Angiotensin-Converting Enzyme Inhibitors and Stroke Prevention: What About the Influence of Atrial Fibrillation and Antithrombotic Therapy?

To the Editor

The Heart Outcomes Prevention Evaluation (HOPE) trial and Losartan Intervention For Endpoint Reduction in Hypertension Study (LIFE) have shown that ramipril and losartan lower the risk of ischemic vascular events, including stroke.1–3 This effect, which is independent of lowering blood pressure, is explained by pharmacological mechanisms, which are further consequences of inhibition of the renin-angiotensin system in the plasma and vascular wall. These potential mechanisms comprise reduction in proliferation of vascular smooth muscle cells, enhancement of endogenous fibrinolysis, stabilization of plaques, decrease in angiotensin II–mediated atherosclerosis, plaque rupture, and vascular occlusion.4 Atherosclerosis, however, is not the only cause of stroke. Stroke may also be due to embolism, vasculitis, or coagulation abnormalities. Stroke may be due to cardiogenic embolism, most frequently in atrial fibrillation. Atrial fibrillation is an independent risk factor for stroke, and ≈16% of ischemic strokes are associated with atrial fibrillation.5

Although the participants in the HOPE study had a 12-lead ECG at baseline, at 2 years, and at study end and some ECG findings have been reported, the prevalence of atrial fibrillation has not been mentioned.1–2,6 It can be expected that the prevalence of atrial fibrillation in the patients of the HOPE study is high, because the same risk factors, which were inclusion criteria for the HOPE study, have been identified by epidemiological studies to also be risk factors for the development of atrial fibrillation: increased age, hypertension, coronary heart disease, elevated serum cholesterol levels, and smoking.7 Uninformed about the prevalence of atrial fibrillation and its distribution among the placebo and ramipril groups, we can assume that differences in the prevalence of atrial fibrillation might have contributed to the differences in stroke incidence between the 2 groups. Possibly, the prevalence of atrial fibrillation was higher in the placebo than in the ramipril group, thus contributing to the lower incidence of stroke in the ramipril group.

In the LIFE study, on the contrary, the prevalence of atrial fibrillation was assessed and was similar in both groups: 3% in the losartan group and 4% in the atenolol group.3 Unfortunately, it is not indicated how many of the atrial fibrillation patients in the LIFE study were on antithrombotic therapy such as oral anticoagulation or aspirin. In atrial fibrillation, stroke prevention can be achieved effectively by antithrombotic therapy, either by oral anticoagulation with 70% reduction of the relative risk or by aspirin with 20% reduction of the relative risk.5 Uninformed about the rate and kind of antithrombotic therapy it is possible that the distribution in the atenolol and losartan groups, we can speculate that differences therein might again have contributed to the differences in stroke incidence.

To better understand the mechanisms of stroke prevention in the HOPE and LIFE studies and to assess the effects of ramipril and losartan on stroke prevention, it would be helpful to know the prevalence of atrial fibrillation and the antithrombotic therapy provided to the patients included in these studies. In addition, in ongoing trials like the ongoing Telmisartan Alone and In Combination With Ramipril Global End-Point Trial (ONTARGET), which aims to randomize 23,400 patients to ramipril, telmisartan, or a combination of them and to follow up patients over 5.5 years for the occurrence of stroke, myocardial infarction, or vascular death, the aspect of atrial fibrillation and antithrombotic therapy should be considered.8 As long as this important clinical information is not available, the importance of other stroke mechanisms and their potential inhibition by angiotensin-converting enzyme inhibitors cannot adequately be assessed.

Claudia Stöllberger, MD
Jörg Slany, MD
Second Medical Department
Krankenanstalt Rudolstiftung
Wien, Austria

Michael Brainin, MD
Neurosciences Centre
Donau-Universität,
Department of Neurology
Donauklinikum
Maria Gugging, Austria

Josef Finsterer, MD
Neurologic Department
Krankenanstalt Rudolstiftung
Wien, Austria

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Claudia Stöllberger, Jörg Slany, Michael Brainin and Josef Finsterer

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