Atrial Fibrillation and Stroke: More Concepts and Controversies

To the Editor:

We wish to congratulate Hart and Halperin1 on their excellent overview of the current “concepts and controversies” surrounding atrial fibrillation (AF) and stroke.

In discussing the formation of thrombus within the left atrial appendage (LAA), they focus a large part of their discussion on the issue of blood stasis in the LAA that occurs in AF, suggesting this mechanism of thrombogenesis to perhaps be of greatest importance, although conceding that “many questions remain about the formation and embolism of left atrial thrombi and, consequently, about the pathogenesis of AF-associated stroke”.2,3 They also comment that “endothelial lesions in the appendage have not been found, and systemic prothrombotic diatheses that contribute to thrombus formation have been suggested but not convincingly identified.”4

We would suggest, however, that there is a growing body of evidence suggesting that endothelial (or endocardial, within the LAA) changes and hemorrheological (or prothrombotic) abnormalities may indeed play a role in the formation of intra-atrial thrombus and subsequent stroke and thromboembolism in AF, thus fulfilling the 3 components of Virchow’s “triad” of thrombogenesis.

Evidence of endothelial abnormalities among patients with AF is suggested by numerous studies documenting elevated plasma levels of circulating surrogate markers of endothelial damage/dysfunction, most notably von Willebrand factor (vWF). The latter has been demonstrated to independently predict the presence of LAA thrombus on transesophageal echocardiography (TEE).2 In addition, direct evidence of atrial endothelial abnormalities has been reported. From necropsy studies, endocardial fibroelastosis in the LAA5 and (among cases of fatal thromboembolic stroke) areas of left atrial endocardial denudation with thrombotic aggregations on scanning electron microscopy (SEM) have been reported,6 being more commonly seen in specimens from patients with AF than those in sinus rhythm.

Furthermore, in specimens collected during mitral valve surgery, we have recently reported SEM evidence of LAA endocardial damage in patients with mitral valve disease, which appears to be more advanced among those with mitral stenosis (compared with mitral regurgitation) and in those with AF (compared with those in sinus rhythm, although not statistically significant due to small numbers).5 Of interest, the patients with more advanced LAA changes on SEM had significantly higher plasma levels of vWF.5 A recent study also reported greater macrophage tissue factor and vWF expression in the atrial tissue of patients with AF, again suggesting a role for the atria in thrombogenesis.6

Evidence of a prothrombotic or hypercoagulable state in AF comes from even more numerous studies, documenting abnormal levels of various markers of intravascular thrombosis, fibrinolysis, and platelet function; these indices appear to be independent of underlying etiology of AF and structural heart disease, and some revert to normal levels after successful cardioversion or the introduction of antithrombotic therapy.7 Furthermore, some indices such as β-thromboglobulin (BTG) have independently predicted LAA thrombus on TEE.2 However, we also note that in the larger Stroke Prevention in Atrial Fibrillation (SPAF-III) TEE substudy, only high levels of plasma fibrinogen (but not BTG) were independently predictive of spontaneous echo contrast on TEE, which is itself predictive of LAA thrombus and stroke.8 Unfortunately, plasma fibrinogen, BTG, prothrombin fragment F1.2, and factor V Leiden levels did not predict stroke among another subgroup of SPAF-III participants,9 but many other endothelial, platelet, and coagulation markers were not assessed.

Despite the failure to date to identify a suitable predictive plasma marker for stroke in AF, the evidence for the presence of endothelial and hemorrheological abnormalities in AF and their relationship to intra-atrial thrombus formation is growing. Some controversy still remains whether the observed abnormalities are caused by AF itself or other underlying cardiovascular conditions.10 Importantly, many previous studies have not fully accounted for differences in hemostatic markers between patients with paroxysmal, persistent, and permanent AF, in light of possible differences in the prothrombotic state between these clinical subgroups.11

We would therefore suggest that continued investigation of endothelial (or endocardial) and prothrombotic abnormalities may still be of critical importance in unraveling the complex pathogenesis of AF-related thrombogenesis.

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Does Antibody to the α4 Integrin Inhibit the Function of Lymphocytes and Monocytes?

To the Editor:

We read with great interest the article by Becker and colleagues1 in the January 2001 issue of Stroke, in which the authors sought to assess the contribution of lymphocytes and monocytes to ischemic brain injury. They found that the administration of TA-2, an antibody against α4 integrin, reduced infarct size and improved neurological outcome when given 2 hours after a stroke. They also observed a peripheral leukocytosis with lymphocyte/monocyte predominance. Because the α4 integrin is thought to be found predominantly on lymphocytes and monocytes rather than neutrophils, they concluded that blockade of the α4 integrin reduced ischemic brain injury by antagonizing the functions of lymphocytes and monocytes. Although TA-2 binding of monocytes has been reported,2 Becker and colleagues neglected to present direct evidence showing that TA-2 administration ultimately blocked lymphocyte/monocyte infiltration and accumulation in the ischemic brain.

We would like to bring to the authors’ attention our study,3,4 on the role of α4 integrin in the cell adhesion process. This study revealed that the alternately spliced connecting segment domain (CS-1) of the extracellular matrix protein fibronectin, which interacts with α4 integrin and inhibits monocyte adhesion, inhibits neutrophil accumulation in ischemic brain and reduces infarct size.5 The reduction of neutrophil accumulation by α4 integrin-binding CS-1 peptide seems inconsistent, because neutrophils are devoid of cell surface α4 integrins. Neutrophils can be detected as early as 30 minutes after and peak at 24 hours after ischemia in rat brain.6 In contrast, monocytes are first detected in ischemic tissue 4 to 6 hours after cerebral ischemia in rats.5 Neutrophil migration into inflammatory tissue has been observed following the infiltration of monocytes,7 and neutrophil migration is thought to be initiated, in part, by a factor released by monocytes.6 Although we did not report direct evidence of the participation of lymphocytes and monocytes in those articles, we hypothesized that antagonizing α4 integrin could result in the reduction of neutrophil accumulation by blocking monocyte function. A companion article2 from Becker’s laboratory also found that the administration of TA-2 reduced neutrophil infiltration into the ischemic brain. Becker et al did not examine lymphocyte/monocyte accumulation in the brain and therefore failed to determine a potential therapeutic mechanism of TA-2 administration in stroke. At a minimum, any alteration of lymphocyte/monocyte accumulation into the ischemic brain after administration of TA-2 should have been determined.

Leukocyte adhesion to endothelium and the extracellular matrix occurs via highly specific receptor-ligand-mediated interactions. Much emphasis has been placed on the interaction between β2 integrin (Mac-1, LFA-1) and intercellular adhesion molecule (ICAM)-1 in mediating neutrophil recruitment to sites of cerebral infarction and on the potential value of blocking this interaction to control neutrophil emigration.7–9 However, the study by Becker et al focused on lymphocyte/monocyte function, and provides an important contribution to the literature. We congratulate the authors on their careful observations.

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Response

We recently showed that inhibition of the α4 integrin decreases infarct size in an experimental model of transient focal cerebral ischemia.1 Very late activation antigen-4 (VLA-4 or α4β1) mediates lymphocyte/monocyte adherence to the endothelium through interaction with VCAM-1,2 an interaction that also results in lymphocyte/monocyte activation.3,4 Because VLA-4 is primarily expressed on lymphocytes/monocytes, we hypothesized the apparent benefit of anti-α4 therapy was related to inhibition of lymphocyte/monocyte trafficking into brain or to inhibition of lymphocyte/monocyte activation. This hypothesis, as Yanaka and colleagues point out, was not directly tested.

Based on their own experiments with synthetic fibronectin peptides, Yanaka and colleagues argue that inhibition of lymphocytes/monocytes may indirectly prevent neutrophil accumulation in brain.5 This argument is based on the fact that administration of synthetic fibronectin peptides results in a decrease in infarct size and in myeloperoxidase (MPO) activity in ischemic brain. Because the fibronectin peptides bind to and inhibit β2 integrins, which are expressed on lymphocytes/monocytes but not β1 integrins, which are found on neutrophils, the authors hypothesize that the decrease in MPO activity, and hence neutrophil influx, results from an effect of the fibronectin peptides on lymphocytes/monocytes. In the article by Relton et al6 that also appeared in the January 2001 issue of Stroke, the authors reported that animals treated with an antibody to the α4 integrin expressed less MPO activity in infarcted brain than animals treated with an isotype control antibody. Both of these studies suggest a role for lymphocytes/monocytes in modulating the initial inflammatory response after stroke. A similar role for lymphocytes/monocytes in modulating inflammation in other organs has also been shown.7 An alternative explanation for the observed effects of anti-α4 therapy is that neutrophils, at least in certain situations, may express VLA-4 and bind to endothelium through VCAM-1.8,9

The comments of Yanaka and colleagues are appreciated. We agree that interpretation of results in experiments using anti-adhesion therapy is complicated, especially without direct visualization of leukocytes in the organ of interest. Quantitative immunocytochemistry on the brains from our experiments is currently being done and will hopefully allow us to determine whether an inhibition of neutrophil or lymphocyte influx was responsible for the observed benefit of anti-α4 therapy.
Letters to the Editor

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Risk of Subarachnoid Hemorrhage From a De Novo Aneurysm

To the Editor:
I read with interest a recent article concerning risk of de novo aneurysm formation and recommendations for future screening for these aneurysms after successful clipping of an intracranial aneurysm. Although the results of the study are reliable, the conclusions are not based on the data of this and previous studies. The patients whose aneurysms have been treated successfully should not unnecessarily be made anxious and fearful for decades because of a very low risk for subarachnoid hemorrhage (SAH) from a potential de novo aneurysm.

In our first angiographic follow-up study (published in 19932), of 31 patients with a mean follow-up of 9 years (range 0.8 to 23.0 years; total follow-up of 279 person-years), formation rate of a de novo aneurysm cases was 2.2%/y, which was similar to that in a recent study (1.8%/y).1 In both of these studies, the formation rate of new aneurysms was likely too high, because new SAH cases were overrepresented in these study populations. Interestingly, in the study of Tsutsumi and colleagues,1 the formation rate of a de novo aneurysm was lower and similar (0.89%/y) to that in our recent study (0.84%/y), obtained among 89 patients with a mean follow-up time of 20.1 years per patient (range 1.2 to 38.9 years; total follow-up time 1789 person-years),4 which suggests that aneurysm formation rate is lower if the follow-up is not restricted to a high-risk population. In our study, there were 15 de novo aneurysm cases, and female gender and cigarette smoking increased this risk. De novo aneurysms developed during a mean follow-up time of 18.8 ± 7.7 years, a period not differing significantly from that of those without de novo aneurysms. In cases in which a de novo aneurysm caused SAH, the follow-up time was somewhat shorter (14.7 ± 8.1 years, range 3.4 to 28.4 years).

When the aneurysm formation rate of our study is adjusted to the population, with an equal sex ratio and a smoking prevalence of 25% as in the general population, the aneurysm formation rate is 0.56%/y.4 It was somewhat surprising that female gender was not associated with aneurysm formation in the study of Tsutsumi and colleagues,1 likely because of too few de novo aneurysm cases or overrepresentation of men among those with angiographic follow-up. It is well known that women have a higher risk for SAH.4 Because female gender does not increase either risk for rupture of a verified unruptured aneurysm5,6 or risk for growth of an intact aneurysm,7 women very likely have an increased risk for aneurysm formation.

Diagnosis of de novo aneurysm is rare, since these are almost always diagnosed after a rupture. Assuming, on the basis of our previous study,4,6 that the risk of rupture of an unruptured aneurysm is approximately 1.3%/y and that the rate of formation of an aneurysm is 0.84%/y, patients whose aneurysms have been treated successfully seem to have a risk for SAH from a de novo aneurysm of 11/100 000 per year. When the aneurysm formation rate is 0.56%/y, the approximate SAH incidence is 7.3/100 000 per year. These incidences of SAH are even lower than those of the general adult population (30 to 60/100 000 per year). Alternatively, risk of SAH from a de novo aneurysm can be calculated directly from data. In the study of Tsutsumi and colleagues,1 it seemed to be 100/100 000 per year or 0.1%/y (4 de novo aneurysm SAH cases per approximately 3980 follow-up years in 142 patients). In our study,4,6 this rate was 78/100 000 per year (95% CI 9 to 276/100 000 per year: 2 de novo aneurysm SAH cases per 2575 follow-up years in 142 patients). Thus, treated SAH patients may have at most a 2- to 3-fold increase of subsequent SAH from a de novo aneurysm. It seems that future screening of new aneurysms is not justified, particularly as it is now controversial whether unruptured aneurysm should even be operated on.5,6 Rupture risk of an unruptured aneurysm is clearly higher than that of a potential de novo aneurysm. In our study,6 33 (currently 34) of 142 patients with unruptured aneurysms suffered SAH from their untreated aneurysm whereas only 2 had SAH from a de novo aneurysm.

In 2 of our 89 patients with aneurysm follow-up,2,3 an aneurysm had developed in the neck of an aneurysm that had ruptured and been clipped. In 4 other patients whose ruptured aneurysms were not totally clipped, the size of the aneurysm increased during follow-up; 2 of the patients suffered a rebleed from that aneurysm (1 rebleed was fatal). These were not considered de novo aneurysms. It seems that clipping of a ruptured aneurysm was relatively efficient from the 1950s to 1970s. Screening of aneurysms may be justified only among patients with a “heavy” family history for these lesions, eg, with 3D CT angiography, which is as reliable as conventional angiography in detecting de novo aneurysms.4

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Letters to the Editor


Response

We appreciate Dr Juvela’s comments on our article, and we also would like to take this opportunity to express our full respect for his numerous important studies that have contributed to the body of knowledge in this specific field.1,2

As Dr Juvela pointed out, whether screening for new aneurysm formation is to be recommended or not can be a difficult issue. However, as we described in our article,3 we did observe 4 cases of SAH from de novo aneurysms in our series of 412 patients, which, as Dr Juvela noted, exceeded his estimation of 11/100 000 person-years. Furthermore, shortly after we submitted our paper, 2 of the 145 patients who did not undergo follow-up angiography in our study developed SAH from a de novo aneurysm at 7 and 11 years, respectively, after surgery; 1 died and the other became bedridden. Therefore, current statistics seem to indicate an even higher risk (≈0.15%/y) of SAH from de novo aneurysms. We wish to make it clear that we are not proposing to screen patients every year after the treatment, thus causing them decades of unnecessary anxiety or fear about fatal SAH. However, the risk is cumulative in each patient, and our study shows that the cumulative risk of SAH, from both de novo and regrowth, is ≈2% and ≈9% after 10 and 20 years, respectively.4 Importantly, most of the SAH from de novo aneurysms (5 of 6, including the 2 additional cases) developed >10 years after surgery. Therefore, we believe that patients who have been fortunate to live >10 years after surgery in good health should benefit from being notified of the risk and being offered screening for aneurysm recurrence at that point. Although there still is controversy, Dr Juvela apparently shares with us the view that unruptured aneurysms accompanying a ruptured aneurysm, once detected, are better be treated surgically.

We did not observe any increased risk of de novo aneurysm formation in females, which did not surprise us. De novo aneurysm formation in patients with verified aneurysms, which is already highly selected, should be considered separately from that in the general population. It seems reasonable to us that women with verified aneurysm did not have increased risk of de novo aneurysm formation compared with men, just as they did not have increased risk of growth or rupture of intact aneurysms. Compared with our unselected series,5 including 20% with multiple aneurysms, the series of Juvela et al.1,2 relied heavily on patients with unruptured aneurysms accompanying a ruptured and clipped aneurysm, which is reflected in the very high ratio (90%) of multiple aneurysms cases. Bearing that in mind, we were somewhat surprised by the similar risk of de novo aneurysm formation in our series and theirs (0.89% and 0.81%, respectively). When we include the 11 cases with newly developing SAH, de novo aneurysms were found more frequently in multiple aneurysm cases (8/31 vs 8/92; P = 0.014, χ² test). Therefore, we felt that the risk of de novo aneurysm formation in the series of Juvela et al was a little lower than we expected from our data. Before referring to the possible “racial difference,” we should continue to collect more information. Meanwhile, how to interpret the data currently available and how to reflect these data in clinical decisions to benefit patients still seems to be open to discussion and also could change with time, considering the rapid progress in medical technology.

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Acupuncture and Stroke Rehabilitation

To the Editor:

In a carefully controlled, randomized clinical trial, Johansson et al.6 concluded that acupuncture had no effect on functional improvement in stroke, thus contradicting most of the previous randomized clinical trials studying this relationship, including their own groundbreaking research.2,3 However, inspection of their Figure 1 indicates that the acupuncture group improved over a 12-month period by approximately 61 Barthel points, while the transcutaneous electrical nerve stimulation group improved by only 46 points and the sham stimulation group by 49 points. In other words, the median improvement of the acupuncture group, over and above the improvement seen in the control groups, was 12 to 15 points. This is not a trivial difference, despite the authors’ claim that this is a small difference in outcomes. Additionally, the interquartile range at 12 months clearly showed a lower boundary much closer to the median than in either of the 2 control conditions, which suggests that a greater proportion of the subjects received some benefit from the intervention when compared with the control conditions. In their original study,2 Johansson et al reported that the acupuncture group improved by 46.9 points while the standard-of-care control group improved by 26.2 points, producing a difference of 20.7 points in favor of the acupuncture group over a no-intervention control group. While the maximum relative improvement in the current study (15 points) is somewhat smaller than the 20.7 points in the original study, the absolute improvement of 61 points in this study certainly compares favorably to the 26.2-point improvement of the original standard-of-care group and the 46.9 points of the acupuncture group in that study.

A similar inspection of their Table 2 shows that after 12 months, the acupuncture-treated subjects had a median walking speed of 0.56 m/s versus 0.23 m/s and 0.38 m/s for the control subjects. Certainly a >100% increase in walking speed would be considered a large improvement by almost any criterion of clinical relevance. Yet this result does not achieve significance. In addition, despite the claim of no statistically significant differences, there is a clear and consistent pattern for the acupuncture group to have better scores (in some cases, much better scores) on most of the Nottingham quality-of-life domains, especially at 12 months.

How could what appear to be large and clinically meaningful results not have even approached statistical significance, given what appears to be adequate power and appropriate methods? My fear is that the choice of nonparametric, categorical statistics, the forcing of a range of scores into 2 categories, and treating...
interval values as ordinal scores drastically reduced power. For example, why is there a clearly equal-interval outcome such as walking speed treated as an ordinal variable and submitted to a less-sensitive statistic than necessary? Failure to use the most powerful statistic appropriate for the data, such as analysis of variance, substantially increases the probability of a type II error.

Why would one want to use less powerful statistics, ones which are less likely to detect an effect, if one exists? My guess is that the use of these techniques stems from the decision to use intention-to-treat (ITT) analysis. While ITT analysis obviously is intended to reflect typical clinical experience, in some situations it can create distortions in the statistical analysis and may make the intervention being studied. To include a functional independence score of zero for effect, as Dr Shiflett proposes that we should abandon the intention-to-treat principle, because acupuncture is not supposed to affect case fatality. This concerns a more general problem in stroke intervention trials. The case fatality rate is high in patients who have poor ADL function. If there are differences in case fatality rates between groups, the mean functional outcome in survivors would seem to be better in the group with the highest case fatality rate, in fact, no treatment effect exists. It therefore seems sound to apply the intention-to-treat principle in stroke trials.

Nevertheless, in the article we reported on sensitivity analyses in which fatal cases were excluded. The differences in outcome between the acupuncture and subliminal groups were still far from statistically significant after such exclusion. Analysis of variance, the statistical procedure proposed by Dr Shiflett for our data set, assumes normal distribution of data. This requirement was not met for the present outcome variables. Analysis of variance is certainly not always the most powerful or statistically appropriate method. Even when the normality assumptions are met, the Wilcoxon test is nearly as powerful as parametric tests. It is difficult to envisage what statistical tests that would be more appropriate and robust and much more powerful and sensitive than the test used in our analyses.

One point raised by Dr Shiflett is open to debate. Different approaches may be used when expressing treatment effects. In his recalculations of our data, Dr Shiflett has used incremental changes in the Barthel ADL score between baseline and 3 and 12 months' follow-up rather than comparisons of absolute scores at follow-up, as we have done. Admittedly, our approach is more conservative. When, instead, we are comparing the degree of improvement from baseline to 12 months, as Dr Shiflett suggests, the difference in Barthel Index between the acupuncture group and the group receiving subliminal stimulation is still far from statistically significant. It is not enough to look at point estimates of the improvements. The variations in treatment effects must also be taken into account, and they were large (Figure 2'). The same applies to differences in walking speed. Because walking speed did not show normal distribution even after various transformations, we used nonparametric rather than the parametric tests suggested by Dr Shiflett. It is also problematic that Dr Shiflett concentrates on single outcome variables that tend to favor acupuncture and ignores others that show tendencies in the opposite direction.

There are now 2 meta-analyses of acupuncture after stroke being conducted, one of them within the framework of the Stroke Module of the Cochrane Collaboration. Hopefully, the statistical power of the combined randomized trials will be sufficient to confirm or refute with greater precision the hypothesis that acupuncture improves functional outcome after stroke. Until then, it seems that the scientific support for acupuncture being used as standard treatment in the subacute phase of stroke is too weak.

**Response**

The Swedish multicenter trial on sensory stimulation after stroke was designed to detect clear differences in functional outcomes between patients treated with acupuncture, high-intensity transcutaneous nerve stimulation, or subliminal transcutaneous nerve stimulation. Thus, it had an 80% power to detect a 20% difference in the proportion of patients with severe activities of daily living (ADL) dependency (Barthel Index score of ≤70 points) at 3 months' follow-up.

In trial design, analyses, and reporting on the results, we were orthodox, adhering strictly to generally accepted principles for randomized controlled trials. This includes (1) intention-to-treat analyses, (2) nonparametric statistical tests of ordinal data (such as the Barthel Index) and of data that did not show normal distribution, and (3) reliance on predefined outcome measures (which, in the present trial, was difference in functional outcome measures at follow-up) and not on post hoc analyses (such as calculations of degree of improvement).

Dr Shiflett proposes that we should abandon the intention-to-treat principle, because acupuncture is not supposed to affect case fatality. This concerns a more general problem in stroke intervention trials. The case fatality rate is high in patients who have poor ADL function. If there are differences in case fatality rates between groups, the mean functional outcome in survivors would seem to be better in the group with the highest case fatality rate, in fact, no treatment effect exists. It therefore seems sound to apply the intention-to-treat principle in stroke trials.

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**Helicobacter pylori and Cerebrovascular Disease**

To the Editor:

We are currently conducting a Canada-wide study of inpatient adverse events after carotid endarterectomy, and as part of that research we have performed analyses exploring associations between a variety of clinical variables and adverse events—specifically, inpatient death or postoperative stroke. These analyses demonstrate an association between peptic ulcer disease (PUD) and adverse events after carotid endarterectomy. We had initially dismissed this association as being spurious, perhaps due to the inevitable type 1 errors that arise when multiple variables are considered in such analyses. However, the recent paper in *Stroke* by Ameriso and colleagues demonstrating *Helicobacter pylori* in human carotid plaques makes us wonder whether our finding is not, in fact, a “true” association.

We identified carotid endarterectomy cases across Canada by screening hospital discharge abstracts compiled by the Canadian Institute for Health Information for the presence of ICD-9-CM procedure code 50.12. The occurrence of inpatient death was determined from the “discharge alive” field in the discharge data, and postoperative stroke was identified by screening for diagnosis codes 997.0, 433, 434, 436, or 438 (for each of these, the and postoperative stroke was identified by screening for diagnosis codes 997.0, 433, 434, 436, or 438 (for each of these, the initial ICD-9-CM diagnosis type indicator had to be coded a “2,” indicating that the corresponding diagnosis is a complication rather than a preexisting diagnosis). We defined a number of clinical risk variables, including PUD, using a published ICD-9-CM coding algorithm for defining comorbidities.2

Bivariate analyses reveal that patients with PUD present as a diagnosis at time of admission were more likely to experience adverse events than were patients without PUD (10.3% versus 4.1%, *P*=0.022). After statistical adjustment to control for age, sex, urgency of admission, and a variety of other comorbidities (eg, diabetes and renal disease), the multivariate OR for adverse events associated with PUD was 2.12 (95% CI 0.95 to 4.76).

We congratulate Ameriso and colleagues for their interesting study. Their article leads us to believe that our finding of an association between PUD and adverse events after carotid endarterectomy may be meaningful and not just a “spurious” result. We await more research on this issue with interest.

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**Response**

We have read with great interest the letter by Ghali and colleagues. It provides a valuable example of the power wielded by a national epidemiological approach on a population database regarding the importance of detectable information.

The reported finding of an association between peptic ulcer disease and adverse events after carotid endarterectomy is interesting, and we agree that it may relate to our recent detection of *Helicobacter pylori* on carotid atherosclerotic plaques.

The medical literature has provided robust evidence of a potential link between infection/inflammation and vascular disease. Peptic ulcer disease, when associated with *H pylori* infection, may be considered an infectious process. Thus, the observation of Ghali and colleagues is provocative and demonstrates the need for further research in the area.

Several questions remain unanswered. Do patients with *H pylori(+) * peptic ulcer disease have an increased prevalence of carotid artery disease? Do patients with carotid artery disease have an increased prevalence of *H pylori(+) * peptic ulcer disease? Are there any meaningful clinical differences between *H pylori(+) * and *H pylori(-) * patients with carotid artery disease?

Our study demonstrated the presence of the microorganism in carotid lesions. However, we were unable to speculate on the role of *H pylori* in the initiation, progression, and/or complication of the atherosclerotic process. Neither were we able to explore the clinical or therapeutic implications of our findings.

The work of Ghali et al, together with research on the basic features of the relationship between infection and atherosclerosis, will undoubtedly expand the knowledge about this intriguing field.

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**More Complications of Spinal Manipulation**

To the Editor:

I read with interest the commentary by Ernst regarding life-threatening complications of spinal manipulation. Recently, I reported 3 cases of stroke that occurred after chiropractic manipulation, 2 involving carotid dissection and 1 involving vertebral dissection. Ernst cites 1 literature case of carotid dissection.4 There is a fourth case his research did not uncover.5 I wish to add an unusual case of intracranial hypotension due to presumed dural tear, a heretofore unreported complication of cervical chiropractic manipulation.

A 34-year-old man suffered a whiplash injury in a motor vehicle accident. He consulted a chiropractor for nonradiating neck pain and improved somewhat. Approximately 1 month after the initial injury, the chiropractor performed a rapid rotatory neck manipulation that caused severe, nonradiating neck pain. Approximately 36 hours after the manipulation he noticed severe, throbbing, positional headache; he would suffer bifrontal and cervico-occipital throbbing on assuming the erect position that resolved promptly on his becoming supine. There was mild dizziness, but no diplopia, otorrhea, rhinorrhea, or other complaints. The clinical diagnosis was intracranial hypotension.

The patient’s vital signs were stable. General and neurological examinations were normal as well. Noncontrast head CT was negative. Lumbar puncture demonstrated an opening pressure of 80 mm H2O. Cerebrospinal fluid analysis showed a red blood cell count of 10/mm3, white blood cell count of 2/mm3, protein 96

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mg/dL, and glucose 63 mg/dL. Brain MRI with gadolinium failed to show any dural enhancement. Lumbar epidural blood patch was of no benefit. The patient was discharged home after he was able to ambulate without incapacitating headache and was instructed to slowly increase his level of activity as tolerated. When mild positional dizziness developed 5 weeks later, complete myelography was performed. Opening pressure was 210 mm H2O. Small bulges were noted at C6-7 and L4-5. There was no evidence of extravasation of intrathecal contrast.

It is my hypothesis that this patient suffered a dural tear due to cervical manipulation. This has been reported after other forms of neck trauma as well. The 36-hour delay from trauma to symptom onset is typical of post–lumbar puncture headache. The initially low opening pressure resolved over several weeks with conservative management, not unlike most cases of dural tears.6

To my knowledge, this is the first reported case of documented intracranial hypotension following chiropractic manipulation.

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**Response**

Dr Jeret points out that my search did not uncover all cases of life-threatening complications of spinal manipulation. This is important, because it contributes to underreporting and under-recognition of such adverse events. We have recently published a survey1 conducted on all members of the Association of British Neurologists. The principal questions related to the number of cases seen by these practitioners of neurological complications occurring within 24 hours of cervical spinal manipulation over a 12-month period. Of the 239 respondents, 24 recalled a total of 35 serious neurological complications. Perhaps the most remarkable aspect of these findings was that none of these cases had been published in the peer-reviewed literature. Thus underreporting, in this series, was exactly 100%. Collectively, these data render all estimates of incidence figures more than questionable. The bottom line, it seems, is that chiropractors and other professions should establish the incidence of complications of spinal manipulation as a matter of urgency. In the absence of reliable data, this therapy cannot be regarded as safe.

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**The Volume of Lacunes**

To the Editor:

With the insight on stroke mechanisms provided by volume measurements of diffusion and perfusion MRI lesions,1,2 it may be time to reassess the dimensions of a lacune. Whether lenticulostriate infarcts as large as 15 mm are commonly due to single perforator occlusion,3 or whether they are more likely to be limited striatocapsular infarcts due to middle cerebral artery embolism4 could be explored by prospective studies with MRI. The upper limit of the size of a lacune was for a long time recorded in terms of diameter and was set at 15 mm, with most being 2, 3, or 4 mm.5 Fisher called lacunes greater than 10 mm in diameter “giant lacunes.” In the classification of subcortical infarction proposed in 1993,3 a lacune was defined as an infarct <1.5 cm (15 mm) in diameter, likely to be due to occlusion of a single perforating artery. Most lacunes are much smaller than 15 mm in diameter. In one recent MRI study, the average lacune volume was 0.5 mL (500 mm3), indicating a diameter of ~10 mm.6

In this light, it is perplexing to see regularly in print, in *Stroke* and elsewhere, that the upper limit of the size of a lacune is 15 mm.7–11 The volume of a cube with sides 15 mm is not 15 mm3 but 15 × 15 × 15 = 3375 mm3. If a particular lacune is spherical, then by the formula for the volume of a sphere, \[ V = \frac{4}{3}\pi r^3 \], the volume of a lacune 15 mm in diameter is 1767 mm3. The figures look less impressive if one does the calculation for the same volume in cubic centimeters: diameter 1.5 cm, volume 1.767 cm3. A lacune of 15 mm3 would not be large at all, having a diameter of ~3 mm. Lacunes may not be spherical, of course,5 and in an important review in *Stroke*7 the size was recorded as “4×4×5 mm” for one lesion. Such a lesion, even if spheroidal, would have a volume at least twice 15 mm3, but it was in that review that the upper limit of the size of a lacune was stated as “15 cu mm.” The reference cited for this referred to the size only in terms of diameter, the upper limit being 15 mm.8 In a recent leading textbook chapter on lacunes, the upper limit of 15 mm3 is discussed in particular reference to the notion of giant or super lacunes.10

There is no justification for setting the limit of the volume of a lacune at 15 mm3. This must be an error that has been repeated at times in the literature and in reputable textbooks. The error is not explained in terms of making the powers of 10 involved in volume calculations with millimeters versus centimeters, nor is it explained by mistaking the nature of volume calculations from length measures. Probably a single transposition error from diameter to volume occurred at some point, perhaps in 1982, and this error has been quoted often enough that it has become entrenched in some quarters.

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Helicobacter pylori and Cerebrovascular Disease
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