J-Shaped Relation Between Blood Pressure and Stroke

To the Editor:
In their interesting study on the J-shaped relation between blood pressure and stroke, Vokó and colleagues\(^1\) found an excess risk of stroke associated with diastolic blood pressure (BP) levels <65 mm Hg in treated hypertensive subjects but not in a group of untreated subjects. On this basis, they hypothesized a harmful effect of excessive BP reduction. The study was not a direct comparison of the prognostic value of pretreatment and in-treatment diastolic BP in the same subjects. By contrast, the authors examined stroke rate in a group of treated hypertensive subjects and in an untreated control group principally composed of normotensive subjects. Therefore, for progressively lower diastolic BPs, pulse pressure (PP) may have been higher in the treated hypertensive group than in the untreated control group. Given the potent prognostic value of PP, such an imbalance could have conditioned the greater stroke risk among the subjects with a diastolic BP <65 mm Hg than among those with a diastolic BP 65 to 74 mm Hg in the treated hypertensive group but not in the untreated group. To clarify this point, the authors should (a) not limit data presentation to the relative risks, but include a table with diastolic BP and PP in each category; (b) compare PP between treated and untreated subjects for each stratum of diastolic BP; and (c) examine PP among the potential determinants of stroke risk. If the J-shaped relation between diastolic BP and stroke risk was due to excessive BP lowering, such a relation should not be noted in an untreated control group with the same levels of diastolic BP and PP. Up to completion of this analysis, we remain skeptical about the reappearance of the J-shaped curve for effect of antihypertensive treatment and suspect that the results of this study are due to the potential confounding effect of PP and improper selection of the control group.

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To the Editor:
We read with interest the article by Vokó et al\(^1\) pointing out for the first time a significant J-curve relating stroke risk to diastolic blood pressure (BP) in treated but not in nontreated elderly hypertensives. On the basis of this prospective cohort study, the authors recommend an optimal BP of 140/80 mm Hg.

If we completely agree for the proposed optimal systolic BP (SBP) since Figure 1 in the Vokó article shows that the range with the lowest stroke risk is 130–149 mm Hg, we wonder how the authors propose 80 mm Hg for the optimal diastolic BP (DBP) since in Figure 2 of the same article the lowest stroke risk is for a DBP range of 65–74 mm Hg, suggesting that 70 mm Hg instead of 80 mm Hg would be the median of the optimal range. We suggest that a printing error may be involved.

The authors have extensively reviewed and excluded possible bias for their worrying observation. They have not evoked however the possibility that all antihypertensive drugs may not be equal in protecting against stroke for the same level of BP decrease. Indeed, the Medical Research Council (MRC) trials have pointed out either in the middle-aged\(^2\) or in the elderly hypertensives\(^3\) that β-blockers are less protective against stroke than diuretics.

Furthermore, angiotensin-converting enzyme inhibitors (ACEI) seem to be less stroke protective than diuretics in hypertensive patients even though the Heart Outcomes Prevention Evaluation (HOPE) study\(^4\) has shown that 10 mg of ramipril was able to decrease the risk of stroke by 32%, a decrease much higher than expected from the associated SBP decrease of 3 mm Hg (13%). This 19% BP-independent decrease of stroke risk with ramipril is however in contradiction with the 25% (analysis by intention to treat) or 43% increase (on treatment analysis) of stroke risk associated with captopril compared to conventional treatment by diuretics and/or β-blockers in the Captopril Prevention Project (CAPPP) trial.\(^5\) The difference of 2.2 and 1.7 mm Hg in SBP and DBP between the 2 groups of CAPPP being of the same order as that between the 2 groups of HOPE, the BP-independent stroke risk increase associated with captopril remains significant at 12% and 30%. This contradiction between the CAPPP and HOPE trials may however be explained by differences in pathophysiological mechanisms related to differences in population. The HOPE population probably had a suppressed endocrine renin-angiotensin system because the ramipril-induced BP decrease was negligible, and this is explained by the lack of heart failure or hypertension since the hypertensive patients were previously treated mainly by β-blockers and calcium antagonists and rarely by diuretics. Therefore, the remarkable antiatherothrombotic effect of ramipril, a tissue specific ACEI, may be only explained by the strong inhibition of the tissue ACE, which is overexpressed by oxidant stress in the case of severe atherosclerosis.\(^6\) This may not be the case in hypertensive patients with low initial prevalence of atherosclerotic complications like in the CAPPP trial in which the mean age was 52 years. In the Swedish Trial in Old Patients (STOP) hypertension-2 trial, there was no difference in stroke risk between ACEI and conventional treatment, but the frequency of thiazide addition to ACEI at the end of the trial was quite high (46%) as well as that of discontinuation of the randomized treatment in both groups (39% and 38%), modifications that have the obvious potential to mask the difference between the groups in the intention-to-treat analysis, which is at present the only available analysis. The lack of protection against stroke (a nonsignificant reduction of 5%) in the Hypertension Optimal Treatment (HOT) study,\(^7\) in spite of an expected 27% reduction for a 4 mm Hg DBP difference again, supports the concept that lack of stimulation of the endocrine renin-angiotensin system by diuretics is deleterious for stroke prevention. Indeed, the difference in DBP was obtained by greater doses of felodipine, β-blockers, and ACEI as well as by a higher use of these drugs, whereas diuretics were used only as the fifth step in 24% of the patients.

Therefore, we suggest that the authors compare the prevalence ratio of ACEI and β-blocker use on that of diuretics in the different SBP and DBP quartiles. Indeed, in agreement with the provocative but relevant hypothesis by Brown and Brown\(^8\) ("Does angiotensin II protect against stroke?"), pathophysiological observations in the gerbil have shown that brain ischemia after unilateral carotid ligation is decreased when circulating levels of angiotensin II are elevated either by angiotensin II perfusion or by previous administration of angiotensin II type I.
receptor antagonist (AT1, RA) and, on the contrary, increased when circulating levels of angiotensin II are decreased by ACEI. These experimental data suggest therefore that non-AT1 receptor stimulation is protective by promoting collateral circulation recruitment in case of cerebral artery occlusion or subocclusion and have led us to propose a trial comparing ACEI versus AT1, RA in the prevention of stroke.

Note Added in Proof
A recent communication of Dr Bruce M. Psaty11 (from the University of Washington, Seattle) at the 40th Annual Conference on Cardiovascular Disease Epidemiology and Prevention (San Diego, Calif) fully supports our hypothesis that brain ischemia is better prevented by antihypertensive drugs stimulating angiotensin II synthesis because in hypertensive patients without cardiovascular complication treated by monotherapy, thiazides divided by 2 the stroke risk comparatively to β-blockers, by 2.3 comparatively to calcium antagonists, and by 2.8 comparatively to ACE inhibitors.

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Response
Verdecchia and Schillaci1 suggest that the J-shaped relationship that we found between diastolic blood pressure and the risk of stroke in treated hypertensives2 could be attributed to the pulse pressure. As discussed in our paper, we considered this possibility and we rejected it for the following reasons. Our results remained materially the same after adjustment for systolic blood pressure or after exclusion of subjects with isolated systolic hypertension. Furthermore, the mean distribution of the pulse pressure was similar in the lowest diastolic blood pressure stratum and in the reference category in treated subjects (mean pulse pressure in the lowest diastolic stratum was 67.9 mm Hg [SD=21.7], and in the reference category, it was 68.9 mm Hg [SD=18.4]). We agree with Verdecchia and Schillaci that the relation between pulse pressure itself and risk of stroke is of interest. In Table 1 we present our results on this relationship. There is no relation between pulse pressure and risk of stroke in treated subjects in our data, which implies that pulse pressure could not be a confounder in our study. The suggestion to compare pulse pressure between treated and nontreated subjects would not help to further clarify the potential confounding effect of pulse pressure since the analysis was done separately for treated and nontreated subjects.

Fournier et al3 rightly point out that in our study the lowest risk of stroke in treated hypertensive subjects was observed in the diastolic blood pressure category of 64 to 74 mm Hg. Our recommendation that optimal blood pressure reduction should attempt diastolic blood pressure levels of ≈80 mm Hg was based, in part, on current clinical practice. However, in our data, the risk of stroke was no different between the categories of 75 to 84 mm Hg and 65 to 74 mm Hg; if anything, it was even slightly lower in the latter category. On the basis of our data, we

TABLE 1. Relationship Between Pulse Pressure and the Risk for Stroke According to Antihypertensive Treatment

<table>
<thead>
<tr>
<th>Quartiles of Pulse Pressure, mm Hg</th>
<th>No Treatment</th>
<th>Subjects Using ACE Inhibitors, %</th>
<th>Subjects Using Diuretics, %</th>
<th>Subjects Using β-Blockers, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;45</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>45-59</td>
<td>1.4 (0.8, 2.5)</td>
<td>0.8 (0.4, 1.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60-70</td>
<td>1.3 (0.7, 2.3)</td>
<td>0.7 (0.4, 1.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;71</td>
<td>1.9 (1.1, 3.3)</td>
<td>1.2 (0.7, 2.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The analysis was adjusted for age, gender, smoking habits, diabetes mellitus, ankle-to-arm index, minor vascular events (intermittent claudication, angina pectoris, history of coronary revascularization procedure), myocardial infarction, atrial fibrillation, and typical and atypical transient ischemic attack.

TABLE 2. Proportion of Different Antihypertensive Drug Users According to Systolic Blood Pressure

<table>
<thead>
<tr>
<th>Quartiles of Systolic Blood Pressure, mm Hg</th>
<th>Subjects Using ACE Inhibitors, %</th>
<th>Subjects Using Diuretics, %</th>
<th>Subjects Using β-Blockers, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;130</td>
<td>15.1</td>
<td>49.5</td>
<td>46.6</td>
</tr>
<tr>
<td>130-149</td>
<td>14.6</td>
<td>46.8</td>
<td>43.6</td>
</tr>
<tr>
<td>150-169</td>
<td>20.3</td>
<td>44.6</td>
<td>43.6</td>
</tr>
<tr>
<td>&gt;169</td>
<td>24.6</td>
<td>44.1</td>
<td>41.3</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme.
agree that a more appropriate recommendation might be to not lower blood pressure too far, ie, below levels of 65 mm Hg. Fournier et al further suggest that different stroke-protective effects of different classes of antihypertensive drugs may at least partly explain our results. However, as is shown in Tables 2 and 3, our data do not support this explanation. There were only minor differences in drug use in the different blood pressure categories, with the exception of the more frequent use of ACE-inhibitors in the two highest blood pressure categories.

We would like to emphasize that treatment of elderly hypertensive subjects has been proven to save lives and to prevent myocardial infarctions and strokes and that our findings do not contradict these general results.4–8 Nevertheless, our results showed that in treated hypertensive elderly subjects, very low diastolic blood pressures increased the risk of stroke. One might consider that a blood pressure below 65 mm Hg is rarely a target blood pressure in everyday practice and that an increased risk associated with very low blood pressure is merely a theoretical problem. However, in our study, 20% of the antihypertensive drug users in this elderly population fell into that category. An important clinical implication of our study is, therefore, that it underscores the importance of careful monitoring of both blood pressure and blood pressure treatment in the elderly.
Response
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Hypertension. 2000;35:e16
doi: 10.1161/01.HYP.35.5.e16

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/35/5/e16

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