Telmisartan for Prevention of Cardiovascular Events

TO THE EDITOR: We have eagerly awaited the results of the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) Study (Sept. 18 issue),1 since a significant benefit of angiotensin-receptor blockers (ARBs) was anticipated based on the findings of several other groups (Losartan Intervention for Endpoint Reduction in Hypertension [LIFE],2 Morbidity and Mortality after Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention [MOSES],3 and Study on Cognition and Prognosis in the Elderly [SCOPE]).4 It was very disappointing to see that telmisartan therapy failed to meet the primary end point—a significant reduction in the rate of recurrent stroke. Furthermore, it was puzzling to see in a subgroup analysis that telmisartan was not effective in the treatment of patients with hypertension (blood pressure >150 mm Hg) or diabetes, two subgroups that were the most expected to derive benefit from ARB treatment. Since blood-pressure reduction has been proved beneficial in the prevention of secondary stroke, and patients with hypertension obtained the greater benefit from perindopril monotherapy in another trial (Lower Target Blood Pressures are Safe and Effective for the Prevention of Recurrent Stroke [PROGRESS]),5 it would be interesting to know whether there were differences in blood-pressure reduction between treated subgroups. If there were no differences, or they were marginal because of the greater use of antihypertensives in the placebo group, then the final outcome may be explained; it would also be of great interest to know whether there were any other differences in baseline characteristics that can explain the negative outcome.

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TO THE EDITOR: The recently published clinical trial by the PRoFESS Study Group failed to demonstrate the efficacy of the telmisartan ARB in preventing recurrent stroke (ischemic or not). It is important to consider that previous hemorrhagic stroke was a major exclusion criterion of this study. The PROGRESS study, however, enrolled patients with both types of stroke, and 11% of the patients included had a history of nonischemic stroke.4 In a subgroup analysis of PROGRESS, the benefit of the perindopril–indapamide combination was even more pronounced in patients with hemorrhagic stroke (relative risk reduction of 50% vs. 24% for ischemic stroke). The exclusion of patients with hemorrhagic stroke may partially explain the main results of the study, since persistent high systolic blood pressure is associated with hematoma expansion and the development of perihematoma brain edema in patients with hemorrhagic stroke.2

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We are puzzled that in the Discussion section of the PROFESS study the authors cite the Acute Candesartan Cilexetil Evaluation in Stroke Survivors (ACCESS) trial in support of dismissing the role of lower blood pressure in the higher risk of stroke observed in patients taking telmisartan during the first 6 months of the study.

In the ACCESS trial, the baseline systolic blood pressure was >180 mm Hg. Among patients given candesartan, as compared with placebo, within 30 hours of stroke onset, blood pressure did not decrease for the first 7 days; after 7 days, systolic blood pressure in the two groups was comparable (at 143 mm Hg) thanks to administration of the same dose of candesartan in the two groups. A 50% reduction in the risk of cardiovascular events was nevertheless observed between 3 and 12 months.

In the PROFESS study, patients given telmisartan had a significantly lower risk of stroke when the baseline systolic blood pressure was between 135 and 150 mm Hg and a higher risk of stroke when the blood pressure was below this range. This suggests that a further decrease in the systolic blood pressure has a deleterious effect on brain perfusion (as reported in several studies cited by the authors). This effect may cancel the brain-specific protective effect of ARBs, as indicated by the lower risk of stroke with eprrosartan than with nitrendipine when administered to patients with comparable blood pressures.1

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The authors reply: Doumas and Papademetriou inquire about the degree to which blood pressure was lowered from baseline measures. The mean difference in systolic blood pressure between the treatment and placebo groups after randomization was −3.5 mm Hg in the upper tertile (systolic blood pressure >150 mm Hg), −3.8 mm Hg in the middle tertile (135 to ≤150 mm Hg), and −4.2 mm Hg in the lowest tertile (≤135 mm Hg). The smallest change in blood pressure (−3.5 mm Hg), which occurred at the highest initial blood pressure, probably resulted from the greater use of antihypertensive drugs (that were not being studied) in the placebo group as compared with the treatment group across all blood pressure levels (at 1 year, 78.5% for the placebo group vs. 71.1% for the telmisartan group in the upper tertile, 68.1% vs. 50.1% in the middle tertile, and 61.2% vs. 52.7% in the lowest tertile). It should be noted that the PROGRESS study included patients with higher initial blood pressure and used a combination of angiotensin-converting–enzyme inhibitor plus a diuretic. Consequently, the difference in systolic blood pressure between the treatment and placebo groups was larger (12.3 mm Hg systolic and 5.0 mm Hg diastolic) than that in PROFESS groups (4.9 mm Hg systolic and 2.8 mm Hg diastolic). In the PROGRESS study, the blood-pressure reduction in those receiving perindopril alone was modest, with no significant reduction in cardiovascular events. Furthermore, the mean duration of the PROGRESS trial was 4 years, whereas that of the PROFESS trial was 2.5 years.

We agree with Fichet and Bressolle that a reduction in blood pressure may be more effective in preventing recurrent strokes after a hemorrhagic stroke, but our study had to exclude such patients because antiplatelet agents were being evaluated simultaneously. In response to Fournier et al., the apparent large benefit reported by the ACCESS group is most likely unreliable, as it was a small pilot study intended to evaluate the safety of candesartan, and there were very few events in the study.

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