Effects of Blood Pressure Lowering on Major Vascular Events Among Patients With Isolated Diastolic Hypertension
The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) Trial*

Hisatomi Arima, MD; Craig Anderson, MD; Teruo Omae, MD; Mark Woodward, PhD; Jun Hata, MD; Yoshitaka Murakami, PhD; Stephen MacMahon, PhD; Bruce Neal, MD; John Chalmers, MD; for the PROGRESS Collaborative Group

Background and Purpose—Despite clear evidence that blood pressure (BP) lowering is effective for prevention of cardiovascular events among patients with isolated systolic hypertension and systolic–diastolic hypertension, there is ongoing uncertainty about its effects in those with isolated diastolic hypertension. The objective of the present analysis is to determine whether BP lowering provides benefits to patients with isolated diastolic hypertension.

Methods—Patients with cerebrovascular disease and hypertension at baseline (n=4283) were randomly assigned to either active treatment (perindopril in all participants plus indapamide for those with neither an indication for nor a contraindication to a diuretic) or matching placebo(s). The primary outcome was total major vascular events.

Results—There were 1923 patients with isolated systolic hypertension (systolic BP ≥140 mm Hg and diastolic BP <90 mm Hg), 315 with isolated diastolic hypertension (systolic BP ≥140 mm Hg and diastolic BP ≥90 mm Hg), and 2045 with systolic–diastolic hypertension (systolic BP ≥140 mm Hg and diastolic BP ≥90 mm Hg) at baseline. Active treatment reduced the relative risk of major vascular events by 27% (95% CI, 10% to 41%) among patients with isolated systolic hypertension, by 28% (29% to 60%) among those with isolated diastolic hypertension, and by 32% (17% to 45%) among those with systolic–diastolic hypertension. There was no evidence of differences in the magnitude of the effects of treatment among different types of hypertension (P homogeneity=0.89).

Conclusions—BP lowering is likely to provide a similar level of protection against major vascular events for patients with isolated diastolic hypertension as for those with isolated systolic hypertension and systolic–diastolic hypertension.

Clinical Trial Registration Information—This trial was not registered because patients were enrolled before July 1, 2005. (Stroke. 2011;42:2339-2341.)

Key Words: antihypertensive agents ■ clinical trials ■ hypertension ■ isolated diastolic hypertension

Recent large-scale observational studies have demonstrated that isolated diastolic hypertension (IDH) as well as isolated systolic (ISH) and systolic–diastolic hypertension (SDH) is associated with a significantly increased risk of cardiovascular disease.1,2 However, patients with IDH have been shown to be less likely to receive blood pressure (BP) lowering treatment than those with ISH or SDH.1,3 One likely reason is ongoing uncertainty about the beneficial effects of BP lowering treatment in patients with IDH, because it is less common and there is a greater clinical emphasis placed on the elevated systolic component of BP.4 The objective of the present analysis was to determine whether BP lowering provides the same protection among patients with IDH as it does among patients with other forms of hypertension.

Methods

Study Design

The design of Perindopril Protection Against Recurrent Stroke Study (PROGRESS) has been described in detail elsewhere.4 Briefly, 6105 participants with cerebrovascular disease who had no clear indication for, or contraindication to, an angiotensin-converting enzyme inhibitor were recruited. In the present analysis, the 4283 participants with hypertension (systolic BP [SBP] ≥140 mm Hg and/or diastolic BP [DBP] ≥90 mm Hg) at baseline were included. Participants were randomly assigned to active treatment (2 to 4 mg perindopril for all participants plus 2 to 2.5 mg indapamide for those with neither an indication for nor a contraindication to a diuretic) or matching placebo(s).

The institutional ethics committee of each collaborating center approved the trial, and all participants provided written, informed
Results

There were 1923 patients with ISH, 315 with IDH, and 2045 with SDH at baseline. Patients with IDH were younger and more likely to be male and Asian (Table). Over a mean follow-up of 3.9 years, 794 major vascular events occurred. During follow-up, mean BP difference between randomized groups was 8.8/3.8, 6.2/2.3, and 10.0/4.4 mm Hg for patients with ISH, IDH and SDH, respectively (P homogeneity=0.003 for SBP and 0.02 for DBP). Active treatment reduced the relative risk of major vascular events by 27% (95% CI, 10% to 41%) among patients with ISH, by 28% (−29% to 60%) among those with IDH, and by 32% (17% to 45%) among those with SDH (Figure). There was no evidence of differences in magnitude of the effects of treatment among different types of hypertension (P homogeneity=0.89). Comparable effects of randomized treatment on major vascular events were observed between patient groups defined by age (<65 versus ≥65 years), sex, geographic region, and baseline use of antihypertensive therapy for each hypertension subtype (all P homogeneity >0.1). BP reductions and risk reductions were consistently greater with combination therapy than single-drug therapy (mean SBP difference 12.3 versus 3.9 mm Hg, 7.7 versus 4.3 mm Hg, and 13.5 versus 5.2 mm Hg; relative risk reduction of major vascular events 34% versus 16%, 63% versus 27%, and

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%) or single-drug therapy (42%) was prescribed. A comparison of treatment effects across patient groups was done by adding an interaction term to the statistical model.

Outcomes

The outcome studied here was major vascular event (nonfatal stroke, nonfatal myocardial infarction, or vascular death).

Hypertension Subtype

BP was measured, to the nearest 2 mm Hg, after 5 minutes of quiet rest in the seated position using a standard mercury sphygmomanometer. After an interval of at least 2 minutes, the measurement was repeated and the results averaged. Three hypertension subtypes (ISH [SBP ≥140 mm Hg and DBP <90 mm Hg], IDH [SBP <140 mm Hg and DBP ≥90 mm Hg], and SDH [SBP ≥140 mm Hg and DBP ≥90 mm Hg]) were defined for the analysis.

Table. Baseline Characteristics by Hypertension Subtype

<table>
<thead>
<tr>
<th></th>
<th>ISH (n=1923)</th>
<th>IDH (n=315)</th>
<th>SDH (n=2045)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age, y (SD)</td>
<td>68 (9)</td>
<td>58 (9)</td>
<td>63 (9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Men, %</td>
<td>65</td>
<td>80</td>
<td>71</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Asian, %</td>
<td>32</td>
<td>46</td>
<td>38</td>
<td>&lt;0.0001</td>
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<tr>
<td>Carebrovascular disease history, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>70</td>
<td>67</td>
<td>72</td>
<td>0.19</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>9</td>
<td>17</td>
<td>12</td>
<td>0.01</td>
</tr>
<tr>
<td>Stroke of unknown type</td>
<td>6</td>
<td>2</td>
<td>4</td>
<td>0.0003</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>24</td>
<td>20</td>
<td>20</td>
<td>0.003</td>
</tr>
<tr>
<td>Other medical history, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>17</td>
<td>23</td>
<td>21</td>
<td>0.006</td>
</tr>
<tr>
<td>Diabetes</td>
<td>15</td>
<td>8</td>
<td>12</td>
<td>0.01</td>
</tr>
<tr>
<td>Coronary heart disease†</td>
<td>18</td>
<td>10</td>
<td>14</td>
<td>0.0001</td>
</tr>
<tr>
<td>Blood pressure, mm Hg (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean systolic blood pressure</td>
<td>154 (12)</td>
<td>132 (5)</td>
<td>161 (15)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean diastolic blood pressure</td>
<td>81 (6)</td>
<td>93 (4)</td>
<td>97 (7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Medication, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypertensive therapy‡</td>
<td>52</td>
<td>49</td>
<td>59</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Calcium antagonist</td>
<td>41</td>
<td>41</td>
<td>43</td>
<td>0.33</td>
</tr>
<tr>
<td>Diuretic</td>
<td>14</td>
<td>10</td>
<td>12</td>
<td>0.13</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>18</td>
<td>12</td>
<td>18</td>
<td>0.61</td>
</tr>
<tr>
<td>Antiplatelet therapy</td>
<td>75</td>
<td>72</td>
<td>71</td>
<td>0.003</td>
</tr>
<tr>
<td>Lipid-lowering therapy</td>
<td>14</td>
<td>13</td>
<td>13</td>
<td>0.35</td>
</tr>
</tbody>
</table>

ISH indicates isolated systolic hypertension; IDH, isolated diastolic hypertension; SDH, systolic–diastolic hypertension; SD, standard deviation.

*Participants recruited from People’s Republic of China or Japan.
†History of myocardial infarction, coronary revascularization, or angina.
‡Currently treated hypertension.

**Figure.** Effects of randomized treatment on the risks of major vascular events by hypertension subtype. Solid boxes represent estimates of treatment effect; horizontal lines, 95% confidence interval (CI); a diamond, the estimate and 95% CI for overall effect. Areas of the boxes are proportional to the number of events. ISH indicates isolated systolic hypertension; IDH, isolated diastolic hypertension; SDH, systolic–diastolic hypertension; CI, confidence interval.
45% versus 10%; $P$ homogeneity = 0.26, 0.009, and 0.03 for patients with ISH, IDH, and SDH, respectively).

**Discussion**

The main results from the PROGRESS trial showed that routine BP lowering treatment reduced the risk of major vascular events by 26% among patients with cerebrovascular disease. These analyses extend the findings of the main report and suggest that BP lowering is likely to be similarly beneficial in patients with IDH as in those with ISH and SDH. Like with the main results, the reductions in BP and major vascular events were greater in patients receiving combination therapy. These results support the current guidelines for management of hypertension, which recommend therapeutic approaches based on DBP as well as SBP.

Although this appears to be the first article to report the beneficial effects of BP lowering in IDH to date, the number of events recorded among participants with IDH was limited and insufficient to provide separately significant results.

**Conclusions**

BP lowering is likely to provide protection against major vascular events for patients with IDH as well as those with ISH and SDH. Although additional data would much more clearly define the effects of BP lowering in patients with IDH, the evidence provided here suggests that clinicians should strongly consider initiation of BP lowering therapy among patients with IDH.

**Sources of Funding**

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

**Disclosures**

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**References**

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고립성 이완기 고혈압을 가진 환자에서
혈압 저하가 주요 혈관 질환 발생에 미치는 영향
뇌졸중 재발에 대한 페린도프릴의보호 효과 연구(PROGRESS) 임상시험

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(Stroke. 2011;42:2339-2341.)

Key Words: antihypertensive agents ■ clinical trials ■ hypertension ■ isolated diastolic hypertension

배경과 목적
고립성 수축기 고혈압(isolated systolic hypertension) 및 수축기-이완기 고혈압(systolic–diastolic hypertension)을 가진 환자에서 혈압(blood pressure, BP) 저하가 심혈관질환 발생을 감소시킨다는 분명한 근거가 있으나, 고립성 이완기 고혈압(isolated diastolic hypertension)를 가진 환자에서 BP 저하가 가지는 효과에 대하여는 아직 논란이 많다. 본 논문은 BP 저하가 고립성 이완기 고혈압 환자에서 이득이 되는지 밝히고자 수행되었다.

방법
뇌혈관질환 및 고혈압을 가진 환자들(n=4,283)이 치료군 (perindopril)을 모든 환자에게 투여하고, indapamide는 적응 증이 되면서 이뇨제에 급기가 없는 환자에게 투여, 혹은 위약군에 무작위 배정되었다. 일자 결과 변수는 모든 주요 혈관 질환의 발생이었다.

결과
연구에 포함된 환자들은 고립성 수축기 고혈압(수축기 BP 140 mm Hg 이상 및 이완기 BP 90 mm Hg 미만)을 가진 환자 1,923명, 고립성 이완기 고혈압(수축기 BP 140 mm Hg 미만 및 이완기 BP 90 mm Hg 이상)을 가진 환자 315명, 수축기-이완기 고혈압(수축기 BP 140 mm Hg 이상 및 이완기 BP 90 mm Hg 이상)을 가진 환자 2,045명이었다. 치료군에 포함된 환자에서 주요 혈관 질환의 발생은 고립성 수축기 고혈압 환자에서 27% (95% CI, 10~41%) 감소되었으며, 고립성 이완기 고혈압 환자에서 28% (~29~60%) 감소되었고, 수축기-이완기 고혈압 환자에서 32% (17~45%) 감소되었다. 고혈압의 분류에 따라 치료 효과가 다르다는 증거는 없었다(동질성 검정 P=0.89).

결론
BP 저하는 고립성 수축기 고혈압 및 수축기-이완기 고혈압과 마찬가지로, 고립성 이완기 고혈압 환자에서도 주요 혈관 질환 발생 위험을 감소시킬 것으로 생각된다.

임상 시험 등록 정보: 본 연구는 2005년 7월 1일 이전에 환자 등록이 완료되었으므로 등록되지 않았다.
### Table: Events / Patients

<table>
<thead>
<tr>
<th>Hypertension Subtype</th>
<th>Active</th>
<th>Placebo</th>
<th>Favors</th>
<th>Favors</th>
<th>Risk Reduction (95% CI)</th>
<th>P for Homogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISH</td>
<td>152/953</td>
<td>205/970</td>
<td>Active</td>
<td></td>
<td>27% (10 to 41%)</td>
<td>0.89</td>
</tr>
<tr>
<td>IDH</td>
<td>22/163</td>
<td>28/152</td>
<td></td>
<td>Active</td>
<td>28% (-29 to 60%)</td>
<td></td>
</tr>
<tr>
<td>SDH</td>
<td>158/1026</td>
<td>229/1019</td>
<td></td>
<td></td>
<td>32% (17 to 45%)</td>
<td></td>
</tr>
<tr>
<td>All Hypertension</td>
<td>332/2142</td>
<td>462/2141</td>
<td></td>
<td></td>
<td>30% (19 to 39%)</td>
<td></td>
</tr>
</tbody>
</table>

*Figure.* Effects of randomized treatment on the risks of major vascular events by hypertension subtype. Solid boxes represent estimates of treatment effect; horizontal lines, 95% confidence interval (CI); a diamond, the estimate and 95% CI for overall effect. Areas of the boxes are proportional to the number of events. ISH indicates isolated systolic hypertension; IDH, isolated diastolic hypertension; SDH, systolic-diastolic hypertension; CI, confidence interval.