The CASANOVA Study: Immediate Surgery Versus Delayed Surgery for Moderate Carotid Artery Stenosis?

To the Editor:

The controversy regarding the efficacy of carotid endarterectomy in preventing stroke in patients with asymptomatic carotid stenosis has prompted the organization of several important prospective clinical trials.1-3 The results of the European trial presented in a recent Stroke article, "Carotid Surgery Versus Medical Therapy in Asymptomatic Carotid Stenosis,"2 does little, in our opinion, to resolve the conflicting data and does much to confuse further the treatment of patients with carotid artery disease. Indeed, the conclusions and even the title of this study are misleading.

The Carotid Artery Stenosis With Asymptomatic Narrowing: Operation Versus Aspirin (CASANOVA) study described by the authors was a randomized prospective comparison of two different therapeutic "policies." Both policies involved surgical intervention in a large percentage of patients (87% in group A and 43% in group B). The primary difference between the two groups was the indication for surgery. In group A, surgery was undertaken immediately after randomization. In group B, surgery was performed selectively on the basis of specific indications, i.e., bilateral lesions, progression of the unilateral stenosis to ≥90%, progression of contralateral lesions to ≥50%, or the development of symptoms. In this so-called medical treatment group, 118 carotid endarterectomies were performed in 87 patients. Of the entire 202 medical group patients, 20% had carotid endarterectomies immediately after randomization (30 patients as part of the protocol for bilateral lesions and 10 in violation of the protocol) and an additional 22% had carotid endarterectomies performed as part of the protocol during follow-up. The CASANOVA Study Group reported no significant difference in outcomes between two very heterogeneous treatment groups, not mutually exclusive surgical and medical treatments, as implied by the title. Any inference made to the efficacy of medical or surgical treatment of carotid artery stenosis based on the relative effectiveness of these two therapeutic policies is inaccurate and misleading. Furthermore, with 17% of the randomized patients violating the protocol and no data presented on the eligible patients who refused participation, there arises the possibility of a "volunteer" bias. The low statistical power of the study, which would not reveal a true 43% reduction in end point incidence, also places the validity of the conclusions in question.

In the "explanatory analysis," the 20% of study patients who violated entry criteria or follow-up protocol or were lost to follow-up were eliminated from consideration. Of the remaining 175 medical group patients, 75 underwent carotid endarterectomy. Because the surgical indications were not considered failures of medical treatment or end points, the stroke incidence of these 75 patients was ascribed to medical therapy. Assigning the end points to a surgical treatment and a medical treatment is clearly a misrepresentation of the data.

The "additional analysis" of stroke incidence in a group of 122 patients undergoing endarterectomies for unilateral disease compared with that of 111 "pure medical treatment" patients suffers from two significant problems. First, an estimated 20% of patients randomized to medical treatment had had a carotid endarterectomy prior to randomization. Second, the medical group was a post-hoc subset of patients remaining after elimination of all patients who had bilateral lesions or who, in the follow-up period, had progression of the unilateral stenosis to 90%, progression of contralateral lesions to >50%, or development of symptoms. Obviously the pure medical treatment group is a subset of the patients treated medically, in which the very patients with theoretically higher risks of stroke while on medical treatment were eliminated from evaluation. This analysis is grossly biased in favor of the medical treatment arm rather than the surgical treatment arm as stated by the authors. Remarkably, even in this group of patients with unilateral lesions, which remained <90% stenotic and free of transient ischemic attacks (TIAs) throughout follow-up, the stroke incidence was reported as 12.6% in 3 years.

Unfortunately, important data collected in the study were not reported. For example, the exact incidence of progression of unilateral and contralateral lesions, the rate of progression, the incidence of TIAs in the medical group, and the complication rates of the first versus the second carotid endarterectomy in patients who underwent bilateral operations were not addressed in the published results. These data may have contributed significantly to our knowledge of asymptomatic carotid artery stenosis.

The results of this study more correctly support the conclusion that, in patients with asymptomatic carotid artery stenosis of between 50% and 90%, there was no significant difference in stroke incidence between patients treated with immediate prophylactic carotid endarterectomy and those who underwent operation selectively based on the hypothetical high-risk factors of bilateral stenosis, stenosis progression, progression to bilateral disease, or development of symptoms. To represent the results of the study more accurately, we therefore suggest a change in title to: "Immediate Prophylactic Surgery Versus Selective Surgery for the Treatment of Asymptomatic, Moderate (50-90%) Carotid Artery Stenosis."

We congratulate the CASANOVA study group for completion of the first prospective trial of patients with asymptomatic carotid stenosis, an impressive undertaking. However, due to its study design, the role of carotid endarterectomy in the treatment of these lesions is still undefined. We must await the results of the other ongoing clinical trials.

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