Perindopril-Based Blood Pressure-Lowering Reduces Major Vascular Events in Patients With Atrial Fibrillation and Prior Stroke or Transient Ischemic Attack

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Background and Purpose—Patients with atrial fibrillation have a high risk of stroke and other vascular events even if anticoagulated. The primary objective here is to determine whether routine blood pressure-lowering provides additional protection for this high-risk patient group.

Methods—This study was a subsidiary analysis of the Perindopril Protection Against Recurrent Stroke Study (PROGRESS)—a randomized, placebo-controlled trial that established the beneficial effects of blood pressure-lowering in a heterogeneous group of patients with cerebrovascular disease. A total of 6105 patients were randomly assigned to either active treatment (2 to 4 mg perindopril for all participants plus 2.0 to 2.5 mg indapamide for those without an indication for or a contraindication to a diuretic) or matching placebo(s). Outcomes are total major vascular events, cause-specific vascular outcomes, and death from any cause.

Results—There were 476 patients with atrial fibrillation at baseline, of whom 51% were taking anticoagulants. In these patients, active treatment lowered mean blood pressure by 7.3/3.4 mm Hg and was associated with a 38% (95% confidence interval [CI], 6 to 59) reduction in major vascular events and 34% (95% CI, −13 to 61) reduction in stroke. The benefits of blood pressure-lowering in patients with atrial fibrillation were achieved irrespective of the use of anticoagulant therapy (P homogeneity = 0.8) or the presence of hypertension (P homogeneity = 0.4).

Conclusions—For most patients with atrial fibrillation, routine blood pressure-lowering is likely to provide protection against major vascular events additional to that conferred by anticoagulation. (Stroke. 2005;36:2164-2169.)

Key Words: antihypertensive agents ■ atrial fibrillation ■ randomized, controlled trials ■ stroke

Atrial fibrillation is common among elderly patients1,2 and is an important cause of ischemic stroke.1,2 Patients with atrial fibrillation obtain substantial benefit from anticoagulant therapy,3,4 although even with effective anticoagulation, the risk of serious vascular complications remains high.5,6 The partial protection afforded by anticoagulation appears to be mediated primarily through the aversion of cardioembolic strokes caused by migration of stasis-precipitated thrombi formed in the left atrial appendage.7 However, stasis-precipitated thrombus does not appear to be the only etiologic mechanism active in these patients, and it is not only the risk of cardioembolic stroke that is elevated.7-9 The effects of hypertension on cardioembolic stroke risk are, for example, well documented,4,8,9 and studies using transesophageal echocardiography have shown hypertension to be associated with increased left atrial appendage stasis mediated by ventricular diastolic dysfunction.10,11 Lowering of blood pressure might therefore ameliorate stasis in the left atrial appendage through reversal of ventricular remodeling and thereby decrease the risk of embolism. In addition, because elevated blood pressure levels in patients with atrial fibrillation are also associated with higher risks of strokes of noncardioembolic etiology,5,9 blood pressure-lowering might also reduce the risks of other stroke subtypes providing important additional protection.

The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) clearly demonstrated the benefits of blood pressure-lowering for the prevention of stroke and major vascular events in a heterogeneous group of patients with cerebrovascular disease.12,13 Previous reports about the beneficial effects of treatment on stroke risk in the subset of 476 patients with atrial fibrillation in PROGRESS have been brief.13 We provide here more detailed information about the effects of randomized treatment in patients with and without
Atrial fibrillation and specifically address uncertainty surrounding the likely value of routine blood pressure–lowering for this large and growing patient population.

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 a cerebrovascular event (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, or contraindication to, treatment with an angiotensin-converting-enzyme (ACE) inhibitor. There were no blood pressure 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 daily) with the addition of indapamide (2.5 mg daily; or 2 mg daily 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).

Definitions and Classification

Stroke and transient ischemic attack were defined according to standard criteria (codes 431, 433, 434, 436, and 437 in the 9th revision of the International Classification of Diseases, Ninth Edition [ICD-9]). All baseline strokes were subclassified as ischemic, hemorrhagic, or unknown type. A diagnosis of atrial fibrillation was made on the basis of either the baseline electrocardiographic examination or a positive disease history confirmed by electrocardiography. Hypertension was defined as systolic ≥160 mm Hg and/or diastolic blood pressure ≥90 mm Hg at baseline, but subsidiary analyses were also done for cuts of 150/95 mm Hg and 140/90 mm Hg. Use of oral anticoagulant therapy was also documented at baseline.

Outcomes

The outcomes of the present investigation were total major vascular event (nonfatal stroke, nonfatal myocardial infarction, or death as a result of any vascular cause), stroke, major coronary heart disease (CHD; nonfatal myocardial infarction or death resulting from CHD), heart failure (congestive heart failure resulting in death, hospitalization or requiring withdrawal of randomized therapy), death resulting from any vascular cause, and total death. Strokes were subclassified into ischemic and hemorrhagic type according to the ICD-9 codes. All these events were reviewed and validated by an end point adjudication committee. Only the first event relevant to each outcome was included in each analysis.

Statistical Analysis

The effects of atrial fibrillation on the risks of events were investigated using Cox proportional hazards models, including the covariates age, gender, current smoking, diabetes, systolic blood pressure, randomized study treatment, and planned use of combination therapy. The effects of randomized treatment on events were calculated using univariate Cox proportional hazards models according to the principle of intention-to-treat, and the effects of randomized treatment on blood pressure were calculated using linear mixed models. Comparisons of treatment effects between participants with and without atrial fibrillation were done by adding an interaction term to the statistical model. The same was done to test the homogeneity of treatment effects for subgroups of patients with atrial fibrillation defined on the basis of use or no use of anticoagulant therapy and the presence or absence of hypertension. Because the overall effect of treatment was greater among participants treated with combination therapy than among those treated with single-drug therapy, treatment effects in subgroups and estimates of numbers needed to treat were standardized for the proportions of the study population for whom combination (58%) or single-drug therapy (42%) was prescribed by taking weighted averages of the estimates obtained for the 2 therapies. Percentage risk reductions were calculated as ([1 − hazard ratio] × 100).

Results

Baseline Characteristics

Of 6105 randomized participants, 476 (8%) had atrial fibrillation at baseline. The characteristics of those with and without atrial fibrillation are summarized by randomized group in Table 1. The patients with atrial fibrillation were older and a smaller proportion was Asian. Despite the similar blood pressure levels at entry, there was less use of combination therapy among patients with atrial fibrillation (48%) compared with those without atrial fibrillation (59%). There were no important differences in these baseline characteristics between randomized groups either for patients with or without atrial fibrillation.

Effects of Atrial Fibrillation on the Risks of Serious Clinical Outcomes

Over a mean follow-up of 3.9 years, a total of 114 major vascular events occurred in the 476 patients with atrial fibrillation (6.9% per annum) (Table 2). Even after controlling for other cardiovascular risk factors and randomized treatment, atrial fibrillation was associated with a 25% (95% confidence interval [CI], 3 to 52) greater relative risk of major vascular events. There were also significantly greater rates of stroke, ischemic stroke, heart failure, deaths from vascular causes, and total deaths in the group with atrial fibrillation that appeared to be independent of other cardiovascular risk factors and randomized treatment (Table 2). There was trend toward increased risk of atrial fibrillation on the risks of hemorrhagic stroke or major CHD but the confidence intervals were wide (Table 2).

Effects of Randomized Treatment on Blood Pressure and the Risks of Serious Clinical Outcomes

During follow-up, the mean difference in blood pressure between participants assigned active treatment and those assigned placebo was 7.3/3.4 mm Hg (standard error [SE] 1.3/0.7) and 9.0/4.0 mm Hg (SE 0.4/0.2) for patients with and without atrial fibrillation, respectively (P homogeneity systolic = 0.2; P homogeneity diastolic = 0.4). Active treatment reduced the relative risk of major vascular events by 38% (95% CI, 6 to 59) among patients with atrial fibrillation and by 25% (95% CI, 15 to 34) among patients without atrial fibrillation (P homogeneity = 0.4) (Figure 1). Point estimates of effect favoring active treatment among patients with atrial fibrillation were obtained for every other outcome reported here, and there was no evidence that the result differed from that obtained for patients without atrial fibrillation (all P homogeneity > 0.05) (Figure 1). It was estimated that one major vascular event was avoided among every 11 patients (95% CI, 6 to 63) with atrial fibrillation treated for 5 years.
compared with one major vascular event avoided among every 23 patients (95% CI, 16 to 41) without atrial fibrillation treated for the same time period (P homogeneity = 0.2).

**Effects of Randomized Treatment by Use of Anticoagulants and Baseline Blood Pressure in Patients With Atrial Fibrillation**

Among the 476 participants with atrial fibrillation, there were comparable reductions in the relative risk of major vascular events associated with active treatment for patients that were (41%; 95% CI, −6% to 68%) and were not using anticoagulant therapy (34%; −19% to 64%) (P homogeneity = 0.8) (Figure 2). Likewise, among these patients, there was no difference in the benefit obtained for patients who were, and patients who were not, hypertensive at baseline for a range of different definitions of hypertension (all P homogeneity > 0.3). There were also comparable benefits from active treatment for each of these patient groups for the outcome stroke (both P homogeneity = 0.9) (Figure 2).

**Discussion**

The main results from the PROGRESS trial showed that a heterogeneous group of patients with established cerebrovascular disease had much to gain from routine blood pressure–lowering with a regimen based on an angiotensin-converting enzyme inhibitor and a diuretic. Subse-
quent analyses have shown these benefits to be consistent across diverse clinical subgroups contained within the study, and a separately significant reduction in stroke has previously been reported for the subgroup of patients with atrial fibrillation. The analyses reported here expand on this earlier report and suggest that the overall benefits of blood pressure-lowering in patients with atrial fibrillation may be larger than for patients without atrial fibrillation.

### Table 2: Effects of Atrial Fibrillation on the Risks of Serious Clinical Outcomes

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Patients With Atrial Fibrillation</th>
<th>Patients Without Atrial Fibrillation</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major vascular event</td>
<td>114 (6.9)</td>
<td>948 (4.6)</td>
<td>1.25 (1.03–1.52)</td>
<td>0.03</td>
</tr>
<tr>
<td>Stroke</td>
<td>77 (4.6)</td>
<td>650 (3.1)</td>
<td>1.29 (1.01–1.64)</td>
<td>0.04</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>64 (3.8)</td>
<td>501 (2.4)</td>
<td>1.39 (1.07–1.81)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>11 (0.6)</td>
<td>100 (0.5)</td>
<td>1.31 (0.70–2.48)</td>
<td>0.4</td>
</tr>
<tr>
<td>Major CHD event</td>
<td>32 (1.8)</td>
<td>237 (1.1)</td>
<td>1.36 (0.93–1.98)</td>
<td>0.1</td>
</tr>
<tr>
<td>Heart failure</td>
<td>31 (1.8)</td>
<td>142 (0.6)</td>
<td>1.80 (1.21–2.68)</td>
<td>0.004</td>
</tr>
<tr>
<td>Vascular deaths</td>
<td>53 (3.0)</td>
<td>326 (1.5)</td>
<td>1.47 (1.09–1.98)</td>
<td>0.01</td>
</tr>
<tr>
<td>Total deaths</td>
<td>81 (4.5)</td>
<td>544 (2.5)</td>
<td>1.35 (1.06–1.71)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*Hazard ratios and P values adjusted for baseline age, sex, smoking, diabetes, systolic blood pressure, study treatment and combination therapy.

CI indicates confidence interval.

**Figure 1.** Effects of randomized treatment on the risks of serious clinical outcomes among patients with and without atrial fibrillation. Annual event rates and treatment effects in subgroups were standardized for the proportions of the study population for whom combination (58%) or single-drug therapy (42%) was prescribed. CHD indicates coronary heart disease. Solid boxes represent estimates of treatment effect on the risk of clinical outcomes. Centers of the boxes are placed at the estimates of effect; areas of the boxes are proportional to the number of events. Horizontal lines represent 95% CI. The “probability value for homogeneity” tested the consistency of the treatment effect in those with versus those without atrial fibrillation.
tion, are accrued on top of benefits gained from anticoagulation and are probably not different for patients with and without hypertension.

The overall risk of major vascular events among PROGRESS participants with atrial fibrillation was 6.9% per annum with persisting high risks of stroke (4.6% per annum) and ischemic stroke (3.8% per annum). Annual stroke risks of this magnitude are, however, directly comparable with the findings of other trials, which have reported stroke rates ranging between 3% and 11% for these patients.5,6 The reasons for the differences in stroke rates between study populations are multiple5,6 but 2 factors consistently identified as determinants of stroke risk, and with particular significance to prevention, are blood pressure5,6 and use of anticoagulant therapy.5,6 Observational studies have clearly implicated elevated blood pressure levels8,9,15,16 and absence of anticoagulation 17 as leading causes of stroke among patients with atrial fibrillation.

Randomized trials of anticoagulant therapies have demonstrated that effective anticoagulation can reduce the risks of ischemic stroke by approximately one half,3 and anticoagulation is accordingly widely recommended by treatment guidelines.18 Baseline use of oral anticoagulants in PROGRESS participants with atrial fibrillation was 51%, and there can be little doubt that this significantly reduced the rate of ischemic stroke among these patients. There also seems to be little doubt that the PROGRESS blood pressure–lowering regimen significantly reduced the risk of major vascular events among the patient subgroup with atrial fibrillation.

Unfortunately, corresponding definitive evidence about the effects of the blood pressure–lowering regimen on each of the major cause-specific vascular outcomes was not provided by these analyses. Although there were trends toward benefit for every category of major vascular event studied, the numbers of events recorded among participants with atrial fibrillation were limited and insufficient to provide separately significant results for each. Likewise, although the effects of blood pressure–lowering appear to have accrued on top of any benefits achieved through anticoagulation, the strength of the evidence is somewhat limited by the small number of events recorded. In particular, there were insufficient data to clearly define the effects of blood pressure–lowering among patients with the very lowest entry blood pressure levels, although these analyses provide no evidence of harm in this patient group.

Few other studies have reported the effects of blood pressure–lowering regimens on stroke risk among patients with atrial fibrillation, and there are only limited trial data to corroborate the findings reported here. The Mortality Assessment in Congestive Heart Failure Trial (MACH-1)19 detailed the effects of a blood pressure–lowering regimen based on the calcium antagonist mibefradil compared with placebo among patients with heart failure. By contrast to PROGRESS, MACH-1 identified no beneficial effect of treatment either overall or among the patient subgroup with atrial fibrillation. This result may, however, reflect an agent-specific lesser effect of calcium antagonist-based blood pressure–lowering regimens among patients with heart failure20 and probably

<table>
<thead>
<tr>
<th>Major Vascular Event</th>
<th>Anticoagulant Therapy</th>
<th>Placebo (n=233)</th>
<th>Favors Active</th>
<th>Favors Placebo</th>
<th>% Risk Reduction (95% CI)</th>
<th>P Value for Homogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>23 (4.6)</td>
<td>33 (8.3)</td>
<td>41 (-6 to 68)</td>
<td>34 (-16 to 64)</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>25 (6.1)</td>
<td>33 (8.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>19 (4.9)</td>
<td>35 (8.0)</td>
<td>49 (5 to 73)</td>
<td>25 (-33 to 58)</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>29 (5.6)</td>
<td>31 (7.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>48 (5.2)</td>
<td>65 (8.2)</td>
<td>38 (-6 to 59)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 2. Effects of randomized treatment on the risks of major vascular event and stroke by use of anticoagulation and baseline blood pressure in patients with atrial fibrillation. Solid boxes represent estimates for individual subgroups and diamonds represent estimates and 95% CI for overall effects in the patients with atrial fibrillation. Vertical broken lines represent point estimates for overall effects in the patients with atrial fibrillation. Other conventions as for Figure 1. Anticoagulant therapy is use of oral anticoagulant agent and hypertension is defined as systolic ≥160 mm Hg and/or diastolic blood pressure ≥90 mm Hg at baseline.
does not constitute good evidence that blood pressure--lowering is ineffectual among patients with atrial fibrillation. The Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) Study\textsuperscript{21} compared the effects of blood pressure--lowering regimens based on an angiotensin receptor blocker and a beta-blocker. This trial, which selected patients on the basis of left ventricular hypertrophy and hypertension, showed a significantly greater protective effect of the angiotensin receptor blocker-based regimen on stroke both overall and separately among the patients with atrial fibrillation. Both PROGRESS and LIFE\textsuperscript{21} have showed beneficial effects on vascular risk of blood pressure--lowering regimens based on agents whose primary action is blockade of the renin–angiotensin system. Recent mechanistic studies suggest that blockade of the renin–angiotensin system may produce particular benefits for people with atrial fibrillation with actions mediated through vascular and electrophysiological remodeling.\textsuperscript{22} However, the relative contribution of blood pressure reduction and blood pressure-independent effects of renin–angiotensin system blockade to the benefits observed remains unclear both overall\textsuperscript{20} and among the subgroup of patients with atrial fibrillation.

In summary, PROGRESS has clearly demonstrated that blood pressure--lowering reduces the risk of major vascular events in patients with atrial fibrillation and prior stroke or transient ischemic attack. Routine blood pressure--lowering appears likely to add substantially to the protection afforded by anticoagulation by reducing the risks of a range of ischemic vascular events and possibly also providing separate protection against serious intracerebral bleeding complications. Although additional data would much more clearly define the effects of blood pressure--lowering in patients with atrial fibrillation, the evidence provided here suggests that clinicians should have a low threshold for initiating blood pressure--lowering therapy among patients with atrial fibrillation.

**Acknowledgments**

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**References**


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