

# Effects of Perindopril-Based Lowering of Blood Pressure on Intracerebral Hemorrhage Related to Amyloid Angiopathy

## The PROGRESS Trial

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**Background and Purpose**—Patients with cerebral amyloid angiopathy (CAA) are at high risk for intracerebral hemorrhage (ICH), but no effective prevention strategies have been established. The objective is to determine whether lowering of blood pressure (BP) provides protection for this high-risk patient group.

**Methods**—This study is a subsidiary analysis of the PROGRESS trial—a randomized, placebo-controlled trial that established the beneficial effects of BP lowering in patients with cerebrovascular disease; 6105 patients were randomly assigned to either active treatment (perindopril for all participants plus indapamide for those with neither an indication for nor a contraindication to a diuretic) or matching placebo. Outcomes were probable CAA-related ICH as defined by the Boston criteria, probable hypertension-related ICH, and unclassified ICH.

**Results**—Over a mean follow-up of 3.9 years, 16 probable CAA-related ICH, 51 probable hypertension-related ICH, and 44 unclassified ICH occurred. Active treatment reduced the risk of CAA-related ICH by 77% (95% CI, 19%–93%), that of hypertension-related ICH by 46% (95% CI, 4%–69%), and that of unclassified ICH by 43% (95% CI, –5%–69%). There was no evidence of differences in the magnitude of the effects of treatment among different types of ICH ( $P$  homogeneity=0.4).

**Conclusions**—BP-lowering treatment is likely to provide protection against all types of ICH. (*Stroke*. 2010;41:394-396.)

**Key Words:** blood pressure ■ cerebral amyloid angiopathy ■ intracerebral hemorrhage  
■ randomized controlled trials

Intracerebral hemorrhage (ICH) is estimated to affect >1 million people worldwide each year, most of whom either die or are left seriously disabled.<sup>1</sup> The most common type of ICH is hypertension (HT)-related ICH, which is related to degenerative changes in the small penetrating arteries of the deep part of the brain.<sup>2</sup> The other type of ICH is associated with cerebral amyloid angiopathy (CAA), which is defined by the deposition of congophilic material, preferentially in vessels of the cortex and leptomeninges.<sup>3</sup> CAA-related ICH is characterized by multiple occurrence of ICH over time, a cortical localization of the hematoma, and an increasing incidence with age.<sup>4</sup> Despite this high rate of ICH, no effective prevention strategies have been established. The objective of the present analysis is to determine whether blood pressure (BP) lowering provides protection against probable CAA-related ICH.

## Materials and Methods

### Study Design

The PROGRESS trial was a randomized, placebo-controlled trial that investigated the effects of BP lowering among patients with cerebrovascular disease.<sup>5</sup> The design of PROGRESS has been described in detail elsewhere.<sup>5</sup> Briefly, 6105 participants with cerebrovascular disease who had no clear indication for, or contraindication to, an angiotensin-converting enzyme inhibitor were randomly assigned to active treatment (2–4 mg perindopril for all participants plus 2–2.5 mg indapamide for those with neither an indication for nor a contraindication to a diuretic) or matching placebo. The institutional ethics committee of each collaborating center approved the trial, and all participants provided written informed consent.

### Outcomes

For patients with possible stroke, a detailed history was taken and neurological and morphological (CT/MRI) examinations were con-

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**Table. Baseline Characteristics of Randomized Participants**

	Active, n=3051	Placebo, n=3054
<b>Demographic</b>		
Mean age, years (SD)	64 (10)	64 (10)
Women, %	30	30
Asian, %	39	39
<b>Cerebrovascular disease history, %</b>		
Ischemic stroke	71	71
ICH	11	11
Stroke of unknown type	4	5
Transient ischemic attack	22	22
<b>Other medical history, %</b>		
Current smoker	20	20
Diabetes	13	12
Coronary heart disease	16	16
<b>BP</b>		
Mean systolic BP, mm Hg (SD)	147 (19)	147 (19)
Mean diastolic BP, mm Hg (SD)	86 (11)	86 (11)

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ducted. Stroke was defined according to standard criteria<sup>6</sup> and subclassified into ICH (ICD-9 code 431) or ischemic stroke (ICD-9 codes 433, 434).<sup>5</sup> The diagnosis of ICH and exclusion of secondary causes were confirmed using CT/MRI. ICH was classified into lobar hemorrhage or nonlobar hemorrhage (basal ganglia, thalamus, brain stem, or cerebellum) according to the originated location based on investigation reports and supporting documentation (medical charts and CT/MRI reports) independently by 2 investigators ( $\kappa$  coefficient=0.84), as described previously.<sup>7</sup> Probable CAA-related ICH was defined according to the Boston Criteria<sup>8</sup> as follows: lobar hemorrhage with evidence of multiple ICH (recurrence of ICH among patients with preexisting ICH or incidence of multiple ICH during follow-up) and age at onset 55 years or older. Probable HT-related ICH was defined as follows: ICH with no evidence of multiple ICH and presence of HT at baseline (BP  $\geq$  140/90 mm Hg or use of antihypertensive agents). Only the first ICH event during follow-up was included in the analysis.

**Statistical Analysis**

The effects of randomized treatment on events were calculated using univariate Cox proportional hazards models, according to the principle of intention-to-treat. The constancy of treatment effects was tested using a  $\chi^2$  test of homogeneity.

**Results**

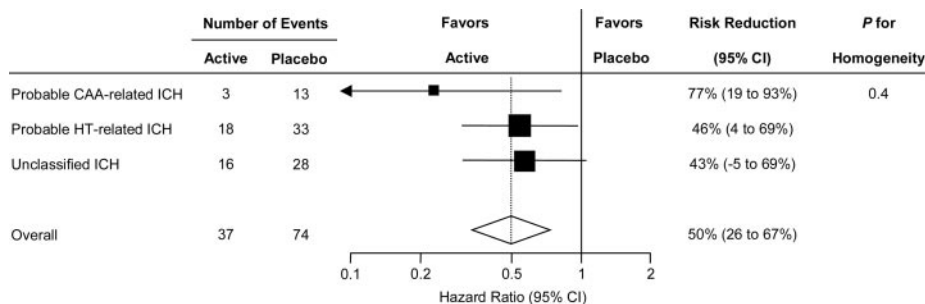
There were no important differences in characteristics between randomized groups (Table).<sup>5</sup> Over a mean follow-up of 3.9 years, 16 probable CAA-related ICH, 51 probable HT-related ICH, and 44 unclassified ICH occurred. Subjects with ICH were more likely to be Asian (65%) than those without ICH (38%). Mean BP levels at baseline were slightly higher among patient with ICH (150/88 mm Hg) than among those without (147/86 mm Hg). Frequency of preexisting ICH was higher among patients with ICH (46%) than among those without (10%). Mean BP levels at baseline were lower among patients with CAA-related ICH (137/81 mm Hg) than among those with HT-related ICH (157/88 mm Hg). Fifty-six percent of patients with CAA-related ICH had HT at baseline and 13% of those had HT newly diagnosed during follow-up. Whereas 88% of patients with CAA-related ICH had preexisting ICH, 84% of those with HT-related ICH had preexisting ischemic stroke.

During follow-up, mean BP difference between randomized groups was 9/4 mm Hg. Active treatment reduced the risk of CAA-related ICH by 77% (95% CI, 19%–93%), that of HT-related ICH by 46% (95% CI, 4%–69%), and that of unclassified ICH by 43% (95% CI, -5%–69%; Figure). There was no evidence of differences in the magnitude of the effects of treatment among different types of ICH (*P* homogeneity=0.4). There were also comparable benefits from active treatment on CAA-related ICH with and without baseline HT (*P* homogeneity=0.4) or baseline and newly diagnosed HT (*P* homogeneity=0.2).

**Discussion**

The main results from the PROGRESS trial showed that routine BP-lowering treatment reduced the risk of ICH by 50% among patients with cerebrovascular disease.<sup>5</sup> The analyses reported here expand on this earlier report and suggest that BP lowering is likely to reduce the risks of CAA-related ICH and other forms of ICH.

Few studies have investigated the effects of BP on the risks of CAA-related ICH. A study of autopsy cases has demonstrated that definite CAA patients with ICH were more frequently hypertensive (50%) than those without ICH (23%).<sup>9</sup> This finding suggests that HT is likely to have an important role in development of ICH among patients with CAA and is consistent with our hypothesis that BP lowering has potential to reduce ICH among patients with CAA.



**Figure.** Effects of randomized treatment on the risks of different types of ICH. Solid boxes indicate estimates of treatment effect on the risks of ICH types; horizontal lines, 95% CI; diamond, the estimate and 95% CI for overall effect. Areas of the boxes are proportional to the event number.

This is the first article to our knowledge to report the beneficial effects of BP lowering on probable CAA-related ICH to date, although the confidence interval was wide because of the small number of events recorded. It is likely that the beneficial effects of BP lowering are applicable to definite CAA-related ICH despite the fact that the diagnosis of probable CAA-related ICH in the present analysis was made clinically and based on the Boston criteria without pathological confirmation. A clinical–pathological correlation study has demonstrated that all patients with clinically diagnosed probable CAA-related ICH based on the Boston criteria had neuropathological evidence of CAA.<sup>10</sup> Although the majority of unclassified ICH most likely comprises possible CAA-related and HT-related ICH, comparable treatment effects were observed among different types of ICH, and this limitation is not likely to invalidate our findings.

### Conclusion

In conclusion, BP-lowering treatment is likely to provide protection against both HT-related and CAA-related ICH, whether hypertensive or not.

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