

# Effects of Blood Pressure Lowering With Perindopril and Indapamide Therapy on Dementia and Cognitive Decline in Patients With Cerebrovascular Disease

The PROGRESS Collaborative Group\*

**Background:** High blood pressure and stroke are associated with increased risks of dementia and cognitive impairment. This study aimed to determine whether blood pressure lowering would reduce the risks of dementia and cognitive decline among individuals with cerebrovascular disease.

**Methods:** The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) was a randomized, double-blind, placebo-controlled trial conducted among 6105 people with prior stroke or transient ischemic attack. Participants were assigned to either 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). The primary outcomes for these analyses were dementia (using DSM-IV criteria) and cognitive decline (a decline of 3 or more points in the Mini-Mental State Examination score).

**Results:** During a mean follow-up of 3.9 years, dementia was documented in 193 (6.3%) of the 3051 randomized participants in the actively treated group and 217

(7.1%) of the 3054 randomized participants in the placebo group (relative risk reduction, 12% [95% confidence interval, -8% to 28%];  $P=.2$ ). Cognitive decline occurred in 9.1% of the actively treated group and 11.0% of the placebo group (risk reduction, 19% [95% confidence interval, 4% to 32%];  $P=.01$ ). The risks of the composite outcomes of dementia with recurrent stroke and of cognitive decline with recurrent stroke were reduced by 34% (95% confidence interval, 3% to 55%) ( $P=.03$ ) and 45% (95% confidence interval, 21% to 61%) ( $P<.001$ ), respectively, with no clear effect on either dementia or cognitive decline in the absence of recurrent stroke.

**Conclusions:** Active treatment was associated with reduced risks of dementia and cognitive decline associated with recurrent stroke. These findings further support the recommendation that blood pressure lowering with perindopril and indapamide therapy be considered for all patients with cerebrovascular disease.

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**I**N 1990, dementia was the eighth leading cause of death and disability in higher-income countries,<sup>1</sup> and by 2020, the disease burden attributable to dementia is projected to increase by one half.<sup>1</sup> The identification of safe and effective interventions for the prevention of dementia is therefore a clinical and public health priority. Observational studies have demonstrated that elevated blood pressure levels<sup>2-5</sup> and a history of cerebrovascular disease<sup>6-8</sup> are each strongly associated with the long-term risks of dementia and cognitive impairment. Blood pressure-lowering interventions may reduce the risk of cognitive impairment by direct effects on the prevention of cerebrovascular disease or by indirect effects on the clinical expression of neurodegenerative processes.<sup>9-13</sup> Three completed large-scale randomized controlled trials of blood pres-

sure-lowering agents have reported the effects of treatment on the risk of dementia or measures of cognitive function.<sup>14-16</sup> While the first identified no clear effect of study treatment on dementia<sup>14</sup> and the second no effect on cognitive function,<sup>15</sup> the third reported a significant beneficial effect of treatment on the risk of dementia.<sup>16</sup> In that study, however, only 32 cases of dementia were recorded, and the confidence intervals about the estimate of treatment effect were very wide. There remains, therefore, substantial clinical uncertainty about the effects of blood pressure lowering on both dementia and other indexes of cognitive impairment.

The recently completed Perindopril Protection Against Recurrent Stroke Study (PROGRESS)<sup>17</sup> demonstrated that a blood pressure-lowering regimen, involving an angiotensin-converting enzyme (ACE) inhibitor and a diuretic, reduced the risks

of stroke and of other major vascular events among individuals with a history of cerebrovascular disease.<sup>18</sup> The effects of the study treatment regimen on the prespecified end points of dementia and cognitive function<sup>17</sup> are reported herein.

## METHODS

### STUDY DESIGN AND PARTICIPANTS

The design of PROGRESS has been described in detail elsewhere.<sup>17,18</sup> Briefly, 6105 participants were recruited from 172 collaborating centers in 10 countries between May 1995 and November 1997. The institutional ethics committee of each collaborating center approved the trial, and all participants provided written informed consent. Participants were eligible if they had a history of cerebrovascular disease (stroke or transient ischemic attack [but not subarachnoid hemorrhage]) within the previous 5 years. In addition, participants were required to have no clear indication for, nor a contraindication to, treatment with an ACE inhibitor. There were no blood pressure criteria for entry. Blood samples were collected at baseline for later DNA extraction and identification of apolipoprotein E gene polymorphisms using standard techniques.<sup>19</sup>

Participants who tolerated and adhered to at least 4 weeks of run-in therapy with perindopril were randomly assigned, in a double-blind manner, to continued active treatment or matching placebo. Randomized treatment allocation was provided by a central computer-based randomization service with stratification by study center, age, sex, entry systolic blood pressure, inclusion diagnosis, and the intention to begin combination therapy (with perindopril plus indapamide or double placebo) or single drug therapy (with perindopril alone or single placebo). Active treatment comprised a flexible treatment 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 participants for whom the responsible study physician believed that there was no specific indication for, nor contraindication to, the use of a diuretic. Those participants assigned to placebo received tablets identical in appearance to the active agents. The rationale for the use, whenever possible, of "combination therapy" (perindopril and indapamide or double placebo) rather than "single drug therapy" (perindopril or single placebo) was to maximize the fall in blood pressure.<sup>18</sup>

### ASSESSMENT OF COGNITIVE FUNCTION AND DEMENTIA

Cognitive function was assessed in all patients at baseline, at the 6- and 12-month visits, and annually thereafter until the end of follow-up, using the Mini-Mental State Examination (MMSE).<sup>20</sup> For each successfully completed item on the MMSE, a score of 1 point (to a maximum of 30) was awarded, with missing items receiving a score of zero. Contextually appropriate translations of the questionnaire were made for Chinese and Japanese participants, since the questionnaire was not available in these languages at the time the study began.

During the study follow-up period, a 2-phase screening and assessment process was used for the diagnosis of dementia.<sup>21</sup> Participants screened positive for possible dementia if they satisfied any of the following criteria during the study follow-up period: (1) an MMSE score of 25 or less at any follow-up visit, (2) a decline in the MMSE score of 3 or more points between any 2 follow-up visits, (3) an MMSE score missing for 2 or more scheduled follow-up visits, or (4) a positive response by the investigator to the question, "In your opinion,

does this patient have dementia?" Participants who screened positive were referred for a formal diagnostic clinical assessment by a local specialist with experience in the diagnosis of dementia.

The clinical assessment included, whenever possible, an interview with both the patient and a close friend or relative. If study participants were not available for assessment or had died, data were sought from all other available sources, including medical records, interviews with family members, and consultations with other medical practitioners. Information was gathered with the aid of a checklist based on the criteria for the diagnosis of dementia as defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*.<sup>22</sup> For all screen-positive cases, the collected information and the diagnosis made by the local specialist were reviewed and either confirmed or refuted by consensus agreement of a 2-person central Dementia Adjudication Committee. Based on the DSM-IV criteria, each screen-positive case was finally categorized by the Dementia Adjudication Committee as (1) certain dementia, (2) fairly certain (probable) dementia, (3) uncertain (possible) dementia, or (4) no dementia. Since all patients had a history of cerebrovascular disease and other vascular risk factors were frequently present, no attempt was made to further classify cases into subtypes of dementia. All screen-negative participants were categorized as "no dementia" and all assessments were made without knowledge of study treatment allocation.

### OUTCOMES

The main outcomes for these analyses were (1) dementia, defined as "certain dementia" or "fairly certain dementia" according to the criteria of DSM-IV, and (2) cognitive decline, defined as a drop of 3 points or more between the baseline and last recorded MMSE scores.<sup>23,24</sup> Both dementia and cognitive function were prespecified secondary outcomes of PROGRESS.<sup>17,21</sup> Since, in observational studies, the risk of cognitive impairment is strongly associated with the occurrence of stroke,<sup>6,8</sup> the effects of treatment on the following 4 additional composite outcomes were studied: (1) "dementia with recurrent stroke" (the diagnosis of dementia after a stroke during follow-up); (2) "other dementia" (all other cases of dementia diagnosed); (3) "cognitive decline with recurrent stroke" (the diagnosis of cognitive decline after a stroke during follow-up); and (4) "other cognitive decline" (all other cases of cognitive decline). Quantitative changes in MMSE score between the baseline and final assessment were also compared between treatment groups.

### STATISTICAL ANALYSIS

We calculated the planned study sample size (6000 participants) and follow-up (4 years) to provide 90% power, using a 2-sided 5% significance test to detect a 30% or greater difference in the relative risk of dementia between the randomized groups. This estimate assumed that the incidence of dementia among individuals with a history of cerebrovascular disease would be about twice that observed among elderly individuals with uncomplicated hypertension (7-10 per 1000 person-years).<sup>6,16,25,26</sup>

All analyses were conducted according to the intention-to-treat principle, and all randomized participants were included in all analyses. Missing baseline MMSE values (n=32) were imputed as the values recorded at the 6-month visit when possible (n=7). The remaining 25 participants and those others for whom there was only a single MMSE assessment (n=192) were assumed not to have met the criteria for cognitive decline. Logistic regression models were used to estimate odds

### Baseline Characteristics of Randomized Participants\*

	Active Treatment (n = 3051)	Placebo (n = 3054)
Age, mean (SD), y	64 (10)	64 (10)
Female	30	30
Asian†	39	39
Full-time education to ≥16 y	53	53
Hypertension‡	48	48
Current smoker	20	20
Current alcohol use§	40	40
Type of qualifying event		
Cerebral infarct	71	71
Cerebral hemorrhage	11	11
TIA/amaurosis fugax	22	22
Type unknown	4	5
MMSE score, median (interquartile interval)	29 (27-30)	29 (27-30)
MMSE ≤25	15	15
ApoE4 allele carrier	22	22
Current HMG-CoA reductase inhibitor (statin) use	8	8

Abbreviations: ApoE4, apolipoprotein E ε4; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; MMSE, Mini-Mental State Examination; TIA, transient ischemic attack.

\*Data are percentage of participants unless otherwise specified.

†Participants recruited from People's Republic of China or Japan.

‡Systolic blood pressure 160 mm Hg or higher or diastolic blood pressure 90 mm Hg or higher.

§Consumes at least 1 alcoholic drink per week.

||Carrier of at least 1 ApoE4 allele.

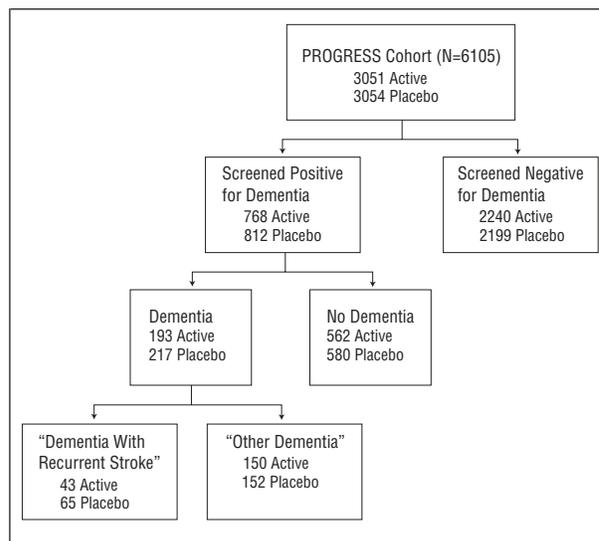
ratios for the effects of study treatment on the dichotomous outcomes of dementia and cognitive decline. Percentage of risk reductions were estimated as  $(1 - \text{odds ratio}) \times 100$ , and all *P* values were calculated from 2-sided tests of statistical significance. The effects of study treatment on mean MMSE scores between baseline and follow-up were determined using general linear models.

Analyses of major subgroups were conducted according to study drug regimen (combination drug therapy or single drug therapy); the presence or absence of hypertension (systolic blood pressure ≥160 mm Hg and/or diastolic blood pressure ≥90 mm Hg) at baseline; and evidence or no evidence of cognitive impairment (MMSE score ≤25 and/or a positive response to the question, "In your opinion, does this patient have dementia?") at baseline (2 participants without any baseline assessment of cognitive impairment were classified as unimpaired at baseline). Standardized estimates of treatment effects in subgroups were calculated by combining subgroup-specific estimates of the effects of combination therapy and of single drug therapy.<sup>18</sup> Tests of homogeneity of the effects in the above subgroups were performed by adding an interaction term to the appropriate statistical model. All analyses were conducted using SAS Version 8.02 (SAS Institute Inc, Cary, NC).

## RESULTS

### BASELINE CHARACTERISTICS

The characteristics of participants in PROGRESS are described in detail elsewhere<sup>18,27</sup> and are summarized in the **Table**. There was good balance between active treatment and placebo groups for those baseline participant characteristics that might influence the risk of dementia



**Figure 1.** Screening and assessment for dementia in the Perindopril Protection Against Recurrent Stroke Study (PROGRESS).

such as age, sex, educational level, MMSE score, and frequency of the ε4 allele of the apolipoprotein E polymorphism.

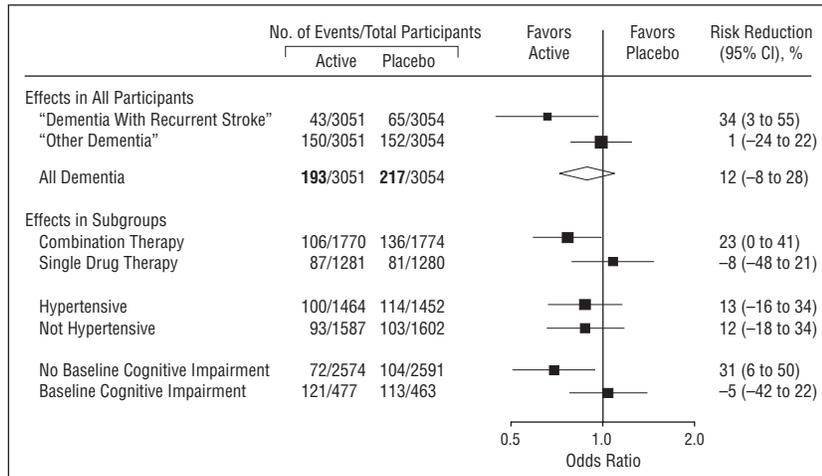
### ADHERENCE TO RANDOMIZED TREATMENT AND EFFECTS OF TREATMENT ON BLOOD PRESSURE

During a mean follow-up period of 3.9 years, 22% of participants permanently discontinued the use of all study tablets prior to death or the final scheduled visit (active, 23%; placebo, 21% [*P* = .02]). The main reasons for permanent discontinuation of treatment were participant decision (active, 7.6%; placebo, 8.2%), cough (active, 2.2%; placebo, 0.4%) hypotension (active, 2.1%; placebo, 0.9%), and heart failure requiring treatment with an ACE inhibitor or diuretic (active, 1.5%; placebo, 2.3%).

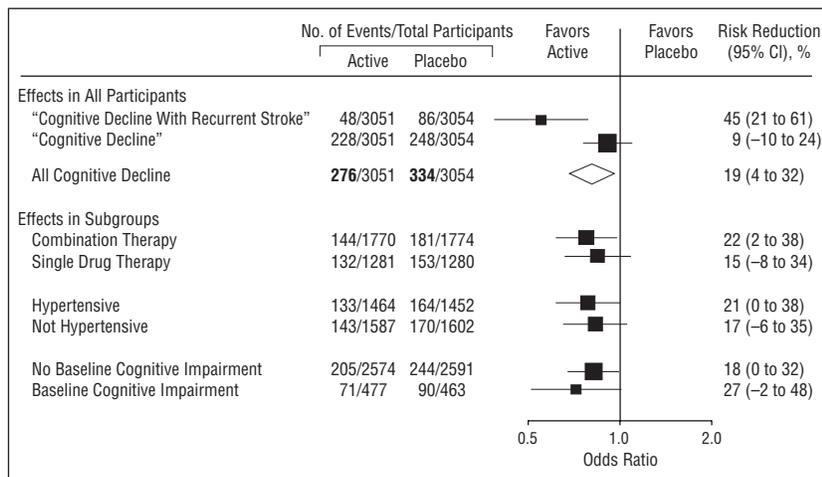
The mean difference in blood pressure between participants assigned active treatment and those assigned placebo was 9/4 mm Hg (SE, 0.3/0.2 mm Hg).<sup>18</sup> Among the 58% of participants treated with combination therapy, the mean difference in blood pressure between active and placebo was 12/5 mm Hg (SE, 0.5/0.3 mm Hg), whereas among those treated with single drug therapy it was 5/3 mm Hg (SE, 0.6/0.3 mm Hg) (*P* for homogeneity < .001 for both systolic and diastolic blood pressure).<sup>18</sup>

### EFFECTS OF TREATMENT ON THE RISK OF DEMENTIA

All randomized participants were screened for dementia on at least 1 occasion, and 1580 participants (768 active; 812 placebo) screened positive (**Figure 1**). Clinical assessments for dementia were performed in 1552 (98.2%) of screen-positive participants; 1049 were assessed "face to face" and the remaining 503 were assessed "in absentia." The 28 screen-positive participants who did not undergo a clinical assessment were



**Figure 2.** Effects of treatment on the risks of dementia. Odds ratios and 95% confidence intervals (CIs) are provided for all dementia, "dementia with recurrent stroke," "other dementia," and for all dementia in major subgroups of participants. The centers of the boxes are placed at the point estimates of effect and the areas of the boxes are proportional to the number of events. The horizontal lines represent 95% CIs. Diamond represents point estimate and 95% CI of the overall estimate of effect.



**Figure 3.** Effects of treatment on the risks of cognitive decline. See Figure 2 for conventions.

assumed not to have dementia. The local specialists diagnosed dementia in 358 individuals and no dementia in 1194 individuals (including 8 for whom there was insufficient information to make a diagnosis). The Dementia Adjudication Committee reclassified 116 (7.4%) local specialists' diagnoses (32 "dementia" to "no dementia" and 84 "no dementia" to "dementia") after comparison of the diagnostic details provided with the DSM-IV criteria. Therefore, a diagnosis of dementia was made in 410 participants, 295 of whom had been assessed face to face and 115 in absentia. Of these 410 participants, 108 (26.3%) also had a stroke during follow-up prior to the diagnosis of dementia and were classified as "dementia with recurrent stroke," leaving the remaining 302 cases classified as "other dementia."

Of the participants in the active treatment and placebo groups, 193 (6.4%) and 217 (7.1%), respectively, were diagnosed with dementia (16 and 19 per 1000 person-years, respectively). Active treatment was associated with a nonsignificant, 12% lower risk of dementia (95% confidence interval [CI], -8% to 28%) ( $P=.2$ ) and a 34% (95% CI, 3% to 55%) ( $P=.03$ ) lower risk of "dementia with recurrent stroke," but no reduction in the risk of "other dementia" (relative risk reduction, 1% [95% CI, -24% to 22%];  $P=.9$ ) (**Figure 2**). Estimates of the effects of treatment on dementia were not materially al-

tered when analyses were restricted to those cases diagnosed "face to face."

### EFFECTS OF TREATMENT ON THE RISK OF COGNITIVE DECLINE

Assessments of cognitive decline were available for 5888 study participants (96.4%). The 217 participants not assessed (active 117; placebo 100) had either no baseline MMSE score ( $n=25$ ) or only 1 measure of MMSE ( $n=192$ ) and for the purpose of these analyses were assumed not to have cognitive decline. Overall, cognitive decline occurred in 610 participants (276 [9.1%] in the active group and 334 [11.0%] in the placebo group), with incidence rates of 23 and 28 per 1000 person-years, respectively. Of the 610 subjects with cognitive decline, 134 (21.9%) had a stroke during follow-up prior to the diagnosis of cognitive decline and were classified as "cognitive decline with recurrent stroke," leaving the remaining 476 cases of cognitive decline classified as "other cognitive decline."

Active treatment reduced the risk of cognitive decline by 19% (95% CI, 4% to 32%) ( $P=.01$ ) and the composite outcome of "cognitive decline with recurrent stroke" by 45% (95% CI, 21% to 61%) ( $P=.001$ ) (**Figure 3**). There was no discernible effect of treatment on "other cognitive decline" (risk reduction, 9%

[95% CI, -10% to 24%];  $P = .35$ ). Estimates of the effects of treatment were not materially altered when analyses were made with cognitive decline defined as either a 2-point fall in MMSE scores (overall risk reduction, 17% [95% CI, 5% to 28%];  $P = .009$ ) or a 4-point fall in MMSE scores (17% [95% CI, -1% to 31%];  $P = .07$ ), or by the exclusion from the calculations of the 217 study participants who were not assessed.

### EFFECTS OF TREATMENT IN PARTICIPANT SUBGROUPS

There was borderline significant heterogeneity ( $P = .05$ ) between the effects of treatment on dementia in participant subgroups defined on the basis of cognitive impairment at entry into the study: there was no apparent effect of treatment among the 964 (16.4%) participants with evidence of baseline impairment (relative risk reduction, -5% [95% CI, -42% to 22%];  $P = .7$ ) but a significant relative risk reduction (31% [95% CI, 6% to 49%];  $P = .02$ ) among the 5141 participants (84.2%) without evidence of baseline cognitive impairment (Figure 2). There was also a trend toward greater effects of treatment on dementia among participants treated with combination therapy (relative risk reduction, 23% [95% CI, 0% to 41%];  $P = .05$ ) than among participants treated with single drug therapy (relative risk reduction, -8% [95% CI, -48% to 21%];  $P = .6$ ) (Figure 2), although these results did not differ significantly ( $P$  for homogeneity,  $.1$ ). However, for neither of these pairs of subgroups, defined by baseline cognitive impairment or study treatment regimen, were there corresponding trends for the outcome of cognitive decline ( $P$  for homogeneity, both  $\geq .5$ ) (Figure 3). There was no evidence of any difference in the effects of treatment on either outcome for participant subgroups defined by baseline hypertension status ( $P$  for homogeneity, both  $\geq .1$ ) (Figures 2 and 3).

### EFFECTS OF TREATMENT ON MEAN MMSE SCORES

Measures of baseline to follow-up change in MMSE were made for 5888 participants (96.4%), but were not available for the 217 participants who had either no baseline MMSE score or only 1 measure of MMSE. For these 5888 participants, the fall in MMSE scores between baseline and final evaluations was smaller among participants assigned active treatment (mean  $\pm$  SE,  $0.05 \pm 0.05$ ) than among those assigned placebo (mean  $\pm$  SE,  $0.24 \pm 0.05$ ). The mean  $\pm$  SE difference between randomized groups in the decline in MMSE scores was  $0.19 \pm 0.07$  ( $P = .01$ ), with no clear evidence of differences in the effects of treatment between any of the subgroups studied ( $P$  for homogeneity,  $> .2$  for all).

### COMMENT

This large-scale randomized trial among individuals with a previous stroke or transient ischemic attack provides the most reliable evidence to date about the effects of blood pressure lowering on the risks of dementia and cognitive decline. While there was no clear effect of treat-

ment on the overall risk of dementia, the risk of the composite outcome of "dementia with recurrent stroke" was reduced by one third. There were also clear beneficial effects of treatment on other indicators of cognitive impairment—the overall risk of cognitive decline was reduced by about one fifth, the risk of the composite outcome of "cognitive decline with recurrent stroke" was reduced by about one half, and the entire decline in mean MMSE scores observed in the placebo group appeared to be averted by active treatment. These benefits were independent of the effects of study treatment on mortality and appeared to be similar in both hypertensive and non-hypertensive individuals.

The observed effects of study treatment on these various indexes of cognitive impairment in PROGRESS appear largely to reflect reductions in the risks of dementia and cognitive decline associated with the occurrence of recurrent stroke during follow-up. This suggests that the benefits of treatment are primarily the consequence of stroke prevention rather than a direct effect on dementia or cognitive decline. This finding is consistent with the results of observational studies, which have demonstrated that the risk of dementia after stroke is high,<sup>6-8</sup> and with the results of previous randomized trials, which have shown that blood pressure lowering reduces the risk of stroke.<sup>28</sup>

These results from PROGRESS add substantially to the available evidence about the effects of blood pressure-lowering regimens on dementia and cognitive impairment. Prior to the completion of PROGRESS, there were only 113 cases of dementia recorded in large-scale trials of blood pressure-lowering agents<sup>14,16</sup> in which the confidence intervals about the estimated effects of treatment were wide and the overall effects on measures of cognitive function were unclear.<sup>14-16</sup> In addition, a recent analysis of data from one of these studies suggested that differential dropout rates between treatment groups may have introduced a bias in the estimate of the treatment effect obtained.<sup>29</sup> The randomized design and the completeness of follow-up achieved in PROGRESS make it very unlikely that the observed effects of treatment are biased. However, while the study was much larger than preceding trials, there were still relatively few events recorded and there is moderate imprecision about the effect estimates calculated. Therefore, whether the absence of a clear overall effect of study treatment on dementia reflects a true absence of benefit for this outcome or whether the limited power of the trial fails to reliably detect a more modest effect of treatment remains uncertain. For example, the 95% confidence intervals for the estimated effect of treatment on dementia in PROGRESS do not exclude a reduction in the relative risk of dementia of 15% to 20%, a treatment effect that would be quite consistent with the result observed for cognitive decline.

Premature discontinuation of study treatment by a proportion of study participants<sup>18</sup> is likely to have resulted in underestimation of the real effects of study treatment on each outcome. Otherwise, there were few sources of systematic error likely to have had substantive influence on the estimates of treatment effect obtained. The comprehensive screening process, the use of specialists in the diagnosis of dementia, and the review of all as-

## PROGRESS Collaborative Group

A complete listing of the members of the PROGRESS Collaborative Group was published previously (*Lancet*. 2001;358:1033-1041).

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assessments by a central Dementia Adjudication Committee should have ensured that the diagnosis of dementia was both sensitive and specific and should have minimized the effects of other features of cerebrovascular disease, which may mimic or mask dementia (eg, aphasia or depression). However, while misclassification of dementia should have been largely avoided, use of the DSM-IV criteria, which require memory impairment for the diagnosis, may have resulted in a slight underestimation of the true incidence of dementia, since memory impairment may be absent in patients who experience dementia following stroke.<sup>30</sup> Although missed cases should have been few, it is possible that more cases were missed in the placebo group, since that group experienced more recurrent strokes, and this too could have resulted in a slight underestimation of any true effects of study treatment on dementia.

For stroke, the primary outcome of the main analysis, patients who received combination therapy with both perindopril and indapamide experienced a much larger reduction in risk (risk reduction, 43% [95% CI, 30% to 54%]) than did those treated with single drug therapy with perindopril alone (risk reduction, 5% [95% CI, -19% to 23%]; *P* for homogeneity <.001).<sup>18</sup> This difference in outcome appears likely to have been the consequence of the markedly greater reduction in blood pressure achieved with combination therapy (12/5 mm Hg) than with single drug therapy (5/3 mm Hg).<sup>18</sup> There were no similarly definitive differences between the effects of these 2 regimens on the outcomes of dementia and cognitive decline, although the results were consistent with combination therapy having a greater effect on dementia compared with single drug therapy. There was stronger evidence of a difference in the effect of treatment on dementia among subgroups of individuals defined by the presence or absence of cognitive impairment at baseline. While a real difference between the effects of treatment on incident and nonincident disease is certainly plausible, the number of events recorded is too few to allow definitive conclusions to be drawn. Moreover, for each of the foregoing subgroup analyses, the case for the exist-

tence of heterogeneity of effects on dementia is reduced by the apparent absence of any such differences in the effects of treatment on cognitive decline.

In summary, as the proportion of elderly individuals increases, the worldwide burden of disease attributable to stroke, dementia, and cognitive impairment is projected to rise substantially.<sup>1</sup> Observational studies have identified high blood pressure and cerebrovascular disease as important determinants of dementia and cognitive impairment, and this study has confirmed the beneficial effects of a preventive strategy based on blood pressure lowering. These benefits, when added to those previously reported, provide further support for the recommendation that blood pressure lowering with perindopril and indapamide be considered for all patients with a history of stroke or transient ischemic attack.

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This article is dedicated to the memory of Lennart Hansson, MD, who died unexpectedly in November 2002.

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