

Response to Letter by D'Anna et al Regarding Article, "Long-Term Mortality in Patients With Stroke of Undetermined Etiology"
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Response to Letter by D'Anna et al Regarding Article, "Long-Term Mortality in Patients With Stroke of Undetermined Etiology"

Response:

We appreciate the interest of Dr D'Anna and colleagues in our recently published article.¹ Dr D'Anna and colleagues raised a question about the definition of incomplete evaluation. They argued that echocardiography should be a routine and essential evaluation for stroke patients. Dr D'Anna and colleagues mentioned that Adams et al² recommended not to classify study patients in a defined category (the cardioembolic one in this case) without performing essential diagnostic tests. However, we cannot find any description that a patient should not be classified in a defined category without echocardiography. Dr Adams stated that, "Diagnoses are based on clinical features and on data collected by tests such as brain imaging (CT/MRI), cardiac imaging (echocardiography, etc.), duplex imaging of extracranial arteries, arteriography, and laboratory assessments for a prothrombotic state. we cannot require that all patients have all diagnostic tests..... To compensate for this situation, the Trial of Org 10172 in Acute Stroke Treatment (TOAST) system allows for a 'possible' stroke subtype diagnosis." Although we agree with Dr D'Anna and colleagues that physicians should make every effort to find potential causes of stroke, cardiac imagings may not be performed because of several reasons in some patients. In many cases, diagnosis of cardioembolism can be made without echocardiographic studies. For example, in a case with atrial fibrillation, which is the most common potential cardiac source of embolism,³ we can classify a patient as cardioembolism without echocardiography. We do not think that such a patient should be classified as an incomplete evaluation simply because of a lack of an echocardiography. This patient even can be classified as a possible cardioembolism without angiographic studies.

Although Dr D'Anna and colleagues did not specify which echocardiography should be essential, the yield for diagnosis of potential cardiac source of embolism is quite different between transthoracic echocardiography and transesophageal echocardiography. The diagnostic yield of transthoracic echocardiography in stroke patients with no history of cardiac disease is much lower than transesophageal echocardiography.⁴ Therefore, transesophageal echocardiography is the modality of choice in patients with unexplained stroke when clinical heart disease is absent.⁴ However, transesophageal echocardiography cannot be performed in many patients because of several reasons.⁵ Therefore, it seems inappropriate that we classify all patients who had not undergone echocardiography into an incomplete evaluation.

Dr D'Anna and colleagues also questioned why 13.5% of patients with cardioembolism did not receive at least an ultrasound study. They were classified as cardioembolism because we aggregated probable and possible categories into the 1 stroke subtype based on the TOAST classification (they were

classified as possible cardioembolism). We do not have an exact answer why angiographic or ultrasound studies were not performed in them because our study was performed retrospectively. However, in general, a carotid Doppler has been less frequently used for stroke evaluation in our institution because intracranial atherosclerosis is more common than extracranial atherosclerosis in Asian patients and a carotid Doppler alone is not good enough for evaluation of entire cerebral arteries.

Dr D'Anna and colleagues suggested that the setting of care should be considered as a confounding factor because admission to an organized stroke care has a positive effect on outcomes. This comment is pertinent. We reanalyzed our data. Among the 3278 patients, 1653 patients (50.4%) were admitted to the stroke unit (SU). Rate of admission to the SU was lower in patients with an incomplete evaluation than those with other stroke subtypes (14.6% versus 52.2%, $P < 0.001$). However, in the univariate analysis, SU care was not related with long-term mortality (odds ratio, 0.90; 95% CI, 0.77–1.06). In multivariate analysis, which included SU care as a confounding factor, the incomplete evaluation still showed higher odds ratio (odds ratio, 2.54; 95% CI, 1.64–3.94). The reason why the SU care was not associated with favorable outcomes is uncertain. Our study was conducted for patients who were admitted between July 1997 and June 2007, whereas our SU was opened at December 2002. Thus, the benefit of the SU might be reduced by this time effect. We further investigated whether an incomplete evaluation was associated with worse prognosis after excluding SU-related factors by analyzing data in the population who were admitted before the SU opened. Multivariate analysis revealed that the patients with an incomplete evaluation in this population still showed high long-term mortality (odds ratio, 2.00; 95% CI, 1.12–3.57). Our reanalyses indicated that SU care was not a contributing factor for high long-term mortality in patients with an incomplete evaluation.

The last opinion of Dr D'Anna and colleagues was that, instead of using small vessel disease as a reference in the multivariate analysis, comparison between determined and undetermined etiology could be more useful to investigate the effects of a stroke diagnostic assessment on prognosis. However, the etiologic mechanism of undetermined etiology in the TOAST classification is very heterogeneous in that the undetermined etiology includes not only incomplete evaluation but also negative evaluation despite extensive work-up and multiple causes identified. Therefore, simple dichotomization of the subtypes into determined and undetermined does not provide accurate information that represents prognosis in each subtype. In addition, we believe that most physicians are familiar with predicting prognosis based on each stroke subtype (for instance, prognosis is good in small artery disease but poor in cardioembolism).

Disclosures

None.

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