tion of vertebral artery disease has not progressed like its carotid artery counterpart. Rocha-Singh insightfully attributed this to the nonspecific symptoms associated with posterior cerebral ischemia, difficulties imaging proximal vertebral artery stenosis with ultrasound, and the absence of a standard surgical therapy for vertebral artery disease.2

The relationship between vertebral artery insufficiency and posterior circulation ischemia is now becoming clear. In a review over 400 cases evaluated for posterior circulation stroke or transient ischemic attack, Wityk et al determined that 20% of patients with posterior ischemia had occlusive disease in the proximal vertebral artery (V1 segment); in 9% of patients a lesion in the V1 segment was the only defined cause of stroke.3 Similarly, the role of vertebral artery disease and other neurological pathologies is now better understood (ie, the relationship between isolated vertigo without other neurological symptoms and vertebral insufficiency). Welsh et al found in a review of patients suffering from long-standing vertigo that 52% of patients demonstrated abnormal configurations or diminished vertebralbasilar flow, 76% of these having the pathology of the vertebral artery.4

Magnetic resonance technology has been used successfully to noninvasively identify vertebral artery disease.5 Similarly, vertebral artery stenting has demonstrated successful procedural outcomes in case series and in this before-mentioned trial.1,2 There should be an increased awareness of the relationship between posterior ischemia and vertebral artery disease, the absence of an acceptable surgical treatment, and the potential vertebral artery stent-supported angioplasty may offer. Ultimately, large-scale randomized trials are necessary to accurately determine the future role of stent-supported angioplasty in the long-term management of vertebral artery disease.

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Carotid Artery Stenting With and Without Cerebral Protection

To the Editor:

We note with interest the finding from the EVA-3S Trial of carotid stenting that the rate of stroke within 30 days of treatment appeared to be higher in patients who were stented without the use of protection device.1 However, we are surprised that the Safety Committee recommended that all patients should be treated with a protection device, although the difference between treatment with and without protection did not reach statistical significance. Moreover, the report does not state whether there were any differences between the two groups in the indications for stenting, the nature of the stenosis, or difficulty of access. Any of these could have led to the decision to stent without protection and at the same time increase the risk of procedural stroke. In the EVA-3S report, age was significantly different between patients treated with and without cerebral protection (66.0 versus 72.7 years, P = 0.013).1 Age has been reported to be a risk factor for carotid stenting2 and this could explain the worse outcome in patients treated without a protection device. There was also a threefold increase in the proportion of patients treated by predilation in the protected group, which might contribute to their better outcome. Only strokes at the time of the procedure would be expected to be prevented by protection devices. In the EVA-3S, only 2 strokes occurred on the day of the procedure without protection, compared with 3 strokes in those treated with cerebral protection. Such a difference could well have arisen by chance. For all these reasons, we believe the recommendation of the EVA-3S Steering Committee was premature. On the other hand, we accept that ethical and research governance considerations may make it difficult to continue a treatment that appears to have a greater risk before the difference reaches statistical significance.

No protection devices were used in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) where the rate of stroke within 30 days of treatment was 10% in patients treated with angioplasty or stenting.3 In the EVA-3S report, the same measure in patients treated with cerebral protection was 10.3%.1 There is therefore no clear evidence that protection reduces the rate of stroke. Thus, we are not convinced that the evidence presented mandates the use of protection devices. Moreover, there are those who argue that protection devices are unnecessary and may increase the risks in some patients.

The protocol for the International Carotid Stenting Study (ICSS or CAVATAS 2) states that when a patient is having stent placement “a cerebral protection system should be used whenever the operator thinks one can be safely deployed.”4 The editorial accompanying the EVA-3S report recommends that ICSS should do an interim analysis of protected versus unprotected patients.1 The ICSS investigators have subsequently presented confidential data on the outcome of stenting with and without protection devices in ICSS to the Data Monitoring Committee. The Data Monitoring Committee acknowledged the need to keep monitoring this issue in future annual reports, but did not recommend any protocol modifications. At present the ICSS investigators have complete data returns for 78 completed stenting procedures of which 66 (85%) were carried out with some form of cerebral protection. The sample of unprotected procedures is very small1,2 and this fact alone can bias any safety data. To take a theoretical example, in an existing series of 10 procedures with 1 stroke, a single stroke in the next procedure would almost double the apparent rate of complications.

In conclusion, we believe that the data from the EVA-3S Trial should be treated very cautiously because of the small numbers of patients analyzed. We do not believe that the current protocols of the other carotid stenting trials need modification.

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3. The CAVATAS Investigators. Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Trans-
Serum Albumin Level as a Predictor of Ischemic Stroke Outcome

To the Editor:

We read with great interest the recent article by Dr Dziedzic et al1 on the relationship between serum albumin level and ischemic stroke outcome. Even though low serum albumin has been associated with an increased incidence of stroke in epidemiologic studies,2 a high serum albumin level in acute stroke patients was described, for the first time, to decrease the risk of poor outcome among hospitalized patients. The neuroprotective effects of endogenous albumin on the capillary microcirculation in the early reperfusion phase were proposed to explain the cellular mechanism of this association, and the role of exogenous albumin therapy in stroke recovery was briefly reviewed.

It is important to recognize the role of serum albumin as a marker of clinical outcomes in vascular disease. Apart from stroke, serum albumin has been associated with adverse vascular events in patients with cardiac3 and renal4 diseases. Among hospitalized patients, hypoalbuminemia was found to be associated with frequent hospitalizations, higher mortality, and readmission,5 and an independent prognostic factor for all deaths among healthy middle-aged individuals in population studies.6 Serum albumin is regulated by factors influencing protein synthesis, breakdown, leakage to the extracellular space, and food intake. In clinical practice, serum albumin is often considered a marker of nutritional status and a negative phase protein that decreases in concentration during injury and sepsis.7

There has been conflicting evidence in the literature on albumin therapy in treating patients with hypoalbuminemia from an underlying vascular disease. Albumin has a molecular weight of about 66 kDa, thus preventing it from passing through the blood–brain barrier by diffusion or by carrier systems through these membranes. Local redistribution, crystallloid dilution, and changes in the metabolism of albumin, which result in ineffective delivery and concentration within the central nervous system, frustrate therapeutic interventions. In septic patients, albumin therapy was not associated with a rise in serum albumin. Instead, a fall in serum albumin was observed and this was hypothesized to be secondary to capillary leakage.8

Until these important questions on albumin therapy are answered in randomized controlled studies, therapeutic options in patients with hypoalbuminemia should be directed toward treating the underlying cause, avoiding or treating salt and water overload, instituting prompt medical and surgical treatment of inflammation and sepsis, and providing appropriate nutritional support to enhance recovery in patients with ischemic strokes.

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Response:

We thank Dr Seet and colleagues for their thoughtful comments to our article. We agree that hypoalbuminemia appears to be a predictor of poor prognosis in different clinical settings and even in apparently healthy individuals.1 It is still unknown in which way hypoalbuminemia can impair the prognosis. The mechanisms responsible for this phenomenon are not limited to energy depletion only, but can be also related to impaired immune and endothelial response, as well as extracellular water expansion.2 On the other hand, experimental studies revealed a beneficial effect of albumin infusion in animal models of cerebral ischemia and it was suggested that this neuroprotective effect is mediated by multiple specific actions of albumin including antioxidative properties, influence on endothelial function, and venular perfusion.3,4 Which of the above-mentioned mechanisms of albumin action are relevant to human stroke remains to be established.

Albumin belongs to negative acute phase proteins. In our study we measured albumin level within 36 hours after stroke onset. We can’t exclude that acute phase response accompanying ischemic stroke can to some degree decrease albumin level in this time period. Inflammatory reaction defined as C-reactive protein level was found to be the most pronounced 3 to 7 days after stroke onset.5 Davalos et al found fall in albumin concentration between day 1 and day 7 of stroke (40.7 ± 4.6 versus 39.5 ± 5.3 g/L) with borderline statistical significance (P = 0.05).6 Other authors observed significant decrease in albumin level 2 and 4 weeks after stroke onset and this phenomenon couldn’t be explained by acute phase reaction.7 Unfortunately there is a lack of studies investigating changes in serum albumin level during acute phase of stroke.

Could albumin infusion be beneficial in human stroke? We share some concerns of Dr Seet and colleagues that this form of the therapy could be ineffective. However, we think that promising results of animal studies warrant the attempt to conduct clinical trials. In our opinion, 2 issues can be addressed in clinical studies: first, if correction of hypoalbuminemia (if possible) can influence the stroke outcome; second, if albumin infusion in early stroke in patients with normoalbuminemia can be beneficial as shown in animal models.

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