used both methods of assessment, the proportional effects of treatment on functional impairment were broadly comparable when measured by each method. This observation, consistent with those of others,\textsuperscript{24,25} suggests that, in cases in which limited resources preclude the use of a more lengthy assessment, the simple question is a reasonable means of quantifying treatment effects in large clinical trials.

In summary, in a population of hypertensive and nonhypertensive subjects with cerebrovascular disease, a blood pressure–lowering regimen involving perindopril for all participants and indapamide for slightly more than half reduced the odds of long-term disability and dependency by approximately one fifth. These benefits were due largely to a reduction in recurrent stroke. The clear benefits of treatment and the high risk of disabling stroke in this patient population provide a strong rationale for the use of perindopril and indapamide among all individuals with a history of stroke or transient ischemic attack, irrespective of their level of blood pressure.

Appendix

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References


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