Underuse of Antithrombotic Therapy in Stroke Patients With Chronic Atrial Fibrillation

To the Editor:
The original contribution of Gage et al1 on the underuse of antithrombotic therapy in Medicare beneficiaries with chronic atrial fibrillation was well received by generalists. However, it still necessary, as a preliminary action, to emphasize to generalists that in a patient with NVAF any thrombotic therapy is better than nothing.

Data from our stroke register further emphasize this problem. In the Emergency Department of Fatebenefratelli Hospital (a central hospital in Milan, Italy), we are following an observational study on acute cerebrovascular accidents. Over approximately 20 months, we have recorded 1009 consecutive patients (884 with ischemic stroke, 88% 125 hemorrhagic, 12%). In patients with ischemic stroke or transient ischemic attack (TIA) and presence of chronic nonvalvular atrial fibrillation (NVAF), we recorded the domiciliary therapy and the presence of additional stroke risk factors: age $>$ 75 years, previous ischemic stroke or TIA, previous diagnosis of arterial hypertension, chronic congestive heart failure, chronic ischemic heart disease, or type I or II diabetes. One hundred twenty-two of 884 ischemic patients (13.8%) had NVAF. Only 49 patients (40.2%) were taking antithrombotic therapy; aspirin (n = 31, 25.4%), ticlopidine (n = 6, 4.9%), indobufen (n = 4, 3.3%), and oral anticoagulant (n = 8, 6.6%); 73 patients (59.8%) were taking no prophylactic antithrombotic therapy. Associated risk factors were present in 96% of the patients: 21 patients (7 with prophylactic therapy and 14 not treated, 17.2%) had 1 risk factor, 39 patients (13 treated and 26 not treated, 31.9%) had 2 risk factors, and 57 patients (28 treated and 29 not treated) had $\geq$ 3 risk factors. The individual risk factors are presented in the Table.

The importance of atrial fibrillation as a risk factor for stroke is well known. It has been demonstrated that the majority of strokes in patients with atrial fibrillation can be prevented by prophylactic antithrombotic therapy. Moreover, the presence of additional cardiovascular risk factors is an indication for antithrombotic therapy. [1, 2, 3, 4].

In our study we have shown that patients with NVAF and other stroke risk factors still do not receive a good treatment. Prophylactic antithrombotic therapy is underutilized in NVAF patients, and despite the recent published guidelines and recommendations, [5] many physicians remain hesitant to prescribe antithrombotic therapy. The actual debate may be whether aspirin or anticoagulation is the treatment of choice; [6] our data show, however, that it is still necessary, as a preliminary action, to emphasize to generalists that in a patient with NVAF any antithrombotic therapy is better than nothing.

Antonio Villa, MD
Ambrogio Bacchetta, MD
Ezio Omboni, MD

<table>
<thead>
<tr>
<th>Individual Risk Factors in Patients With Ischemic Cerebrovascular Disease and Nonvalvular Atrial Fibrillation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age $&gt;$ 75 y</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>With prophylactic therapy, n</td>
</tr>
<tr>
<td>No prophylactic therapy, n</td>
</tr>
<tr>
<td>Total, n (%)</td>
</tr>
</tbody>
</table>

PIS indicates previous ischemic stroke or TIA; HYP, previous diagnosis of arterial hypertension; CHF, chronic congestive heart failure; IHD, chronic ischemic heart disease; and DIA, type 1 or 2 diabetes.

Response
By combining our findings with those of Villa et al and others, [2] we conclude that approximately one third of the atrial fibrillation population, especially the very elderly, receives no antithrombotic therapy. We found that the underuse of antithrombotic therapy was associated with an increase in the rate of death and ischemic events (stroke, TIA, or myocardial infarction). The effectiveness of warfarin and aspirin that we observed in the Medicare population (24% and 5%, respectively) was considerably lower than the reductions reported from the clinical trials, but the absolute risk reductions associated with these therapies were clinically significant: Approximately 1 death or hospitalization for an ischemic event was averted for each 11 patient-years of warfarin therapy and for each 54 patient-years of aspirin therapy.

As Villa et al highlight, patients with atrial fibrillation often have additional comorbid conditions that place them at high risk of stroke if they receive no antithrombotic therapy. Patients who have 1 or more of these stroke risk factors should be offered therapy with warfarin (or other oral anticoagulant) if they have no contraindication to its use, because anticoagulation is likely to prolong their quality-adjusted survival more than antiplatelet therapy would. [3] Medicare-aged patients who have atrial fibrillation but who lack additional stroke risk factors can be treated with either warfarin or aspirin, depending on their risk of hemorrhage and personal preferences. Further efforts are needed to increase the appropriate use of antithrombotic therapy in the atrial fibrillation population.

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The relative risk in case fatality for treatment in an SU of this collective was a modest 0.91. In contrast to the findings reported by Jørgensen et al.,1 outcome of patients with more severe strokes (impaired consciousness at admission) did not show a significant difference in any of 15 outcome measurements, whether treated in an SU or a GW. Furthermore, 27-day case fatality of all patients treated in GWs was 17% (B. Stegmayr, MD, PhD, written communication, 2000), which is considerably lower than the rate of 23% reported in the SU in Copenhagen some years earlier.

Preliminary unpublished results (J. Slany, MD, 2000) of 300 totally unselected stroke patients of an ongoing Austrian stroke registry conducted in general medical wards show an inhospital mortality of 17%, which is well in accordance with the Swedish data.

It is reassuring to see that improvements in the management of acute stroke seem to have leaked out of the boundaries of SUs and to have caught hold also in general medical and neurological wards. Thus, the results and conclusions of Jørgensen and coworkers seem to reflect past glories rather than present-day facts.

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Jørgen H. Jørgensen, Lars Peter Kammersgaard, Hirofumi Nakayama, MD, PhD

Letters to the Editor

To the Editor:

In the February issue of Stroke, Jørgensen and coworkers1 report that treatment of stroke patients in a stroke unit (SU) compared with a general ward (GW) offers benefits on the order of odds ratios of 0.17 to 0.66. Consistently, their conclusion is that all patients with acute stroke should be treated in a dedicated SU. Moreover, their findings raise serious considerations of whether further treatment of stroke patients in GWs is ethically justifiable.

In an earlier publication of the same investigation,2 Jørgensen and coworkers described an inhospital mortality of 23% in patients treated in the SU, which was 21% lower than that in patients treated in a GW. That is in fair agreement with the findings of the meta-analysis presented by the SU Trialists,3 which depended on studies predominantly performed in the 1980s.

Logistic multiple regression analysis blew up this benefit to an odds ratio for poor outcome of 0.50 for the total stroke population and 0.17 for patients with severe stroke treated in the SU. However, these figures depend heavily on the reliability of comorbidity assessment. Why should the comorbidity of patients treated in Bispebjerg, where the SU was located, have been much greater than in Frederiksberg? The only hint given is the lower income of people in Bispebjerg. However, very little information is provided: how and by whom comorbidity was assessed and whether any control of these data was performed. Evaluation of previous myocardial infarctions and ischemic heart disease may be difficult in stroke patients. Diagnosis of hypertension and possibly also of diabetes depends on corresponding treatment. Especially in hypertension, decision to treat blood pressure may have changed to lower levels between 1989 to 1990, when GW patients were evaluated, and 1991 to 1993, when SU patients were studied.

Furthermore, neither treatment in the SU nor in the GW is detailed. The only information provided about the GW is that that traditional treatment was given. Both Bispebjerg and Frederiksberg hospitals reportedly possessed all major medical and surgical specialities, but again we are left in uncertainty of whether that included a neurosurgery department that might provide life-saving services for at least a small portion of patients with severe strokes.

The main question, however, is whether the findings reported by Jørgensen et al.1 still hold true, since at least those for the GW date back for more than 10 years. As pointed out by the authors1 and others,3,4,5 the mainstay of SU treatment appears to be team approach, earlier and more intensive mobilization and rehabilitation of patients, and prompt and determined correction of fever, infections, hyperglycemia, and other medical problems. It is the undisputable merit of SUs to have elaborated these treatment principles, but they may be easily adopted by general wards. That this has happened is suggested by more recent findings from Sweden and from Austria. A multicenter observational study6 of over 10 000 stroke patients admitted to Swedish hospitals in 1996 shows mortality and other outcome benefits of SU treatment only for patients who were fully conscious on admission.

Jörgen Jørgensen, Lars Peter Kammersgaard, Hirofumi Nakayama, MD, PhD


Response

Jörgen Jørgensen questions the validity of the assessment of comorbidity in our study. Comorbidity was assessed by the same person (the principal investigator of the study, Henrik Stig Jørgensen) in both study groups. Definitions of comorbidities were identical in the 2 study populations. There is, therefore, no reason to believe that the difference found in comorbidity between the 2 study groups is an artifact. The higher comorbidity in patients treated on the stroke unit probably reflects that the catchment area for the stroke unit is a working-class district, whereas the catchment area for the hospital offering treatment on general wards is an upper class district.

Throughout the 80s and 90s, treatment and rehabilitation on dedicated stroke units have consistently been proved superior to treatment on general wards.1–3 This is true even in completely unselected patients with stroke.4–6 Slany argues that this may no longer be true. It would be interesting to see scientific proof for this statement.

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Hirofumi Nakayama, MD, PhD

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Low Incidence of Stroke in the Chiquitanos Tribe in the Bolivian Lowlands

To the Editor:

We read with great interest the article on stroke prevalence in rural Bolivia by Nicoletti et al.1 We greatly appreciate their study in this remote rural area in the Cordillera province of the Santa Cruz Department. The living conditions, the difficulties in primary health care, and the impact of stroke on this population are meticulously described. The results of the 2-phase study show a crude prevalence of first stroke of 174/100 000 in this area. In men the prevalence was more than twice as high. The authors conclude that the crude prevalence is lower than rates from developed countries and that it is similar to those reported in studies carried out in rural developing countries.1

Using the letter file of this journal, we would like to comment on some aspects. First, we feel that the description of the calculation of the prevalence is a little unclear. It is not clear enough to us exactly how the adjustment of the crude incidence rate for area and clustering was performed. We cannot follow in detail, for instance, how from 1 case in a observed population of 471 individuals a crude prevalence rate of 295 can be calculated. In addition, we suggest that it might have been useful to give the crude annual incidence figures alongside the prevalence data. This would make it easier, despite the valid difficulties reported by the authors, to draw comparisons with other studies in developed countries.

The crude annual incidence rate may be more useful in healthcare planning also, such as when assessing the need for acute stroke care. For instance, a recently published study in our area—Erlangen, in southern Germany—showed a crude annual incidence of first-ever stroke of 174/100 000 and was extremely helpful for planning and establishing our stroke unit.2 Second, the result in the study of Nicoletti et al that stroke was more than twice as prevalent in men than women is very interesting. In the Erlangen study mentioned above, the age-adjusted annual incidence rates were only slightly higher for men than women. It would be interesting to see the prevalence rate adjusted to the WHO standard, not only for both sexes but also separated for men and women.

Third, we would like to draw attention to a neuroepidemiological study3 with some similarities to that of Nicoletti et al,1 which we performed in another rural Bolivian region: the area of the indigenous tribe of the Chiquitanos. Some aspects of this study are interesting in comparison to the work of Nicoletti et al. The Chiquitano tribe lives in the southern Amazon region in Bolivia, in the northeast part of Santa Cruz Department, remote from larger towns (Figure). Its population has an age and sex distribution similar to that of the study population.4 Our study covered a total population of 5652 individuals in 1995. The acute care for the whole region is provided by 1 hospital, including outpatient department (“consultorio”). Ambulatory care in the area is guaranteed by 7 specially trained nurses (“sanitarios”), who screen for neurological disease and refer the patient to the hospital if neurological disorder is suspected. If a patient dies before seen by professionals, the study general practitioner reviews the patient’s history to assess probable diagnosis. Because the hospital is supported by the Catholic church and Erlangen’s Medical Association for Bolivia, consultation and inpatient treatment are very cheap and available to everyone. Therefore, the rate of stroke patients not seen by professionals is assumed to be low. Over a 1-year period (April 1995 through March 1996), a total of 1514 individuals consulted the hospital staff or ambulatory care. One hundred thirty-nine patients suffered from neurological diseases (Table). A first-ever stroke was possibly diagnosed in 2 patients (2 women, aged 71 and 62 years). Therefore, a crude annual incidence of 35/100 000 could be estimated. In contrast, cervical and lumbosacral pain syndromes were the most common neurological problems and were caused by sleeping in hammocks and by hard agricultural labor. Tropical pyomyositis was also very frequent and was the most common muscle disease. Epilepsy was found in 11 patients and extrapyramidal syndromes in 2. Although direct comparison with the study of Nicoletti et al is difficult, our findings seem to support their contention that stroke is uncommon in the indigenous population in Bolivia. The authors suggest in their conclusion that the low incidence of stroke among the inhabitants of Cordillera might be attributed to the age distribution, difficulties in reaching a hospital, and ethnic factors. Our study, interestingly, had a similar age distribution but good access to health care and a higher ethnic population. In our study, nearly all individuals (98%) are indigenous, whereas in the Nicoletti study only 30% are indigenous. This might indicate that ethnicity is perhaps the more important factor in the low stroke occurrence in rural and indigenous Bolivia.

Fourth, we agree with Nicoletti et al that neuroepidemiological studies are necessary for the organization and planning of health care in underprivileged areas. The department of Santa Cruz in Bolivia is particularly strongly marked by immigration from the

Neurological Diseases of the Chiquitano Tribe Referring to 1514 Consultations at the Local Health Center Over a 1-Year Period*

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Number and Severity†</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS diseases</td>
<td></td>
</tr>
<tr>
<td>Epilepsy</td>
<td>11 (11 moderate severe)</td>
</tr>
<tr>
<td>Migraine</td>
<td>8 (8 moderate severe)</td>
</tr>
<tr>
<td>Tension-type headache</td>
<td>9 (9 slightly impaired)</td>
</tr>
<tr>
<td>Stroke</td>
<td>2 (2 severe)</td>
</tr>
<tr>
<td>Meningitis, encephalitis</td>
<td>2 (2 severe)</td>
</tr>
<tr>
<td>Movement disorder</td>
<td>2 (1 severe, 1 moderate severe)</td>
</tr>
</tbody>
</table>

Cranial nerve diseases

Idiopathic facial nerve palsy     | 2 (2 moderate severe) |
Hemifacial spasm                  | 1 (1 moderate severe) |
Syndrome of skull base lesion     | 1 (1 severe)         |

Spinal disorders

Syndrome of cervical disc disease | 25 (14 slightly impaired, 11 moderate severe) |
Syndrome of lumbar disc disease   | 45 (21 slightly impaired, 24 moderate severe) |
Postpolio syndrome               | 1 (moderate severe) |

Diseases of the peripheral nerves

Intercostal neuralgia             | 4 (4 moderate severe) |
Plexopathy                        | 3 (3 moderate severe) |
Carpal tunnel syndrome            | 1 (1 slightly impaired) |
Varicella zoster neuropathy       | 2 (2 moderate severe) |
Polyneuropathy due to pellagra    | 1 (1 moderate severe) |

Myopathies

Tropical myositis                 | 18 (14 moderate severe; 4 severe) |

Inborn abnormalities              |
Spina bifida                      | 1 (1 moderate severe) |

Total                             | 139 |

*Population of 5652 individuals.
†Severity was classified as slightly impaired (capable of performing daily work), moderate severe (not capable of working, but rest at home), and severe (hospitalization).

highlands. The indigenous population of the Altiplano—where subsistence is increasingly perilous—are migrating to the Bolivian lowlands to build new lives. A zone with great problems is the “Brecha Casarabe” area near the capital Santa Cruz, where new settlers daily join the 25 000 population and where until now no sufficient infrastructure, including health care, has been in place. Fifth, in addition, the phenomenon of “transition epidemiologica” should be considered. This refers to the new health problems associated with increasing life expectancy and urbanization: the treatment of older and chronically diseased people, the rehabilitation of stroke-handicapped patients, and the care of patients with socially caused diseases (AIDS, drug addiction, consequences of violence).4,5

We would like to conclude that the issues of neurological morbidity in underprivileged areas are an important and underresearched field and that the work by Nicoletti et al is an important step with regard to stroke epidemiology in this area. At our university we have reacted to this challenge by introducing the field of “Tropical Neurology and Neurology of the Underprivileged” into our neurology training program, by preparing teaching posters at our yearly German neurological meeting, and by directly supporting aid organizations in underprivileged areas.

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Hospital San Xavier
San Xavier


Response

First and foremost, we very much appreciated the interest and the comments of Dr Heckmann and colleagues, and we enjoyed reading data on neurological patients observed in hospitals and ambulatory facilities in another area of the Santa Cruz Department.

Concerning the question raised by Heckmann and colleagues about the calculation of the prevalence, as reported in our survey: to select the sample of about 10 000 inhabitants from the 10 areas of the Cordillera Province, a cluster sampling method was used, with the 10 areas acting as strata. Within each stratum, communities were selected at random, and each constituted 1 cluster. The complex sampling methods, as random cluster sampling, result in additional variability in the sample estimate. The effect of the design on the variability of a sample estimate is measured by the ratio of the variance of estimates from the design used to the variance that could come from the same sample size if simple random sampling were used; it is called “design effect.” To account for the additional variability at the different stages of complex designs, the sample size and sample estimates were adjusted by the design effect. The design effect for each estimate is reported in the Table. As previously reported, our estimates were calculated by using the csample module of the EPI-INFO 6.

Our survey was designed and carried out to determine the point prevalence of the major neurological diseases (epilepsy, stroke, peripheral neuropathy, parkinsonism). Therefore, it is not possible to provide incidence data. As stressed in our article, because of the lack of census data, death certificates, and hospital registers, the way to assess the true incidence in this rural population should be a follow-up of the population for a long period of time, implying high cost and organization problems.
Age- and Sex-Specific Prevalence of Stroke

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Population</th>
<th>Cases</th>
<th>Cases/100,000</th>
<th>DE</th>
<th>Population</th>
<th>Cases</th>
<th>Cases/100,000</th>
<th>DE</th>
<th>Population</th>
<th>Cases</th>
<th>Cases/100,000</th>
<th>DE</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–34</td>
<td>3902</td>
<td>0</td>
<td>...</td>
<td></td>
<td>3796</td>
<td>2</td>
<td>63</td>
<td>1.2</td>
<td>7698</td>
<td>2</td>
<td>31</td>
<td>1.2</td>
<td>0–74</td>
</tr>
<tr>
<td>35–44</td>
<td>471</td>
<td>1</td>
<td>295</td>
<td>1.4</td>
<td>445</td>
<td>0</td>
<td>...</td>
<td>...</td>
<td>916</td>
<td>1</td>
<td>151</td>
<td>1.4</td>
<td>0–444</td>
</tr>
<tr>
<td>45–54</td>
<td>323</td>
<td>1</td>
<td>165</td>
<td>0.5</td>
<td>318</td>
<td>2</td>
<td>796</td>
<td>1.4</td>
<td>641</td>
<td>3</td>
<td>472</td>
<td>1.2</td>
<td>0–1057</td>
</tr>
<tr>
<td>55–64</td>
<td>206</td>
<td>5</td>
<td>2419</td>
<td>0.8</td>
<td>198</td>
<td>0</td>
<td>...</td>
<td>...</td>
<td>404</td>
<td>5</td>
<td>1216</td>
<td>0.8</td>
<td>240–2192</td>
</tr>
<tr>
<td>≥65</td>
<td>133</td>
<td>5</td>
<td>4419</td>
<td>1.2</td>
<td>163</td>
<td>0</td>
<td>...</td>
<td>...</td>
<td>296</td>
<td>5</td>
<td>1933</td>
<td>1.2</td>
<td>230–3635</td>
</tr>
<tr>
<td>Total</td>
<td>5035</td>
<td>12</td>
<td>247</td>
<td>0.91</td>
<td>4920</td>
<td>4</td>
<td>99</td>
<td>0.86</td>
<td>9955</td>
<td>16</td>
<td>174</td>
<td>0.95</td>
<td>94–254</td>
</tr>
</tbody>
</table>

95% CI: 322*
119–374 16–183

DE indicates design effect.

*Age-adjusted to the world standard population.

Regarding the hypothesis of a possible effect of the ethnic group on the low prevalence rate, other types of analytic epidemiological design are necessary to test it, but at any rate we believe that the most important factors to explain our low prevalence rates could be case-fatality rates, low hospitalization rates, and the age structure of our population.

Concerning the higher prevalence found in men, as reported in our article, it is in agreement with data reported in literature.

We enjoyed reading the study by Roh et al., in which MRI diffusion-weighted imaging (DWI) within 4 days of acute stroke showed that multiple noncontiguous lesions were seen in nearly 30% of their cases. In addition, they reported a difference in the presumed embolic pathophysiology on the basis of the involved vascular territories, suggesting that topographical variations are in part related to hypercoagulable states as well as anatomical variations. This observation adds further to the nascent clinical utility of this relatively new technique.

We would draw the authors’ attention to studies performed within hours of the acute stroke, showing that similar multiple lesions can be detected, with topography again suggesting embolism. Furthermore, complementary MRI techniques now available include perfusion-weighted imaging (PWI) and angiography (MRA), which can be applied concomitantly with acute DWI. We have recently reported in Stroke the predictive utility of consideration of the qualitative topography of these combined techniques in hyperacute stroke. DWI lesions in humans are usually predictive of transition to histological infarction, whereas PWI delineates the presence and severity of ischemia, including regions where infarction is not inevitable. Similar multiple lesions, and hence presumed similar pathophysiology, are seen where PWI lesions occur even without DWI lesions. Thus, the combination of techniques is considerably more powerful in identifying both pathophysiology and potential response to intervention.

It is our hope as stroke physicians that further characterization of hyperacute PWI/DWI ischemic patterns in appropriately designed prospective studies will be shown to predict which patterns are reversible with selectively targeted therapies. There is every reason to include those patients with noncontiguous multiple DWI and PWI deficits in these trials.

Response
We thank Drs Darby, Parsons, Barber, and Davis for their interest in our work1 on the significance of multiple acute brain infarction on DWI. DWI has made it easier to discriminate small, multiple, silent ischemic lesions that would have gone unrecognized before the era of DWI. Another study,2 performed mostly within 24 hours of acute stroke, showed that multiple acute ischemic lesions were present in 17% of patients and that the stroke mechanism was mainly embolic. The different frequency of multiple lesions from ours may be partly due to the different time interval between stroke onset and imaging and the different sample size. The main mechanism of acute multiple ischemic lesions was presumed to be embolic. Additionally, we showed that hypercoagulability and vascular anatomic variations may also play a role in the pathogenesis of bihemispheric ischemic lesions.

Acute multiple ischemic lesions may have clinical significance with regard to acute stroke therapies. Darby and colleagues3 have reported the predictive utility of pathophysiological topography of acute ischemia through the combination of DWI, PWI, and MRA. PWI lesions without DWI lesions can occur even though they compose a small proportion of acute ischemia. Thus, multiple PWI lesions may have underlying pathophysiology similar to that of the multiple DWI lesions. We agree with the opinion of Darby and colleagues in that the combination of these new techniques is more powerful in determining stroke pathophysiology and therapeutic intervention.

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Is the Acetazolamide Test Valid for Quantitative Assessment of Maximal Cerebral Autoregulatory Vasodilation?

To the Editor:
I read with great interest the article by Demolis and colleagues1 and the short editorial by Dr Alkayed that followed. The study by Demolis et al is an important contribution to the literature. Although the acetazolamide is commonly used to assess the vasodilatory capacity of the cerebral circulation, the physiological significance of an abnormal blood flow or blood velocity response to this stimulus is not known. As Dr Alkayed correctly states, the degree to which blood flow responses to this agent indicate autoregulatory capacity is unclear. The results from the study of Demolis et al serve to further underscore this fact. I am writing to point out 2 minor, but important, errors in the thoughtful editorial by Dr Alkayed that followed.
First, the vasodilatory effects of acetazolamide are complex and very likely caused by different mechanisms that P CO2-induced vasodilation.2,3 Hemodynamic studies of patients with carotid occlusive disease comparing the vasodilatory effects of acetazolamide to hypercapnia or physiological activation have reported striking discordances.4,5 Kazumata and colleagues6 measured an increase in cerebral blood flow with hypercapnia in 10 of 11 patients with an absent increase or paradoxical reduction in cerebral blood flow after acetazolamide. The study by Nishimura and coworkers7 reported an association between P CO2 effects (not acetazolamide) and the effects of induced hypotension using PET measurements of cerebral blood flow. The findings of Demolis and colleagues and the study by Nishimura are therefore not contradictory.
Second, indirect methods of hemodynamic assessment such as these require empiric validation as predictors of stroke risk.8,9 Dr Alkayed cited 2 studies as reporting an association between stroke risk and impaired blood flow responses to acetazolamided. The first, a pioneering study by Yonas and colleagues,8 suffered from several methodological flaws, including mixed patient populations and a retrospectively defined hemodynamic threshold to identify normal and abnormal acetazolamide responses.9 The second study, by Yokota et al,9 is mistakenly cited as supporting an association between stroke risk and impaired blood flow responses to acetazolamide, when, in fact, it found just the opposite. This was a well-designed, prospective study of 105 patients. Over a mean follow-up period of 2.7 years, the risk of stroke in patients with normal acetazolamide-induced blood flow responses (6 in 39 patients) was the same as the risk for patients with abnormal response (7 of 39 patients).9
The study by Demolis and colleagues supports the hypothesis that the vasodilatory effects of acetazolamide are mediated by a different mechanism than vasodilation due to autoregulation. The physiological and clinical significance of an absent increase or paradoxical reduction in cerebral blood flow after acetazolamide remains to be determined.

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Response

Whether CO₂ and acetazolamide cause vasodilation by the same mechanism is unclear. Clinically, a dissociation between hypercapnic and acetazolamide vasoreactivities has been reported.¹ I agree with Dr Derdeyn that evidence for or against an association between stroke risk and abnormal response to CO₂ and acetazolamide should be considered separately. The study by Yokota et al² was mistakenly used as supportive of an association between impaired vasodilator capacity and stroke risk. The clinical significance of an abnormal response to acetazolamide, as Dr Derdeyn points out, remains unclear.

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Ischemic Preconditioning and Tolerance in Human Brain

Response

Dr Cheung raises the important issue that the results of our study might be biased by inadequate inclusion and exclusion criteria. We included only Canadian Neurological Scale (CNS) scores from 4 to 10.5 to adjust the presumed stroke severity to the experimental situation. In experimental models, focal ischemic tolerance has been consistently shown for hemispheric infarcts of reproducible size, whereas very small or very large infarcts have not been examined in detail. It is true that TIAs and strokes represent different manifestations of the same disease, but most TIAs last <1 hour,¹ whereas the majority of stroke patients presently reach the hospital only after several hours, as was the case in our study. We believe that a clear distinction can be made between TIA and stroke in most cases. We excluded patients with a visible infarction on CT, because the preconditioning stimulus per definition should cause no or only minimal damage. Probably 30% of TIAs <1 hour in duration show corresponding diffusion-weighted imaging (DWI) abnormalities on MRI, but the volumes are rather small.² In another study,³ the MRI abnormalities were not related to the TIA symptoms. We agree that the power of our study would have been improved by an admission MRI (including DWI) and follow-up scans at fixed time points. Unfortunately, this is currently not the standard institutional diagnostic regimen of our and many other stroke units. We excluded patients with TIA in another vascular territory because we were concerned whether they would represent a “positive control.” In rat brain⁴ and rabbit hearts⁵ “remote preconditioning” has been observed, which means that ischemia in the other hemisphere or even in another organ would induce ischemic tolerance. The death rate between the groups was not different. Because the follow-up time was up to 4 years and the cause of death often was unknown, we found it inappropriate to select this as a primary end point of our study. Finally, most patients had their qualifying TIA only several days before stroke, a time at which the “delayed window” of ischemic tolerance has been demonstrated in numerous experimental studies. When the cases with a very long interval between TIA and stroke are excluded, the results do not change. The mean CNS score of all TIA patients was 8.7; for the subgroup with a TIA within 7 days before stroke, the CNS was 8.9. In contrast, patients with unblemished strokes had a worse CNS score on admission (7.4). For the patients with TIAs that occurred long before stroke, other factors, such as collateral development, have to be taken into account that a prodromal TIA can induce immediate and long-lasting “ischemic tolerance.” I wonder if the authors would include more patients into the group with a prodromal TIA, subdivide the whole group into a subgroup with a recent TIA and another subgroup with a remote TIA, and repeat some of the analyses.

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Response

Weih and colleagues¹ conducted a retrospective case-control study of 37 patients with a transient ischemic attack (TIA) before their ischemic stroke and compared the outcome with that of 111 control patients with no TIA before the cerebral infarction. Their results revealed that milder strokes and favorable outcome were associated with the presence of a prodromal TIA. I would raise the following issues for clarification and discussions by the authors.

First, I do not understand the rationale behind adopting some of the exclusion criteria. Patients with a Canadian Neurological Scale score of ≤4 or ≥10.5 were excluded.¹ Why should patients with a milder stroke be excluded? Patients with a severe stroke and/or aphasia may be noncommunicative, but the prior history of TIA can be sought from the spouse or other relatives. The success of acute thrombolysis with tissue plasminogen activator and the conduct of multicenter trial on acute ischemic stroke have blurred the distinction between a TIA and an ischemic stroke.² In addition, small cerebral infarction has been documented by MRI in patients with clinically defined TIA.³ Thus, excluding patients with previous infarction on CT within the same vascular territory is unnecessary. On the other hand, patients with TIA in a vascular territory other than that of the index stroke may represent a “positive” control group to show whether the induced “ischemic tolerance” is confined to the vascular territory of the prodromal TIA.

Second, patients who died before completion of follow-up were excluded from the outcome analysis, and patients had varying durations of follow-up.¹ I think the cause of death is relevant, and excluding stroke-related deaths would bias toward a better outcome. In any case, death following stroke is the worst outcome. On the other hand, assessment of independence and favorable outcome should be made at a comparable time after the index stroke.

Finally, the interval between the prodromal TIA and the index stroke varied from 6 hours to 2 years.¹ It is rather unconvincing
Low Plasma Antioxidant Activity Is Associated With High Lesion Volume and Neurological Impairment in Stroke

To the Editor:

We read with great interest the article by Leinonen et al.1 in the January 2000 issue of Stroke. In this study, low total peroxyl radical-trapping potential (TRAP) of plasma, but not of cerebrospinal fluid, was found to be associated with high lesion volume and high neurological impairment. An inverse correlation between plasma TRAP and infarct volume (r = −0.53, P = 0.01 for TRAP and r = −0.56, P = 0.007 for TRAPmean), in addition to higher lesion volume in patients with a lower-than-mean level of plasma TRAP (1190 μmol/L) than patients with a TRAP level higher than that (15.3 ± 14.1 versus 5.6 ± 7.1, P = 0.03), was the affirmative underlying statistical findings for this result. The infarct volume–plasma TRAP level correlation analysis was performed in 21 patients with right hemisphere acute infarction. Their NIH Stroke Score was not correlated to the plasma TRAP levels in these patient groups (in the patients with infarction >1.5 cm³, n = 15, r = −0.314, P = 0.253; in the patients with infarct volume ≥3 cm³, n = 12, r = 0.115, P = 0.722, by the Pearson correlation test). We thought that omission of lacunar infarction was important because of the title of the article by Leinonen et al.: “Low Plasma Antioxidant Activity Is Associated With High Lesion Volume and Neurological Impairment in Stroke”. By reanalyzing of their data, this statement did not seem to be relevant to territorial infarctions. If so, their paper may mislead casual readers.

According to aggregated data from a large number of experimental in addition to a limited number of human stroke studies, the generation of free radicals and/or antioxidant depletion leading to oxidative stress plays an important pathophysiological role in ischemic brain injury. Currently, there is evidence that oxidative damage to membrane lipids and proteins is increased during cerebral ischemia and reperfusion. Even though it remains difficult to determine which part of the damage is caused by hypoxia and which part by reperfusion, it seems possible that this type injury may occur in all types of territorial infarction. However, lacunar infarction shows very different pathogenetic properties. The presence of ischemic penumbra and occurrence of reperfusion are not, indeed, expected in lacunar infarctions. Apart from demonstration of elevation of plasma lipid peroxides in diabetics with multiple lacunar infarction2 and lowered vitamin A/cholesterol and carotenoids/cholesterol ratios in small-artery ischemic stroke3 in some studies, the oxidative injury similar to territorial infarct is never believed to exist in lacunar infarcts. Also, in some studies of oxidative injury in ischemic stroke, patients with lacunar infarction have served as the control group.4

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Hormone Replacement Therapy and Intima-Media Thickness of the Common Carotid Artery: The Rotterdam Study

To the Editor:

We read with interest the population-based study by Westendorp et al.,1 in which the authors describe an inverse association between hormone replacement therapy (HRT) use and carotid artery intima-media thickness. Nevertheless, we feel that the results of this study must be viewed with a little caution. Cross-sectional population studies of HRT use have provided us with often-conflicting results of the effect of HRT on cardiovascular risk. Some studies, such as the Nurses’ Health Study,2 have suggested that HRT may have a significant cardioprotective effect. However, in the Framingham study,3 a retrospective analysis of estrogen use in 1234 postmenopausal women suggested that estrogen use was associated with a 50% increase

in cardiovascular mortality and morbidity with no difference in all-cause mortality.

Cross-sectional studies, by the nature of their design, have biases which cannot all be accounted for. Although some confounding factors such as age and cigarette smoking can be identified and allowed for when calculating risk ratios, other important factors such as social deprivation, educational levels, and access to health care professionals are more difficult to assess and quantify. Indeed, some of the supposed benefits of HRT may be attributable to a “healthy cohort effect.”

For this reason, randomized prospective studies provide us with more clear evidence on which to base clinical practice. The first large, randomized, placebo-controlled study of HRT use with cardiovascular death as an end point raised significant concerns regarding its safety in women with preexisting coronary artery disease. 5 At the recent American College of Cardiology meeting in March 2000, the prospective randomized Estrogen Replacement and Atherosclerosis (ERA) trial did not demonstrate any significant benefit of HRT on coronary atherosclerosis progression.

The proposed cardiovascular protective properties of HRT were purported to be due to modifications in the lipid profiles. Indeed, HRT reduces LDL levels and raises HDL levels. 6, 7 A closer analysis of lipid profiles, however, suggests that these assumptions regarding HRT may need to be reassessed.

For example, one longitudinal study 7 found that surgical menopause is associated with an increase in total cholesterol, which was reduced by HRT. However, in a prospective longitudinal study of 17 women with surgically induced menopause, 6 weeks of treatment with HRT was associated with an increase in the proportion of small, dense LDL subfractions (P≤0.01) despite a decrease in total cholesterol. 8 These small, dense LDL subfractions are significantly more atherogenic and indeed, a lipid profile with a high proportion of these subfractions has been identified as an independent risk factor for both coronary and carotid artery disease. 9, 10 Because LDL subfractions are not routinely measured in clinical practice, the reduction in total cholesterol: HDL ratio with HRT use may give physicians a false reassurance.

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Leptomeningeal Enhancement After Carotid Stenting

To the Editor:

We were very glad to see the recent study by Wilkinson et al 1 to show the leptomeningeal enhancement by head MRI. We agreed with authors that the enhancement was mainly over the leptomeninges and that the leakage of contrast medium resulted in this leptomeningeal enhancement. However, we did not think such leakage was due to injury of the blood-brain barrier. It would be more accurate to say that the contrast medium leaked out of the vessels associated with the subarachnoid space/pia mater. A physiologist unselectively termed “blood-brain barrier” as the interface between blood and brain; in a strict sense, the blood-brain barrier should exist within the brain. Actually, it is the absence of blood-brain barrier in those vessels within the subarachnoid space. 2 We would like to present our similar experience in brain CT here to demonstrate injury of the blood-brain barrier after stenting. Our patient was an 82-year-old woman who had left hemiplegia during the stenting of the right internal carotid artery. Therefore, she underwent a brain CT examination (with no further injection of contrast medium), approximately 7 hours after the beginning of the stenting procedure. Brain CT showed obvious enhancement at the hemisphere ipsilateral to stenting. The enhancement was mainly noted at the pia mater within the sulci as well as at the basal ganglion and surface of superficial cortex (Figure 1). Interestingly, there was no more enhancement in these areas in the next day (Figure 2). We observed such a phenomenon but could neither fully understand its significance nor draw a conclusion at that time, because the patient number was so small and because there were

Figure 1. Brain CT scan of an 82-year-old woman who had stenting in the right internal carotid artery at approximately 7 hours after the beginning of the stenting procedure. There was enhancement over the surface of the cortex as well as within the left basal ganglion, where the blood-brain barrier had broken down.
To the Editor:

Wilkinson et al.1 describe the very interesting phenomenon of abnormal leptomeningeal enhancement in the territory of the middle cerebral artery after ipsilateral carotid stent insertion. In our view, Figures 1E and 1F of the above-mentioned article not only show leptomeningeal contrast enhancement but also indicate extravasation of contrast medium into the cerebrospinal fluid (CSF) space. The authors do not believe that a reaction of leptomeningeal vessels to the x-ray contrast medium (Optiray, Mallinckrodt Medical Ltd; dosage not mentioned) was a likely cause. The phenomenon of contrast medium extravasation into the CSF space following disruption the blood-CSF barrier, however, has been observed by using CT2 and MRI.3 During the last 10 years we have found extravasation of contrast medium into the CSF space in 11 patients, who suffered from cardiovascular and cerebrovascular arteriosclerosis often associated with severe hypoxic brain damage (Figures 1 and 2).

We believe that a latent, regional alteration of the blood-brain barrier in patients with severe stenosis of the internal carotid artery might become obvious in terms of enhancement of the leptomeninges and the adjacent subarachnoid space under certain conditions: (1) repeated intra-arterial application of x-ray contrast media; (2) short periods of hypoxemia during angioplasty; and (3) in accordance with Wilkinson et al.,1 an obviously temporary reperfusion phenomenon exists, the mechanism of which is not completely understood.

Enhancement of the ventricular system (Figure 2) is a result of extravasation of the “tight junctions” between the cuboidal cells resting on the basement membrane of the choroid plexus.4 Enhancement of the subarachnoid space may result from alteration of the blood-brain barrier of cortical blood vessels via “sink action” or as a direct consequence of disruption of the tight capillary junction of the outer layer of the arachnoid.4 Neurological and psychiatric symptoms can be expected in primarily parenchymal brain lesions. Despite the possibility of contrast medium diffusion into the extracellular space of the brain parenchyma, enhancement of the CSF space is rarely associated with clinical symptoms. This observation is supported by the paucity of side effects after intrathecal application of x-ray contrast media.

We are impressed by the regularity of leptomeningeal enhancement in MRI after carotid stenting, as shown by Wilkinson et al.1

Leptomeningeal Enhancement and Extravasation of Contrast Medium into the CSF Space?

et al. The authors’ diagnostic strategy enables us to study asymptomatic forms of blood-brain barrier disruption for scientific purposes and in clinical practice.

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Response to the Preceding 2 Letters

We thank Drs Bretschneider and Strotzer and Drs Lu, Sun, and Huang for their interest in our recently published findings.¹

We agree with the interpretation of Drs Bretschneider and Strotzer that the images in our article (along with the other 10 cases from our study that demonstrated unilateral leptomeningeal enhancement) appear to show localized extravasation of MR contrast into the CSF space. In the discussion section we defined leptomeningeal enhancement as the abnormal accumulation of contrast media in the pia and/or the arachnoid mater. Intravenous contrast media are normally prevented from entering subarachnoid CSF by tight junctions within the endothelium of the capillaries in the outermost layers of the arachnoid.² However, once present within the arachnoid mater, water-soluble contrast media may be free to diffuse into the CSF. It is interesting that qualitative image interpretation does not reveal enhancement of the brain extracellular fluid itself, since it is known that water-soluble substances can freely diffuse from the brain into the CSF via the pia mater.² Quantitative studies are indicated to exclude the presence of subtle enhancement of brain parenchyma adjacent to areas of leptomeningeal enhancement.

As set out in the discussion section of our article, we also believe that a latent, regional alteration of the blood-brain barrier in patients with severe stenosis of the internal carotid artery might become obvious in terms of enhancement of the leptomeninges (including the adjacent subarachnoid space) under certain conditions. The administration of iodinated contrast medium may be one such condition. However, our data from 2 patients who had intra-arterial angiography with repeated contrast injections but did not undergo stent insertion and did not demonstrate leptomeningeal enhancement suggest that this is not the case. Our apologies for omitting the dosage of iodinated contrast used (Optiray, Malinckrodt Medical Ltd): 30 to 50 mL was injected directly into the internal carotid artery for the stenting procedure, and approximately 130 mL was applied into the aorta for an arch angiogram. As stated in our article, we believe that more control data would be needed to further limit the possibility that x-ray contrast is the causative agent that leads to the observed enhancement.

We are most interested in the observations of Drs Bretschneider and Strotzer of extravasation of contrast into the CSF space in 11 patients who suffered from cardiovascular or cerebrovascular atherosclerosis. In the context of carotid stenting at our institution, the suggestion that short periods of hypoxemia during angioplasty are responsible relates to 2 episodes of <15 seconds of balloon inflation. This would seem to be unlikely, in view of transcranial Doppler ultrasound findings, not specifically in these patients but in others, which show that the middle cerebral artery flow is usually maintained despite balloon occlusion. None of the patients undergoing procedures in our study¹ showed changes in consciousness at the time of balloon inflation, which suggests that the degree of hypoxemia was minimal at the time of angioplasty. This really leaves us with what we believe to be the most likely explanation: reperfusion damage to the leptomeningeal vasculature which has been put at risk from long periods of low arterial input pressure brought about by severe atherosclerotic carotid stenosis.

Drs Lu, Sun, and Huang outline the case of a patient who demonstrated enhancement throughout the territory of the middle cerebral artery on x-ray CT after carotid stenting. In contrast to the patients in our study,¹ this patient suffered neurological deficit during the interventional procedure, although it is not clear whether this represented a transient ischemic attack or a completed stroke. This is a different scenario from the cases we previously reported.¹

Drs Lu, Sun, and Huang pose the question, “How long would this phenomenon last?” Further investigation is needed to fully address this question. However, there is some published evidence: (1) in our study, fluid-attenuated inversion-recovery images obtained after intervention and after the administration of the second bolus of MR contrast showed stronger enhancement than those obtained after intervention but before the administration of the second bolus (on average, approximately 2 hours after stenting), and (2) the study by Gillard et al³ did not show leptomeningeal enhancement 24 hours after endarterectomy. Of course, this second point is useful only if we assume that surgery can lead to the same observation.

We thank Drs Bretschneider and Strotzer and Drs Lu, Sun, and Huang for details of their experience and thought-provoking comments. We hope that our diagnostic strategy promotes a flurry of research activity which in turn leads to a better understanding of the blood-brain, blood-CSF, and perhaps CSF-brain barriers.

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Continuous Infusion Versus Bolus Injection Of Ultrasound Contrast Agents in Vascular Doppler Flow Imaging

To the Editor:
The recent report from Germany by Droste et al1 in this journal reinforces the benefits of echocontrast-enhanced transcranial Doppler imaging of the collateral circulation with use of the echocontrast agent Levovist (Schering AG). Their results, showing that ultrasound contrast improved imaging resolution and diagnostic confidence, parallel our American experience with this same ultrasound contrast agent in a similar clinical application.2 We note with interest the investigators’ mention of using a new type of administration for this echocontrast agent (namely, continuous infusion by means of a pump), whereas our early clinical trial experience with Levovist has been limited to intravenous bolus injection. Medical searching revealed that several European centers have now reported experience with the continuous infusion of ultrasound contrast during Doppler studies of the intracranial,3–6 carotid and peripheral,7–9 and coronary arteries.10,11

A comparative evaluation of the advantages of continuous infusion and bolus injection in transcranial Doppler applications would be timely to standardize ultrasound contrast delivery parameters for broad general usage. Such a study could also incorporate analysis of the influence of total dose and the time-intensity curve on side effect profiles. Because continuous infusion appears to be clinically effective in transcranial Doppler indications, it may be prudent to adopt this method of administration over bolus injection for the additional theoretical benefit of avoiding steep concentration gradients and acute microbubble loading in the entire vasculature. Albrecht et al10 compared both modes of administration in the setting of peripheral vascular Doppler imaging in 6 healthy volunteers with the Doppler gain set to a low level to simulate suboptimal scanning conditions. This pilot investigation demonstrated that continuous infusion yielded a steady-state concentration of the echocontrast agent and greater examination time at optimal enhancement, avoided bloom and possibly other artifacts, and reduced the need to alter Doppler system settings. Continuous infusion also permitted the sonographer to titrate echocontrast enhancement tailored for the individual patient and vessel under examination with the additional benefit of being more “dose effective,” ie, required a lower overall microbubble burden in the patient in order to achieve the desired diagnostic result.

We would be interested in the viewpoints of our European counterparts, Droste et al, who have reported separately their transcranial Doppler experiences with the bolus injection method.12,13 The use of ultrasound contrast has ramifications beyond the technical specifications of Doppler examinations. In the United States the demand for access to vascular ultrasonography, including transcranial Doppler, has moved beyond the finite number of academic investigator-sonographer laboratories into widespread application by nonvascular specialty practitioners. In this context, there exists the possibility that a majority of patients with clinical indications for transcranial Doppler studies may exhibit “suboptimal” imaging characteristics relative to the sonographer’s level of expertise. Therefore, another important purpose and benefit of ultrasound contrast agents may ultimately become its use to enhance access to quality care in vascular ultrasonography by reducing operator dependency and enabling sonographers throughout a spectrum of expertise to achieve clearly visible, standardized, and dependable results.

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This, however, often led to the initial appearance of blooming artifacts and a relatively short enhancing period, both of which resulted in a reduction of the effective examination time to approximately 2- to 3 minutes. Consecutively, we tried the fractionated use 4 g of the echocontrast agent Levovist (Schering AG) in a concentration of 400 mg/mL (ie, 10- to 11 mL). Five mL of the echocontrast was given as a bolus via a cubital vein with use of a butterfly. The next 2.5 mL was added when the effect of the echocontrast was fading, and finally the residual 2.5 mL was injected. This prolonged the investigation time to approximately 4- to 5 minutes and smoothed the agent’s enhancing effect.1 Eventually, we applied one 4-g vial of the echoenhancer Levovist (10- to 11 mL suspension) in a concentration of 400 mg/mL, using a specifically configured infusion pump with a continuous infusion rate of 2.5 mL/min. This procedure allowed for an enhancement time of more than 5 minutes, minimized the effect of blooming, and could be performed by 1 investigator without the need to interrupt the investigation and to relocate the vessels.2,3 We therefore feel that continuous infusion offers many advantages over the manual (bolus) injection. Other centers in Europe, as mentioned in the letter by Drs Boyajian and Otis, are also increasingly using this method. Infusion rates from 0.5 mL/min up to 2.5 mL/min were reported. We have never observed any major side effects of Levovist, either during manual injection or during continuous infusion. This is in line with a recent post-marketing surveillance by Schering, in which 585 Levovist applications (416 by manual injection, 169 by infusion pump) were monitored. No relevant side effects were observed (unpublished data, S. Weber, MD, Schering AG, 2000). We agree with the statement of Drs Boyajian and Otis that echocontrast agents could enable sonographers throughout a spectrum of expertise to achieve clearly visible, standardized, and reliable results. However, echocontrast cannot replace adequate training of technicians and doctors involved in diagnostic ultrasonography. Echocontrast agents help to further promote this cost-effective, noninvasive, and easy-to-repeat bedside technique by minimizing the number of patients who cannot be investigated because of technical problems.

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Leptomeningeal Enhancement and Extravasation of Contrast Medium into the CSF Space?
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