Letters to the Editor

Poststroke Sexual Function

To the Editor:

We read with great interest the recent article by Korpelainen et al.1 Despite the fact that the majority of their patients reported a marked decline in all the measured sexual functioning, there was increased libido in 19 of their 192 patients. These patients did not differ from other patients as to the site of the lesion, as reported before.2-4 However, no information was presented about intercourse frequency, deviant sexual behavior, or spousal satisfaction.

We have recently seen a 69-year-old right-handed man, who presented with acute left hemiplegia. His medical history was significant for coronary artery disease diagnosed 6 years before this admission. He had stopped smoking and drinking alcohol since that time. His examination showed dense left hemiplegia, and CT showed massive infarction involving the entire right middle cerebral artery territory. Three months after the ictus, he was walking with a cane; his arm, however, showed no improvement. His wife complained that he became hypersexual and wanted to have sexual intercourse daily. She denied any deviated sexual behavior; socially, his behavior was appropriate. She stated that before ictus they had intercourse every 2 weeks and she is now unsatisfied with her husband’s behavior. The patient at that time was not on any drugs reported to increase sexuality.5 Seven months later, the patient developed poststroke seizures, and 3 years later he died of acute myocardial infarction.

This case is different from the other reported cases in that the hypersexuality developed before the seizures, and the involvement of the frontal, temporal, and basal ganglia regions occurred at the same time. As Korpelainen et al1 stated, sexual counseling after stroke is usually needed, as most of the patients will not disclose their sexual problems spontaneously.

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Response

We thank Hamed et al for their interesting comments regarding our article.1 Hypersexualism related to cerebral lesions is an interesting phenomenon that has been associated particularly with temporal lobe lesions and temporal lobe seizures. Its pathophysiology is not yet clearly known, however. In their classic study, Klüver and Bucy2 described behavioral changes resulting from bilateral temporal lobectomies in rhesus monkeys. These changes included increased sexual activity, marked changes in dietary habits, and antisocial behavior. Terzian and Ore3 reported that bilateral removal of human temporal lobes may result in symptoms similar to Klüver and Bucy’s syndrome.

It also seems that stroke may sometimes increase libido and sexual activity leading rarely to hypersexualism, as Hamad et al and other authors have previously reported.4-6 It is still unclear whether this is related to epileptic activity or to the cerebral lesion itself.

In our study, all the patients and their spouses independently completed a questionnaire that included their prestroke and poststroke sexual functions and habits. Interviews were not used. Nineteen of our 192 stroke patients reported increased libido after the stroke in comparison with the prestroke libidio, but as far as we know, none of these patients suffered from a real hypersexuality. Interestingly, many of these patients and their spouses also reported increased satisfaction with their sexual life, in contrast to the majority of other patients and spouses reporting dissatisfaction with their poststroke sexual life. Therefore, it seems that increased libido after the stroke may sometimes improve the quality of sexual life. We suggest that this may be caused by improved relations between the patient and the spouse or by other positive changes in psychosocial elements.

In future, the phenomenon of poststroke hypersexuality should be studied using qualitative (ie, interviews) instead of quantitative studying methods to obtain more information about its psychological and social significance. In addition, modern functional brain imaging techniques could be used to study its pathophysiology.

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Poststroke Sexual Dysfunction and Quality of Life

To the Editor:

We read with great interest the article recently published in Stroke by Korpelainen et al,1 who reported an increasing sexual dysfunction and dissatisfaction with sexual life in stroke patients and their spouses. In that study, poststroke sexual dysfunction in patients was also closely related to the degree of depression as measured by the Geriatric Depression Scale. The authors recognize that a limitation in their study was using only the Rankin scale to score the degree of patients disability.

We developed a study to measure the variables (depression, disability, or psychological) that could interfere in the sexual life of stroke survivors and their spouses. During 1997, we followed up for 1 year a cohort of 118 patients consecutively admitted to our Stroke Unit at San Carlos University Hospital in Madrid, Spain. The final series consisted of 90 survivors (41 women and 49 men; mean age 68 years, range 32 to 90 years), of whom 70 had experienced an active sexual life before stroke and had been recruited to participate in our study. They completed a questionnaire that included questions on their prestroke and poststroke sexual function, in addition to the Hamilton Depression Scale,2 the Sickness Impact Profile (SIP),3 the Short Form 36 (SF-36),4 the Barthel Index,5 the Rankin scale,6 the Scandinavian Stroke Scale,7 and the Bamford stroke classification.8 We developed an ANCOVA model for statistical analysis.

The main outcomes measures were libido, impotence, sexual satisfaction, and disability, measured by Rankin Scale and Barthel...
Index; depression, measured by Hamilton Scale; Psychosocial Dimension of SIP; SF-36 Vitality; and SF-36 Mental Health. A marked decline in sexual function was reported by 71.5% of the stroke patients 1 year after stroke (72.7% of women and 70.8% of men who were sexually active before stroke); 48.5% of the stroke patients experienced diminished libido. These data are similar to those in the study conducted by Monga et al., who reported diminished libido and erection disorders in 79% and 62% of male stroke patients, respectively.

In our study, impotence was diagnosed in 48% of men 1 year after stroke and was correlated with Physical Dimension of the Sickness Impact Profile. Mean value of Physical Dimension was 17.1 in patients with impotence and 8.8 in normal sexually functioning patients ($P=0.001$).

Libido decline was not correlated with stroke etiology, laterality (right/left) of brain lesions, disability measured by Barthel Index, or age. Libido decline was statistically correlated with the Hamilton Depression Scale (mean value scale 17 versus 9.4 in patients without libido decline; $P=0.001$) and the Psychosocial Dimension of the SIP (mean value 43.7 versus 22.2 in patients without libido decline; $P=0.009$). SF-36 Vitality and SF-36 Mental Health were statistically significantly diminished in stroke patients with reduced libido.

We found no statistically significant differences in the Barthel Index and Rankin scale scores in stroke patients with and without sexual dysfunction (mean score value of 95 versus 90, respectively) 1 year after stroke. Thus, psychological factors seem to exert a strong impact on libido decline in stroke patients 1 year after stroke. Disability and physical functioning exert only a specific impact on impotence, not on sexual dysfunction related to libido decline.

Quality of life instruments are useful instruments for studying physical and psychological factors related to poststroke sexual dysfunction.

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Risk Assessment and Anticoagulation in Atrial Fibrillation in the Elderly: Malpractice or Accuracy?

To the Editor:
We read with interest the paper by Kalra et al recently published in Stroke.1 We would like to contribute to this topic with our experience in 97 patients newly admitted to our Acute Care for the Elderly Medical Unit selected for chronic or recent-onset atrial fibrillation. Seventeen patients had atrial fibrillation of recent onset (>48 hours and <6 months), and the remaining patients had chronic atrial fibrillation (>6 months). By strictly following the recommendations of the most commonly cited trials,2,3 all patients potentially needed anticoagulation to prevent thromboembolic strokes. On the contrary, although our hospital guidelines indicate the use of warfarin, the retrospective analysis of our charts revealed that 21 patients (21.6%) had neither anticoagulation nor aspirin, 49 (50.6%) had only aspirin, and 27 had only warfarin (27.8%). Of 21 patients who received neither warfarin nor aspirin, 4 had a diagnosis of active peptic ulcer, 3 severe liver cirrhosis, 3 gastric cancer, 3 cachexia, 3 anemia secondary to gastrointestinal bleeding, 2 multiple myeloma, 1 lung cancer, 1 ovarian cancer with lung metastasis, and 1 hepatocellular carcinoma. Among the remaining 76 patients, factors associated with aspirin treatment (in 49 patients) were age, cognitive impairment, functional impairment in basic activities of daily living, APACHE score, chronic obstructive pulmonary disease, and liver diseases; independently, factors were living alone, being female, number of somatic diseases, mood depression, and impairment in ≥3 instrumental activities of daily living.

These data indicate that many different factors have been barriers to warfarin prescription, but they are not based on clinical criteria alone; in fact, functional, psychological, and social factors in addition to strictly clinical factors influence the use of anticoagulation. It is indeed intuitive that people affected by terminal diseases or by pathologies involving bleeding problems are not treatable with warfarin and that persons living alone or with a cognitive or functional impairment are seriously disadvantaged in carrying out the periodic laboratory procedures related to anticoagulant prescriptions.

Warfarin therapy is logistically difficult, requiring frequent visits for blood sampling, communication, and dose adjustment, all of which are more difficult for elderly people. We suggest that before starting warfarin therapy it is necessary to assess the realistic
Letters to the Editor

To the Editor:

We read with great interest the article by Proust et al on the sonographic diagnosis of cerebral vasospasm that was recently published in Stroke. Although we do agree with their conclusions, two important methodological aspects of their article deserve further comment and clarification to make their results reproducible.

First, the authors state that they measured the diameter of the middle cerebral artery (MCA) as well as the velocity at a distance of 2 cm from the internal carotid artery (ICA) bifurcation. Even ignoring the fact that the site of measurement of the MCA diameter, demonstrated in their article in Figure 1, appears to be at a distance of 8 mm from the ICA bifurcation, the average length of the M1 segment is, according to most data from the literature, only 15 mm. This strongly suggests that velocity measurements must have been sampled at a main branch of the MCA instead of its main trunk. The authors point out that they adopted “a standard technique to identify the basal cerebral arteries.” However, the sources they cite, Bogdahn et al and Tsushiya et al, do not specify the site of MCA insonation, whereas Schöning et al, to whose results the authors relate their own findings, preferred to obtain the sample volume close to the ICA bifurcation. Taking into account that highly disturbed flow tends to be the rule at this location, the optimal site for MCA insonation still has to be pinpointed, even more so because a distant lateral placement of the sample volume results in less favorable angle of insonation of the vessel.

This latter point leads us to another methodological remark, concerning the angle of insonation of the MCA. The authors maintain that their mean angle of the MCA insonation is 21±14.6°. They claim the angle obtained was so favorable that its necessary correction was only slight and TCCS velocities obtained were the same as those measured with TCD sonography. The authors claim the results to be similar to those of Schöning et al. Nevertheless, that source and others do clearly state that angle-corrected velocities in the MCA are significantly higher than those obtained by conventional TCD. Moreover, Schöning’s mean angle of MCA insonation was 26.6±14.4°, with the velocity predominantly taken close to the bifurcation. We also found a similar angle of insonation (29±14°) at a distance of 10 mm lateral to the bifurcation.

At the MCA insonation site reported by Proust et al, ie, at 2 cm from the ICA bifurcation, the angle of insonation was reported elsewhere to be mainly between 30° and 50°, a value evidently different from that of the authors. For the critical velocity of 120 cm/s, obtained with TCD at the angle of insonation 30°, velocity would have become 139 cm/s.

These methodological inconsistencies imply that the velocity threshold proposed for diagnosis of vasospasm of the MCA may be imprecise and may need recalculation. This conclusion is strengthened by the fact that blood flow velocity declines steeply within the age span into which fall most of the patients examined by Proust et al. Our results, similar to those obtained by Martin et al, indicate that the average value of mean velocity in the MCA decreases from 81 cm/s in the people aged 40 to 59 cm/s in those above 60 years. Therefore, the age factor should not be ignored in the attempt to establish velocity thresholds for the diagnosis of cerebral vasospasm.

Velocities of 120 cm/s are encountered as an upper limit of normal values in the TCCS technique in healthy subjects up to the age of 40 years.

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Usefulness of Transcranial Color-Coded Sonography in the Diagnosis of Cerebral Vasospasm

To the Editor:


3. Atrial Fibrillation Investigators; Atrial Fibrillation, Aspirin, Anticoagulation Study; Canadian Atrial Fibrillation Anticoagulation Study; Stroke Prevention in Atrial Fibrillation Study; Boston Area Anticoagulation Trial for Atrial Fibrillation Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation: the Copenhagen AFASAK study. Lancet. 1989;1:175–179.extended...
Letters to the Editor

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To the Editor:

The recent article by Crawley et al.1 understates the increasing case against screening for familial intracranial aneurysms by overestimating the risk of aneurysm rupture and the accuracy of MR angiography (MRA) in a screening context, as well as underestimating the costs and risks of screening.

The calculations of Crawley et al. are based on an annual rupture risk of 0.4% to 1.5%.2 This figure is derived from a systematic review, but since then the International Study of Unruptured Intracranial Aneurysms,3 the largest study of unruptured aneurysms to date, found an annual rupture risk of only 0.05% for aneurysms <10 mm in size and 0.5% for aneurysms >10 mm (or aneurysms in patients with a previous aneurysmal subarachnoid hemorrhage). The figure of 0.05% should be regarded as the more applicable to screening for aneurysms in asymptomatic relatives of subarachnoid hemorrhage patients.

The value of MRA as a screening tool for the detection of intracranial aneurysms is still controversial, and the sensitivity and specificity of 90% quoted may be optimistic. We have systematically reviewed the world literature and identified 20 prospective “blinded reader” studies (of ≥10 subjects) comparing MRA with digital subtraction angiography and published between 1988 and 1997 that met quality criteria.4 The sensitivity of MRA ranged from 56% to 97% (median 88%) and specificity from 75% to 100% (median 95%), although not all papers provided sufficient data to calculate specificity. However, most intracranial aneurysms detected by a screening program would be <10 mm in size and more than a third would be <5 mm.5 MRA is much less accurate for small aneurysms (<5 mm), with a sensitivity as low as 54%.6 Crucially, 19 of 20 studies were performed in populations in which the prevalence of aneurysms was >50% (and it was 10% in the remaining study), whereas a very low prevalence would be expected in a screening context. While it had been thought that prevalence did not influence sensitivity or specificity,7 more recent evidence indicates that a high disease prevalence leads to an increase in the calculated sensitivity and specificity of a diagnostic test.8 Therefore, if MRA is used as a screening tool in a low-prevalence population, the sensitivity will be less, possibly much less, than 90%.

The costs of screening may be significantly higher than those used in the model. The quoted cost for MRA of $290 ($274) is conservative. For a full screening study incorporating MRI of the brain, MRA plus targeted maximum intensity projection reconstructions and reported by a neuroradiologist, a figure approaching $450 ($425) is more realistic. No evidence is quoted to support the assertion that screening would need to be repeated at least every 10 years. This is a very long time interval, and de novo intracranial aneurysm formation and rupture within 3 years has been observed in familial intracranial aneurysms.9

It is also important not to underestimate the risk of surgery for an unruptured intracranial aneurysm. The estimate of death or dependence of 8% used by Crawley et al excludes less-severe morbidity of 5.5%.10 The prospective International Study of Unruptured Intracranial Aneurysms data give the even higher rate for combined morbidity and mortality of 15.8%.11 People identified through a screening program for familial asymptomatic unruptured aneurysms would, in general, be healthy, therefore all morbidity after surgery should be included in the cost-benefit analysis of screening. There is a case for taking into account the benefit from reduction of anxiety from screening, but the effect of this has not been established.

The omission of coiling of aneurysms is disappointing. Even though data on the risks and benefits of coiling are more limited, it would have been a useful inclusion in the model for comparison with an earlier study on this subject.11

The available evidence indicates that the case against routine screening for familial intracranial aneurysms is stronger than that stated by Crawley et al. One way forward may be to identify which individuals within an affected family are at most risk. Although risk factors such as female sex, smoking, and heavy alcohol intake are recognized, more information is needed on the genetic basis and patterns of inheritance of familial intracranial aneurysms and subarachnoid hemorrhage.

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**Response**

We thank White et al for their letter supporting our conclusions that screening for aneurysms is not justified in asymptomatic patients with a family history of subarachnoid hemorrhage. The fact that White et al believe we understated the case against screening while others have criticized our model as overstating the case suggests that we got the balance about right at the time we wrote our article. In our model we deliberately chose conservative figures to avoid any possibility of bias against screening. However, many of the figures quoted by White et al were not available when we submitted our original article and we agree that the new data further increase the possibility of bias against screening. However, many of the figures quoted by White et al were not available when we submitted our original article and we agree that the new data further increase the case against routine screening.

**Increased Intensity of Physiotherapy After Stroke**

*To the Editor:* The article by Lincoln et al in the March issue of *Stroke* raises some questions regarding their method of data analysis. The authors evaluated the effects of variations in the intensity of physical therapy on arm function after stroke. The patients were randomized into 1 of 3 treatment groups: routine physical therapy (RPT) or 10 hours of additional physical therapy with either a qualified senior research therapist (QPT) or an assistant physical therapist (APT). There was no significant benefit reported from the additional therapy. The authors acknowledge that almost 50% of the treatment group did not complete the additional treatment. The patients who did not complete treatment pose some interesting questions that warrant further explanation by the authors.

The authors report on page 576 that “20% of QPT and 14% of APT patients” were excluded from the final analysis because they were unable to tolerate the additional therapy. Could the authors provide information on how many patients in the RPT group were unable to tolerate routine therapy? If the percentages are similar, one must consider the possibility that a certain percentage of patients simply cannot tolerate any level of therapy provided in an acute inpatient rehabilitation setting. Although it may not be feasible to give more therapy, it may be just as difficult to give regular therapy.

Larger concerns are raised when looking at the group of patients with the second-most-common reason for noncompletion. The authors report that “10% of QPT and 13% of APT patients” were not included in the final analysis because they recovered to “minimal arm impairment” during the intervention period. The major goal of any therapy program is the recovery of function; therefore, why was this group excluded from the analysis of potential benefits from additional therapy? Would not recovery to this level be a desired outcome? Also, what percentage of patients in the RPT group achieved minimal arm impairment during the intervention time frame? If the percentage was low, a significant difference may actually have been achieved with increased physical therapy.

Many challenges are encountered in the rehabilitation of patients after a stroke, and any treatment program must reflect the diversity of impairments. We must continue the efforts to identify which patients can benefit from and tolerate intensive rehabilitation versus those who will respond better to lower-level, subacute programs. The emphasis should be on meeting the individual needs of each patient. This article adds to the literature that assists with these decisions, but we must be cautious that we do not overlook potential interventions by excluding the very group of patients that may demonstrate the most benefit.

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**Response**

We would like to thank Drs Shutter and Whyte for their comments and requests for further information about our trial, and particularly about the patients who did not complete treatment.

Before providing further information, we must first clarify that, as described in the footnote to Table 2 (page 576) in our article,1 the only patients excluded from our “final” comparison of outcomes were those who had been lost to follow-up or had died prior to the particular outcome point. This was an “intention-to-treat” analysis. For results to be applied in clinical practice, information is needed about the effectiveness of providing the service to all patients, even though some may withdraw from it. We did conduct an analysis wherein we excluded noncompleters of treatment. The differences in outcome between the groups remained nonsignificant. The information that we provide about noncompleters of treatment on page 576 and in Table 3 is provided for completeness of reporting compliance with the intervention, because this is important information for clinicians in their consideration of both the feasibility and effectiveness of providing additional therapy.

Having clarified which patients were included in our analysis, we would like to make some further points and provide what information we can. Shutter and Whyte suggest that a certain percentage of patients simply cannot tolerate any level of therapy in an acute inpatient rehabilitation setting. We would agree with them on this point. As we note on page 575, we excluded a considerable proportion of the 1265 patients who were admitted to this large general hospital, including 181 (14%) who were unable to tolerate a half-hour session of physiotherapy per day even by 5 weeks after...
stroke. Besides this 14%, a further 64 (5%) were significantly physically or mentally disabled premorbidly such as to rule out “typical” routine therapy.

We are unable to answer completely the request for information on the number of patients in the routine therapy group who were unable to tolerate routine therapy. To be recruited into the study, all patients had to be able to tolerate 30 minutes of physiotherapy daily. As reported, 20% of QPT and 14% of APT patients were unable to tolerate the full amount of additional therapy. Some of these patients deteriorated after recruitment; others could tolerate their 30 minutes of routine treatment but not more. We have no reason to expect that this would have been different in the RPT group, particularly as we collected information on the routine treatment in order to check for differences between the groups and found none.

We provide further information on the routine treatment another article, which reports a post hoc subgroup analysis examining the effects of severity of arm impairment on the response to additional therapy.

The second concern of Shutter and Whyte, regarding patients who recovered to minimal impairment, should be allayed by our clarification that these patients were indeed included in the “final analysis.” Again, we cannot completely answer their question regarding the numbers in the RPT group who achieved minimal arm impairment during the intervention time frame. However, we have no reason to expect that the proportion in the RPT group differed from that in the intervention groups, particularly in light of the similar medians across the groups for the various arm measures at the postintervention assessment (Table 2).

We appreciate the call by Shutter and Whyte for continued efforts to identify which patients can benefit from intensive rehabilitation. We also agree that there should be an emphasis on meeting the ethnic differences between the Greek and Japanese.

There is one factor that may have limited the apparent strength of the relationship found by Kallikazaros et al: their data were based solely on angiographic findings. In determining the optimal treatment strategy, it is important to examine both angiographic findings and clinical features. The indications for CEA at our hospital are as follows: (1) either symptomatic or asymptomatic patients with a carotid stenosis >70%; (2) symptomatic patients with a stenosis of 50% to 69% with ulcer formation; and (3) patients with hemodynamically significant stenosis, such as bilateral lesions. Therefore, angiographic findings do not always show the clinical significance. However, our results based on the analysis of both angiographic and neurological findings confirm, although indirectly, their conclusion that carotid disease is significantly correlated with severe CAD.

In addition, if the patient had a left main stem stenosis, the patient was classified as severe CAD in their study despite the number of diseased vessels. We also performed CAGB instead of PTCA in patients with a left main stem stenosis because cannulation of the narrowed left main stem was thought to be too risky. Although classification of the extent of CAD based on the number of disease vessels may not be precise, the stenosis of the left main stem can be regarded as a severe arteriosclerotic change.

The question still remains of whether screening for carotid disease is mandatory in patients with 1– or 2– coronary vessel disease or whether carotid screening should be limited to patients with severe coronary disease. The optimal strategy for the management of such patients should be established by a well-designed randomized trial.

We congratulate the authors for their careful observations, which describe the relationship between the prevalence of carotid disease and CAD.

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We appreciate the comments of Yanaka et al about our recent study may partially reflect our different definition of carotid disease candidates was significantly higher (2.7%) in patients who received 1- or 2-vessel disease, and severe CAD (defined as 3-vessel disease or left main stem disease with or without other vessel disease) was 5.30%, 13.5%, and 30.7%, respectively.

In a parallel way, they reported that the number of the CEA conclusions that carotid disease is significantly related to severe CAD. However, we followed a different approach to this matter. We studied patients who underwent coronary angiography for evaluation of chest pain suggestive of ischemic heart disease, and we also excluded subjects with a history of any cerebrovascular disease. In contrast, their team studied subjects who underwent CABG and/or CEA or PTCA. We found that the incidence of carotid disease in patients with 1-vessel disease, 2-vessel disease, and severe CAD (defined as 3-vessel disease or left main stem disease with or without other vessel disease) was 5.30%, 13.5%, and 30.7%, respectively.

In a parallel way, they reported that the number of the CEA candidates was significantly higher (2.7%) in patients who received CABG (those with left main stem disease or 3-vessel disease) than in patients who received PTCA (0.25%; those with 1- or 2-vessel disease).

In our study we may partially reflect our different definition of carotid disease (lumen diameter stenosis of $\geq 50\%$). They included either symptomatic or asymptomatic patients with a carotid stenosis $>70\%$ or symptomatic patients with a stenosis of $50\%$ to $69\%$ with ulcer formation. Furthermore, in our population the number of patients with significant carotid stenosis (80% to 100%) who were possible candidates for CEA was found to be 5%, a value very close to their results.

Regarding their comment about the evaluation of carotid stenosis, we must stress that we estimated the degree of carotid stenosis by ultrasonography and not by angiography.

Our primary purpose was to elucidate whether carotid disease can be a clinical useful marker for the presence of CAD and not to determine the optimal treatment strategy in each patient. Accordingly, we found that carotid disease has a high negative predictive value (92%) for the presence of severe CAD in our population. In addition, the knowledge of the left ventricular ejection fraction, which can be estimated by echocardiography, along with the carotid atherosclerotic status provide further useful information for the presence or absence of severe CAD.

According to our results, we think that patients with severe CAD may be evaluated for carotid artery stenosis. Whether screening for carotid disease is useful in patients without severe CAD, such as patients with 1- or 2-vessel disease, will be determined by a well-designed randomized study, as suggested by Yanaka et al.

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Response

We appreciate the comments of Yanaka et al about our recent article, which gave us the opportunity to clarify the relationship between carotid disease and CAD.

Their results confirm our conclusions that carotid disease is significantly related to severe CAD. However, we followed a different approach to this matter. We studied patients who underwent coronary angiography for evaluation of chest pain suggestive of ischemic heart disease, and we also excluded subjects with a history of any cerebrovascular disease. In contrast, their team studied subjects who underwent CABG and/or CEA or PTCA. We found that the incidence of carotid disease in patients with 1-vessel disease, 2-vessel disease, and severe CAD (defined as 3-vessel disease or left main stem disease with or without other vessel disease) was 5.30%, 13.5%, and 30.7%, respectively.

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According to our results, we think that patients with severe CAD may be evaluated for carotid artery stenosis. Whether screening for carotid disease is useful in patients without severe CAD, such as patients with 1- or 2-vessel disease, will be determined by a well-designed randomized study, as suggested by Yanaka et al.

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Plasma Homocyst(e)ine Concentrations in Cerebrovascular Disease

To the Editor:

We read with interest the article, "Plasma Homocyst(e)ine Concentration, but Not MTHFR Genotype, Is Associated With Variation in Carotid Plaque Area.

The authors showed that compared with reference control subjects, homocysteine concentrations were increased (13.7±0.73 versus 10.6±5.6 μmol/L) in 307 patients (148 women, 159 men) with stenotic artery disease (as indicated by carotid plaque area in 2D ultrasound). They observed a strong association between extent of carotid artery disease and homocysteine concentrations but not with the termolabile mutation (677TT) in the gene encoding the methylenetetrahydrofolate reductase (MTHFR). Thus, their observations are in accordance with earlier reports.

We would like to comment on 2 points. First, recently we differenially investigated homocysteine concentrations in 144 patients (55 females, 89 males) with cerebral large-vessel disease (plaques or stenoses of the extracranial arteries and/or increase of cerebral blood flow velocity of $\geq 140$ cm/s in the large intracranial vessels) and small-vessel disease (ie, subcortical vascular encephalopathy).

The latter disease is clinically characterized by stepwise progressive mneic deficits and cognitive decline, typical gait disorders, and incontinence and neuroradiologically by diffuse periventricular white matter abnormalities and central lacunar lesions.

We observed that patients with this cerebral macroangiopathy exhibited surprisingly high concentrations of homocysteine (18.2±8.5 μmol/L).

Logistic regression analysis revealed that hyperhomocysteinemia is an independent risk factor for subcortical vascular encephalopathy (OR=5.7).

Surprisingly, we did not find significantly increased levels in patients with cerebral large-vessel disease, after the exclusion of patients with cerebral macroangiopathy.

Therefore, elevated homocysteine concentrations in carotid artery disease observed in the study of Spence et al and in earlier studies could be, in part, due to the presence of some patients with undiagnosed cerebral microangiopathy in their study populations, because microangiopathy and macroangiopathy often occur together.

Without exclusion of cerebral macroangiopathy by exact neurologi-

cal, neuropsychological, and neuroradiological examinations, it is difficult to attribute elevated homocysteine concentration to cerebral large-vessel disease.

Second, regarding possible causes of homocysteinemia, Spence et al could not find an association between carotid artery disease and MTHFR genotype. They observed that the majority of subjects with elevated plasma homocysteine concentrations did not have the MTHFR 677TT genotype and suggested further causes contributing to hyperhomocysteinemia.

This is in accordance with our observation of decreased plasma concentrations of vitamins $B_6$ (9.9±5.2 versus 15.2±14.1 μg/L) and $B_12$ (371.2±226.9 versus 451.3±270.0 ng/L) in cerebral microangiopathy and a significant correlation between concentrations of vitamin $B_12$ ($r=-0.24, P<0.05$) and folate ($r=0.29, P=0.01$). These associations suggest—although they do not demonstrate—that hypovitaminosis rather than genetical factors could have contributed to hyperhomocysteinemia in cerebrovascular disease.

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Response

Dr Fassbender and colleagues correctly suggest that plasma homocyst(e)ine should be studied for its association with other well-characterized cerebrovascular phenotypes, such as cerebral microangiopathy. However, their assertion that it is “difficult” to associate an elevated plasma homocysteine concentration with cerebral large-vessel disease without determining cerebral microangiopathy is incongruous with our results. Our data strongly suggested that carotid arterial changes were associated with elevated plasma homocyst(e)ine. Whether or not some of our study subjects might also have had cerebral microangiopathy is immaterial to the observed association of homocyst(e)ine with carotid plaque area. Because we could measure carotid plaque area with a high degree of accuracy, we used carotid plaque area as a dependent quantitative trait in a linear regression model to determine the sources of its variation. This analysis led us to conclude that plasma homocyst(e)ine was a significant determinant of carotid plaque area whereas MTHFR genotypes were not. Some subjects might have been ascertained because their presenting symptoms had resulted from cerebral microangiopathy, however, our subsequent phenotypic analysis indicated that almost 80% of study subjects had detectable carotid plaque area. We were not interested in, nor can we now exclude, a possible association between plasma homocyst(e)ine and unmeasured cerebral microangiopathy in some subjects. However, the existence of such a possibility does not affect our interpretation that plasma homocyst(e)ine is significantly associated with variation in carotid plaque area.

We also agree that an inadequate intake of vitamins is probably an important confounder to hyperhomocysteinemia. Most published studies to date have little or no information on the vitamin status of the study subjects. This data gap is notable, because gene–environment interactions certainly play a role in homocyst(e)ine metabolism. Future studies will need to carefully document dietary intake of vitamins and also possibly assay from blood and other tissues the concentrations of those vitamins that play a role in homocysteine metabolism.

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Antiplatelet Therapy in Acute Cerebral Ischaemia

To the Editor:

The review by Bednar and Gross1 of antiplatelet therapy in acute cerebral ischaemia mistakenly suggested that “only 1 study, the Multicentre Acute Stroke Trial–Italy (MAST-I), entered patients within 6 hours of the ictus.” The International Stroke Trial (IST) and the Chinese Acute Stroke Trial (CAST) randomized a total of 5629 patients within the first 6 hours.1,2 finding good evidence of benefit.2–4 Thus, antiplatelet therapy has already been evaluated in the acute phase of cerebral ischemia, and indeed, the number of patients randomized in aspirin trials within 6 hours is approximately the same as those randomized in all the trials of thrombolytic therapy for acute ischemic stroke.3 We disagree with Bednar and Gross that “larger studies are needed to confirm these findings.”

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Response

We appreciate the interest by Drs Sandercocck, Warlow, Dennis, and Chen in our review.1 In this review, we have correctly stated that there were “two large-scale, randomized, prospective clinical trials, the International Stroke Trial (IST)2 and the Chinese Acute Stroke Trial (CAST) … in which aspirin … was administered within 48 hours of the ischemic event.” Our review also correctly stated that MAST-Italy3 is the only randomized clinical study to administer aspirin within 6 hours of the ictus. These statements certainly do not exclude the fact that a small subset of patients from IST and CAST were entered from hours 0 to 6.

We find it very surprising that Dr Sandercocck and coauthors would categorically state that the combined randomization of 5629 patients to aspirin or placebo alone or combined in the IST and CAST trials demonstrates “good evidence of benefit.” In fact, there is absolutely no statistical support for this contention. Moreover, when one analyzes patients from both IST and CAST who received aspirin in the acute period (0 to 3 hours), the results are very different: one finds that patients receiving aspirin in the IST trial derived absolutely no benefit from aspirin, whereas this subpopulation of patients received the greatest benefit in the CAST trial!

Drs Sandercocck, Warlow, Dennis, and Chen further note that they “disagree . . . that larger studies are needed to confirm” the benefit of aspirin within 6 hours of stroke. We strongly disagree. Indeed, their statement appears to be completely contradictory to the statement by Dr Sandercocck in the IST study. In that study, Dr Sandercocck and coauthors noted that “the combination of low-dose subcutaneous heparin plus aspirin looked as if it might be better in the short term than aspirin alone. However, these analyses were based on a relatively small number of patients (6,000) and . . . this hypothesis needs to be tested by a further trial.”2

Thus, although combination aspirin plus low-dose heparin showed even greater early benefit and randomized even more patients than seen for acute (0 to 6 hours) aspirin therapy, Drs Sandercocck, Warlow, Dennis, and Chen disagree that there is a need for larger studies to confirm the findings seen with aspirin, yet contend that the
“small number” of patients studied with low-dose heparin warrants a further trial!

It would appear that there is a lack of consistency in the application of study design and robust statistical analysis by Drs Sandercock and coauthors. It is our hope that future studies will continue to study the role of aspirin as a potential strategy for both acute (0 to 6 hours) and delayed stroke therapy to more clearly define the benefit.

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Heart Rate Variability Following Ischemic Stroke

To the Editor:

We have read with interest the article by Korpelainen and colleagues1 regarding heart rate variability (HRV) in patients with ischemic stroke. The authors report impaired beat-to-beat HRV as measured by traditional spectral components and impaired long-term continuous HRV as measured by SD2 PoinCare plots in patients with hemispheric and medullary brain stem but not pontine brain stem stroke compared with control subjects. These findings raise a number of important questions regarding cardiovascular autonomic control after acute ischemic stroke.

First, previous work from our department has not identified impairment of HRV, whether assessed by time domain2 or frequency domain3 techniques, in keeping with the authors’ own findings with regard to SD1 Poincare, complexity, and fractal measures of HRV.1 Furthermore, absolute levels and variability of blood pressure (BP) are an important consequence of abnormalities of cardiovascular autonomic control after acute ischemic stroke.1–5 An Update in Human Studies with Larger Numbers of Stroke Patients.

Second, if impaired HRV is a reproducible finding after acute ischemic stroke, it would be important to speculate on the underlying mechanism. One presumes that it reflects sympathetic hyperactivity, though the low-frequency power is reported as significantly lower in those groups with impaired HRV.1 Of course, this measure has considerable variability and, it would be important to compare either the normalized low-frequency power or the low-frequency/high-frequency ratio.

Third, it is interesting to note the authors’ findings with respect to right- and left-hemisphere strokes. This is an important observation if sympathetic hyperactivity is the only explanation for impaired HRV, given the reported right hemisphere dominance for sympathetic effects.4 Furthermore, the authors report differences between medullary and pontine brain stem strokes, in contrast to their own previous observation that patients with both medullary and pontine infarcts had a more pronounced suppression of HR responses to parasympathetic stimuli than hemisphere strokes.5

Finally, frequency domain analysis of cardiovascular parameters can be difficult in poststroke patients, particularly over prolonged recording periods because of the well-recognized increased ventricular ectopy rate.4 It is unclear from the article how the authors accepted the data for subsequent analysis on the basis of ectopy and spike rates, which is clearly an important factor in the subsequent interpretation of the findings.

It is clear that cardiovascular autonomic dysfunction is an important aspect of acute stroke. However, further studies should address its clinical relevance in terms of prognosis and in the dilemma surrounding the therapeutic manipulation of BP in acute stroke.

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Response

We thank Drs Robinson, Panerai, and Potter for their interest in our recent article concerning abnormalities of HR regulation following ischemic stroke.1 Comments of this research group with known interest in cardiovascular autonomic regulation are valuable.

First, they ask about absolute levels and variability of BP of our patients. We agree that stroke-related abnormalities of BP are interesting and clinically important, reflecting dysfunction of the cardiovascular autonomic regulatory system. During the study, however, no suitable equipment was available for ambulatory BP measurements in our laboratory. Therefore, data about BP variability could not be presented.

The pathomechanisms of impaired HR variability are still unclear and speculative. Our view is that its etiology is multifactorial, including at least neuronal as well as hormonal components. We have also calculated the low-frequency/high-frequency power ratio and presented the data in one of our previous works.2 This ratio is not generally accepted, however, and we decided to exclude it from the last study.

A lot of clinical and experimental data are available for cortical asymmetry in the regulation of HR and other cardiovascular functions. Although our research group has failed to show such an asymmetry using measurements of HR and BP, there has been a trend toward more pronounced abnormalities in patients with right-sided strokes.1,4 Further experimental and human studies with larger numbers of stroke patients that we have presented may solve this problem.

We are all well aware of the technical problems related to long-term ambulatory ECG recordings. All the artifacts and ectopic beats were first deleted automatically and then manually with our customized software. All the segments (8000 R-R intervals) with less than 15% sinus beats were excluded from the final analysis.

We agree that further studies should focus on the clinical relevance of HR and BP variability in order to create new therapeutic strategies.

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Response

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The Natural History of CADASIL

To the Editor:

I read with much interest the article by Desmond et al1 about the natural history of CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy). Similar work I conducted previously was published 1 year ago2 and unfortunately ignored by the authors. The methods we used were similar: making a review of the literature on MEDLINE and collecting documented cases on pathological or genetic bases. A preliminary communication of this work was presented at the 8th meeting of the European Neurological Society held in Nice in June 1998.3 During the same session, Dichgans et al presented the work they later published,4 which was not included in our own review submitted in 1997. Similarly, the cohort described by Chabriat et al5 was not included in our work. Our own data included all the references listed by Desmond et al up to References 27 to 36, which appeared later. A few documented pathological cases, either familial or apparently sporadic, were included in our review and not in that of Desmond et al.

Our data, including 134 documented cases, showed similar results, with a mean age at onset of 40.3 ± 13.8 years. Major initial symptoms were stroke, transient ischemic attacks, or stroke-like episodes in 36.5% of the cases and migraine in 34.6%, with a significant difference of age at onset (24.8 ± 11.6 years versus 43.9 ± 9.8 years for stroke and 47.7 ± 8.7 years for transient ischemic attacks). Other initial symptoms, including depression, dementia, and other psychiatric or neurological presentations, were much less frequent (each <10%). We found similar data about the duration of the disease (mean 13.6 ± 10.7 years) and age at death (56.7 ± 10.9 years), much lower than those published in the cohorts of Chabriat et al6 and Dichgans et al5 (21.5 and 23.3 years for mean duration of the disease and 64.3 and 61 years for mean age at death, respectively). It was suggested in our study that stroke or transient ischemic attacks were a little less frequent (70%) than as published in the French and German cohorts (84% and 87%, respectively), a result confirmed (67%) by Desmond et al.1 Additional data were collected from our review about causes of death, showing stroke in 26 documented cases to be the most frequent cause (32%), followed by bronchopneumonia and other decubitus complications. One of the diagnostic criteria of CADASIL is the absence of vascular risk factors related to the pathology, particularly hypertension. In the 79 cases screened in the literature for such factors, we showed that 11 patients (14%) had a mild hypertension. Signs or symptoms of any other vascular disease were unusual, but myocardial infarction occurring at a young age, sometimes antedating the neurological signs, was documented in 7.5%.

From our review, we suggested diagnostic criteria for probable and possible forms of CADASIL in order to give to clinicians guidelines for identification of the patients on clinical and imaging bases for further genetic analysis. Alternative etiologies were presented, with the diagnoses of multiple sclerosis and vascular dementia being the most frequently encountered. We conclude that the work of Desmond et al, although subject to the same methodological weakness as ours, was not unique, as they assumed, but instead a valuable confirmation of previously published data. However, in the context of expansion of the spectrum of genetically determined cerebral arteriopathies, the confirmative data of the natural history of CADASIL by 2 independent studies looks worthwhile.

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Response

We regret that we failed to acknowledge the related study of Dr Davous1 in our article,2 but we did not know of its existence because the journal in which it was published is not referenced in MEDLINE. In addition, that journal is not a part of the otherwise extensive holdings of the Health Sciences Library of Columbia University, and his article was not referenced in any of the previous publications on CADASIL that we reviewed. Finally, it should be noted that the abstract cited by Dr Davous,3 which was published after our initial presentation of our findings at the 50th annual meeting of the American Academy of Neurology in 1998,4 summarized his important proposal of operationalized criteria for the diagnosis of CADASIL, but made no reference to any formal pooled analysis of previously published cases relevant to the clinical characteristics and natural history of that disorder. We are pleased to recognize the inconsistencies between the findings of our 2 studies, however, and it is our hope that future collaborative efforts crossing national boundaries will help us to gain an increased understanding of the features of CADASIL and move toward the development of an effective therapy.

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Small but Quantifiable Patient Preference for MRA Versus Catheter Angiography

To the Editor:

In our previous article1 we used decision analysis to examine the cost-effectiveness of various test strategies for both screening and diagnosing carotid artery disease. While our conclusions for screening were contingent on several factors (ie, prevalence of significant stenosis, benefits and risk of surgery, and quality of life with stroke),
for presurgical patients the best test strategy was clear. 3D time-of-flight (TOF) magnetic resonance angiography (MRA) is more cost-effective than catheter angiography (CA), as long as the MRA sensitivity and specificity are at least 86% and 90%, respectively. Missing from this analysis, however, was data on patient preference for CA or MRA. Swan and Langlotz point out that a patient’s attitude about an intervention is an essential component in cost-effectiveness models. Therefore, we undertook a patient preference study of CA versus MRA in presurgical patients and report our results here.

Sixty-nine patients were recruited prospectively and randomized to first undergo either an MRA or CA examination. The second study was performed on the same day and followed by a patient questionnaire. The questionnaire was modeled after one developed by Mushlin et al in a study of multiple sclerosis patients. We first asked the patients which modality they would prefer if one had to be repeated. We then asked them to give the number of days with a severe headache that they would be willing to endure to avoid the less-desirable modality. Finally, the patient used a visual analog scale (VAS) to locate a “severe headache” on a scale from 0 (representing perfect health) to 10 (representing death). From these data we estimated the number of quality-adjusted life-years (QALYs) lost when a patient undergoes the less-desirable modality. QALYs were estimated as the product of the number of days (converted into years) of a severe headache and the severity factor from the VAS divided by 10.

For the 69 patients who gave consent and were randomized, there were technical problems on 3 MRA examinations, and 4 patients refused the MRA. These 4 patients did not appear to be claustrophobic, but rather refused MRA because it was purely for research purposes. Sixty-two patients successfully underwent both examinations and completed the questionnaire. Ten patients (16%) indicated no preference for MRA or CA. Of the remaining 52 patients, there was a statistically significant preference for MRA ($P < 0.0001$): 46 (88%) preferred MRA over CA, and 6 (12%) preferred CA over MRA. There was no difference in average age, gender, or symptomology between those who preferred MRA versus those who preferred CA.

Five patients had complications on CA (2 had small hematomas, 1 a moderate hematoma with numbness on the right upper extremity, 1 a pseudoaneurysm, and 1 supraventricular tachycardia/chest pain that required overnight observation). Four of these patients preferred MRA; 1 patient with a small hematoma preferred CA. Although most patients preferred MRA over CA, the disutility of CA was small. The average QALYs that a patient was willing to give up to avoid a CA was 0.0024 (95% CI 0.0014 – 0.0034), equivalent to <1 quality-adjusted day. The minimum was −0.0041 (1.5 days willing to be given up to avoid an MRA) and maximum 0.0201 (1 week to avoid a CA). When we factor into our decision analysis model an average reduction in QALYs of 0.0024 when a CA is performed instead of MRA, there is no effect on our overall conclusions.

3D-TOF-MRA is a cost-effective alternative to CA for presurgical evaluation because of its good accuracy, noninvasiveness, and modest price. It is the modality preferred by the majority of patients, though the magnitude of the preference is small.
Small but Quantifiable Patient Preference for MRA Versus Catheter Angiography
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