Concerns Regarding Carotid Endarterectomy Guidelines

To the Editor:

We were surprised to read the rather unequivocal endorse-ment1 by the American Heart Association writing group of carotid endarterectomy (CE) for asymptomatic stenosis of greater than 60%. This position does not represent the viewpoint of all stroke neurologists or surgeons, and some professional groups have recently come to the exact opposite conclusion, not recommending CE for asymptomatic stenosis.2

The writing group states that CE is beneficial if the surgical complication rate is less than 3%. Current evidence indicates that CE complication rates are not being closely monitored at US hospitals.3 A recent study found that the surgical complication rates were either unknown or not being monitored at over 50% of teaching hospitals in the United States.4 In the “real world” of CE practice, it is unlikely that a complication rate this low can be uniformly achieved, and a 1991 analysis of Medicare data found that the death rate associated with CE was 2.3%.5

In addition, we and others have concerns that the Asymptomatic Carotid Atherosclerosis Study (ACAS) results cannot be generalized.6–9 Only 4% of the eligible patients were entered into the study.10 In addition, 29% of the surgeons who applied for participation in the trial were either rejected or did not complete the credentialing process.11 Thus, in the ideal setting for producing a positive surgical result (namely, combining low-surgical-risk patients with surgeons vetted for their excellence), a statistically significant result was obtained, which may not be clinically meaningful to all clinicians.

Finally, for full disclosure, it would be of interest to know how many members of the writing group were actual ACAS participants. This may affect the panel’s objectivity, and we would suggest that when controversial studies are involved, future writing groups should include a balance between study participants and nonparticipants.

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References

Response
I believe that every member of the writing committee was and is intimately familiar with all of the arguments advanced by both the ACAS supporters and the ACAS detractors. Nevertheless, the ACAS study is level I evidence (grade A recommendation) that documented a statistically significant benefit of CEA for stroke prevention in patients with ≥60% diameter reduction asymptomatic carotid stenosis. We can argue forever about the clinical significance of this finding, but it does not change the conclusions of the study. We did not use terms such as “so compelling” or “unequivocally,” but rather outlined the rules of evidence used and presented that study as well as other studies in the context of those rules. As noted in the paragraph above the recommendation, “… some investigators consider it acceptable to delay surgery until there is >80% carotid stenosis…” we assume that Drs Chaturvedi and Halliday and many other distinguished and respected colleagues fall into that category. In short, we believe the statement in the AHA guidelines is evidence based and perfectly reasonable.

The writing group was composed of a well-balanced panel of recognized experts in carotid artery disease from the disciplines of neurology, vascular surgery, and neurosurgery. Parenthetically, we believe the composition of the writing group is irrelevant if an evidence-based approach to guideline development is used. That is the value of such methodology.

The relative clinical benefits of CEA for severe and moderate symptomatic stenosis and asymptomatic stenosis are well known. The data alone do not help us decide where to draw the line that divides a “worthwhile” procedure from one that is “not indicated” from a cost-to-benefit analysis viewpoint. We believe that kind of decision requires economic, social, ethical, and political analysis, and it was considered beyond the scope of this guidelines paper.

We do not recommend the blanket use of carotid endarterectomy in asymptomatic populations of patients in our AHA report. We simply endorse surgery on asymptomatic patients with ≥60% diameter stenosis by a surgeon who does surgery with <3% risk. We cannot be held responsible for people who misapply guidelines, whether it be this set of guidelines or any other set of guidelines.

The statement that only 4% of eligible patients were entered in the study is not true. The JAMA article states that 42,000 patients were screened and 1662 patients randomized.1 Screened means evaluated to determine eligibility. Study participants were
screened from ultrasound vascular labs, and many patients were not eligible because of symptomatic status, degree of stenosis, or other reasons. Complete data on exclusion criteria were not provided in the manuscript.

In short, we think that the AHA CEA Guidelines are, by and large, evidence based and do not need to be amended. While investigators may respond to any scientific study with their own degree of questions, we think the facts on this speak very clearly for themselves, and we endorse that result unless otherwise equally careful studies suggest an alternative result.

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Ischemic Strokes Arriving Too Late for tPA Are an Ideal and Ethical Control Group for Continuing Studies of tPA Efficacy

To the Editor:

The report of Chiu et al1 showed that a single university hospital and 2 community hospitals could achieve results comparable to those of the recent NINDS rt-PA Study. Thirty patients were treated from a possible 267 patients appearing in the 3 emergency rooms.

Thirty-seven percent of the remaining 237 patients were rejected because the time limit for treatment was exceeded. This group accounts for nearly 3 times the number of patients actually treated. No mention in the paper was made of how these people fared or whether there was any attempt at follow-up. An age- and sex-matched control for those who were selected for treatment ought to be buried in this group of nearly 90 patients; the only distinguishing variable would be the time of onset.

It would be of great interest to know whether this control group had a worse outcome than the people receiving therapy. The report’s authors already may have the data or could obtain it. For most neurologists in practice over 10 years, their first experience with thrombolytic therapy was being called to the ICU after intracerebral hemorrhage when the therapy had been used for myocardial infarction. They next read the 4 negative studies on thrombolytic therapy before the NINDS Study. Their subsequent experience is likely to have been intense pressure from the media and academic powers—that-be to ignore the first 4 studies and to apply the therapy, along with pressure from hospitals in competition with others to use the latest (if not the best). The therapy may work as advertised, but further confirmatory data would be welcome.

Such data may already exist; Chiu and colleagues may actually have the data but have not written it up. Even if the patients rejected for therapy were not followed up in their study, it would not be difficult to do such a study and publish the results, since tPA appears to be the standard of care at present. My experience is that for every patient reaching the emergency room within 3 hours of stroke onset while awake, there are 2 or 3 otherwise identical patients who present after the 3-hour limit. Withholding thrombolytic therapy poses no ethical problem, as it is more likely to hurt these patients than to help.

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to interpret, as is the case with any nonrandomized clinical trial. Stroke patients who present to the emergency room within 3 hours of onset of symptoms are not average stroke patients in at least one respect—they have disproportionately severe strokes. Patients with mild neurological deficits are more likely to delay seeking medical attention. Patients with massive strokes tend to show up early. A statistical adjustment could be made for initial NIH stroke score, but a given NIH score at 1 hour may have a different prognostic significance from the same score at 24 hours.

Fortunately for those of us attempting to examine our performance in clinical practice, the main challenge to thrombolytic therapy is the issue of safety rather than efficacy, although of course it is axiomatic that treatment decisions be based on risk-benefit ratio. For most centers, it is probably sufficient to ascertain that the incidence of complications and protocol violations is acceptably low (not significantly greater than 6.4% for symptomatic intracerebral hemorrhage).

As for the 4 negative studies on thrombolytic therapy to which Dr Robinson refers, they teach an important lesson as well. Their results indicate that we should not be using intravenous streptokinase or high-dose tPA beyond 3 hours for stroke. Whether 0.9 mg/kg intravenous tPA or intra-arterial thrombolysis are efficacious up to 6 hours after onset are questions being actively investigated in randomized clinical trials.

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Surgery for Primary Intracerebral Hemorrhage: Meta-analysis of CT-Era Studies To the Editor:
I read with interest Hankey and Hon’s recent review of studies of surgery for primary intracerebral hemorrhage. Their systematic review of case series is a novel contribution to the literature. There is some precedent, however, for their meta-analysis of extant randomized controlled trials of surgical versus medical therapy. The authors may have been unaware of my brief meta-analysis of the same 4 trials, published 3 years earlier, as it appeared in a book chapter rather than a Medline article. Contrasts between the two meta-analyses are illuminating.

My formal systematic overview examined the clinical end point of mortality rather than the combined clinical end point of death or dependency used by Hankey and Hon. Collating all 4 studies, I found no major effect of surgery, with an odds ratio of 1.48). This finding is similar to the 0.97 (95% CI, 0.64 to 1.62) finding of Hankey and Hon for the fatal outcome of 0.97 (95% CI, 0.64 to 1.62). Employing Hankey and Hon’s abstraction of data, pooled analysis of these 3 studies for the end point of death or dependency reveals a trend toward lower odds of death or dependency at 6 months (odds ratio, 0.72; 95% CI, 0.38 to 1.44). These promising trends should encourage further clinical trials of decompressive surgery for primary intracerebral hemorrhage. Our current database is pitifully small, even in pooled analysis. As Hankey and Hon note, a trial large enough to definitively identify the benefits and risks of surgery is urgently needed.

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Response
We thank Dr Saver for his interest in our paper and for drawing our attention to his meta-analysis of the trials of surgery for primary intracerebral hemorrhage, which we had not identified.

We agree that the trial of McKissock et al., carried out in the pre-CT era, is now perhaps anachronistic, but we included it in our overview because one of the principles of a sound meta-analysis is to include all the evidence (ie, randomized trials) and not just selective studies. Having done that, however, we then examined the data from the 3 more recent trials in which primary intracerebral hemorrhage was diagnosed by CT brain scan. Because the combined sample size was so small (only 85 in the control group and 84 in the surgically treated group) and the 95% confidence intervals of the odds ratio (0.72) of death or dependency so wide (ranging from 0.38 [surgery being very effective] to 1.44 [surgery being harmful]), we elected not to present this analysis in our paper. We did not carry out a further analysis of the effect of surgery on mortality in the 3 CT-era trials but are interested to see Dr Saver’s results, which suggest that surgery may reduce the odds of death by 8% to 72%. However, because these results are derived from a post hoc analysis of a very small number of outcome events (death), they are statistically unstable and imprecise, and hypothesis generating rather than conclusive. Furthermore, the effect of surgery on functional outcome among survivors is unknown. There remains considerable uncertainty surrounding the risks and benefits of surgery for primary intracerebral hemorrhage and the need for more data from randomized controlled trials. The results of Saver’s analysis of the effects of surgery for primary intracerebral hemorrhage on mortality should not precipitate any ethical restraint on the conduct of future large randomized controlled trials.
Since the publication of our article, we have been informed that Prof David Mendelow and Dr M.S. Siddique at the Department of Surgery (Neurosurgery), University of Newcastle, UK, have initiated a multicenter (UK and Germany), randomized controlled trial of surgery for primary intracerebral hemorrhage. To date, 35 patients have been recruited, and the target is 1000 patients. We congratulate them on this endeavor and wish them well.

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Apoptosis and Matrix Vesicles in the Genesis of Arterial Aneurysms of Cerebral Arteries
To the Editor:

It was pleasing to see the electron microscopic study of early experimental aneurysms by Kondo et al., a natural sequel to previous experimental work on cerebral aneurysms by Profs Hashimoto and Hazama. More space devoted to electron micrographs at higher magnifications would have been preferable, and I concur with Dr Rosenblum that apoptosis of vascular smooth muscle cells (SMCs) is unproved.

Their mural thinning or atrophy progressing to aneurysmal dilatation is similar to early aneurysmal changes in human cerebral arteries and the experimental mural atrophy produced by hemodynamic stress in experimental arterial bends, forks, and afferent arteries of arteriovenous fistulas and classified as atrophic lesions of atherosclerosis. Occurring at specified anatomic sites, they are readily reproducible and in humans and experimentally may eventually exhibit proliferative atherosclerotic lesions. They develop initially as transversely oriented tears of the internal elastic lamina (IEL) that precede endothelial disruption and secondary thrombus on the floor of early IEL tears appearing in rabbits in 5 days and 2 days postoperatively in common carotid and iliofemoral arteries, respectively. Following rapid endothelialization, tears continue appearing in the IEL and deep medial elastic laminae without endothelial disruption or thrombi, until eventually elastic tissue and SMCs may disappear completely. Elastic disruption should not be attributed, therefore, to a few platelets or leukocytes, notable for their absence in the wall in these initial lesions. The abrupt edges to the tears and microfractures in the IEL are notable for their absence in the wall in these initial lesions. Should not be attributed, therefore, to a few platelets or leukocytes, fragmentation of plasma membranes and matrix vesicle production, are characteristic of human atherosclerosis and reproducible in proliferative lesions of venous pouch aneurysms and arteries and veins of experimental arteriovenous fistulas.

Necrotic debris in the matrix derives primarily from SMCs by granuloveascular degeneration, whereas that from endothelium is readily washed downstream. Similar vesiculation occurring in erythrocytes is accentuated by hypertension, vigorous sport, and marathons, with the production of hemolytic anemia. Turbulence associated with cardiac valve stenosis and arteriovenous fistulas is accompanied by a shortened erythrocyte life span, thus supporting the concept that the vesiculogranular degeneration of SMCs (and probably of endothelium) is also mechanically induced, resulting from bioengineering fatigue and usage rather than genetically programmed cell death.

Matrix vesicles are unlikely to be lysosomal, although lysosomes and nuclear debris may appear in the matrix with progressive degeneration of SMCs, which at times disintegrate into a myriad of vesicles of variable size lying in the midst of dystrophic basement membranes. Matrix vesicles in early atrophic lesions are not as plentiful as in proliferative lesions, which include early intimal thickenings in human cerebral arterial forks and rabbit renal arterial forks. These matrix vesicles occur in arteries of all sizes, including arterioles, and are augmented in experimental hypertension, experimental arteriovenous fistulas (arteries and veins), and experimental venous pouch aneurysms and atherosclerosis. They are associated with the early appearance of lipid in cerebral arteries and sheep arteriovenous fistulas as nonphagocytosed cell debris and necrotic cells that have an affinity for lipid and calcification. These ultrastructural, degenerative cellular changes are hemodynamically induced and are not apoptotic or programmed cell death, as so often alleged. “Apoptosis” is frequently used indiscriminately and at times assumed, the necrosis occurring secondarily to as-yet undetermined or ill-understood causes.

There is no scientific evidence to support a dominant role of shear stress in atherogenesis and aneurysm formation. When analyzed, shear stress at the wall/blood interface proves to be an insufficient explanation. Atrophic lesions must be due to transmural stress and have been attributed to the pulsatile pressure head of the main flux of blood impacting on the wall at arterial forks and the greater curvature of bends superimposed on the repetitive distensile and elongating effect of the rapidly traveling pulse pressure of 40 to 100 mm Hg. Affenter arteries of arteriovenous fistulas are subjected to greatly increased flow and pulse pressures immeasurable larger than the relatively insignificant shear stresses (12 to 15 dynes/cm²) transmitted through the thin endothelium and its attachments to the underlying matrix. For the wall to dilate, yield of all mural connective tissues, including the adventitia, is necessary, and this presupposes transmural stress.

Hypothetical explanations currently in vogue regarding underlying mechanisms do not detract from the important contribution of Profs Hashimoto and Hazama in the experimental production of cerebral aneurysms, their observations lending further evidence to the assertion that such lesions are indeed biomechanically (hemodynamically) induced.

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Response

We would like to express our gratitude to Prof Stehbens for his interest in our recent article in Stroke1 and thank the editor for the opportunity to reply to his letter. We also regret that more space was not available for electron micrographs.

In our article, we demonstrated the apoptosis of the medial smooth muscle cells not only by electron microscopy but also by specific immunolabeling of nuclear DNA fragmentation with terminal deoxynucleotidyl transferase, although the frequency was not so high.

The disappearance of cells through apoptosis, or rather of the apoptotic bodies of such cell death leaves behind, is extremely rapid.2 Therefore, it is difficult to definitively prove as well as deny the apoptosis in vivo with only ultrastructural findings. A small proportion of apoptotic cells visualized in a tissue section can represent a cell loss of considerable magnitude.2 Although there may have been relatively few apoptotic cells at any point in time, this does not deny the participation of apoptosis as a mode of cell death, as Prof Rosenblum mentioned in the editorial comment on our article.4 Although our study implied the importance of apoptosis in the production of the aneurysms, the evidence was not definitive, and we do not assume that only apoptosis (that is, programmed cell death) is responsible for the disappearance of smooth muscle cells in the development of cerebral aneurysms in rats.3

Prof Stehbens stated that mechanical hemodynamic stress directly causes bioengineering fatigue of internal elastic laminae6 and “vesticulogranular degeneration” of medial smooth muscle cells and endothelial cells.7 We agree that this direct mechanical force can play an important role in the development of cerebral aneurysms. Release of smooth muscle cells by direct hemodynamic stress from the extracellular matrix, a cell survival factor,9 may be a trigger of apoptosis. Furthermore, increased hemodynamic stress may induce synthesis of endonucleases via expression of the required genes and their message.

In vessels, as in other organs, complex systems may be involved in the control of their structure in response to surrounding conditions. The role of the endothelial cell as a mecha

References


**Quantitative Brain SPECT and the NIH Stroke Scale**

To the Editor:

The excellent article by Grotta and Alexandrov¹ not only provides objective evidence in a small number of patients that intravenous tissue plasminogen activator (tPA) improves cerebral perfusion but also provides important data about the National Institutes of Health Stroke Scale (NIHSS) rating system. If the NIHSS scores data from their article are plotted against the corresponding single-photon emission computed tomography (SPECT)-graded scale score, a relationship becomes apparent, as shown in the Figure. If one omits the 4 outlying points with high NIHSS scores with less-than-expected asymmetries on SPECT in this group of 21 SPECT scans, the relationship becomes fairly linear. Without these 4 pairs of outlying data, approximately 10 points of deficit on the NIHSS roughly correlates with 40 points on their SPECT-graded scale scoring system, which quantifies the severity and extent of asymmetries in cerebral perfusion over 4 SPECT slices.

Rankin Scale scores at 1 month after stroke have been shown to correlate with the degree and size of hypoperfusion on SPECT scans of hypoperfusion within 36 hours after symptom onset in a group of 55 patients.² Whereas the baseline NIHSS score was found to have an overall accuracy of 83% in predicting 3-month outcome in a study of 373 acute stroke patients,³ more research is needed on the predictive value of quantitative SPECT and how it correlates with the NIHSS, Rankin Scale, and other functional outcome measurements. A firm correlation remains to be made between NIHSS and the degree and size of cerebral hypoperfusion in acute stroke; one or more SPECT indices of volume and severity of hypoperfusion may need to be considered.

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**Response**

We thank Dr Meyer for his comments. We have also noted the nice correlation between the neurological status of the patient on arrival as measured by the baseline NIHSS and the perfusion defect as measured by SPECT. In evaluating the acute stroke patient, we all want a physiological test that is convenient, safe, inexpensive, widely available, and informative. SPECT fulfills many of these criteria. Perhaps clinical trials incorporating such studies will show that these tests can help us select our therapeutic strategies. However, until then, it is reassuring that in the first few hours after stroke onset, the neurological exam accurately reflects what is going on inside the brain physiologically.

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**Complications and Outcome Following Acute Stroke: Revised Table**

To the Editor:

It has come to our attention that Table 2 in our 1996 article published in *Stroke*¹ contains some errors. The revised numbers do not alter our conclusions. Indeed, some of the changes are greater than the ones published.

The corrected Table 2 appears below.

TABLE 2. Changes in Mean Skinfold Thickness (Triceps, Midarm Circumference, and Arm Muscle Circumference) Related to Presence of Swallowing Difficulties

<table>
<thead>
<tr>
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<th>Mean Skinfold Thickness, mm (SEM)</th>
<th>Mean Difference, mm (SEM)</th>
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<tbody>
<tr>
<td></td>
<td>Day 0</td>
<td>Day 7</td>
</tr>
<tr>
<td>Triceps</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safe</td>
<td>14.9 (1.2)</td>
<td>14.6 (1.1)</td>
</tr>
<tr>
<td>Unsafe</td>
<td>16.7 (1.1)</td>
<td>15.5 (1.2)</td>
</tr>
<tr>
<td>VF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No aspiration</td>
<td>16.2 (1.1)</td>
<td>15.5 (1.0)</td>
</tr>
<tr>
<td>Aspiration</td>
<td>13.8 (1.0)</td>
<td>13.1 (1.3)</td>
</tr>
<tr>
<td>Midarm circumference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safe</td>
<td>288.5 (7.9)</td>
<td>287.5 (8.4)</td>
</tr>
<tr>
<td>Unsafe</td>
<td>300.9 (7.9)</td>
<td>295.4 (8.6)</td>
</tr>
<tr>
<td>VF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No aspiration</td>
<td>299.0 (6.5)</td>
<td>297.0 (7.1)</td>
</tr>
<tr>
<td>Aspiration</td>
<td>276.4 (10.4)</td>
<td>270.3 (9.9)</td>
</tr>
<tr>
<td>Arm muscle circumference</td>
<td></td>
<td></td>
</tr>
<tr>
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<tr>
<td>Safe</td>
<td>283.8 (7.6)</td>
<td>280.8 (8.3)</td>
</tr>
<tr>
<td>Unsafe</td>
<td>295.3 (7.6)</td>
<td>286.3 (9.9)</td>
</tr>
<tr>
<td>VF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No aspiration</td>
<td>293.7 (6.2)</td>
<td>288.2 (7.6)</td>
</tr>
<tr>
<td>Aspiration</td>
<td>272.0 (10.2)</td>
<td>266.3 (9.9)</td>
</tr>
</tbody>
</table>

BSA indicates bedside assessment; VF, videofluoroscopy. Mean differences were calculated using data from the surviving patients at each time point. Changes in indices over time were analyzed with the use of the paired t test. Results at each time interval were compared with those at day 0.

†P<0.01; ‡P<0.02.
Concerns Regarding Carotid Endarterectomy Guidelines
Seemant Chaturvedi and Alison Halliday

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