Clopidogrel and Its Use in Stroke Patients

To the Editor:

Substantial clinical data support the use of antiplatelet therapy in reducing the incidence of secondary atherothrombotic events in individuals who have experienced a transient ischemic attack (TIA) or stroke. The consensus based on recent trials is that antiplatelet therapy can reduce the incidence of subsequent ischemic events in those patients for whom carotid endarterectomy is not indicated and for whom atrial fibrillation is not a contributing factor. Aspirin has been the antiplatelet drug most frequently evaluated, and numerous trials support its efficacy. Ticlopidine, a thienopyridine antiplatelet agent, is also effective in preventing recurrent ischemic events in the stroke patient, but the risk of bone marrow depression and questions about its superiority to aspirin in reducing ischemic vascular events other than subsequent stroke have been raised. Recently clopidogrel, an analog of ticlopidine that has not demonstrated bone marrow toxicity, was approved by the Food and Drug Administration for use in patients at risk of recurrent ischemic events, including stroke, myocardial infarction, and limb claudication. The clinical data supporting the use of clopidogrel, however, may provide no compelling justification for using clopidogrel in preference to aspirin in stroke patients.

Although the CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) trial found a statistically significant reduction in the combined incidence of stroke, myocardial infarction, and vascular death for clopidogrel compared to aspirin, the magnitude of the therapeutic advantage was small (an 8.7% relative risk reduction, or a decrease in the absolute event rate from 5.83% to 5.32% with clopidogrel). A difference of this magnitude would require switching 200 patients from aspirin to clopidogrel to see even 1 less atherothrombotic event per year. Furthermore, the therapeutic advantage attributable to clopidogrel was observed only when data from stroke patients were pooled with those enrolled in the study on the basis of a recent myocardial infarction or clinically active peripheral arterial disease. When stroke patients, a group totaling over 6400 individuals with over 12,000 patient-years of treatment, were evaluated in a post hoc analysis, no significant difference in efficacy was seen between clopidogrel and aspirin. The majority of the benefit of clopidogrel over aspirin in CAPRIE occurred in the group enrolled because of clinically active peripheral arterial disease. Also, it has been suggested that high-dose aspirin may be more effective than low-to-moderate-dose aspirin in the secondary prevention of stroke. Thus, the possibility exists that at higher doses aspirin may be more effective than clopidogrel in the prevention of recurrent stroke.

Given these uncertainties surrounding the relative efficacy of clopidogrel compared with aspirin in stroke patients, it is difficult to justify switching patients to clopidogrel. No safety advantage for clopidogrel was evident in CAPRIE. Both agents produced similar side effect profiles (e.g., upper gastrointestinal discomfort and general bleeding disorders were the most common adverse events for both drugs). Although upper gastrointestinal effects were somewhat more common in the aspirin-treated patients, it is possible that the incidence of these events would have been more comparable if a lower dose of aspirin or an enteric-coated formulation had been used in CAPRIE. If one considers the higher cost of clopidogrel over aspirin and the absence of a substantive safety advantage of clopidogrel over aspirin, there is little basis for switching stroke patients to clopidogrel.

There is however, a place for clopidogrel in the treatment of stroke patients. The questionable status of clopidogrel utilization relative to aspirin should not detract from the conclusion that clopidogrel is an effective antiplatelet agent that would most likely demonstrate superiority to placebo if such a trial were ethically possible. There are, for example, a number of patients who are unable to tolerate or who have failed aspirin therapy. For whom clopidogrel may be indicated. Also, the CAPRIE trial suggests there may be a role for clopidogrel in the treatment of patients with peripheral vascular disease. However, at present, aspirin must still be considered the antiplatelet agent of choice for use in the prevention of recurrent ischemic events in stroke patients.

Note: Dr. Gorelick is on the Speakers Bureau for Janssen/Excerpta Medica, Dupont, Roche Laboratories, and he has consultant agreements with NPS, Esaot, Searle/Lorex.

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Trials of Community Rehabilitation Need To Be of Adequate Sample Size

To the Editor:

Evaluations of the most cost-effective ways of providing rehabilitation after stroke are central to planning stroke care. Although reporting of good-strength, randomized controlled trial evidence is necessary in the era of evidence-based medicine, basic principles have to be adhered to. Both the trials by Holmqvist and colleagues and Rogers are useful pilot studies but are statistically weak and do not provide conclusive evidence for clinicians and health care planners on how to provide care.
In the Swedish trial\textsuperscript{1} the results are applicable to less than 10% of stroke patients. The main outcome measure for the trial is not specified, and the sample size for detecting a specific difference for this main measure is not detailed. The authors state that 130 patients would be required to detect an unspecified difference in costs; however, the trial includes only 81 patients. Hence, like the evaluation by Rodgers,\textsuperscript{2} the results must be considered as pilot data. There is not sufficient power to detect important clinical differences in outcome, and the authors do not discuss the fact that the nonsignificant differences could, with an adequate sample size, become negative outcomes in a larger study.

In a similar trial of early discharge from hospital to a community rehabilitation team in London, UK, we randomized stroke patients in hospital and followed them up for 1 year. There were no significant clinical differences between the groups at 1 year, but the early discharge from hospital to a rehabilitation team option has been shown to be effective.\textsuperscript{3} This trial required 260 patients to have sufficient power to detect clinically significant differences in Barthel score at 1 year.

If trials are to be undertaken, we as clinical researchers have an obligation to ensure that hypotheses can be answered, and this requires rigorous trial design, with adequate numbers of patients to detect differences in outcome should they exist.

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\textbf{Response:}

The excellent publication of Rudd and colleagues\textsuperscript{1} published simultaneously with ours\textsuperscript{2} and that of Rodgers et al\textsuperscript{3} add to the growing recognition that early supported discharge with continuity of rehabilitation at home can be feasible in combination with a considerable reduction in the use of bed-days for stroke patients.

We read with interest the comments by Rudd and colleagues,\textsuperscript{1} as mentioned by Rudd and colleagues, we do not specify one main outcome measure. To our knowledge, there is no consensus on appropriate main outcome measure for studies that focus on moderately disabled stroke patients. As in the study by Rodgers et al,\textsuperscript{3} we used several main outcome measures to capture possible effects on impairment, disability, and/or handicap level. Several authors\textsuperscript{5,6} have recently pointed out that the assessment of stroke disability should take into account not only the patients’ ability to perform basic or instrumental ADL (eg, the Barthel ADL index) but also the patients’ perceptions of their emotional, social, and physical functions and the ease with which they are performed. The battery of stroke disability measurements chosen for our trial fulfills such requirements and has subsequently been recommended by authorities in the field.\textsuperscript{5,6}

In a rigorous trial design of community rehabilitation, it is important, in our opinion, to reduce the discrepancies in initial medical attention, care, and rehabilitation. A stroke unit is thus far the only known organization producing services for which an impact on mortality, long-term care, and the level of dependence in ADL has been demonstrated.\textsuperscript{7} Unlike those in other studies,\textsuperscript{1,3} all of our patients received similar initial medical attention and early rehabilitation at the Department of Neurology at Huddinge University Hospital, organized as a stroke unit.\textsuperscript{2} Thus, when the admittance procedures for stroke patients were altered at the Huddinge Hospital and not all patients from the catchment area received care at the Department of Neurology, we were no longer able to recruit all stroke patients from the population (as was previously the case) nor were we able to ensure similar initial medical attention, care, and rehabilitation. A nursing strike, a physical therapy strike, and periods of shortage of speech therapists were other factors beyond our control that reduced the number of patients included in the study.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|}
\hline
\textbf{Comparison Variable} & \textbf{Minimum No. of Patients} \\
\hline
\textbf{Effect (odds ratio)} & \\
2 & 296 \\
3 & 130 \\
4 & 90 \\
\hline
\textbf{Savings (SKr)*} & \\
5,000 & 212 \\
10,000 & 54 \\
15,000 & 24 \\
\hline
\end{tabular}
\caption{Required Sample Size Calculated on the Basis of Different Magnitudes of Expected Effects or Savings*}
\end{table}

\textsuperscript{*}Savings are expressed in Swedish krona (SKr).


Rudd and colleagues point out that our results are applicable to less than 10% of the stroke population. In our opinion, it is not likely that there will be one best way of organizing the rehabilitation service that will be feasible for such a heterogenous group as stroke patients. Our study focused on moderately disabled stroke patients who, in line with prior experience, are those who might benefit most from specific interventions. Our patient selection criteria, based on level of cognitive function and ADL capacity at 1 week, would strengthen the appropriateness of our stroke population for the purposes of experimental evaluation research into rehabilitation techniques. Nevertheless, the results of our study should not be used for planning stroke services for the more severe or unspecified type of stroke patients.

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Coincidence of Factor V Leiden Mutation and a Mutation in the Prothrombin Gene at Position 20210 in a Patient With Puerperal Cerebral Venous Thrombosis

To the Editor:
Cerebral venous thrombosis (CVT) is a rare cause of stroke with a variable clinical picture. A search for underlying disorders may be successful in 65% to 80% of cases. Over the past few years, activated protein C (APC) resistance has been identified as the most common hereditary thrombophilic factor in CVT. More recently, a mutation in the prothrombin gene at position 20210 has been found in pedigrees with venous thrombosis. We report the case of a patient with puerperal CVT with hereditary APC resistance, who in addition showed a heterozygous mutation in the prothrombin gene at position 20210.

A 30-year-old, previously healthy woman suffered a generalized seizure after a 10-day-long headache episode 5 weeks after she had given birth to her first child. After the ictus she was confusion and disorientation for several days. A cranial CT showed a 2×3-cm hypodense area in the right temporal lobe. A cranial MRI revealed a 3-cm lesion in the right parietal lobe that was hyperintense in T2-weighted images and hypointense in T1-weighted images and showed no contrast enhancement. MR angiography subsequently showed no flow signal in the right lateral sinus. An EEG showed a right parietotemporal focus with delta and theta waves. The family history was negative for epilepsy, cerebrovascular events, and thromboembolic events, except for an occurrence of deep venous thrombosis in the patient’s grandmother. The patient was treated with unfractionated heparin IV (partial thromboplastin time adjusted) during the acute phase, followed by oral anticoagulation with phenprocoumon (international normalized ratio adjusted to 2.5 to 3.0) for 2 years by her private physician. Due to persistent sharp waves during the patient’s follow-up EEGs, phenytoin treatment was continued for 20 years. During this time she recovered completely and showed no signs of relapse. Two years 3 months after the thrombosis she was referred to our clinic for assessment of future treatment, particularly during a desired pregnancy. A workup for thrombophilic factors showed normal values for thrombocytes, prothrombin time, plasma thromboplastin time, antithrombin, fibrinogen, protein S, protein C, antinuclear, double-stranded DNA antibodies, and antiphospholipid IgG. Antiphospholipid IgM levels were markedly elevated but normalized after control. In contrast, the APC resistance ratio (assay by Chromogenix) was markedly decreased to 1.5 (normal, >2.0).

Prothrombin activity was found to be in the upper normal range (108%). Restriction analysis with Mnl I of a 267-bp fragment...
spanning the exon 10 fragment of the factor V gene with Mnl I revealed a heterozygous point mutation at position 1691 from G to A within the factor V Leiden gene as described.5 Restriction analysis with Hind III of a 345-bp fragment in the 3'-UT region in the prothrombin gene showed a heterozygous point mutation at position 20210 from G to A, as described previously.5 To date, no family screening for both mutations has been performed.

It has been shown that the presence of more than one thrombophilic factor increases the penetrance of a thrombotic event.7-9 In addition, approximately 50% of thrombotic episodes occur in association with circumstantial factors such as immobilization or pregnancy, suggesting that multiple risk factors might be necessary before clinically evident thrombosis is likely to develop. To our knowledge, this is the first report of factor V Leiden mutation in coincidence with a mutation in the prothrombin gene at position 20210 in CVT. More recently, a similar combination has been reported in a female with pregnancy-associated deep-vein thrombosis.10

In general we recommend testing for inherited thrombophilia in CVT in addition to a complete workup for other possible thrombotic factors. In our case we recommended primary prophylaxis with heparin during immobilization, pregnancy, and puerperium. However, the question of whether patients with combined thrombophilia benefit from long-term anticoagulation after the first incidence of CVT cannot be answered. The decision on treatment of hereditary thrombophilia after CVT must be made on a case-by-case basis as long as prospective studies are lacking.

(We would like to thank Dr. Schulz, Department of Neurology, Ernst v. Bergman Hospital Potsdam, for the EEG description, and Mrs S. Ziemer, Department of Pathologic and Clinical Biochemistry, for the coagulation tests.)

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Ambulatory Blood Pressure in Lacunar Infarct Patients

To the Editor:

We read with interest the recent paper by Yamamoto and colleagues1 evaluating longitudinal changes in MRI in patients with lacunar infarcts. The main conclusion reached by these authors is that high average ambulatory blood pressure, especially nighttime blood pressure, and a reduced nocturnal blood pressure dip may facilitate the development of silent ischemic lesions as well as symptomatic stroke recurrences in patients with lacunar infarcts. Before accepting these important conclusions, we believe that some comments are pertinent. We have also evaluated the effects of blood pressure in patients with first-ever lacunar infarcts and its association with the coexistence of silent lacunar infarcts2 and periventricular white matter intensities.3 Our main results suggest that both types of radiological signals react to separate hemodynamic mechanisms. Whereas silent lacunar infarcts seem to be related to elevated diurnal diastolic blood pressure, periventricular white matter intensities are better explained by elevated diurnal systolic blood pressure. A reduced heart rate, especially in lacunar infarct patients with a previous history of heart disease (symptoms of coronary heart disease, congestive heart failure, or electrocardiographic proof of ischemic changes or nonvalvular atrial fibrillation), is an additional factor associated with the severity of white matter abnormalities. It is likely that the angiarchitectural characteristics of the supplying vessels to the periventricular white matter explain why this region is vulnerable to different components of arterial blood pressure compared with the arterial territory of the lenticulostriate, thalamoperforant, or perforant branches of the basilar artery, where most silent lesions are located. In opposition to Yamamoto and colleagues, we did not find significant differences between the nocturnal blood pressure dip and the extent of silent subcortical or periventricular ischemic lesions. Yamamoto and colleagues did not observe significant blood pressure differences between patients who took antihypertensive agents and those in whom blood pressure followed its natural course. However, if Yamamoto et al are right, hypotensive medication should be increased at night to augment the nocturnal blood pressure dip. Conversely, if our findings prove correct, the medication should be adjusted mainly to avoid elevated diurnal systolic and diastolic blood pressure and to prevent an excessive reduction in heart rate, which frequently occurs at night. Nevertheless, our results also suggest that therapeutic decisions should be tailored to individual patients according to the coexistence of other risk factors, such as the presence of cardiac abnormalities.

The study of Yamamoto et al differs with our own work in several methodological aspects that deserve attention. Although both our group and Yamamoto et al examined patients with lacunar infarcts, they evaluated Japanese patients and we studied a white population. Yamamoto et al excluded patients with “obvious atheromatous stenotic lesions as detected by MR angiography,” but from the methods of the study it is unclear whether this technique was specifically performed to rule out the presence of intracranial atherosclerosis, particularly prevalent in this population.4 Unlike the Japanese study, we performed multivariate analysis to test the independent contribution of
variables that in univariate analysis showed a significant association with the radiological abnormalities. Although we initially observed a relationship between elevated nocturnal systolic blood pressure and white matter disease, the association did not remain significant when multivariate analysis was performed. Finally, rather than a dichotomous classification of the extent of white matter disease, we quantified the total area of all lesions detected by MRI to obtain a volumetric value for each subject. To what extent our conflicting results obey methodological disparities is difficult to establish. Certainly, we both agree that further investigation is necessary to clarify these important issues.

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**Response**

We thank Dr Chamorro for his interest in our recent article and critical comments. We fully agree with Dr Chamorro’s concept that silent lacunar infarcts and periventricular white matter intensities react to separate hemodynamic mechanisms. While lacunar infarcts are defined as the occlusion of a branch of perforating arteries, including lenticulostriate and thalamoperforant arteries, the most consistent histological substrate of periventricular white matter intensities is considered to be a diffuse pallor of the white matter attributed to rarefaction of the myelin sheaths. The periventricular white matter is considered to be an arterial borderzone in terms of the pattern of vascularization and to be susceptible to low flow ischemia. Thus, consistent with Dr Chamorro’s idea, we speculated before starting this study that periventricular white matter intensities could be accelerated by lowered blood pressure. However, the results were unexpectedly contrary to this speculation. Periventricular white matter intensities, with or without silent lacunes, developed in patients with higher blood pressure than patients with a good outcome. It looks like high blood pressure develops periventricular white matter intensities by accelerating microvascular disturbances accompanied by a breakdown of the blood-brain barrier. Differences from in the results of Chamorro et al and ours may be due to the fact that we carefully excluded those patients who had heart disease and obvious atheromatous stenosis (>30%) in carotid, middle cerebral, and vertebral arteries.

Furthermore, there might be another difference between silent lacunar infarcts and periventricular white matter intensities in regard to their location. While periventricular white matter intensities are located in the periventricular and subcortical white matter, multiple lacunes involve deep and specific cerebral regions, including the striatum, thalamus, diencephalon, and their connections, which are strongly associated with control levels of the autonomic regulation system. We have considered that multiple lacunes, especially when accompanying injury to the central autonomic nervous system, might play an important role in causing reduced nocturnal blood pressure dip, whereas periventricular white matter intensities do not relate to nocturnal blood pressure dip.

The most remarkable finding in our study is that high diurnal blood pressure values and reduced nocturnal dip were observed in those patients who showed the development of both silent lacunes and diffuse white matter lesions. If both silent lacunes and diffuse white matter lesions develop, they might cause Binswanger’s disease. The relationship between reduced nocturnal dip and the development of both these lesions might be explained by two possibilities: the first is that sustained high nighttime blood pressure might accelerate arteriolosclerosis in small penetrating arteries; the second is that autonomic disturbances coexisting with nondippers might have adverse effects on cerebral blood flow regulations. In the first situation, hypotensive medication should be administered to control nighttime blood pressure as well as daytime blood pressure. In this case, however, we would not recommend only lowering nighttime blood pressure in order to change to dipper pattern, but rather trying to control blood pressure throughout the whole day. In the second situation, controlling blood pressure would not be enough to prevent the development of ischemic lesions. Because nondippers have recently been shown to have an adverse prognosis, the strategies for these patients, including the medication for ameliorating autonomic disturbance and consequently normalizing the diurnal blood pressure pattern, should be considered or developed.

We detected atherosclerotic stenosis using MR angiography and ultrasonography, and excluded large lacunes (>15 mm) to which atherosclerotic changes are considered to contribute. Although it has been suggested, as Dr Chamorro pointed out, that intracranial artery disease has tended to be frequently found in Japanese, recent studies have shown extracranial atherosclerotic changes are also increasing in Japanese. Actually, we found and excluded a small number of patients with intracranial artery disease by MR angiography.

Although we have demonstrated that high diurnal blood pressure values accelerate the development of silent infarcts and diffuse white matter lesions, longitudinal study suggested that blood pressure tends to become lower over the course of development of vascular dementia. Further longitudinal studies are necessary to clarify these issues.

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Symmetrical Infarction of the Cervical Spinal Cord Due to Spontaneous Bilateral Vertebral Artery Dissection

To the Editor:

Vertebral artery (VA) dissection is a well-known cause of vertebrobasilar ischemia in young people and may be due to preceding chiropractic maneuvers, cystic medial necrosis, mucopolysaccharidosis and reticular fiber diseases, vasculitis, or a yet-unknown arteriopathy. Common findings in VA dissection are unilateral or bilateral neck pain associated with cerebellar and brain stem (usually medullary) infarctions, which are rarely associated with clinical signs of spinal cord lesions. Recently, 1 patient each was described with bilateral spinal cord infarction and Brown-Séquard’s syndrome as the sole manifestation of spontaneous unilateral VA dissection. We add another patient with spontaneous bilateral VA dissection causing MRI-documented bilateral cervical cord infarction without clinical, electrophysiological, or radiological signs of brain stem or cerebellar lesions.

A 31-year-old, previously healthy woman with a history of an episode of spontaneous right-sided neck pain 3 weeks before noted sudden onset bilateral neck pain radiating into both arms. Within some hours, she developed progressive unsteadiness of gait, weakness of the left arm and leg, and urinary retention. There was no history of neck trauma, chiropractic manipulation, or abrupt head movements. On examination, she had normal cranial nerve functions. There was a severe left-sided hemiparesis with loss of deep tendon reflexes on the left and weak knee and ankle jerks on the right side. The plantar responses were flexor. She had bilateral loss of pain and temperature sense below C5. Touch, vibration, and position sense were unimpaired. She had bilateral loss of pain and temperature sense below C2 to C5 vertebral levels.

MRI revealed symmetric infarction of the ventral one third (“snake-eye” conformation) of the spinal cord segments C2 to C5 (Figure). Cerebral angiography showed bilateral VA dissection with nearly total proximal stenosis and low blood flow in the basilar artery. MRI of the cerebellum and brain stem was normal. Direct current electro-oculography, brain stem auditory evoked potentials, and masseter and blink reflexes were also within normal limits. The patient was initially treated with intravenous heparin with clotting time increased to 2 times to normal and later put on phenprocoumon. The clinical course was favorable, and within 3 weeks only mild urinary retention was still present. Spinal cord infarction may be the sole manifestation of unilateral or bilateral VA dissection, followed by clinical signs of bilateral posterior cervical cord infarction.

Spinal cord infarction may be the sole manifestation of unilateral or bilateral VA dissection, followed by clinical signs of bilateral posterior cervical cord infarction.

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patients due to hemodynamic compromise continues to be debated, as does the potential role of extracranial-intracranial (EC-IC) bypass surgery for the treatment of that subgroup. Unfortunately, in our opinion, the author’s conclusion that cerebrovascular reactivity defined by the cerebral blood flow response to acetazolamide did not identify a subgroup at high risk for stroke is not substantiated by the study design or the data presented.

While the study began with a relatively large population of 105 patients with advanced occlusive vascular disease, 11 were lost to follow-up and 16 went on to surgical interventions. Although an explanation for the carotid endarterectomies is presented, none is given for the 9 EC-IC bypass procedures. This point alone invalidates this study as a prospective natural history study because of the withdraw of a significant number of patients without meeting a prospectively decided end point, ie, stroke or death. Because these patients underwent a purely hemodynamic procedure, the authors must have perceived that these individuals were at increased risk of stroke. These 9 individuals were the ones who were likely to have been of greatest interest to this study.

Despite the authors’ claim that single-photon emission computed tomography (SPECT) with \textsuperscript{N}-isopropyl-p-\textsuperscript{[123]I}\textsuperscript{-}iodoamphetamine (\textsuperscript{[123]I}IMP) is a useful technology for identifying patients with hemodynamic reserve compromise, there is ample literature to make this claim doubtful. The SPECT study used by Yokota et al\textsuperscript{1} involved 2 studies performed 3 days apart. This long separation of baseline and acetazolamide-activated studies is a less-than-desirable study format, because many variables may have changed significantly between studies. Both the transcranial Doppler and xenon-enhanced CT cerebral blood flow studies that the authors criticize as being flawed were based on challenge studies performed 20 minutes apart.\textsuperscript{2-4}

It must be remembered that \textsuperscript{[123]I}IMP SPECT is a qualitative technology which must base its conclusions on patterns and changes of patterns of flow between a symptomatic and an asymptomatic vascular territory. Because this qualitative technology is only able to examine the change of ratios, such a study is unable to distinguish a negative flow response from an asymmetrical positive response. Because only a negative cerebral blood flow response (“steal phenomenon”) was found to be predictive of an increased stroke,\textsuperscript{5,6} as well as an increased oxygen extraction fraction,\textsuperscript{6} it is very likely that patients with a bilateral drop of flow as well as an asymmetrical activation of flow were misclassified by Yokota et al\textsuperscript{1} in regard to a vascular reserve compromise. In an analysis of the value of quantitative versus qualitative data in making the above “correct” decision, qualitative data had a 50% error of prediction (sensitivity and specificity).\textsuperscript{7}

Unfortunately, only 32 patients with carotid occlusion were enrolled into the study, with the remainder of the patients having either internal carotid artery or middle cerebral artery stenosis. Because the recognized important role of continued embolic events in patients with internal carotid artery stenosis (and, from the authors’ personal experience, with middle cerebral artery stenosis), this study, despite its claim of being a large, prospective trial based on a reliable methodology, has fallen short in all regards.

The authors’ conclusion that reduced vasodilatory capacity does not play a major role in stroke recurrence would seem premature. The weight of the literature, including a recent study by Powers et al,\textsuperscript{8} has demonstrated that a hemodynamically compromised subgroup at increased risk for stroke does exist and can be identified by quantitative technologies capable of identifying either a steal phenomenon or an increased oxygen extraction fraction. A future study for examination of this question should ideally examine both the ideal methodology for identifying the subgroup at risk as well as the efficacy of a surgical revascularization procedure randomized for only the group at increased risk of stroke.

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Response

In our recent article,\textsuperscript{1} we reported that reduced cerebral hemodynamic capacity, determined by SPECT and acetazolamide (ACZ) challenge in patients with cerebral artery occlusive disease, does not play a major role in occurrence of subsequent stroke. The study was performed in a prospective manner. Each subject was evaluated on admission by CT scan, cerebral angiography, and ACZ-SPECT. Patients with infarcts of medium to large size and those with multiple, bilateral carotid, or vertebrobasilar arterial lesions were carefully excluded, because these lesions not only make the judgment of ACZ reactivity difficult but also affect the patients’ outcome. We examined a total 105 patients for up to 7.8 years. We believe this to be the most comprehensive and informative study concerning the effect of vasoreactivity on the outcome currently available in the literature. Drs Yonas and Pindzola raise several important questions regarding our study.

Their first question concerns the 9 patients who underwent the EC-IC bypass procedure. Our protocol did not put any restrictions on the medical management or surgical procedures. Within these guidelines, EC-IC bypass surgery was performed on 9 patients, including 6 ACZ-positive patients who had reduced vasodilatory capacity. Withdrawal of these patients might have appeared to affect our results; however, when they were included in the survival analysis with respect to stroke recurrence at the time of the surgery, no significant differences were observed in the overall recurrence-free survival rate between the ACZ-positive and ACZ-negative groups.

The second point raised by Drs Yonas and Pindzola relates to the SPECT methodology. We used a relative change in CBF distribution between 2 hemispheres to evaluate ACZ reactivity. The absolute CBF value may be affected by many variables, including arterial CO\textsubscript{2} tension, arousal level, and measurement...
conditions. However, the flow pattern tends to remain stable. Because all patients had an angiographically proved unilateral occlusive vascular lesion, vasodilatory capacity in the contralateral hemisphere could be used as an internal control for each patient. All SPECT studies were performed at least 1 month after the ischemic event. During the 3-day interval between baseline and ACZ challenge, the cerebral hemodynamics were assumed to be stable. We demonstrated that our SPECT method with ACZ challenge was reliable on the basis of the close correlation between these results and those obtained with the oxygen extraction fraction and cerebral blood volume/cerebral blood flow ratio simultaneously measured by positron emission tomography (PET) using $^{15}$O-labeled gas. Drs Yonas and Pindzola suggest that the steal phenomenon is predictive of a subsequent stroke. A varying degree of vasodilatory capacity may correlate with severity of local hemodynamic failure as demonstrated by PET. However, the clinical accuracy of the predictive ability of the steal phenomenon for stage II hemodynamic failure remains in question. We demonstrated that the paradoxical decrease phenomenon is highly specific to stage II failure (98% specificity) but its sensitivity is very low (45% sensitivity), based on simultaneous measurement of absolute cerebral blood flow change after the ACZ challenge and several other PET parameters using PET with $^{15}$O-H$_2$O injection and $^{15}$O-gas inhalation.

As for the patient characteristics, stenosis of the middle cerebral artery (MCA) causes less than 5% of the ischemic strokes among Western populations. Furthermore, intracranial arterial lesions occur more frequently in Japanese than in Western populations. A report by the National Cardiovascular Center Stroke Registry that included 2192 stroke patients showed that the frequency of extracranial arterial lesions among atherothrombotic stroke patients was 50% and that of intracranial lesions 40%; the lesion responsible could not be determined in the remaining 10% (authors’ unpublished data, 1998). These values are similar to those of the present study. Thus, the relatively small number of patients with internal carotid artery (ICA) occlusion in our study appears to reflect the ethnic differences in the distribution of atherosclerotic vessels. The ACZ reactivity became normal within an average of 2 years in 11 of 24 patients who initially demonstrated reduced ACZ reactivity in our study. Of those 11 patients, 5 had MCA stenosis, 1 had MCA occlusion, 3 had ICA stenosis, and 2 had ICA occlusion. These data indicate that spontaneous improvement in reduced vasodilatory capacity can also be expected in cases of carotid occlusion.

The significance of chronic hemodynamic insufficiency in stroke occurrence has been a matter of controversy. As recently discussed by Barnett, uncontrolled case series reports and retrospective studies may raise hopes but will prove nothing. Only a well-designed prospective, randomized study can solve this important question. However, before starting such a large trial, we should systematically accumulate data on stroke occurrence in patients with major cerebral artery disease, clarify the target population for a future study, and most importantly, standardize the method of evaluating “chronic hemodynamic insufficiency.”

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Clopidogrel and Its Use in Stroke Patients
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