Letters to the Editor

Stoke in the Very Elderly

To the Editor:

Atrial fibrillation (AF) is the most common, potent, and independent risk factor for ischemic stroke,1 the incidence of which increases with age.2 To determine the influence of advanced age on anticoagulation therapy in elderly patients with AF, a retrospective cohort study of all patients admitted to our department (from 1995 to 2003) was conducted. These patients were >90 years of age and had an acute stroke. The following parameters were analyzed: age, sex, cardiovascular risk factors and their treatment, and outcome. Among the 404 patients experiencing acute stroke, 39 (9.65%) were >90 years old (average age 91.73±2.34), and 82% were females. Four patients had cognitive impairment (Alzheimer disease) whose quality of life was average for their age. Major risk factors for stroke were AF (64%), hypertension (51%), and diabetes mellitus (7%). Smoking habits, before stroke or transient ischemic attack (TIA), had not been found. None of the patients with AF had been treated with anticoagulant drugs except 4 who received acetylsalicylic acid. However, all patients with hypertension or diabetes were receiving drugs. All episodes of stroke were ischemic (hemispheric 28; TIA 8; and lacunar 3). Thirteen patients died (12 in the first 72 hours), all of whom with AF. The death rate among the elderly patients was 33.3% and 10.35% in the remaining patients diagnosed with acute stroke over the same time period. Seven patients fully recovered previous health state and functions, whereas 19 did not. After discharge, 14 patients with no AF received antiplaquetary drugs. In the remaining with AF, 4 received warfarin, 2 received antiplaquetary drugs (because of the refusal of the family to receive anticoagulants), and no treatment was received by 6 patients, all of whom had an important cognitive impairment and disability after stroke. Incidence of stroke increases with the age, and 75% of strokes occur in the elderly.3 AF is the most important single cause of ischemic stroke in this age group.4 Several clinical trials have demonstrated that warfarin sodium treatment reduces risk of stroke and death compared with placebo in persons with AF. In addition, this benefit is accompanied by a relatively low annual bleeding rate. Unfortunately, these findings have not been adequately implemented in clinical practice.1,3,5 Reduced odds of receiving warfarin is associated with the >85 age group, previous intracranial or gastrointestinal hemorrhage, or cognitive impairment.1 However, pharmacological treatment for risk factors such as hypertension, diabetes, heart failure, and dyslipemia are currently applied. Stroke has high rates of mortality (31% versus 16.7%) and disability (78% versus 48%) in the aged patient versus the younger one.5 We think that warfarin could reduce the stroke risk in persons with AF and should be used independent of age, especially in the elderly with other associated risk factors. This may be an opportunity to improve the quality of life and care of our elderly patients.

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1. Go AS, Hylek EM, Borowosky LH, Phillips KA, Selby JV, Singer DE. Warfarin use among ambulatory patients with non valvular atrial fibril-

Response:

In their retrospective study of acute stroke patient admissions, Marti and Anton focused on the very elderly, >90 years of age. The majority (64%) exhibited atrial fibrillation (AF), but none were under warfarin before the stroke. The death rate was high in these very old patients, especially in AF patients. Physicians are usually reluctant to apply recommendations in elderly with AF because they fear hemorrhagic side effects of long-term use of warfarin.1 Although the risk of life-threatening hemorrhage is higher in elderly under anticoagulation, there is an alternative higher risk of ischemic stroke in AF patients >80 to 85 years, which overwhelms the former.2 Warfarin has been shown to reduce stroke rates by 68%.3 Therefore, as a rule, warfarin is mandatory in at-risk patients with AF, whatever their age. Neurologists have to make a special effort because they underuse anticoagulation compared with cardiologists.3 It was suggested in elderly AF patients to lower intensity of anticoagulation (international normalized ratio [INR], 1.5 to 1.9) in view of the balance between prevention of thromboembolism and the adverse effect by warfarin (ie, bleeding).4 However, in a recent retrospective study, INRs <2.0 were not associated with lower risk for intracranial hemorrhage compared with INRs between 2.0 and 3.0.5 Ximelagatran, a new oral direct thrombin inhibitor, might provide a more physician- and patient-friendly method of stroke prophylaxis, especially in the elderly.1 We must keep in mind that because of the rapidly aging population, physicians are challenged with more and more older patients with AF, for whom optimal prevention of stroke is crucial.

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4. Yamauchi T. Optimal intensity of warfarin therapy for secondary pre-
vention of stroke in patients with nonvalvular atrial fibrillation: a multi-
center, prospective, randomized trial. Japanese Nonvalvular Atrial

Embolic Detection and Differentiation Using Multifrequency Transcranial Doppler

To the Editor:

In our articles in Stroke in August 2002,1,2 we presented our findings using the first multifrequency transcranial Doppler (TCD) to detect and differentiate cerebral emboli. Since this time, we have had considerable experience using multifrequency TCD in medical patients during invasive cardiovascular investigations and perioperatively during heart surgery. We found that results are most reliable for embolus differentiation when the Doppler signal enhancement, ie embolus-blood-ratio (EBR), is >28 dB/ms (ie, a Doppler power increase >7 dB, which lasts >4 ms) simultaneously in 2.0-MHz and 2.5-MHz channels. The lower EBR limit for the classification of solid microemboli should also not be horizontal but have a slight slope of y = −0.1x–0.12 dB, where y = dEBR and x = 2.0 MHz EBR.

Embolus detection and differentiation is also very difficult when there are bursts of gaseous or solid emboli, when several emboli may enter the sample volume at the same time. Ultrasound contrast bubbles may make detection and differentiation difficult because of changes in the background signal or resonance effects of single contrast bubbles.

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Postcarotid Endarterectomy Hyperfusion or Reperfusion Syndrome

To the Editor:

I read with great interest the study by Karapanayiotides et al.1 This study highlighted several important features of the hyperfusion syndrome and raises several questions.

It is not entirely surprising that the middle cerebral artery mean flow velocities do not reliably predict the occurrence of the hyperfusion syndrome. The relationship between velocity and volumetric flow is complex and not always predictable. As suggested, it is likely that volumetric flow may contribute to microvascular trauma. Furthermore, the relationship between the release of free radicals and metabolic products after reperfusion and their contribution to intracerebral endothelial dysfunction has not been studied adequately in this setting.

In addition, did the authors find any correlation between the degree of contralateral internal carotid artery stenosis and the risk of hyperfusion syndrome? It would be interesting to determine whether the precarotid endarterectomy relative interhemispheric difference of cerebral blood flow predicted the hyperfusion syndrome postcarotid endarterectomy.

Finally, in light of this complex process, the suggestion that “reperfusion syndrome” rather than “hyperfusion syndrome” be used to describe this process may be appropriate.

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Response:

We deeply appreciate Dr Dieter’s interest in our study. We agree with Dr Dieter’s statement that the relationship between velocity and volumetric flow is complex. However, in the case of patients undergoing carotid endarterectomy, this complexity has been elegantly demonstrated only once before.1 The authors concluded that for all pairs of measurement at a regional cerebral blood flow (CBF) of >20 mL/100 g per minute, there was little relationship between regional CBF and middle cerebral artery (MCA) mean flow velocity. Furthermore, posts ischemic hyperemia after the release of clamping was evident in measurements of mean velocity but not of regional CBF. Accordingly, in a case report studied with single-photon emission computed tomography,2 equally increased MCA mean flow velocities were found in the hyperperfused and the contralateral hemisphere. We believe that our data offer the stimulus for further research on the relationship between transcranial Doppler ultrasonography and other techniques of CBF measurement.

We also agree that the hemodynamic modifications observed after endarterectomy are coupled tightly to delicate neuroeffector mechanisms triggered after reperfusion,3 which amply merits investigation.

In our study, we cannot document any relationship between the degree of contralateral internal carotid artery stenosis and the risk of hyperfusion syndrome because of the small number of patients. Among the patients who developed symptoms of hyperfusion, only 1 had bilateral internal carotid artery stenosis >90%. This patient had initially undergone an uncomplicated right endarterectomy, and 1 week later, she underwent a left endarterectomy that was followed 5 days later by a massive intracerebral hemorrhage. This was the only patient who had abnormally increased MCA mean flow velocities ipsilateral to the endarterectomy site (and interestingly, contralateral to it), but most unfortunately, this patient was not studied with perfusion- or diffusion-weighted MRI. We also compared the mean relative interhemispheric difference of the MCA mean flow velocity between patients who developed hyperfusion syndrome and those who did not and found no difference (27±11 versus 24±10; P = 0.3; Mann–Whitney test). However, this analysis has limited value because of the small number of patients and the aforementioned limitations of transcranial Doppler ultrasonography to assess interhemispheric CBF differences over the cortical convexity.

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Emerging Therapies: Clopidogrel and Aspirin
To the Editor:

We read with interest the commentaries regarding the recently published Management of Atherothrombosis with Clopidogrel in High-Risk Patients (MATCH) trial and wish to contribute some additional perspectives. Patient baseline characteristics have been cited as reasons for the neutral results and detrimental outcomes observed.¹

The large number of patients with small-vessel qualifying events is one reason cited for treatment failure, and Dr Caplan notes that there were “too few patients with documented large-artery disease in MATCH.” On the contrary, the prevalence of lacunar infarctions among participants in MATCH was similar to or less than that of other recent large randomized cerebrovascular trials (53% versus 56% to 67%),²⁻⁴ whereas the proportion of patients with large-vessel infarctions was greater (34% versus 12% to 20%).²⁻⁴ Additionally, as Dr Caplan himself states, some patients with large-artery disease may have been misdiagnosed as “lacunar” if adequate intracranial artery studies were not performed. Given the preponderance of diabetes in the MATCH study population, intracranial atherosclerosis may well have been underestimated, and thus the total percentage of large-vessel qualifying infarctions may have exceeded the reported 34%.² Notably, outcome analyses were negative for lacunar and large-vessel subgroups.²

The frequency of hypertension was also greater than that of most previous studies (78% versus 51% to 68%)²⁻⁵⁻⁶ but less than that of a recent trial evaluating ticlopidine against aspirin in black patients (86%).⁴ In contrast to MATCH, no increase in intracranial hemorrhages was observed in the ticlopidine study.⁴ There was also no increase in intracranial hemorrhages in the 2 trials that had comparable or greater frequencies of lacunar infarctions as qualifying events (53% versus 56% to 67%).³⁻⁴ Drs Amarenco and Donnan argue that the greater rate of severe hemorrhages from clopidogrel/aspirin may have been attributable to the low risk incurred from clopidogrel alone because clopidogrel has been found to cause fewer (mostly gastrointestinal) hemorrhages when compared with aspirin.⁵ However, the rate of intracranial hemorrhage has not been shown to be significantly different between aspirin and clopidogrel,⁶ and thus the increase in intracranial hemorrhages in MATCH must be considered cautiously. Further, the severe systemic hemorrhagic complications in MATCH recapitulate the adverse events seen in previous cardiovascular thienopyridine–aspirin combination trials.⁷⁻⁸

In MATCH, the prevalence of diabetes exceeded that of any previous cerebrovascular study (68% versus 15% to 40%),²⁻⁶ and as Drs Amarenco and Donnan point out meta-analyses of antiplatelet agents have demonstrated reduced efficacy in diabetic patients with vascular disease.⁹ However, the data referred to did not specifically pertain to patients with cerebrovascular disease, and in fact patients with carotid disease were grouped separately in that analysis.⁹ Information regarding the effectiveness of antiplatelet agents in cerebrovascular patients with diabetes is lacking, but to date there is little evidence for diminished efficacy.

Finally, Drs Amarenco and Donnan mention that many patients included in MATCH had experienced recurrent infarctions while on aspirin, and that the MATCH patients did not represent the population for whom many neurologists prescribe aspirin plus clopidogrel. Our experience has been the opposite, in that it is exactly these patients for whom combination treatment with aspirin/clopidogrel is so often prescribed inappropriately.

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