Racism and tPA Use in African-Americans

To the Editor:

The investigation of Johnston et al1 into the influence of ethnicity on thrombolysis raises the spectre of racism in health service provision. However, as shown in the case of cardiac catheterization after myocardial infarction, racism is not always the reason for differences in treatment.2

Although the authors used a simple dichotomous definition of stroke severity in their regression analysis, they did not account for stroke subtype (or National Institutes of Health Stroke Scale [NIHSS] score). The proportion of ischemic stroke due to small-vessel disease in African-Americans is 52% compared with 25% in whites.3 Lacunar strokes tend to be less severe (maximum NIHSS of 10) and have a better prognosis than cortical ischemic strokes.4 The authors’ Table 2 demonstrates that despite American Heart Association guidelines, physicians are reluctant to give tPA to patients with less-severe stroke (only 8% of all eligible patients). Furthermore, physicians may not offer thrombolysis to those with suspected small-vessel stroke on pathophysiological grounds.5 This is in spite of no differential effect found in the NINDS study6 and that initial lacunar syndromes poorly predict eventual lacunar stroke.7

White patients arrived in the emergency department sooner than African-Americans. Although the percentage arriving within 3 hours was similar, a more realistic criterion for eligibility would be 2.5 hours, given that imaging, examination, and consent to treatment must all be completed prior to administration.

Another possible explanation is mistrust of health services. Even a few minutes’ prevarication can result in the 3-hour time window being exceeded. This may not be recorded as a refusal of treatment.

As one of the few centers outside the United States offering thrombolysis to a population with a high proportion of Afro-Caribbean patients, we have encountered the above problems, which cannot be attributed to racial prejudices. Racism in medicine, whether conscious or subconscious, individual or institutional, is to be deplored. However, ethnic variation in pathophysiology and behavior should be thoroughly examined before assuming that racism is the explanation for observed differences.

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Response

The causes of disparities in healthcare delivery—including the use of tPA in ischemic stroke—are likely to be complex, as suggested by Dr Evans and colleagues. In our article, we never imply that racism is the only cause of the ethnic disparity in tPA delivery. However, we do suggest that it contributed to the disparity, and appreciate the opportunity to clarify our reasoning.

We doubt that stroke subtype contributed importantly to the disparity. We know of no evidence to suggest that small-vessel strokes are responsible for a significantly larger portion of ischemic strokes in blacks. In fact, the article1 referenced by Evans and colleagues appears to report that small-vessel strokes account for 21% of ischemic strokes in blacks and 17% in whites—a difference that is neither clinically nor significantly important. Findings were similar in Northern Manhattan.2

Stroke severity was an important predictor of tPA use in our study, and a more detailed analysis would have been interesting. However, we found no difference in the portion with severe strokes (blacks 18% versus whites 16%), and others have found that outcomes are worse after ischemic stroke in blacks.3 Timing also does not appear to account for the disparity in our study. When we limited analysis to those arriving within 2 hours, black tPA candidates were still less likely to receive tPA than white candidates (8% versus 24%; P = 0.04).

We agree that mistrust of the medical system may have contributed to the disparity. Though no black patient was documented to decline tPA, it is possible that documentation was incomplete. Of course, some may postulate that mistrust itself is rooted in racism.

When are data adequate to raise the possibility that racism is contributing to a disparity in healthcare delivery? Should we require more solid proof of racism than other factors, such as age or insurance type? The answer must depend in part on the consequences of being wrong: What are the implications of suggesting that racism is a contributor to a disparity when it is not? Regardless of cause, taking greater care in offering tPA to blacks with ischemic stroke may reduce a very large disparity in its use at minimal additional cost.

S. Claiborne Johnston, MD, PhD
Leslie A. Gillum, MD, MPH
Wade S. Smith, MD, PhD

Re: Utilization of Intravenous Tissue-Type Plasminogen Activator for Ischemic Stroke at Academic Medical Centers

To the Editor:
We write in response to the recent significant article of Johnston et al. The authors' hypothesis is that racism, even on an unconscious level, may contribute to the disparity between administration of tissue plasminogen activator (tPA) to blacks and the administration of tPA to whites for acute ischemic stroke at academic medical centers in the United States.

While we do not dispute their findings, we wish to introduce an additional point that was not considered in their article, and to forward a means to partially remedy the disparity. Their findings were based on a retrospective analysis at 42 academic medical centers in the United States. tPA may have been administered at some of these institutions under the auspices of a phase II or III clinical study. If so, a community consultation should have been performed prior to this emergent research, per FDA and NIH requirements. However, the community consultation requirement has not been appropriately explained by the FDA or the NIH, and researchers may be at a loss as to how to effectively inform the community that experimental treatments are being administered without consent of either the patient-subject or a surrogate.

If physicians knew that an effective community consultation had been performed, one that reached all segments of the community, they would be less likely to unconsciously bias themselves against administering experimental treatment to minority populations. The specter of unethical research may account for some of the unconscious bias against administering experimental therapies to populations that have experienced historical injustices in clinical research. Rather than discriminating on the basis of racism, physician-researchers may be overly cautious in administering experimental therapies. Knowledge that an effective community consultation had taken place may allow physician-researchers to confidently administer experimental, albeit potentially lifesaving, treatments.

Johnson et al may have told us something we already knew: more work needs to be done to determine what counts as an effective community consultation before emergent research, which in turn may be one step toward remedying racial disparities in emergent research subject populations. Researchers must do more to understand both the procedures as well as the value systems that shape effective community consultations.

The authors are currently performing research on effective community consultations prior to emergent research, supported by Summa Health Foundation.

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Kent State University
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Glenda Wickstrom, MD, MS
Summa Health System
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Summa Health System

Life-Threatening Complications From Spinal Manipulation Are Rare

To the Editor:
The letter by Dr Ernst is misleading from the title. Are long thoracic nerve palsy and “local discomfort” life-threatening? The estimated annual incidence of spontaneous vertebral artery dissection (VAD) is 1 to 1.5 cases per 1000.

Estimates of cerebrovascular events associated with cervical manipulation range from 0.1 to 5.0 per 100 000. These are estimates of events and do not extrapolate to deaths or permanent impairment, which is an even smaller percentage that would be considered “life-threatening.”

In contrast, the risk of stroke from pregnancy is between 26 and 69 per 100 000.1 “Iatrogenic” arterial dissection as a complication of cerebral angiography has an “underreported” incidence rate of 400 per 100 000.

“Spontaneous” VAD can be caused by innocuous movements, and one would wonder whether the reports of manipulation being involved in VAD are just reports of the same entity. The concept of “spontaneous” lends to an idea of “instantaneous,” further confusing to etiology of this disease entity when manipulation is involved.

While some stress the temporal coincidence of trivial movements/chiropractic care with the onset of cervical artery dissection, easily concluding cause, suspicion should be raised with the discrepancy between relatively minor forces resulting in such severe vascular lesions.

An underlying arteriopathy leading to weakness of vessel walls and predisposing patients to “spontaneous” and/or chiropractic dissections has been proposed. In a rare autopsy examination after manipulation, the histopathological study by Peters et al of cervical arteries revealed widespread underlying disease of the arteries, with focal and segmental degeneration of smooth muscle tunica media and cystic transformation of the vessel walls. Additional predisposing factors were also described.

It would appear to be of more benefit to the public if articles identified the genetic, environmental, and maladaptive factors, rather than hyping the rare life-threatening complications of chiropractic care.

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9. Touze E, Randoux B, Meary E, Arquiza C, Meder JF, Mas JL. Aneu-
rysmal forms of cervical artery dissection: associated factors and
I, Hacke W. Ultrastructural connective tissue abnormalities in patients
zum Buschenfelde KH. Dissection of the internal carotid artery after

Response

Dr Di Duro’s interest is much appreciated. In my view, however,
his arguments are of debatable validity. Firstly, my editorial1 did discuss many life-threatening complications and
also included, for the sake of completeness, some minor adverse
events. Thus, I do not feel that the title was misleading. Second,
estimates of cerebrovascular accidents (CVAs) after spinal ma-
nipulation may well be invalid. They are built on certain
assumptions regarding the level of underreporting. We have
recently shown that, in the United Kingdom setting, underreport-
ing seems to be 100%.2 This renders estimates hardly worth the
paper they are printed on. Third, a recent, large case-control
study has demonstrated that spontaneous and chiropractic-
induced CVAs are, in fact, not the same.3 At least some
populations seem to be at risk of suffering a CVA from
chiropractic spinal manipulation which is significantly above that
of spontaneous CVAs.

In essence, this leaves us with the following situation. There is
preciously little hard evidence that upper spinal manipulation
produces significant health benefits for any type of patient. There
is mounting evidence that these procedures are associated with
relevant risks. Thus, there is considerable uncertainty regarding
the risk benefit profile of upper spinal manipulation. It is now up
to the chiropractic profession to convincingly demonstrate that
the benefits outweigh the risks. Until such data are available, it
is legitimate, I would even say prudent, to be cautious and
critical—primum non nocere!

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1. Ernst E. Life-threatening complications of spinal manipulation. Stroke.
2. Stevinson C, Honan W, Cooke B, Ernst E. Neurological complications of
3. Rothwell DM, Bondy SJ, Williams SJ. Chiropractic manipulation and
stroke: a population-based case-control study. Stroke. 2001;32:
1054–1060.

Retinal and Cerebral Artery Embolism After
“Shiatsu” on the Neck

To the Editor:

We read with great interest the articles by Ernst1 on the
life-threatening complications of spinal manipulation and by
Rothwell et al2 on the relation of chiropractic manipulation and
stroke, as we recently experienced a case of serious complication
caused by acupressure “shiatsu” on the neck. With the great
demand throughout the industrialized world for complementary
and alternative medicine, not only chiropractic and spinal ma-
nipulation but also shiatsu, an oriental technique of massage, are
becoming increasingly popular in western countries as a support
for general health and well-being.3,4 There are many accumpoints
on the body surface for shiatsu known as “tsubos,” and it is
accepted that by applying pressure on these tsubos one can achieve physically healing effects with hardly any serious side
effects.5 There are two such tsubos on the nape, and shiatsu on
these is known to improve tension headache due to neck and
shoulder stiffness; however, we recently experienced a very
suggestive complication of shiatsu on these tsubos.

Transient ischemic attack was diagnosed in an 80-year-old
man after he experienced a sudden onset of weakness in his left
hand in December 1999. Although he was asymptomat on
admission, MRI demonstrated a small infarction in the right
frontal lobe. MR angiography demonstrated bilateral internal
carotid artery stenoses just distal to the carotid bifurcation.
Cerebral angiography with contrast media was not performed at
that time due to mild renal impairment. After anticoagulant
therapy with argatroban for 7 days, he was discharged, free of
any neurological symptoms, with a prescription for ticlopidine
hydrochloride. On the evening of the day of discharge, he
received shiatsu massage on the neck in a prone position, with his
face buried in a pillow, for approximately 10 minutes to improve
a mild headache associated with neck and shoulder stiffness.
Immediately after rising, he was aware that the nasal half of his
right visual field was impaired. When this ocular symptom did
not improve, he returned to our hospital the following morning.
Ophthalmologic examination disclosed that his right visual
acuity was only counting fingers at 10 cm, and neurological
examination showed slight left hemiparesis dominant in the
upper extremity. Fundus examination disclosed diffuse retinal
dehema with multiple emboli in many branches of the central
retinal artery, and fluorescein angiography was compatible with
multiple branch oclusions of the central retinal artery (Figure,
left). Fluid-attenuated inversion recovery MRI of the brain
showed multiple small infarctions in the right frontoparietal lobe
(Figure, right). The patient was hospitalized and treated with
intravenous infusion of urokinase for 7 days, with almost full
recovery of left hemiparesis and minimal improvement of ocular
symptoms.

As Ernest1 mentions, it is important to generate reliable incidence
figures on complications of spinal or chiropractic manipulations.
The same holds true for shiatsu; however, very few serious com-
lications of shiatsu therapy could be found in the literature. Mumm
et al6 reported an interesting case of probable traumatic zoster that
might have resulted from direct trauma to the nerve or nerve roots
during shiatsu massage. On the other hand, direct pressure to or
around the extracranial carotid artery, such as carotid sinus massage,
can cause embolic accidents, especially in elderly people.7 It would
not be unexpected that shiatsu on the neck could cause similar
complications; however, we were unable to find any medical reports
cerebral or retinal artery embolisms directly caused by shiatsu.
We are not denying the traditional healing effects of shiatsu, but
we would like to call to attention the fact that it may cause serious
neurological symptoms in patients with atherosclerotic extracranial
carotid artery disorders, the incidence of which is greater in
Caucasians than in Japanese,8 and the potential risk of embolic
accidents associated with shiatsu may be higher than generally
accepted. Although Rothwell et al2 successfully demonstrated ob-
jective data on the association of vertebrobasilar accidents and
chiropractic manipulation by a population-based case-control study,
they mention that the rarity of vertebrobasilar accidents makes this
association difficult to study. The same problem can be predicted
when studying the association between shiatsu and embolic acci-
dents originating in the extracranial carotid artery. However, it
should be stressed that these complications can be avoided if
patients at high risk are properly informed beforehand of the
potential association between embolic stroke and manipulation on
the neck.

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Is Retrospective Study Reliable in Genetic Studies?

To the Editor: We read with great interest the preliminary study by Niskakangas et al.1 “Association of Apolipoprotein E Polymorphism With Outcome After Aneurysmal Subarachnoid Hemorrhage.” Although in this paper the authors concluded that there is a significant association between apolipoprotein E e4 (apoE e4) and the outcome of subarachnoid hemorrhage (SAH) patients, we have some reservations about the methodology and its data analysis.

The classification of CT findings used in this study was different from the original study of Fisher et al:2 there are only 4 grades in Fisher’s grading scale, instead of the 5 grades shown in the article by Niskakangas et al. Each grade was clearly defined in the Fisher study, whereas the scale used in the Niskakangas study falls short of a clear definition. In their statistical analysis section, the authors then mention that the CT findings were allocated to 1 of the 4 categories. It would be helpful if the authors could clarify how they grouped the 5 grades into 4 categories during the statistical analysis.

We noticed there was a fundamental problem with the data collection and presentation on the neurological outcome of patients. Patients from groups both with and without apoE e4 had a 0- to 57-month follow-up. This may contribute to inaccuracy and bias in the assessment of the patients’ neurological outcome after a SAH. The convention in neurological outcome assessment prescribes a duration of at least 6 months from the time of hemorrhage to the time of assessment, in order to ensure that the patient’s clinical condition and recovery are stable before assessment.3 Information on the distribution (SD) of the duration of follow-up may indicates the proportion of patients who had their neurological outcome assessment too early during their recovery period. The other possibility is that these 0-month follow-up cases were all mortalities.

Results presented in Tables 1, 2, and 3 of the article by Niskakangas et al may contain an error. All variables, including the demographic, clinical, and radiological data and the neurological outcome, that compared with the apoE e4 group were not carried out by the Fisher exact test as mentioned in the Statistical Analysis section. The probability values presented were, in fact, the standard errors of the difference of the 2 proportions compared; neither the scale of measurement was comparable (eg, 0.029 instead of 2.9%) nor was the calculation was based on the exact method.

Apart from the misleading probability value calculated, it was inappropriate to compare each subgroup separately. For example, the authors compared each level of initial Hunt and Hess score with and without apoE e4 separately using the same data. Instead, the Fisher exact test (or \( x^2 \) test), as originally proposed, for this 5 \times 2 contingency table is the appropriate method.

The authors mentioned that there were 4 patients who were dead, but their apoE genotypes were unknown. We have also included these patients into the analysis, assuming that none, 1, 2, 3, or all 4 harbor the apoE e4 allele. The association between apoE e4 and outcome disappeared when none of these patients were assumed to have the gene \( (P=0.068; OR 2.15, 95\% CI 0.94 \) to 4.97). This article clearly demonstrated the limitation of a retrospective study. It is difficult to convince the readers that there is an association between APOE polymorphism and SAH recovery with a retrospective study as shown in this paper, especially when there was a significant number of missing patients (14.3%). Although we have queries regarding the methodology, data analysis, and the conclusion of this article, it did demonstrate the necessity of having a well-designed prospective clinical study that may be in a better position to investigate the association.

The Fisher Grading Scale

<table>
<thead>
<tr>
<th>Grade</th>
<th>Subarachnoid Blood on CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No blood detected</td>
</tr>
<tr>
<td>2</td>
<td>Subarachnoid blood &lt;1 mm thick</td>
</tr>
<tr>
<td>3</td>
<td>Subarachnoid blood &gt;1 mm thick</td>
</tr>
<tr>
<td>4</td>
<td>Diffuse or no subarachnoid blood, but intracerebral or intraventricular clots</td>
</tr>
</tbody>
</table>
between apolipoprotein E polymorphism and outcome in patients with aneurysmal SAH.

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Response

We wish to thank Poon et al for their interest and very valuable comments concerning our recent article in Stroke.1 We agree that we did not use the original Fisher’s grading scale, but properly noted that a modified Fisher scale was used. We should have defined the grading system more clearly already in the article. Differences are as follows: in grade 1, we saw only a very small amount of blood locally in the subarachnoid space (can be seen); in grade 2, there was subarachnoid blood <1 mm thick; grade 3, >1 mm thick, diffusely spread throughout the subarachnoid cisterns; and in grade 4, there was diffuse subarachnoid hemorrhage (SAH) and/or large hematoma or intraventricular bleeding. Although we did not use the original Fisher grading scale, in our opinion it was mainly based on that, and therefore we considered it fair to reference the original article. Regrettably, there is an error in the text in the Statistical Analysis section. We have allocated CT findings to 5 groups in statistical analysis, 0 through 4.

We agree that there is heterogeneity in the follow-up times of the patients. However, the length of the follow-up time partly describes the outcome of a patient, and the different distribution of the ε4 allele is already seen here. Patients with good outcome returned to normal life after a convalescence period of approximately 2 to 3 months, were clinically stable, and had no clinical indication to be followed up after that. Patients who were primarily in poor condition were followed up for a longer period, enabling us to better estimate the final clinical condition of these patients. The majority of those 0-month follow-up cases were patients who died, and in addition 3 patients (followed up for 1 to 2 weeks) who were primarily in good condition when leaving the hospital.

As Poon et al point out, there were unforgivable calculation errors concerning the statistics of the patient characteristics (Table 2). The probability values in the Table 2 are erroneous statistical raw data. The differences between the patients with and those without the APOE ε4 allele were tested using the χ² test. All probability values for the group differences were statistically insignificant, as follows. In the Table 2, concerning the initial Hunt and Hess score, the P value was 0.21 (df=4, χ²=5.82), and in the initial CT findings the P value was 0.91 (df=4, χ²=0.97).

Poon et al have presented an interesting view about considering those 4 missing dead patients, presenting 3% of the whole series. That was very valuable point, and it emphasizes the problem of the selection bias in retrospective association studies. We hypothesized that the ε4 allele is a risk factor for poor outcome after SAH. In a recent publication by Dunn et al, the ε4 allele frequency of SAH patients was lower than in normal population, suggesting that the ε4 allele could be associated with an excess rate of early mortality after SAH and therefore causing a selection bias, while patients with poor outcome are not included to clinical patient series. The same could have happened in our series.

Poon et al have stated some of the potential weaknesses of retrospective study design in genetic studies in general and in our study in particular. The complexity of the natural cause of this devastating disease and possible complications in therapy itself make the design of outcome studies quite difficult. Thus far, there has been one prospective clinical series studying the association of APOE genotype with SAH outcome, and even in it there were some problem with selection bias.

We do not suggest that our hypothesis is the final truth. It is a preliminary report, as we stated in the subtitle of our article. There is, indeed, a need for a prospective, properly designed population-based studies that includes patients who die before admission to hospital. Future studies will show whether the APOE gene polymorphism has a role in the prognosis of subarachnoid hemorrhage. Considering the fundamental role of APOE in neurobiology,3 we think that APOE is an important area for studies of subarachnoid hemorrhage and of hemorrhagic stroke in general.

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IMT for the Elderly?

To the Editor:

I would like to respond to an article published in a recent issue of Stroke, entitled “Is Carotid Intima-Media Thickness Useful in Cardiovascular Disease Risk Assessment?”

The title of the article caught my eye because my profession involves extensive use of carotid intima-media thickness (CIMT) for detection of atherosclerosis. However, I was surprised that the title did not reflect the misleading nature of the article, and it appears to refute the authors’ earlier published works.2

The title of the article suggests that certain cardiovascular risks were compared with assessment of CIMT. The authors of this article concluded that as a screening tool, CIMT does not represent a substantial increase in the predictive value for
CIMT alone as a predictor of cardiovascular and cerebrovascular disease clearly indicate the value of measurement and interpretation of a risk factor is not all that normal lifespan in 40% of the cases studied. Would this imply levels has been demonstrated by Sijbrands et al not to limit detection. We remain confident that our ounce of prevention is worth a pound of cure.

CIMT is not appropriate for screening when the patient would have known cardiovascular disease risk factors in development. The key to controlling the disease is prevention, rather than dealing with it after it has progressed to riskier stages. A typical screening setting is for new patient discovery, and the methodology for screening was not optimal here. Unlike other screening methods, the purpose of CIMT is to look at the disease itself, instead of examining the risk factors. Risk factors are often arbitrarily selected by the investigator out of a pool of sometimes more that 246 suggested factors in every patient. In a different Netherlands study, a major risk factor like elevated cholesterol levels has been demonstrated by Sijbrands et al to not limit normal lifespan in 40% of the cases studied. Would this imply that measurement and interpretation of a risk factor is not all that relevant, but viewing the disease itself would be? The well-established statements by the American Heart Association and American College of Cardiology clearly indicate the value of CIMT alone as a predictor of cardiovascular and cerebrovascular events. This article gives the misleading impression that the technique of measurement of CIMT used in the Rotterdam Study is widely used. This important point was overlooked by the authors. The procedure described using calipers is clearly outdated; so is the aggregate maximum measurement of the IMT. Our group uses carotid IMT (IMTHeartScan) to screen different populations with a proprietary edge contour detection technique (ARTIS, Prevention Concepts Inc) in a screening setting, as well as a risk factor management setting. Our procedure allows us to predict with a high degree of confidence both an absolute and relative risk of cardiovascular complication in ethnically diverse populations. We disagree, however, that such measurements have no value in patients in which disease has progressed to some extent. Even in those at higher risk of coronary heart disease it may be of great importance to be able to identify those who are at a relative higher risk compared with those at a relative lower risk in order to target treatment.

Instead of an arbitrary selection out of 246 risk factors, as Dr Barth suggested, our selection of established risk factors was based on the ability for a general practitioner to easily obtain that information, since in the Netherlands the general practitioner is usually the first line of the medical circuit to contact. The focus of our study was to evaluate the added value of the CIMT measurement when added to easily obtainable risk factors.

With respect to the CIMT measurement as performed in the Rotterdam Study, Dr Barth is of the opinion that we used an outdated measurement technique and that an aggregate maximum measurement of CIMT is also outdated. We would like to point out that the CIMT measurement technique used in the Rotterdam study is based on manual tracing over a 10-mm segment as well as on an automated edge technique that has been shown to be state of the art and is used in trials and population-based studies. Furthermore, we disagree with the “outdatedness” of aggregate measures. Clearly, the far wall of the common carotid is perhaps easier to measure and may yield a high reproducibility, but the aggregate measures reflect the entire carotid atherosclerosis burden and are and will remain a major outcome in trials.

Finally, our CIMT measurement predicts future disease in a magnitude similar to that in other population-based studies that use either manual tracings or automated edge detection tracing.

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Response

Our article on the usefulness of carotid intima-media thickness measurements in cardiovascular risk assessment concluded that in a general population aged 55 years or older, when information on established risk factors (medical history, smoking, blood pressure, cholesterol, and body mass index) is available, the measurement of CIMT does not add substantially in distinguishing high-risk from low-risk patients. When, however, only age, sex, and CIMT were present, there was a considerable increase in the diagnostic ability of the model. We agree with Dr Barth that our data pertain to subjects 55 years or older, and it may be different in younger populations and in high-risk populations.

We disagree, however, that such measurements have no value in patients in which disease has progressed to some extent. Even in those at higher risk of coronary heart disease it may be of great importance to be able to identify those who are at a relative higher risk compared with those at a relative lower risk in order to target treatment.

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J.C.M. Witteman, PhD
M.L. Bots, MD, PhD


6. Barth JD. Which tools are in your cardiac workshop? Carotid ultrasound, endothelial function, and magnetic resonance imaging. Am J Cardiol. 2001;87:8A–14A.
11. Hodis HN, Mack WJ, LaBree L, Selzner RH, Liu C, Liu C, Azen SP. The conclusion which results from the interpretation of Table 2 of Gibbs et al (although not documented in our experience, however) is that a correlation probably exists between recent or established carotid atherosclerotic disease and increased correlation between soft plaques and C pneumoniae infection results from the interpretation of the table. More investigation of the carotid plaque with ultrasonography is required, however, with an adjunct TCD, for better corroboration of the final result.

In our work, an attempt was made to combine the recent or chronic disease due to C pneumoniae, as shown from the results of the titers of immunoglobulin (Ig)G and IgM. Our results were as follows3,4: 20 of 35 (57.1%) of the patients had an increased IgG titer of antibodies; 2 patients had high IgG and IgM antibody titers and were PCR positive, while both were symptomatic. It should be noted that we had also examined samples of thyroid artery in all of the patients in whom C pneumoniae was not traced in the arteries. Sixty-five percent of the 20 patients with increased IgG antibody titer were symptomatic; in the subgroup of 8 patients with IgG and IgM antibodies (recent disease), 85% were symptomatic; and in the subgroup with active disease (IgG+IgM+polymerase chain reaction [PCR]), both patients were symptomatic. Moreover, we examined the quality of the atheromatous plaque with use of color-coded duplex sonography; however, we were not able to connect the soft plaques of type I and II with the symptomatic patients, while the majority of the symptomatic patients had plaques of the III, IV, and V type. The basic conclusion is that there was a high affinity between recent disease and signs of C pneumoniae in the plaques when PCR was used. In our work, we concluded that the symptomatic patients, in the majority of the cases, were seropositive.

In any case, there is no etiological connection between the systematic disease arising from C pneumoniae, as shown by the titer of the antibodies, and the specific localization on the carotid plaque.

More studies focused on this matter might connect the titer of the antibodies and carotid stenosis, or, better still, the influence of the ratio in the presence of cerebral episodes.

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Re: Chlamydia pneumoniae Does Not Influence Atherosclerotic Plaque Behavior in Patients With Established Carotid Artery Stenosis

To the editor:
We read the interesting paper of Gibbs et al.1 We believe that, just as in other cases, the inflammatory response to infection probably plays a significant role.2 The basic incentive in writing this letter is to underline the following assertion that results from the original idea of the authors to check the rhythm of emboli by means of transcranial Doppler ultrasonography (TCD).

The fact that most patients without Chlamydia pneumoniae infection present with a cerebral episode does not discard the relationship between infection from C pneumoniae and embolization. It is simply the reporting of the results, which the authors suggest, that the plaques can be influenced by C pneumoniae infection, because wherever we find C pneumoniae infection we discover more embolic episodes.

The conclusion which results from the interpretation of Table 2 of Gibbs et al (although not documented in our experience, however) is that a correlation probably exists between C pneumoniae infection and plaques (soft, or not taking under consideration that many embolic episodes do not provoke many cerebral episodes as well in the C pneumoniae–positive group), despite the fact that the discovery of the rhythm of emboli with TCD had not resulted in an increase in the number of cerebral episodes. The reasoning that there may likely exist some kind of increased correlation between soft plaques and C pneumoniae was not traced in the arteries. Sixty-five percent of the 20 patients with increased IgG antibody titer were symptomatic; in the subgroup of 8 patients with IgG and IgM antibodies (recent disease), 85% were symptomatic; and in the subgroup with active disease (IgG+IgM+polymerase chain reaction [PCR]), both patients were symptomatic. Moreover, we examined the quality of the atheromatous plaque with use of color-coded duplex sonography; however, we were not able to connect the soft plaques of type I and II with the symptomatic patients, while the majority of the symptomatic patients had plaques of the III, IV, and V type. The basic conclusion is that there was a high affinity between recent disease and signs of C pneumoniae in the plaques when PCR was used. In our work, we concluded that the symptomatic patients, in the majority of the cases, were seropositive.

In any case, there is no etiological connection between the systematic disease arising from C pneumoniae, as shown by the titer of the antibodies, and the specific localization on the carotid plaque.

More studies focused on this matter might connect the titer of the antibodies and carotid stenosis, or, better still, the influence of the ratio in the presence of cerebral episodes.

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Response
We thank the authors for their comments, and were interested in their hypothesis that C pneumoniae is more likely to be found in soft, lipid-rich plaques compared with harder fibrous plaques. Ultrasound assessment of plaque density was not a factor assessed in this work, so any comment is conjectural. However, we disagree with their interpretation of the results presented. Soft plaques have been reported to be more likely to embolize and cause cerebral ischemia than hard plaques. If there were an association between C pneumoniae and soft plaque content, the results would have been biased in such a way that C pneumoniae would have been more likely to be associated with embolization
and infarction. This was manifestly not the case; if the results had shown a significant correlation between embolization, infarction and \textit{C} \textit{pneumoniae} DNA, then plaque content would have had to be analyzed to ensure it was not a confounding factor. Whether \textit{C} \textit{pneumoniae} has a causal or disease-modifying effect has yet to be established. We suggest that if the case is proven, the underlying mechanisms in atherogenesis or alteration of plaque behavior are likely to be at the subcellular level, and interpretation of plaque content either by ultrasound or histology is unlikely to shed light on cause and effect.

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\textbf{A Novel TCD Grading System for Residual Flow in Stroke Patients}

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\textit{To the Editor:}

We read with great interest the article of Demchuk and colleagues\textsuperscript{1} regarding the clinical significance of transcranial Doppler flow grades for stroke patients. However, there appeared to be a few discrepancies in the manuscript that require clarification.

In the first paragraph of the Results section on page 91, the authors indicate that data from 94 patients were analyzed. However, in the summary table, the total patient number is 92. The authors should clarify why 2 patients were not included in their summary data.

In the third paragraph of the Results section on page 91, the authors state that TIBI flow improvement to grades 4 or 5 occurred in 35\% of patients (19/54) with an initial grade of 0 or 1. The results appear to be different in the results summary table. In contrast, in that table, 21 of 53 patients had flow improvement from 0 –1 to 4 –5. Therefore, the percentage of TIBI flow improvement to grades 4 or 5 instead of the 35\% (19/54) rate of flow improvement occurred in 35\% of patients (19/54) with an initial grade of 0 or 1.

\vspace{1em}

\textbf{Meihui Ma, MD, PhD}

\textbf{Joseph Berger, MD}

\textit{Department of Neurology}

\textit{University of Kentucky}

\textit{Lexington, Kentucky}

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\vspace{1em}

\textbf{Response}

We appreciate the interest and are grateful for the opportunity to reply to the comments of Drs Ma and Berger on our study.\textsuperscript{1} The authors requested clarification of some inconsistencies in the data. Ma correctly points out that the summary table includes only 92 patients. The reason 2 patients were not included in the summary data was that no follow-up TCD studies were performed in these cases, and therefore a change in Thrombolysis in Brain Ischemia (TIBI) flow grade from baseline to follow-up could be evaluated in only 92 cases. The full complement of 94 cases was included in the analysis of baseline TIBI grade.

The authors correctly point out that the summary table results reveal a 39\% (21/53) rate of flow improvement from TIBI 0 to 1 to 4 to 5 instead of the 35\% (19/54) rate of flow improvement from TIBI 0 to 1 to 4 to 5, as stated in the abstract and the Results section. The 35\% rate was based on the initial scoring of TIBI grades, which were later readjusted after final interpretation of TIBI scores. The summary table reflects the correct number in each TIBI group at both baseline and follow-up, on which all statistical analyses were based. We regret this error, but do not feel this error has significantly affected the results of the study.

\vspace{1em}

\textbf{Andrew M. Demchuk, MD, FRCPC}

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\vspace{1em}

\textbf{Inflammation, Statins, and Outcome After Ischemic Stroke}

\vspace{0.5em}

\textit{To the Editor:}

In the recently article by Jonsson and Asplund,\textsuperscript{1} the authors demonstrate that statins have a moderate effect in improving the prognosis of ischemic stroke patients, underlying the possible complex role of statins in determining prognosis after ischemic stroke. Their data are in agreement with our preliminary results on the concurrent use of statins in patients with first-ever ischemic stroke.\textsuperscript{2} Previously, we found that the use of statins reduces the levels of \textit{C}-reactive protein (CRP) after ischemic stroke, the initial neurological deficit, and improves the prognosis of stroke patients with a significant reduction of the 1-year risk of death or new vascular events.\textsuperscript{2} Recently, we have extended these observations in the same ischemic stroke cohort that had concluded the 2-year follow-up. All patients (n=193) were recruited in the period between March 1, 1998, and March 31, 1999. Design, methods, and baseline characteristics of our stroke data bank have been previously reported.\textsuperscript{3,4} We measured levels of CRP after stroke (within 24 hours), at 3 months, and at the end of the 2-year follow-up, together with total cholesterol, HDL and LDL subfractions, and triglycerides. Differences in proportions were evaluated by \textit{χ}\textsuperscript{2} test. Continuous variables are described as mean±SD or median values with 25th and 75th percentiles, and comparisons between groups were evaluated with the Student \textit{t} test or Mann-Whitney \textit{U} test, when appropriate. The Kaplan-Meier technique (log-rank test) was applied in survival analysis. Log-normalized values of CRP were used to evaluate correlations over time.

At the entry, mean total cholesterol concentrations were 4.62±1.25 mmol/L in men and 5.31±1.06 mmol/L in women (\textit{P}=0.001; Student \textit{t} test). Mean HDL cholesterol concentrations were 0.95±0.39 mmol/L and 1.02±0.31 mmol/L (\textit{P}=0.1977), respectively. Mean LDL cholesterol concentrations were 3.97±1.32 mmol/L and 4.64±1.06 mmol/L (\textit{P}=0.001), and mean triglyceride concentrations were 1.50±0.73 mmol/L (\textit{P}=0.0255), respectively. Median CRP concentrations were 1.85 mg/dL in men (0.70 to 5.40) and 1.0 mg/dL in women (0.23 to 2.65; \textit{P}=0.0020, Mann-Whitney \textit{U} test) at the entry. Ninety-three patients (48.2\%) had a total cholesterol concentration ≥5.0 mmol/L at the time of ischemic stroke, 122 (63.2\%) had a ratio of total cholesterol to HDL cholesterol ≥5, and 175 (90.7\%) had LDL cholesterol ≥3.0 mmol/L. Fifty-two patients (26.9\%) took statins: simvastatin (\textit{n}=37; dose range 10 to 20 mg/d), pravastatin (\textit{n}=10; range 20 to 40 mg/d), and atorvastatin (\textit{n}=5; range 10 to 40 mg/d) at the time of qualifying stroke; of these only 16 (8.3\%) had a total cholesterol concentration <5 mmol/L.

Younger age (70.5±9.8 versus 73.7±8.8 years; \textit{P}=0.0321, Student \textit{t} test), a greater prevalence of arterial hypertension (90.4\% versus 68.8\%; \textit{P}=0.0022, \textit{χ}\textsuperscript{2} test), and history of dyslipidemia (51.9\% versus 31.2\%; \textit{P}=0.0081) were noted in statin group. Significantly lower median levels of CRP (0.6 mg/dL [0.3 to 1.5]) versus 1.9 mg/dL [0.8 to 3.75]; \textit{P}<0.0001, Mann-
Bar graph showing the cumulative risk at 1 year of death or new vascular event according to tertiles of CRP and statin treatment. The number of patients without concurrent statin treatment were as follows: lower C-reactive protein tertile (<0.5 mg/dL), 23; middle tertile (0.6 to 3.3 mg/dL), 73; highest tertile (>3.3 mg/dL), 38. The number of patients with concurrent statin treatment were as follows: lower C-reactive protein tertile (<0.5 mg/dL), 24; middle tertile (0.6 to 3.3 mg/dL), 28; highest tertile (>3.3 mg/dL), 7.

Whitney U test) within 24 hours after stroke, together with a significantly lower score on the Canadian Neurological Stroke Scale (7.5 [6.0 to 9.0] versus 6.0 [4.5 to 8.0]; \( P = 0.0003 \)) were also found in patients with statin therapy. No differences were found in terms of neuroradiological findings such as large infarcts, cortical involvement, hemorrhagic transformation, brain edema, or of stroke subtypes.

There was not a compulsive lipid-lowering treatment during follow-up, so only an additional 7 (3.6%) patients received statin therapy during their in-hospital stay. Diet control was prescribed in all patients with total cholesterol level \( \geq 5 \text{ mmol/L} \). No lipid-lowering drug therapy was prescribed by the referring physician. No patients stopped statin treatment. During the 2-year follow-up period, 76 patients (40%) had a combined end point (death or any new vascular event): 36 patients died (vascular death in 29), and 40 had a nonfatal vascular event (cardiac in 21 and cerebral in 19). Only 12 combined end points (3 death and 9 new nonfatal vascular events) were registered in those without statin therapy, median CRP levels and the mean HDL cholesterol levels (difference, 0.5 mg/dL; \( P = 0.147 \)). In the statin group, 31 (68.9%) had a total cholesterol concentration \( \geq 5 \text{ mmol/L} \), and 38 (84.4%) had a ratio of total cholesterol to HDL cholesterol \( >5 \) at the end of the 2-year follow-up.

The concomitant use of statins at the time of stroke appears to reduce the neurological deficit and improves the prognosis. This effect is apparently independent from the lipid concentrations, because at the end of the follow-up there were no significant differences in lipid concentrations between 2 groups. In the short-term period, the effect of statins is probably related to their anti-inflammatory properties more than lipid concentration reduction. A greater risk reduction was found in the subgroups of patients with higher levels of CRP, while lipid profile was similar in the 2 groups at the end of 2-year follow-up. However, some patients have an intense activation of inflammation system in response to a stroke with persistent elevated CRP levels.\(^4\) This activation is only partially reduced by statins.\(^5\) These patients, therefore, may benefit from a more careful clinical follow-up and probably from a more appropriate anti-inflammatory treatment.\(^6\)

A direct neuroprotective effect of statins in ischemic brain damage has been suggested.\(^7\) There was no evidence of this effect in our stroke population, because no associations were found between statin therapy and neuroradiological findings. However, a strong and persistent acute-phase response after stroke is associated with larger infarcts,\(^5\) so the neuroprotective effect of statins is more complex in humans than that we can actually realize.

In conclusion, the proportion of patients with ischemic stroke who received statin treatment is low, and even an even lower proportion of them received efficacious control of hypercholesterolemia. A more extensive and aggressive use of statins in all patients at risk for and with first-ever ischemic stroke, and especially in patients with persistently higher CRP levels after ischemic stroke, should be developed into specific screening programs that will be appropriately funded and developed in a public health perspective.\(^8\)

Written on behalf of the Villa Pini Stroke Data Bank Investigators, whose members also include Vittorio Bocola, MD, Donato Melchionda, MD, Rocco Santarelli, MD, and Antonina Faricelli, MD.

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Inflammation, Statins, and Outcome After Ischemic Stroke
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