Re: Characteristics, Outcome, and Care of Stroke Associated With Atrial Fibrillation in Europe

To the Editor:
I read with great interest the detailed study of atrial fibrillation in the context of acute stroke with particular relevance to the higher 3-month mortality of acute stroke patients who have atrial fibrillation (AF). We have previously reported\(^1\) the higher 3-month mortality of AF patients presenting with a stroke. It should be recognized, however, that AF is only one aspect of the cardiovascular disease (CVD) of these patients and does not usually exist independently of other types of CVD (eg, ischemic heart disease and cardiac failure) in the older age group. It is vital that a more detailed assessment be performed for outcome measurement in patients with AF to take into account the presence of other CVDs. We have reported\(^2\) that although AF was associated with a higher 3-month mortality in acute stroke patients (\(P=0.05\)), there was no significant association of AF with acute phase mortality, ie, death in acute wards (\(P=0.24\)). More significantly, we found that it is the presence of any degree of cardiac failure in addition to AF or other CVDs that is significantly associated with higher mortality both in the acute phase and at 3 months (\(P<0.001\)). Any future studies of the relationship of AF in the context of acute stroke should also study the influence of coexistent cardiac failure and other CVDs, eg, ischemic heart disease. In addition, it is also difficult to completely separate the independent influence of higher age on stroke mortality, because the patients with AF are much older than those without AF. Higher age is an independent factor that influences mortality after acute stroke.\(^3\) It is similarly important that these factors be considered in intervention studies in acute stroke.

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Response
We thank Dr Sharma for his interest in our article evaluating the impact of atrial fibrillation (AF) on survival and function of acute stroke patients. The problem of comorbidity is obviously relevant when considering stroke outcome, especially in the elderly population. In fact, the multivariate OR (1.57; 95% CI 1.29 to 1.94) indicating the relationship between AF and 3-month death was controlled for all baseline variables, including age, sex, hypertension, diabetes, smoking, alcohol consumption, previous myocardial infarction, and previous transient ischemic attacks. We did not include heart failure in our assessment in the acute phase. While heart failure may reveal an additive independent impact on stroke outcome, this cardiac disease is an end stage of different conditions,\(^4\) for the great part considered in our analyses.

The effect of age on survival has already been reported in our study population.\(^5\) Although no statistical method is perfect in separating the effect of single exposures on considered outcomes, the above reported multivariate OR was age controlled. We entirely agree with Dr Sharma that all demographics and risk factors have to be carefully considered when planning intervention studies in acute stroke.

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Re: Systematic Comparison of the Early Outcome of Angioplasty and Endarterectomy for Symptomatic Carotid Artery Disease

To the Editor:
In the recent article by Golledge et al.,\(^1\) the authors attempted to compare the early outcome of angioplasty and endarterectomy, or more specifically, the early complication rates of these 2 procedures.

Notwithstanding the methods, which were well detailed, I wish to draw attention to the authors’ inclusion of 2 specific series (the fourth and fifth series of their Table 2). These 2 series comprised 7 and 9 patients, respectively, in which the disabling stroke or death rates were 43% and 11%. Even though the 2 series account for only 2% of the total 714 patients treated, these complications represent 4 of 28, or 14%, of the disabling strokes or deaths in the overall numbers. Clearly, there is a significantly disproportionate representation of morbidity from these 2 small series, and by comparison the smallest series among the carotid endarterectomy studies numbered 62 patients. Indeed, exclusion of the 2 small angioplasty series leaves 24 disabling strokes/deaths out of 698 carotid arteries, or a 3% incidence, rather than the 4% given. While this is still a significant difference (\(\chi^2=3.939, 2\)-sided \(P=0.0472\)), and does not refute the authors’ conclusions, it is not “twice as common” but rather 1% greater than the serious complications of carotid endarterectomy.

Stephen P. Lownie, MD, FRCS
Neurosurgery and Endovascular Therapy
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Letters to the Editor


Response

I would like to thank Dr Lownie for his careful comments regarding our recent article. He correctly points out the very high disabling stroke rate in 2 small series of endovascular treatment of carotid stenoses. Because this therapy is an evolving technique, it would be hoped that these poor outcomes reflect part of the learning curve of a new technique. However, with the availability of an established treatment for symptomatic carotid artery disease, referring clinicians and patients alike need to be aware of the potential complications of this new technique, even in the hands of those taking up this procedure for the first time. As Dr Lownie points out, excluding these 2 more unfavorable series does not distract from the conclusion that the present publications suggest a significantly higher complication rate of carotid stenting: The disabling stroke or death rate (with exclusion of the 2 series mentioned) is 24/698 (3.4%) compared with 107/4973 (2.1%) for the carotid endarterectomy series. Equally, if the 2 most unfavorable series are also removed from the carotid endarterectomy list (numbers 8 and 17 in our Table 3), the serious complication rate of surgery is reduced to 74/4428 (1.7%), i.e., half that of carotid stenting (3.4%), as originally stated.

Jonathan Golledge, MChir
Repatriation General Hospital
Adelaide, South Australia

Re: Chiropractic Manipulation and Stroke

To the Editor:

The study of Rothwell et al, recently published in Stroke,1 attempts to add some light to the considerable heat generated by a long series of case studies,2– 6 some of which have implied that spinal manipulation is exceedingly dangerous, suggesting that “patients, chiropractors, and physicians should be aware of the potential adverse neurologic outcomes following chiropractic adjustment”2 or (even worse) “since possible complications cannot be predicted and may be very severe, it seems of utmost importance to carefully evaluate the benefit-risk ratio of each cervical manipulation.”3 By adding a control patient population that did not report a vertebrobasilar accident (VBA) stroke but saw a chiropractor nevertheless, Rothwell and colleagues have attempted to clarify whether a visit to a chiropractor constitutes a significant risk factor leading to a VBA. Their design represents an improvement over the previous simplistic and largely undocumented recollections of patients and therapists attempting to attribute VBAs directly to cervical manipulations.

Unfortunately, the authors miss the point. Comparing stroke with nonstroke patients visiting the chiropractor begs the question; the fact remains that the vast preponderance of VBA stroke victims most likely never visited the chiropractor’s office before the vascular event in the first place. No less than 68 everyday activities have been implicated in disrupting cerebral circulation.7– 9 Among these activities, 18 (including childbirth, overhead work, turning the head while driving a vehicle, swimming, and beauty parlor events) have actually been associated with vascular accidents but are decidedly nonmanipulative.9

Assuming that VBAs are the result of blunt trauma may actually exonerate most cervical adjustments as a causative agent. Peak elongations of the vertebral artery during neck manipulative treatments have recently been shown to be at most approximately 11% of the elongations observed at the arterial failure limit; in fact, these elongations are consistently lower than those seen during routine range of motion and diagnostic testing.10 What is becoming more and more apparent is that VBAs must be considered the result of cumulative events over an extended period of time rather than recent visits to the chiropractor.

In concrete terms, this would suggest that a subset of stroke patients who had sought chiropractic treatment for neck pain were already well on the way to experiencing a VBA accident. The study of Rothwell et al omitted the most obvious and convincing control group, which would have been a cohort of patients with neck pain seeking treatment by practitioners other than chiropractors, such as allopathic physicians. This would have more directly reflected the development of VBAs and avoided the highly conjectural attempt to lay the blame directly to chiropractic manipulation, as has been done in the studies of inferior design cited earlier.2– 6

As shown in their Table 1, the entire argument as to whether spinal manipulation is a significant risk factor appears to hinge on a total of 5 cases over 5 years, or 1 case per year. To put this matter in the proper perspective, one should be forever cognizant of the fact that death rates following cervical manipulation calculate to be anywhere between 1/100 to 1/400 the rates seen in the use of NSAIDs for similar conditions.11,12 Death rates from lumbar spine operations have been reported to be 300 times higher than those produced by cerebrovascular accidents in spinal manipulation.13,14 For cervical surgeries, recent death rates have been estimated to be 700-fold greater.15 As Rome16 has pointed out, risks for “virtually all” medical procedures ranging from the taking of blood samples15 or use of vitamins or drugs16 are routinely accepted by the public as a matter of course.

Until these lifestyle risks are properly bundled into a study of the proper design, the public will continue to be misled by studies that appear to have magnified out of proportion the extremely low but admittedly problematic risk of cervical manipulation. One would hope that future studies would maintain a more balanced perspective on the likely causes of VBA and not miss the forest for the trees.

Anthony L. Rosner, PhD
Brookline, Massachusetts


**A Minor Revision of Hunt and Hess Scale**

*To the Editor:*

The following patient who was admitted to our department could not be rated as grade 1 or 2 according to Hunt and Hess (HH) scale for subarachnoid hemorrhage assessment. The patient presented with mild headache, unilateral third nerve palsy, and absence of nuchal rigidity. A brain CT scan verified a subarachnoid hemorrhage, and angiography disclosed a posterior communicating artery aneurysm, which was clipped successfully.

The HH subarachnoid hemorrhage grading does not anticipate the above condition. According to the HH scale, the grade 1 patient is “asymptomatic or with minimal headache and slight nuchal rigidity.” Our patient did not fit this description because the neurological examination disclosed a unilateral total loss of third nerve function. The HH grade 2 patient would present with “moderate to severe headache, nuchal rigidity, no neurological deficit other than cranial nerve palsy.” Our patient could not be classified as grade 2 because there were no complaints such as moderate or severe headache, nor was there any nuchal rigidity. On the other hand, he did have a third nerve deficit.

Consequently, we propose that the HH scale should be reconsidered. Grade 1 should include patients who are “asymptomatic or with minimal headache, no or slight nuchal rigidity, and with or without cranial nerve palsy,” with grades 2, 3, 4, and 5 as before.

**George Stranjalis, MD**

**Damianos E. Sakas, MD**

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**Neurobiology of Depressive Symptoms Predictive of Stroke Among Japanese**

*To the Editor:*

Ohira et al find that depressive symptoms predict risk of stroke, specifically ischemic stroke among Japanese. Neurobiological features are suggested by reports linking vasospasm and dysregulation of coping behavior, cortical silent periods, and mood with dopamine abnormalities lateralized to the right hemisphere. This hypothesis is supported by optimal response organization and working memory at intermediate dopamine tone in a mediofrontostriatal activation system, and deactivation of the right hemisphere, a state marker of depression, which promotes dominance of the left hemisphere associated with cardiac dysrhythmia and vasoconstriction. These findings are supported by an exaggerated cerebral cortical response and exaggerated asymmetry to mental stress in patients with coronary artery disease.

Therefore, prevention of ischemic stroke through intervention on depression may be attained by cognitive-behavioral and/or pharmacotherapeutic intervention that balances asymmetric brain functions and alleviates depressive symptoms, such that patients rely less on inappropriate emotion-focused coping strategies.

**Ernest H. Friedman, MD**

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**Response**

Dr Friedman raises the hypothesis that the right hemisphere is more likely to be affected in depression-related ischemic strokes, pointing out that the intervention on depression balancing asymmetric brain functions may be useful for the prevention of ischemic stroke.

We explored whether the lesions of incident ischemic strokes among persons with higher depression scores at baseline were more likely to be localized to the right hemisphere compared with those among persons with lower depression scores. The findings of CT scan or MRI were available for 37 of the 39 ischemic strokes. The proportions of ischemic strokes with the lesion in the right hemisphere were 50% (4/8) in cases in the low tertile (≤30) of the Zung Self-Rating Depression Scale, 56% (5/9) in the medium tertile (31–34), and 60% (12/20) in the high tertile (≥35). This trend was far from statistically significance (P=0.63), in part due to a small number of cases. Therefore, our result neither supports nor negates Dr Friedman’s hypothesis. Further follow-up of our cohort or the exploration of the data from larger follow-up studies is necessary.

**Tetsuya Ohira, MD**

**Hiroyasu Iso, MD**

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*University of Tsukuba*

*Tsukuba, Japan*


**Physician Knowledge of the Benefits, Risks, and Contraindications of Tissue Plasminogen Activator for Acute Ischemic Stroke**

*To the Editor:*

Emergency room (ER) physicians and neurologists are critical in ensuring a prompt evaluation of patients arriving at the ER within 3 hours of symptom onset and in initiating therapy with tPA. Suboptimal institutional readiness for evaluating patients with acute stroke and fear about the hemorrhagic complications among neurologists are some of the factors that can limit the widespread use of tPA, as reported by Katzan et al. Family physicians play an important role in educating patients at risk for stroke about the warning signs of stroke and the importance of contacting 911 as soon as these appear. Limited knowledge about
Knowledge of Benefits, Risks, and Contraindications of tPA for Acute Ischemic Stroke

<table>
<thead>
<tr>
<th></th>
<th>General Practitioners (n=147)</th>
<th>Emergency Physicians and Neurologists (n=28)</th>
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<tr>
<td></td>
<td>Percentage 95% Cl</td>
<td>Percentage 95% Cl</td>
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<tr>
<td>Approval of tPA for use in acute stroke</td>
<td>54 46–63</td>
<td>89 78–100</td>
</tr>
<tr>
<td>Magnitude of beneficial effect</td>
<td>10 5–15</td>
<td>11 0–22</td>
</tr>
<tr>
<td>Time window</td>
<td>41 33–49</td>
<td>79 63–94</td>
</tr>
<tr>
<td>Rate of symptomatic ICH</td>
<td>12 7–18</td>
<td>39 21–57</td>
</tr>
<tr>
<td>Rate of fatal ICH</td>
<td>21 15–28</td>
<td>39 21–57</td>
</tr>
<tr>
<td>Mechanism of action</td>
<td>73 66–80</td>
<td>93 83–100</td>
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Knowledge of contraindications*

<table>
<thead>
<tr>
<th></th>
<th>General Practitioners (n=147)</th>
<th>Percentage 95% Cl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of antiplatelets</td>
<td>41 33–49</td>
<td>82 68–96</td>
</tr>
<tr>
<td>Use of anticoagulants</td>
<td>40 32–48</td>
<td>68 51–85</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>38 30–46</td>
<td>64 47–82</td>
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<tr>
<td>Glucose levels</td>
<td>17 11–23</td>
<td>46 28–65</td>
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<tr>
<td>Acute high blood pressure</td>
<td>36 28–44</td>
<td>46 28–65</td>
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<tr>
<td>Seizure at onset</td>
<td>27 20–34</td>
<td>29 12–45</td>
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<tr>
<td>Rapid improvement</td>
<td>25 18–32</td>
<td>75 59–91</td>
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<tr>
<td>Age</td>
<td>54 46–63</td>
<td>68 51–85</td>
</tr>
<tr>
<td>Peptic ulcer disease</td>
<td>54 46–62</td>
<td>71 55–88</td>
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<tr>
<td>Symptoms on awakening</td>
<td>19 12–25</td>
<td>68 51–85</td>
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*Not all conditions listed are contraindications to tPA. Knowledge of contraindications was evaluated by presenting a brief clinical scenario and asking respondents whether the use of tPA was contraindicated in that situation.

Regardless of specialty, physician awareness about the benefits, risks, indications, and contraindications of tPA for acute stroke is insufficient. Limited knowledge of the benefits and unjustified fear of the side effects may limit stroke patients’ access to this treatment. For tPA to be widely used, coordinated efforts by multidisciplinary teams focusing on patient education, rapid access to emergency care, and prompt evaluation in the ER are essential. These steps will take place only if physicians are fully aware of the risks and benefits of available treatments. Acute stroke teams should consider the education of their peers an integral part of their mission. Educational efforts should be specialty driven: family physicians need to know about the time constraints, benefits, and risks associated with the use of tPA; ER physicians and neurologists need to be familiar with the indications and contraindications of this therapeutic tool.

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Review of this letter was directed by Graeme J. Hankey, MD.

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4. Albers MJ, Hademenos G, Latchaw RE, Jagoda A; Marler JR; Mayberg MR; Starke RD; Todd HW; Viste KM; Girgus M; Shephard T; Emr M; Shwayder P; Walker MD. Recommendations for the establishment of primary stroke centers. JAMA. 2000;283:3102–3109.
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