Letter to the Editor

To the Editor:

Hypertension at middle age is a risk factor for vascular and neurodegenerative dementia later in life. Because populations are aging, the number of demented patients will grow 2-fold every 20 years, from 24.3 million people in 2000 to 81.1 million by 2040, with >60% living in developing countries. The question of whether hypertension is a modifiable risk factor for dementia is therefore of great clinical importance. Our 2007 meta-analysis1 included 4 placebo-controlled trials of blood pressure–lowering therapies for prevention of dementia (18 196 patients and 642 dementia cases).2–4 The common odds ratio was 0.89 (CI, 0.75 to 1.04) and did not reach statistical significance (P=0.15). However, sensitivity analyses revealed a difference (P=0.04) that depended on whether active treatment started with or included a diuretic or dihydropyridine calcium channel blocker compared with an inhibitor of the renin system. The pooled odds ratios were 0.75 (CI, 0.60 to 0.94; P=0.01) for Systolic Hypertension in the Elderly Program (SHEP),3 Syst-Eur,5 and the combination therapy arm of PROGRESS,4 and 1.08 (CI, 0.84 to 1.38; P=0.54) for SCOPE6 and the perindopril-only subgroup of the PROGRESS trial.4

Since our 2007 review,1 4 additional placebo-controlled trials reported on the prevention of dementia by blood pressure–lowering therapies, including ADVANCE,7 HYVET-COG,8 PRoFESS,9 and, most recently, TRANSCEND.10 We therefore updated our meta-analysis (Figure). In all trials combined, blood pressure lowering did not reduce the risk (−5%). For trials involving a diuretic or dihydropyridine calcium channel blocker as part of active treatment, the reduction was significant (−18%), whereas this was not the case in trials of renin system inhibitors (+1). This difference between drug classes might be explained by the amount of blood pressure reduction because in weighted metagression analysis, lowering of systolic pressure explained 41% (P=0.08) of the risk reduction. However, several quantitative overviews11–13 support the idea that diuretics and dihydropyridine calcium channel blockers have a small (5% to 10%) benefit beyond blood pressure lowering in the prevention of stroke. Moreover, 2 trials, respectively on prevention9 and

### Placebo-Controlled Trials of Blood Pressure–Lowering Therapies for Primary Prevention of Dementia

**Table.** Effects of blood pressure lowering on the incidence of dementia in placebo-controlled clinical trials. Solid squares represent the odds ratios in individual trials and have a size proportional to the inverse of the variance. Horizontal lines and diamonds denote the 95% CIs for individual trials and summary statistics, respectively. Pooled estimates of risk were computed from a fixed-effect model and are weighted for the inverse of the variance. The vertical dotted line marks the position of the point estimate of the pooled effect size for all trials combined. The individual studies were: the SHEP;3 the Systolic Hypertension in Europe trial (Syst-Eur);5 the Perindopril Protection Against Recurrent Stroke Study–monotherapy (PROGRESS/Per) and combined therapy (PROGRESS/Com) arms;4 the Hyper-tension in the Very Elderly substudy on cognition;8 the Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation (ADVANCE);7 the Study on Cognition and Prognosis in the Elderly (SCOPE);6 the Prevention Regimen for Effectively Avoiding Second Strokes trial (PRoFESS);9 and the Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND).10 Pooled estimates of the between-group differences in systolic blood pressure (ΔSBP) and median or average follow-up (∆FU) were weighted for the number of patients. DIU indicates diuretic; CCB, calcium channel blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

<table>
<thead>
<tr>
<th></th>
<th>ΔSBP FU</th>
<th>Control</th>
<th>Active</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHEP</td>
<td>12.0</td>
<td>4.9</td>
<td>44/2371</td>
</tr>
<tr>
<td>Syst-Eur</td>
<td>10.1</td>
<td>2.0</td>
<td>21/1180</td>
</tr>
<tr>
<td>PROGRESS/Com</td>
<td>12.8</td>
<td>3.9</td>
<td>136/1774</td>
</tr>
<tr>
<td>HYVET-COG</td>
<td>15.0</td>
<td>2.2</td>
<td>137/1649</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>5.6</td>
<td>4.3</td>
<td>37/5571</td>
</tr>
<tr>
<td>All DIUs/CCBs</td>
<td>9.9</td>
<td>3.5</td>
<td>375/12545</td>
</tr>
</tbody>
</table>

**Figure.** Effects of blood pressure lowering on the incidence of dementia in placebo-controlled clinical trials. Solid squares represent the odds ratios in individual trials and have a size proportional to the inverse of the variance. Horizontal lines and diamonds denote the 95% CIs for individual trials and summary statistics, respectively. Pooled estimates of risk were computed from a fixed-effect model and are weighted for the inverse of the variance. The vertical dotted line marks the position of the point estimate of the pooled effect size for all trials combined. The individual studies were: the SHEP;3 the Systolic Hypertension in Europe trial (Syst-Eur);5 the Perindopril Protection Against Recurrent Stroke Study–monotherapy (PROGRESS/Per) and combined therapy (PROGRESS/Com) arms;4 the Hyper-tension in the Very Elderly substudy on cognition;8 the Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation (ADVANCE);7 the Study on Cognition and Prognosis in the Elderly (SCOPE);6 the Prevention Regimen for Effectively Avoiding Second Strokes trial (PRoFESS);9 and the Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND).10 Pooled estimates of the between-group differences in systolic blood pressure (ΔSBP) and median or average follow-up (∆FU) were weighted for the number of patients. DIU indicates diuretic; CCB, calcium channel blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

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progression\textsuperscript{14} of dementia, showed positive effects of dihydropyridine calcium channel blockers. Experimental studies, reviewed in this journal,\textsuperscript{1} also support the hypothesis that inhibiting the inward current of calcium ions in neuronal cells protects against necrosis and apoptosis. In conclusion, the issue of whether blood pressure lowering reverses the risk of Alzheimer’s disease remains unsettled. A sufficiently powered trial comparing a diuretic or long-acting dihydropyridine calcium channel blocker with a renin system inhibitor in the primary prevention of dementia is needed, but such an orphan trial will not easily find a sponsor unless public agencies take up the challenge.

Disclosures

J.A.S. did consultancies for pharmaceutical companies and received funding for studies, seminars, and travel from manufacturers of blood pressure–lowering drugs. All other coauthors have no conflicts of interest to declare.

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