Effects of Blood Pressure Lowering on Intracranial and Extracranial Bleeding in Patients on Antithrombotic Therapy
The PROGRESS Trial

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Background and Purpose—Observational studies demonstrate strong associations between blood pressure and bleeding complications of antithrombotic therapy. The objective was to determine whether blood pressure lowering reduces risks of bleeding in patients on antithrombotic therapy.

Methods—This is a subsidiary analysis of the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) trial, a randomized, placebo-controlled trial. A total of 6105 patients with cerebrovascular disease were randomly assigned to either active treatment (perindopril/indapamide) or placebo(s). The outcomes were intracranial and extracranial bleeding.

Results—There were 4876 (80%) patients on antithrombotic therapy at baseline. Over a mean follow-up of 3.9 years, 119 intracranial and 123 extracranial bleeding events were observed. Among patients with and without antithrombotic therapy, active treatment lowered blood pressure by 8.9/4.0 and 9.3/3.8 mm Hg and reduced the risks of intracranial bleeding by 46% (95% CI, 7%–69%) and 70% (39%–85%), respectively. However, active treatment did not reduce the risks of extracranial bleeding significantly in either group. Among patients on antithrombotic therapy, the lowest risk of intracranial bleeding was observed in participants with the lowest follow-up systolic blood pressure levels (median, 113 mm Hg).

Conclusions—Blood pressure lowering provides protection against intracranial bleeding among patients with cerebrovascular disease including those receiving antithrombotic therapy.

Clinical Trial Registration Information—This trial was not registered because patients were enrolled before July 1, 2005.

Key Words: antihypertensive agents ■ antithrombotics ■ bleeding ■ clinical trials ■ hypertension

Antithrombotic therapy is beneficial for secondary prevention of ischemic stroke, coronary heart disease, and other cardiovascular disease but is associated with a modest increase in bleeding.1 Although observational studies have demonstrated strong associations between blood pressure (BP) and bleeding complications of antithrombotic therapy,2–4 there remains uncertainty about the effects of BP lowering on the risks of bleeding during antithrombotic therapy. As a result, many guidelines for prevention of cardiovascular disease do not refer to the importance of BP control during antithrombotic therapy.5,6 The objective of the present analysis was to determine whether BP lowering reduces the risks of bleeding in patients on antithrombotic therapy.

Methods

Study Design

The design of the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) trial has been described in detail elsewhere.7,8 Briefly, 6105 participants with stroke (ischemic, hemorrhagic, or unknown) or transient ischemic attack were randomly assigned to active treatment (2–4 mg perindopril for all participants plus 2–2.5 mg indapamide for 3544 participants) or matching placebo(s).

The trial was approved by the institutional ethics committee of each collaborating center, all participants provided written, informed consent; and the trial was registered with ClinicalTrials.gov (NCT00002051).

Analysis

The primary endpoint was the occurrence of any stroke or transient ischemic attack, which was defined as new or worsening symptoms consistent with cerebrovascular disease; these events were adjudicated by an independent stroke committee. Secondary endpoints included all-cause mortality, myocardial infarction, all-cause bleeding, intracranial bleeding, and extracranial bleeding. Blood pressure was measured at least every 4 weeks for the first 3 months, then every 6 months, and was recorded in the trial database.

Analysis of intracranial and extracranial bleeding as adverse effects of BP lowering was performed in a subgroup of patients with cerebrovascular disease (n = 4876; 80% of the total study population). The outcomes were intracranial and extracranial bleeding.

Baseline characteristics were compared between treatment groups using chi-square tests for categorical variables and analysis of variance for continuous variables. The outcomes were analyzed using a Cox proportional hazards model with time in days to any endpoint and treatment group as the main explanatory variables. The proportional hazards assumption was tested by visual inspection of plots of log-log survival versus follow-up time.

Results

During a mean follow-up of 3.9 years, 119 intracranial and 123 extracranial bleeding events were observed. Among patients with and without antithrombotic therapy, active treatment lowered blood pressure by 8.9/4.0 and 9.3/3.8 mm Hg and reduced the risks of intracranial bleeding by 46% (95% CI, 7%–69%) and 70% (39%–85%), respectively. However, active treatment did not reduce the risks of extracranial bleeding significantly in either group.

Among patients on antithrombotic therapy, the lowest risk of intracranial bleeding was observed in participants with the lowest follow-up systolic blood pressure levels (median, 113 mm Hg).

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consent, and procedures followed were in accordance with institutional guidelines.

Outcomes

The outcomes were intracranial (intracerebral [International Classification of Diseases, 9th Revision code 431], subarachnoid [430], and subdural hemorrhages [432.1]) and extracranial bleeding (gastrointestinal [530.7–8; 456.0; 531.2, 4, 6; 532.2, 4, 6; 533.2, 4, 6; 534.2, 4, 6; 578] and other hemorrhages [599.7; 626.5–8; 627.1; 784.7–8; 786.3]), which were life-threatening or resulted in hospitalization, disability, or death. Fatal bleeding and nonfatal intracranial hemorrhage were validated by an end point adjudication committee.7

Statistical Analysis

The effects of randomized treatment on events were estimated using univariate Cox proportional hazards models according to the principle of intention to treat. Treatment effects in subgroups were standardized for the proportions of the study population for whom combination (58%) and single-drug therapy (42%) was prescribed. Comparisons of treatment effects across patient groups were performed by adding an interaction term to the statistical model.

The association of achieved follow-up systolic BP levels (\( <120, 120–139, 140–159, \) and \( \geq 160 \) mm Hg) and outcomes was investigated using time-dependent Cox proportional hazards models including age, sex, region, history of hemorrhagic stroke, smoking, diabetes, randomized treatment, and combination therapy as covariates. CIs were estimated by treating the hazard ratios as floating absolute risks.9

Results

Of 6105 randomized participants, 4876 (80%) received antithrombotic therapy at baseline. Patients on antithrombotic therapy were older and less frequently Asian and had a smaller proportion with a history of hemorrhagic stroke (online-only Data Supplement Table I).

Over a mean follow-up of 3.9 years, 119 intracranial (111 intracerebral, 4 subarachnoid, and 4 subdural hemorrhages) and 123 extracranial bleeding events (97 gastrointestinal and 29 other hemorrhages) occurred. During follow-up, the mean BP difference between randomized groups was 8.9/4.0 (SE, 0.3/0.2) and 9.3/3.8 (0.6/0.3) mm Hg for patients with and without antithrombotic therapy, respectively (\( P_{\text{homogeneity}}=0.54/0.74 \)). Active treatment reduced the relative risk of intracranial bleeding events by 46% (95% CI, 7%–69%) among patients with antithrombotic therapy and by 70% (39%–85%) among patients without antithrombotic therapy (Figure 1). Conversely, there was no significant reduction in the risk of extracranial bleeding for patients who were and were not using antithrombotic therapy.

Among 4876 patients on antithrombotic therapy, the association between achieved follow-up systolic BP and the risk of intracranial bleeding was strong and continuous (\( P_{\text{trend}}=0.007 \); Figure 2), whereas there were no clear associations for extracranial bleeding.

Discussion

The present analysis demonstrated that BP lowering was beneficial for prevention of intracranial bleeding among patients with cerebrovascular disease including those receiving antithrombotic therapy. Separate observational analyses have also shown that the lowest achieved follow-up systolic BP down to approximately 115 mm Hg was associated with the lowest incidence of intracranial bleeding in patients on antithrombotic therapy. These findings are supported by a number of prospective cohort studies, which demonstrated significant associations between BP and antithrombotic therapy-related bleeding.2–4 The present findings are also consistent with the Atrial Fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE-I) trial, which demonstrated 40% reduction in intracranial bleeding associated with BP lowering in patients with atrial fibrillation on antithrombotic therapy.10
Another important finding of the present analysis was that BP lowering had no demonstrable effects on the risk of extracranial bleeding. This is consistent with the Bleeding With Antithrombotic Therapy (BAT) study, which demonstrated no clear associations between BP and extracranial hemorrhage.2 Gastroprotection strategies are likely to provide additional protection against upper gastrointestinal bleeding, the main cause of extracranial bleeding associated with antithrombotic therapy.11,12

Although this is one of the largest randomized controlled trials to have investigated the effects of BP lowering on bleeding among patients on antithrombotic therapy, the limited number of events makes it difficult to conduct further subgroup analysis by type of antithrombotic therapy. Another limitation is that nonfatal extracranial bleeding events were not reviewed by the end point adjudication committee.

Summary

BP lowering provides protection against intracranial bleeding among patients with cerebrovascular disease including those receiving antithrombotic therapy.

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The PROGRESS Study was funded by grants from Servier, the Health Research Council of New Zealand, and National Health and Medical Research Council (NHMRC) of Australia. The study was designed, conducted, analyzed, and interpreted by the investigators independent of all sponsors.

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