Letters to the Editor

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Systematic Review of Cost-Effectiveness Research of Stroke Evaluation and Treatment

To the Editor:

Holloway and colleagues' review of cost-effectiveness studies in stroke evaluation and treatment1 may have inadvertently introduced major biases by the selection criteria used for inclusion of studies. They decided to include only studies that used quality-adjusted life-years (QALYs) as the indicator of health effect. The justification for this criterion is not given. By doing this, cost-effectiveness studies that used indicators such as lives saved or strokes avoided are excluded, and the authors do not provide information on study exclusions to allow the reader to assess the potential bias created.

The review is biased in two ways. First, the use of QALYs is inappropriate in many areas of stroke evaluation and management where measures of diagnostic accuracy, patient satisfaction, or reduction in symptoms are of relevance. It is noteworthy that the review excluded consideration of the most effective intervention for stroke management—organized stroke care and rehabilitation—for which reviews of cost-effectiveness studies have been performed.2,3 Thus, the review is biased in describing the range of cost-effectiveness studies in stroke.

Second, the review provides biased estimates of cost-effectiveness. To illustrate this bias, consider the use of anticoagulation for patients with nonvalvular atrial fibrillation. The cost-effectiveness studies they present show that warfarin dominates among high- and medium-risk patients but in low-risk patients it has a high cost per QALY. The authors concluded that anticoagulation was the preferred option for all but the low-risk patients.

A cost-effectiveness study comparing anticoagulation only, anticoagulation or aspirin, or aspirin only that reported cost per stroke prevented was excluded but comes to remarkably different conclusions.4 In this study, the cost per stroke prevented (which may arguably be a more relevant outcome than a QALY to most patients and doctors) was substantially lower for the aspirin-only regimen at US$1300 (Table).

The most effective treatment is anticoagulation for those who can tolerate it and aspirin for the remainder, as this prevents 1300 strokes a year if complications are low, and even in complications are high still prevents more strokes than simply giving everyone aspirin—but this approach ignores the higher costs involved in anticoagulation. If complications of anticoagulation are high, which tends to be the case in older patients, the aspirin only policy is the most cost-effective option.

I hope the authors of this review will consider updating it by using more appropriate inclusion criteria and thereby arriving at more relevant decisions to aid clinicians and policy makers.

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References

Response

We thank Dr Ebrahim for taking an interest in our article. He states that our analysis was biased because we excluded studies that did not report quality-adjusted life-years as the health effect. We excluded such studies because we wanted a measure of cost-effectiveness that we could compare across health care interventions: the cost-per-QALY metric allows for such comparisons. Including studies using different outcomes (eg, cost per stroke avoided) would limit our ability to make such comparisons. We agree with Dr Ebrahim that measures of diagnostic accuracy, patient satisfaction, and reduction of symptoms are relevant in evaluating the effectiveness of diagnostic and management strategies of patients with stroke. We also believe that the QALY effectively incorporates those attributes into a single health measure of both quality and quantity. Cost-effectiveness studies that use measures other than QALYs, however, are important and should be the subject of future systematic reviews. We consider our project an important step in improving the evidence base upon which cost-effectiveness data can be used by clinicians and policy makers.

Dr Ebrahim also asserts that we provided biased estimates of cost-effectiveness and refers to one of our cited studies.1 This study addressed the cost-effectiveness of warfarin compared with

| Cost-Effectiveness of Anticoagulation and Aspirin Regimens in Prevention of Stroke in Patients With Atrial Fibrillation |
|-------------------------------------------------|----------------|--------------|
| Anticoagulation Only | Anticoagulation or Aspirin | Aspirin Only |
| No. eligible for treatment | 22 000 | 75 000 | 75 000 |
| Annual cost (US$) of treatment | 800 | 250 | 16 |
| Net reduction in stroke, low risk | 630 | 1 300 | 910 |
| Net reduction in stroke, high risk | 260 | 930 | 910 |
| Cost (US$) per stroke prevented, low risk | 28 000 | 14 000 | 1 300 |
| Cost (US$) per stroke prevented, high risk | 68 000 | 19 900 | 1 300 |

Low risk and high risk refers to the risk of bleeding on anticoagulation.

aspirin or no therapy in patients with nonvalvular atrial fibrillation. He states that we “conclude that antiocoagulation was the preferred option for all but low-risk patients.” In our article, we presented only the data on the cost-effectiveness of warfarin compared with aspirin, since this was a primary objective of the referenced article. By not presenting the aspirin data, we never meant to imply that aspirin was not cost-effective in some patients. In fact, Gage and colleagues1 found that aspirin was the preferred therapy in low-risk patients if their estimated stroke rate was 1.1% per year—a finding more in keeping with the data from the article provided by Dr Ebrahim.2 We also note that the table provided by Dr Ebrahim uses the terms “low risk” and “high risk” to describe the risk of bleeding on anticoagulation; our article used these terms to describe the annual risk of stroke.

A major conclusion in our study was that analyses employing methodologically sound methods and studying the same condition (ie, screening and treating for asymptomatic carotid stenosis) yielded very different estimates of cost-effectiveness. Further research is needed to determine why such similarly framed questions could lead to such disparate results. These results suggest, however, that readers of such analyses should exhibit a healthy skepticism toward any study making cost-effectiveness claims. Therefore, as we indicate, it might be premature to use the results from such analyses to develop stroke policy and guidelines. Such a conclusion is relevant to aid clinicians and policy makers in making decisions.

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Treatment for Ruptured Aneurysms and Screening for Unruptured Aneurysms

To the Editor:

I read with interest the letter to the editor from Yamashita et al, “Trend in Outcome of Cerebral Aneurysmal Rupture Since 1985: A Proposal for Future Treatment,” and would like to comment on a couple of points.

I think that the population-based study of cerebral aneurysms conducted by Yamashita et al has greatly contributed to our understanding of the epidemiology of subarachnoid hemorrhage (SAH) and the recent results of treatment. In the letter, 3119 patients with SAH between 1985 and 1997 in Yamaguchi prefecture were enrolled, corresponding to 240 patients annually. All of these patients were admitted to 1 of 28 neurosurgical centers. Thus, the average number of patients treated per institute was only 8.6 per year. I basically agree with the opinion of the authors that, judging from the trend of treatment results over the last 13 years, the outcome of SAH patients will not improve dramatically in the near future. However, I think that it may be possible to improve the outcome by concentrating these 240 patients in 3 or 4 institutes. It has been shown that in many kinds of diseases, treatment results in hospitals managing a larger number of patients are superior to those in hospitals treating a smaller number of patients. Therefore, after initial resuscitation, patients with SAH should be transferred to such institutes, where intensive care, including surgery for aneurysms and management of cerebral vasospasm, should be managed. Because the present situation in Yamaguchi prefecture could also apply to most of the other parts of Japan, it would be desirable to reform our medical system with such a perspective in mind.

Second, as the authors discussed, considering the high mortality due to SAH, it is reasonable to shift our attention to the screening of asymptomatic populations for unruptured aneurysms in order to prevent SAH in future. In the same issue of the journal, we reported the results of cost-effectiveness analysis of such screening.3 We demonstrated that the cost-effectiveness of screening depends largely on assumptions about the annual rate of SAH (rupture rate) from unruptured aneurysms. A program of screening is cost-effective for a rupture rate of 1% to 2% per year, as reported previously.4,5 In contrast, such screening is neither cost-effective nor beneficial if the rupture rate is 0.5% per year. A rupture rate of at least 0.75% per year of the rupture rate would be necessary to justify screening. Thus, the rationale for such screening would seem to be lost, based on data from the recent large-scale international study.6

So far, several comments about the international study—both favorable and unfavorable—have been reported.7–12 Although this was the largest study of its type, it appeared to include some inconsistent data. In particular, the risk of subsequent rupture of aneurysms smaller than 10 mm was extremely low (0.05% per year) if patients had no history of SAH. In fact, it may be as low as the incidence of SAH in the general middle-aged or elderly population.2,13 By contrast, most ruptured aneurysms in patients with SAH are of this size.1 I have some concern about the 424 patients in this subgroup of the retrospective cohort, details of which did not appear in the paper. These patients would not have been representative of the overall population of patients with unruptured aneurysms. Why were they not treated surgically, but merely followed up? These patients may constitute a group who were judged by their physicians to have a low risk of aneurysm rupture (eg, intracavernous aneurysms or those with calcified walls, or thrombosed). It seems we should at least be prudent in applying these data to any decision making. I would like to reemphasize that an understanding of the natural history of unruptured aneurysms, ie, the “rupture rate,” is essential for discussion of the screening and/or treatment of unruptured aneurysms.

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Small Chronic Hemorrhages and Ischemic Lesions in Association With Spontaneous Intracerebral Hematomas

To the Editor:

Tanaka et al1 have cited my article2 concerning fibrinoid necrosis, miliary aneurysms and cerebral hemorrhage, in a misleading way. I did NOT, as their text suggests, offer support for the concept of “pseudoaneurysms” or “bleeding globes.” In fact, I reported no such lesions. Rather, one important finding in my paper was that the miliary aneurysms [ie, true aneurysms] can become fibroed, rather than rupture, and then become fibrous balls. I pointed out that when cut in cross-section and thus isolated from their parent arteriole in histological section, these balls may not be recognized for what they are—healed, TRUE aneurysms. The proof of their identity was the presence of remnants of arteriolar wall elastic tissue at their margins. In longitudinal sections I clearly illustrated the continuity of this elastic tissue with the elastic of the parent arteriole at the point where the neck of the fibroed aneurysm joined with the fibrous ball. As Tanaka et al point out, if there are pseudoaneurysms caused by organization of hemorrhages from nonaneurysmal sites of bleeding, these would have a completely different structure and would be, in their words, rimmed by fibrin and later supposedly transformed into masses of collagen (without remnants of elastica). This point remains extremely important as I pointed out elsewhere:3 the failure to recognize fibrous balls as true miliary aneurysms will lead to great underestimation of the incidence of miliary aneurysms in benign hypertension; the failure to use elastic stains to distinguish between healed aneurysms and “bleeding globes” (which are simply small hemorrhages adjacent to a vessel) will also lead to underestimation of the incidence of miliary aneurysms. Both errors continue to contribute to the failure of many persons to recognize the importance of miliary aneurysms as potential sources of cerebral hemorrhage.

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Response

In our article, the term “fibrous ball” was used to mean an organized military pseudoaneurysm. This is not consistent with Dr Rosenblum’s definition of the term as a fibrosed true aneurysm with endothelium and internal elastic laminae, in patients with intracerebral hemorrhage. Our diagnosis of pseudoaneurysm has been based on both light- and electron-microscopic observations of 7 milia raneurysms that were found among 48 specimens of hypertensive intracerebral hemorrhage. The aneurysmal walls invariably consisted of dense layers of fibrin and plasma protein admixed with a few hematogenous cells. Endothelial cells, however, were totally absent on the luminal surface. The wall of the aneurysm contained no remnants of arteriolar elements such as internal elastic laminae. Our findings of milia raneurysms are completely consistent with the descriptions in the textbook Pathology of the Cerebral Blood Vessels: “Vessels bearing milia raneurysms usually exhibit a severe degree of arteriosclerosis. The aneurysmal wall consists of hyaline and collagenous tissue, the media and internal elastic lamina in most cases. Mutating near the entrance to the sac. In some aneurysms a considerable amount of fibrin occurs in the thickened aneurysmal wall, and red cells and remnants of a hyaline or collagenous tissue are recognizable within the fibrin laminations. A few leukocytes, macrophages and siderophages are not infrequent. The lesions could be false aneurysms if formed as the result of rupture of the wall. Milia raneurysms undergo partial or complete thrombosis and eventually be replaced by a collagenous mass.”

As mentioned in our article, however, an abrupt breakage of the arterial wall is more common than microaneurysms at the site of rupture in hypertensive intracerebral hemorrhages. This is also consistent with the descriptions in the textbook, Greenfield’s Neuropathology: “The long-lived controversy about the role of microaneurysms is still unsettled. Challa and co-workers who presented strong evidence for microaneurysms being actually complex coils and twists of small arterioles regarded rupture of non-aneurysmal arteriolar wall damaged by hypertension as the likely cause of hypertensive haemorrhages.” Thus, we maintain our belief that hypertensive intracerebral hemorrhage is caused by a direct rupture of the arteriosclerotic arterial wall at the bifurcation, with or without a secondary formation of pseudoaneurysms.

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Diffusion MR Imaging and Transient Ischemic Attacks

To the Editor:

With great interest we read the excellent study of Kidwell et al1 about diffusion MRI in patients with transient ischemic attacks (TIAs). In 48% of their 42 TIA patients, they found abnormal diffusibility on diffusion-weighted imaging (DWI). The frequency of positive DWI findings increased with increasing TIA duration. In DWI-positive TIA patients, diffusion abnormalities were smaller and alterations of apparent diffusion coefficients (ADC) less pronounced than in stroke patients.

We were pleased to present a study with similar results. We studied 40 consecutive patients (mean±SD age 61±10.5 years; 20 men) eligible for MRI scanning, in whom TIA diagnosis was assumed based on patient history. All included patients reported an acute focal neurological deficit that lasted <24 hours. Because symptoms had completely resolved before they reached the hospital, clinical deficits had not been witnessed by a physician. DWI was performed within 7 to 72 hours after symptom onset (mean 36.5 hours), on a 1.5-T MR imaging system (General Electric Medical Systems) using a single-shot, multislice spin-echo echo planar imaging sequence. (TR 12000 ms, TE 101 ms, flip angle 90°, field of view 40×20 cm, matrix 128×64 mm, axial slices, thickness 5 mm, interslice gap 2.5 mm, inversion recovery pulse TI 2200 ms). Diffusion gradients were applied in 3 orthogonal directions, with a maximum b value of 1000 s/mm².

In 14 patients (35%), DWI revealed a hyperintense lesion indicative of acute ischemic compromise. Five of those patients had multiple lesions on T2-weighted images, which suggested small-vessel disease. In these patients DWI was useful to identify the acute ischemic lesion among preexisting white matter lesions. For DWI-positive TIA patients, the mean relative ADC value of the entire DWI lesion was calculated (ADC = -log(signal intensityb = 1000)/signal intensityb = 0) and expressed as relative ADC compared with contralateral normal-appearing tissue. Relative ADC values of TIA-associated DWI lesions ranged from 0.67 to 0.90, with a mean±SD of 0.81±0.07, which was significantly higher compared with values in stroke patients, who had a mean relative ADC value of 0.62±0.1 when measured within the same time window of 72 hours (P<0.001, Mann-Whitney test).

TIA duration differed significantly between DWI-positive patients, who had a mean TIA duration of 7.1±9.2 hours, and DWI-negative patients, with a mean TIA of 3.2±6.7 hours (P<0.05, Mann-Whitney test). When patients were sorted into groups according to TIA duration, the frequency of positive DWI findings ranged from 0% to 67% (Figure). These results
are similar to data from Kidwell et al., who found that among patients with TIA lasting for <1 hour, 33% had DWI lesions, compared with 71% among patients with TIA duration of 12 to 24 hours. However, in their study no details were mentioned about patients with a very short TIA duration of only several minutes. All of our patients who reported symptoms lasting for 5 minutes or less had normal DWI results. On the other hand, among patients with positive DWI findings the shortest TIA duration was 10 minutes, and only 2 of 26 patients (8%) had TIA lasting for <30 minutes. These data may indicate pathophysiological differences between the very brief ischemia lasting for a few minutes and ischemic events lasting for hours. However, TIA duration should be interpreted cautiously, because it represents the patient’s estimate rather than an exactly measured time period. Nevertheless, the DWI studies on TIA seem to indicate that ischemic tissue injury may occur if clinical symptoms last longer than a few minutes. The likelihood of ischemic injury seems to increase with advancing duration of clinical symptoms, even if they eventually disappear within 24 hours (the threshold chosen to discriminate TIA from stroke).

For patients who present in clinical practice with a history of acute focal neurological deficits which have already resolved rather than with identifiable clinical symptoms, DWI might be useful to verify the suspected ischemic etiology. Furthermore, according to a recent abstract, in DWI-positive TIA patients further diagnostic evaluation is more likely to reveal an underlying cardiac or cerebrovascular etiology.

Response

We thank Dr Engelter and colleagues for their thoughtful comments on our study. Their observations from an additional 40 TIA patients undergoing diffusion-weighted MR imaging confirm and extend our report.

With regard to TIA of very brief duration, the briefest TIA in our cohort was 10 minutes, which occurred in 3 patients. Only 1 of these exhibited a DWI abnormality. Ten patients in our cohort had TIA ≤30 minutes in duration. Thirty percent of these exhibited DWI lesions.

The convergent results of Engelter and colleagues and ourselves demonstrate that the likelihood of DWI abnormalities developing in TIA patients increases with the duration of ischemia. However, as brief an ischemic episode as 10 minutes may produce DWI alteration. The severity of ischemia is likely also an important determinant of diffusion abnormality. Clinicians should be aware that in a substantial minority of patients with TIAs as brief as 10 to 60 minutes in length, diffusion MR can demonstrate abnormalities, and these findings can alter the diagnosis of stroke mechanism and the treatment plan.

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Noninvasive Vascular Assessment in Suspected Acute Basilar Artery Occlusion

To the Editor:

Brandt and colleagues concluded in their recent article in Stroke that CT angiography (CTA) was superior to Doppler sonography (DS) in the assessment of occlusion or patency of the basilar artery (BA) and that the usefulness of combined extracranial and transcranial DS was confirmed in proximal BA occlusion. I agree with the first conclusion but disagree with the second one and would like to raise the following comments.

First, digital subtraction angiography (DSA), the gold standard for diagnosis or exclusion of BA occlusion, was performed in only 6 of the 19 patients. Although I understand the reasons for not performing DSA in all patients, the absence of the gold standard does not allow a direct comparison between DSA and CTA, nor does it permit full validation of the accuracy of CTA in the assessment of patients with suspected BA occlusion.

Second, I am concerned about the accuracy of the “final diagnosis” of some patients. The method of deriving the final diagnosis was not explained in the Subjects and Methods section. Transient BA occlusion was implied in 3 patients when infarcts in the posterior circulation were seen on the follow-up CT of the brain. Nevertheless, CT is inferior to MRI in revealing small infaracts, especially in the posterior fossa. I wonder whether MRI was performed in the other patients (1, 3, 4, 12, 16, and 18) to exclude small posterior circulation infarcts which, in turn, would indicate transient BA occlusion. On the other hand, transient BA occlusion should have been diagnosed in patient 7, who had a lower brain stem infarct. Patient 17 did not have DS before CTA; heparin was listed as the treatment, and DSA was listed as not performed in the Table, but DSA and local thrombolysis were done, according to the text in the Subjects and Methods and the Results sections.

Third, CTA was performed in 20 patients with suspected BA occlusion, and 1 patient was excluded because DSA was not done. If one adopts the authors’ clinicoradiological diagnostic criteria for BA occlusion, 10 patients with complete BA occlusion and 2 with incomplete BA occlusion were detected by CTA. I patient with BA occlusion was missed by CTA because of “dense” BA calcification, and patient 7 was also missed (as explained above). The sensitivity, specificity, positive predictive value, and negative predictive value became 12/14 (85.7%), 6/6.
(100.0%), 12/12 (100.0%), and 6/8 (75.0%), respectively, which indicates the usefulness of CTA in patients with suspected BA occlusion. In addition to the limitations of CTA, which were described by the authors,1 the extra dose of nonionic contrast medium may limit the volume of contrast permitted for DSA and/or local intra-arterial thrombolysis.

Fourth, I am interested to know the CT number over the hyperdense BA of patient 19 (Figure 1), since the differential consideration is a “hyperdense” BA from thrombosis. Finally, the potential role of DS in BA occlusion appears to be very limited, because findings of DS were not helpful in almost half (9/19 or 47.4%) of the target patients with suspected BA occlusion.1 More importantly, time is a critical factor in acute therapy for ischemic stroke. Precious time will be lost in attempting to complete the extracranial and transcranial DS when 5% to 19% of patients have poor temporal bone windows; findings of DS are not helpful nearly half of the time,1 and BA occlusion cannot be excluded by “normal” DS findings.1

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Response

We appreciated the detailed comments of Dr Cheung, which allow us to further underscore some aspects of our study.

As there exists no prospective study of CTA controlled by DSA in patients suspected of BA occlusion, we published a series of such patients who all had undergone CTA as well as DS to analyze the CTA potential in emergencies.1 For ethical reasons DSA was performed only on patients considered suitable for thrombolysis. We concluded cautiously that—although we found CTA a reliable non-invasive technique in showing BA occlusion—“the small number of patients studied precludes definite conclusion on the accuracy of CTA in BA occlusion” and that “further evaluation of CTA especially in high-grade BA stenosis is necessary.” Further, we avoided to determine sensitivity and specificity which can only be done in trials with DSA in all patients.

Since the end of our study in February 1997, we and others continued to find CTA reliable in the diagnosis of both BA occlusions and arterial occlusions in the anterior circulation.2,3 In 16 additional patients who underwent DSA and intra-arterial thrombolysis for BA occlusion following CTA, diagnostic accuracy was similar. Moreover, Dr Cheung, while correctly calling DSA the “gold standard,” did not point to any diagnostic failure of CTA in his own experience.

Regarding the use of Doppler sonography (DS) in the emergency assessment of suspected BA occlusion, we are not aware of any larger series. We concluded that “the decision not to perform DS is not to be based reliably on negative DS findings alone if BA occlusion is clinically suspected.”1 However, this does not preclude any use of DS in BA occlusion. Indeed, we found positive results by DS in 3 of 4 proximal BA occlusions. With such positive signs for BA occlusion as a high-resistance pattern, sudden loss of signal, or retrograde flow in the distal BA, diagnosis of BA occlusion can be made. BA occlusion can be excluded with a high degree of certainty if there are normal DS findings, including absence of indirect signs for BA occlusion such as pathological flow patterns in the vertebral or posterior cerebral arteries and a sufficient insonation depth of the BA of at least 110 to 120 mm by transcranial Doppler sonography.2 We encountered false-negative results or uncertain DS findings of BA occlusion only in patients with an insonation depth below these values or due to technical problems (e.g., intubation, adipose necks); in these cases, further imaging studies became necessary. Both patients in our study with false-negative DS results and distal BA occlusion had a maximal insonation depth of only 90 and 100 mm, respectively. Furthermore, a particular strength of DS is the assessment of hemodynamics, which can also be used in monitoring indirect signs of BA occlusion. Thus, DS may complement the information gained by CTA in the decision for thrombolytic therapy. In fact, only recently we treated by intra-arterial thrombolysis a patient in good clinical condition with a short distal BA occlusion diagnosed by CTA, because DS revealed a severe flow reduction in the BA and both posterior cerebral arteries. Moreover, the vascular region of interest must be known before CTA is performed, as the scanning range is relatively narrow. DS further assists—along with the clinical findings—in identification of this region (ie, extracranial versus intracranial, anterior versus posterior circulation). The diagnostic value of DS and the time spent for the examination strongly depend on the experience of the examiner, though; experienced examiners need no more than 10 minutes if the clinically relevant arteries are focused on. By contrast, CTA is less dependent on the experience of the examiner.

Definition and accuracy of “final diagnosis”: All patients were emergency patients initially suspected clinically of having acute BA occlusion as defined in the Methods section.1 Not all patients were eventually admitted to our maximal-care hospital. Therefore, or due to poor clinical condition, MR imaging could not be performed in some patients. The final diagnosis was defined by clinical course and final imaging results. In most cases brain stem ischemia caused by BA occlusion or associated with posterior circulation infarcts shown by MRI in some of these patients (2, 5, 6, 7, 8, 13, 14, and 15) or by follow-up CT was the final diagnosis. In patient 7, a lower brain stem infarct in the territory of the posterior cerebellar artery was found on MRI, which made a transient BA occlusion highly unlikely. There were, however, 3 patients without BA occlusion and brain stem infarct even on follow-up imaging, in whom could be identified other etiologies, such as intoxication (patient 18, proven by laboratory test), postictal coma, and a large hemispheric infarct detected on follow-up CT.

In patient 17 with BA occlusion, no DSA was performed because of thalamic and occipital lobe infarcts and age (77 years). The CT number (in Hounsfield units) over the hyperdense BA of patient 19 (Figure 1)1 was 280, which corresponds to calcification. Finally, as stated in our previous article of CTA in the anterior circulation, the use of 130 mL of nonionic contrast agent for CTA does not preclude subsequent DSA.2

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Cerebrovascular Reactivity in Internal Carotid Artery Occlusion

To the Editor:

Vernieri and colleagues\(^1\) concluded in their recent article that treatment options in internal carotid artery occlusion can be differentiated on the basis of cerebral hemodynamic status. Specifically, their results have demonstrated that the breath-holding index (BHI) in the middle cerebral artery detected by transcranial Doppler ultrasonography (TCD) is predictive of cerebrovascular ischemic symptoms ipsilateral to the internal carotid artery occlusion. Finally, the authors suggest the use of BHI in selecting patients for the classic or a new type of surgical extracranial/intracranial bypass study. I would like to raise the following comments.

First, “carotid stump syndrome” is a well-known phenomenon: continual episodes of transient ischemic attack (TIA) and/or stroke ipsilateral to an occluded internal carotid artery; embolism has been implicated in the pathogenesis, and border-zone infarction is less common.\(^2,3\) The source of emboli includes the ipsilateral internal carotid artery stump, the ipsilateral external carotid artery, the contralateral internal and external carotid arteries, the vertebrobasilar system, and the heart. In the study by Vernieri and colleagues,\(^1\) patients with significant stenosis of the contralateral carotid artery system, significant vertebral artery disease, or cardiac source of emboli were excluded. These exclusions might have resulted in a lower rate of ischemic stroke, especially on the side contralateral to the carotid artery occlusion, and augmented the importance of hemodynamic mechanisms in producing cerebrovascular ischemia. In addition, I am interested in knowing whether there was any significant stenosis in the external carotid artery ipsilateral to the internal carotid artery occlusion.

Second, CT or MRI of the brain was performed at baseline in all the patients with internal carotid artery occlusion, but the neuroimaging findings were not described in the article.\(^4\) This information may be important because some “asymptomatic” patients and some symptomatic patients with “TIA only” could have “silent” cerebral infarcts. Specifically, I wonder whether the neuroimaging findings at baseline can predict outcome events and whether there is an alternative way of categorizing the patients with internal carotid artery occlusion.

Third, TCD findings are affected by both intracranial and extracranial arterial diseases,\(^5\) and near-occlusion may be misdiagnosed as occlusion by carotid ultrasonography.\(^6\) Conventional angiography was performed in all 42 symptomatic patients and in 3 of 23 asymptomatic patients. I would like to know the reasons for performing conventional angiography in these patients, because carotid endarterectomy is not considered in patients with an occluded internal carotid artery.\(^7\) If the invasive angiography was performed to detect significant intracranial disease, this information was not available from 20 of 23 asymptomatic patients; I wonder whether MR angiography was used in some of the patients.

Fourth, apnea for 30 seconds after a “normal” inspiration was used to elicit changes in the mean flow velocity at the middle cerebral artery and generate the BHI, and some training was arranged for the patients.\(^1\) Thirty seconds of apnea is quite long, and I wonder whether hyperventilation (and thus hypocapnia) was present before the definitive recording. A difference between the initial end-tidal CO\(_2\) and the end-tidal CO\(_2\) prior to breath-holding would reveal any significant hyperventilation. I also wonder whether the BHI should be corrected for or adjusted according to the degree of change in the end-tidal CO\(_2\), since this is the chief driving force for changes in the mean flow velocity.

Fifth, I am interested in knowing how “stable” or reproducible the BHI is in an individual patient. This is an important factor in determining the usefulness of the BHI in selecting patients with internal carotid artery occlusion for any type of surgical extracranial/intracranial bypass study.\(^1\) It would be interesting to have repeated measurements of the BHI during follow-up to see whether a change in the BHI may occur before any cerebrovascular ischemic event.

Finally, the authors emphasized the importance of hemodynamic mechanism in producing ischemic cerebrovascular events, and hypertension was present in 39 of 65 patients.\(^1\) I am interested in knowing the aggressiveness of blood pressure control in these 39 patients, because treatment of hypertension may compromise the cerebral hemodynamics in the presence of internal carotid artery occlusion and inadequate collaterals.\(^7\) In addition, the authors did not elaborate on the use of medical treatment such as aspirin and the control of vascular risk factors, nor explain how the outcome events were documented.

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of the embolic and hemodynamic mechanisms of ischemic cerebrovascular events. In the Discussion section, we have emphasized that the relationship between impaired cerebral hemodynamics and the risk of ischemic events does not automatically mean that all TIAIs and strokes occurring in patients with carotid occlusion are exclusively on an hemodynamic basis. It is probable that the hemodynamic and embolic mechanism can act synergically. Moreover, in the final part of the Discussion section, we have acknowledged that the possible application of our results to some of the conditions mentioned by Dr Cheung (ie, significant stenosis of the carotid system contralateral to the occlusion) should be validated by additional studies. For these considerations, we do not share all the concerns expressed in the first comment of Dr Cheung’s letter. Regarding the second point, information about baseline brain CT or MR is required. The inclusion of patients and their classification as TIA, stroke, and asymptomatic patients was based on clinical criteria confirmed by neuroradiological findings. We agree that the study of any further way of categorizing the patients (including the neuroimaging finding) and predicting their outcome can be of interest. However, as clearly specified in the article, our aim was to study the possibility of obtaining prognostic indications on the basis of intracranial hemodynamic status and clinical characteristics of patients, with particular attention to vascular risk factors. Basal neuroimaging findings, as well as other variables, were not the object of our study. Conventional angiography was performed in hospitalized patients as part of a routine investigation aimed to optimize treatment and exclude significant contralateral carotid or ipsilateral external carotid stenosis as well as severe intracranial atherosclerotic disease. The problem of the possible presence of intracranial significant stenosis cannot be fully excluded in asymptomatic patients, in whom angiography was not performed. However, no sign of such a condition was detected on transcranial Doppler basil investigation. Moreover, we would like to add that in Caucasian subjects, the presence of severe intracranial steno-occlusive disease, as opposed to extracranial atherosclerosis, is not frequent. MR angiography was performed in about one-third of asymptomatic patients, as part of an ongoing study. The results of this evaluation were always in accordance with ultrasonographic findings.

The breath-holding method has been widely employed in the study of cerebrovascular reactivity. A recent study on functional MRI confirmed the ability of voluntary apnea to provide information about cerebral hemodynamic status. We agree that a hyperventilation before apnea can alter the results. For this reason, as clearly described in the Subjects and Methods section, subjects hold their breath for 30 seconds after normal respiratory activity, which was checked by means of a respiratory monitor. At the end of the apnea period, the end-tidal CO2 does not reach a stable value, so that the recording of such a variable can only be used to confirm the efficacy of the apnea and the full cooperation of the study subjects. The problem of the reproducibility of the breath-holding index (BHI) values in individual patients, as underlined by Dr Cheung, is of fundamental importance for determining the usefulness of this method in selecting patients with carotid occlusion for any type of surgical extracranial/intracranial bypass surgery. We have experience that with all the methodological precautions used in our study, individual BHI values are highly reproducible. As a further confirmation of this, 15 patients with normal and 12 with pathological BHI were investigated on 2 (18 patients) or 3 occasions (9 patients) at 2- to 3-month intervals. In all cases, the results confirmed the inclusion of every single patient in the normal or pathological BHI group. The problem of pharmacological treatment in patients with carotid occlusion is debated. All patients included in our study were on antithrombotic treatment with aspirin 325 mg orally daily (88%) or ticlopidine 500 mg daily (12%). Furthermore, all patients had the best medical treatment for any treatable vascular risk factor. In particular, careful attention was paid in the treatment of hypertension, with the aim of obtaining values of systolic and diastolic pressure, respectively, in the range of 130 to 145 and 80 to 85 mm Hg. A more aggressive treatment was avoided, as suggested by the study of Widder et al.

Finally, patients in our study were followed up by telephone every 3 months and reevaluated clinically every 6 months by 1 designated individual, who was unaware of the transcranial Doppler data investigator. In the case of events not directly observed in our hospital, clinical records were acquired for an exact description. In particular, special attention was paid to transient neurological deficits that were accepted as TIAIs only if a rigorous evaluation had been performed during the first hours/days after the onset of symptoms, including the exclusion of other possible causes of transient neurological deficits.

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References

Computed Tomographic Findings and Prediction of Malignant Middle Cerebral Artery Infarction

To the Editor:

In their recent Stroke article, Haring and colleagues presented recent data from 31 patients with malignant middle cerebral artery infarction (mMCAI) and 31 control patients with non-mMCAI and concluded that absence of attenuated corticomedi¬ullary contrast over the entire MCA territory is the crucial CT criterion for predicting mMCAI with high sensitivity and specific¬ity. I have major concerns about their methods and wish to make the following comments.

I fully agree that patients with mMCAI have a high mortality rate and that decompressive craniectomy may be a life-saving procedure. Randomized clinical trials are awaited to confirm the benefit of decompressive craniectomy in reducing mortality and, hopefully, in improving the functional outcome in patients with mMCAI. One major obstacle in the design of the aforementioned clinical trial or in routine clinical management of individual patients is the unpredictable occurrence of mMCAI despite similar neurological deficits and CT findings in the initial stage. In other words, some patients with dense hemiplegia, fixed head and eye deviation, and rapid deterioration of consciousness plus angiographic or sonographic evidence of occlusion of internal carotid artery and/or middle cerebral artery run a stable improv-
Marfan Syndrome and Intracranial Aneurysms

To the Editor:

Two brain autopsy series of patients with Marfan syndrome have now been published and, in contrast to the conclusions drawn by Conway and colleagues, they strongly suggest that patients with Marfan syndrome are at an increased risk of harboring an intracranial aneurysm. Combining the 2 autopsy series, incidental intracranial aneurysms were found in 2 (6.5%) of 31 patients with Marfan syndrome. This could be compared with the 0.8% to 1.3% prevalence of incidental intracranial aneurysms in the general autopsy populations at the 2 institutions. However, the mean ages of the patients in the series with Marfan syndrome at autopsy were only 28 and 39 years, respectively, and intracranial aneurysms are now well recognized to be acquired lesions. The expected prevalence of incidental intracranial aneurysms in the third and fourth decades of life would be much lower. For example, in the Johns Hopkins autopsy study used by Conway and colleagues as representative of the general autopsy population, the prevalence of incidental intracranial aneurysms was 0% in individuals less than 40 years of age.

Conway and colleagues mention that their patient with Marfan syndrome and an intracranial aneurysm had a brother who also had Marfan syndrome, but no aneurysm was found at autopsy in the brother, although he was 5 years older at the time of his death. They then suggest that this indicates that their patient’s intracranial aneurysm was probably sporadic and not associated with the underlying arteriopathy of Marfan syndrome. This may be an overly simplistic interpretation of their data, because intracranial aneurysms are acquired lesions with multiple risk factors, both genetic and environmental. For example, Chauveau and colleagues described monozygotic twins with autosomal dominant polycystic kidney disease who were examined at age 47 with MR angiography. Two aneurysms were found in the twin with untreated hypertension and none in the twin with treated hypertension. Autosomal dominant polycystic kidney disease is a well-studied connective-tissue disease that is generally believed to be associated with intracranial aneurysms.

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Response

We appreciate Dr Schievink’s interest in our article. After careful consideration of his 3 points, however, we have to take exception to the same and reiterate our conclusion that there exists no evidence that Marfan syndrome is associated with an increased prevalence of intracranial aneurysms.

Schievink proposes that we pool the results of his autopsy study and ours and change our conclusion. He reported an autopsy series of 7 Marfan patients, 2 of whom had an aneurysm. We object to a “meta-analysis” of these 2 series (which would add up to 32 patients, not 31 as Schievink calculated) for the following reason. Doing so would dilute the epidemiological strength of our series, namely, the fact that it is derived from an

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unselected sample of 1400 Marfan patients accumulated over 40 years, with the sampling error of a small series of 7 patients that we suspect carries an inadvertent sampling bias. As we stated in our article, it is difficult to derive any firm statistical conclusions from Dr Schievink’s series because of its small number of patients combined with the sampling bias in the cerebrovascular patient population at that hospital, which has been previously recognized, documented, and reported by a different group from the same institution.3

Schievink goes on to state erroneously that in our previous study4 we reported a prevalence of aneurysms of 0% in individuals less than 40 years of age. We would like to clarify that in our autopsy series of 13,042 patients, we documented a prevalence of intracranial aneurysms of approximately 0.9% in the second decade of life, 2% in the third decade, 3% in the fourth decade, and 3.3% in the fifth decade. Moreover, the prevalence of intracranial aneurysms observed in our series in individuals younger than 40 years of age was actually higher than the overall prevalence of 1.3%, but for our statistics we chose the more conservative number of 1.3%.

Finally, Schievink states that our comment concerning the brothers in our series, one who had an aneurysm and one who did not, is “overly simplistic.” Although we are indeed aware that multiple genetic and environmental factors may contribute to aneurysm formation, we simply wanted to report this curious finding. We did not need to draw any absolute conclusions from the same, since we felt that the data presented in the paper were more than sufficient to support our conclusion.

After we submitted our paper, Dr Vincent Gott from our institution published a multi-institutional study of 675 patients with Marfan syndrome who underwent replacement of the aortic root and reported the cause of death of 86 of these patients.5 Similar to what other investigators reported in the 5 clinical series of Marfan patients that we cite in our paper and what we noted in our own series of 710 neurosurgical patients, Gott and colleagues did not identify any Marfan patient who died from an intracranial aneurysm.

We therefore reiterate our conclusion that there exists no evidence that Marfan syndrome is associated with an increased prevalence of intracranial aneurysms, but we nevertheless thank Dr Schievink for his interest in our work.

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