Letters to the Editor

Lubeluzole Treatment of Acute Ischemic Stroke

To the Editor:

The final conclusion of the recently published article 1 on lubeluzole treatment of acute ischemic stroke, that “treatment with lubeluzole within 6 hours of the onset of ischemic stroke resulted in improved clinical outcome at three months with no safety concerns,” may not result from the data presented and the way they were analyzed. The primary aim of this trial was to test the null hypothesis that treatment with lubeluzole results in outcome similar in terms of death at 3 months to placebo treatment. As the primary end points “all deaths” showed no statistically significant difference between groups, the null hypothesis cannot be rejected. The fact that the number of deaths were (not statistically significant) lower in the lubeluzole group may well be due to chance because of small numbers or to differences in baseline characteristics; fewer males and fewer patients with various types of cardiac disease in the lubeluzole-treated group may have favored better outcome in the treatment group. From the analysis description, adjustments for these differences cannot be inferred. Secondly, fewer patients in the lubeluzole group died from hemorrhage, but no reason other than a possible effect of lubeluzole explaining this difference was discussed. Was there perhaps a higher number of patients with hemorrhage in the placebo group in the first place, thus favoring better outcome in the lubeluzole group? The statistically insignificant lower death rate in the lubeluzole group was due in part to the apparently lower number of deaths from congestive heart failure. However, can this be explained by a specific mode of action of lubeluzole, by chance, or by the fact that there were fewer patients with congestive heart failure in the lubeluzole group at baseline? A most prominent effect of lubeluzole might have been expected in deaths directly related to stroke. However, it turns out that lubeluzole did approximately 10% (not statistically significant) worse: odds ratio (OR), 1.11; 95% confidence interval (CI), 0.48 to 2.57 (31/368 lubeluzole versus 27/353 placebo). Considering deaths that were primarily vascular related, lubeluzole again fared worse: OR, 1.19; 95% CI, 0.74 to 1.92 (57/368 lubeluzole versus 47/353 placebo), a finding mainly due to a statistically significant increase in cardiovascular deaths in the lubeluzole-treated group compared with the placebo group (21 versus 7; OR, 2.99; 95% CI, 1.22 to 7.34). This finding is all the more surprising considering the lower number of patients with cardiovascular disease at baseline in the lubeluzole group, and it raises a serious question about the cardiovascular safety of lubeluzole. In this respect, I do not think it is appropriate to conclude that lubeluzole might worsen instead of improve stroke patients’ outcome. Therefore, neither primary nor (relevant) secondary end point analysis allows a definite conclusion in favor of lubeluzole. Some stroke patients (those with ischemic heart disease?) seem to be at an increased risk for myocardial infarction or sudden death by lubeluzole. Until a more reliable estimate of a possible favorable treatment effect or adverse effects in stroke in general and patient subgroups becomes available, the conclusion that lubeluzole improves clinical outcome in stroke patients remains premature.

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Response

We agree with Dr Lodder that we found no statistically significant effect on overall mortality, as is clearly stated several times in our article. Therefore, his speculation regarding differential effects of lubeluzole versus placebo on mortality due to various causes, such as hemorrhage, congestive heart failure, and stroke, is not justified. None of these differences reached statistical significance (for example, 31/368 lubeluzole patients versus 27/353 placebo patients having stroke-related deaths; CI, 0.48 to 2.57). Had we embarked on such a “fishing expedition” in our analysis, we would have been appropriately criticized.

The secondary analyses of the effect of lubeluzole versus placebo on good outcomes as measured by the Barthel Index, Rankin Scale, and National Institutes of Health Stroke Scale scores were prespecified. Furthermore, dichotomization of these scales into “good” versus “poor” outcome is appropriate, given the nonnormal distribution of scores on all of these scales in stroke patients at 3 months. There is precedent for such analysis in previously successful clinical therapy trials in stroke.1 Finally, all patients were included in the analysis. The positive effect of lubeluzole was detected by a logistic regression analysis across all three possible outcomes: good, poor, or dead.

We stand by our conclusion that in this study, treatment with lubeluzole was associated with improved clinical outcome with no safety concerns. These findings need to be corroborated.

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Fou Rire Prodromique and Ischemic Stroke

To the Editor:

The recent article by Carel and colleagues 1 describes an ischemic stroke preceded by a transient fit of laughter, or fou rire prodromique; they found two previous cases2,3 in the literature.

We recently reported a case of an embolic stroke preceded by an episode of pathological laughter. The patient was a 78-year-old man with a history of atrial fibrillation and a previous ischemic stroke 20 days before, characterized by dizziness and visual disturbance. He was shopping and suddenly began to laugh; the fit of laughter lasted 15 minutes and was followed by Wernicke’s aphasia and right hemiparesia. A CT scan in the emergency room showed an infarction in the posterior division of the right middle cerebral artery. In a CT control scan performed 48 hours later, a recent infarction in the posterior division of the left middle cerebral artery, sparing deep subcortical territory, was additionally shown. An EEG recording demonstrated theta-delta activity in posterior areas with no epileptic activity. Hemiparesia disappeared within 48 hours; the patient remained agitated the first days, and looked blind. Six months later the aphasia and hemianopia persisted. The fit of laughter did not recur.

Fou rire prodromique is a descriptive term for a condition whose precise mechanism is not well known. Carel and colleagues found no conclusive evidence regarding the nature of the symptom, although they argued against an epileptic seizure. In our patient it is impossible to distinguish the fou rire prodromique, a descriptive expression, from a gelastic seizure as the first sign of an embolic cortical stroke.

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Transcranial Doppler and Stump Pressure During Carotid Endarterectomy

To the Editor:
We read with great interest the article by Finocchi et al. on the role of transcranial Doppler (TCD) and stump pressure (SP) during carotid endarterectomy (CEA). Having recently published a paper on the same subject, we would like to offer some considerations as an adjunct to the issues raised by Finocchi et al.

We understand that it was the intention of the authors to assess the usefulness of SP as an indicator of hemodynamic changes predicting intraoperative cerebral ischemia. In order to do so, 112 patients who underwent CEA for symptomatic and asymptomatic severe carotid stenosis under general anesthesia were monitored by TCD and SP measurement. After examining duration of clamping, values of TCD flow reduction and of SP at clamping, microembolic signals, and perioperative complications, the authors concluded that the major complications of CEA may result from hemodynamic factors and that SP alone is not a reliable indicator of hemodynamic changes that predict clamping ischemia.

In our study, we evaluated a series of 175 CEAs monitored by SP measurement and TCD and performed under local anesthesia. The need for shunting was compared between SP/TCD flow velocity reduction and the awake response. Since there is no general consensus on the appropriate SP cutoff value that indicates the need for shunting, we constructed a receiver operating characteristic (ROC) curve to determine the relationship between specificity and sensitivity of SP and TCD. Values that combined the highest sensitivity with the highest specificity for both SP and TCD, using the ROC curve, were ≤50 mm Hg (100% sensitivity, 83% specificity) and ≥70 mm Hg flow velocity reduction from baseline (83% sensitivity, 96% specificity), respectively. In our experience, both SP and TCD showed limitations, because they overestimate or underestimate CEAs in need of a shunt. We believe that sensitivity is more important than specificity in CEA and thus concluded that SP is a more dependable indicator of cerebral perfusion than TCD. We acknowledge the usefulness of intraoperative monitoring with TCD for testing adequacy of shunt flow and detection of embolism.

We believe that drawing conclusions about reliability of SP while not being able to actually document the neurological status of patients at clamping is speculative. In our opinion, a gold standard should be used to test the effectiveness of a monitoring technique. In our study, patients were operated on under local anesthesia, which allowed us to effectively test the response of patients to carotid cross-clamping and thus assess the reliability of the monitoring techniques. Furthermore, we believe that the arbitrarily chosen cutoff value of 40 mm Hg is rather low. This value appears to be associated with a low sensitivity. According to our analysis, a cutoff value of 40 mm Hg implies an undershunting rate of 18%. In other words, using this cutoff value, 18 patients of 100 who exhibited either focal or global ischemia at clamping would not have been shunted (sensitivity 82%, specificity 95%). The opposite is true with a 50 mm Hg cutoff: there is an overshunting rate of 17%, but all of the patients with neurological deficits at clamping would have been shunted (sensitivity 100%, specificity 83%).

We believe that drawing conclusions about reliability of SP while not being able to actually document the neurological status of patients at clamping is speculative. In our opinion, a gold standard should be used to test the effectiveness of a monitoring technique. In our study, patients were operated on under local anesthesia, which allowed us to effectively test the response of patients to carotid cross-clamping and thus assess the reliability of the monitoring techniques. Furthermore, we believe that the arbitrarily chosen cutoff value of 40 mm Hg is rather low. This value appears to be associated with a low sensitivity. According to our analysis, a cutoff value of 40 mm Hg implies an undershunting rate of 18%. In other words, using this cutoff value, 18 patients of 100 who exhibited either focal or global ischemia at clamping would not have been shunted (sensitivity 82%, specificity 95%). The opposite is true with a 50 mm Hg cutoff: there is an overshunting rate of 17%, but all of the patients with neurological deficits at clamping would have been shunted (sensitivity 100%, specificity 83%).

With respect to postoperative neurological complications, the authors state in their discussion that the major complications of CEA may be related to hemodynamic factors. This estimate is in conflict with other reports, and in our opinion this conclusion is not supported by the findings on postoperative cerebral CT scans: in the 5 nonshunted patients who developed neurological postoperative complications, 3 postoperative CT scans remained unchanged, and 2 showed new "small deep infarcts." Based on these findings, it is reasonable to believe that the "small deep infarcts" are lacunar infarctions, the pathophysiology and causes of which are still controversial. Therefore, we believe that it is hypothetical to consider the hemodynamic changes that occur at clamping the only factors responsible for these two ischemic events. Likewise, the authors suggest that in the two postoperative large cerebral infarctions detected on CT scan (which occurred in 2 shunted patients), a relevant role for embolism cannot be excluded. According to the high SP values in those 2 patients (52 and 60 mm Hg), shunt and potential embolism from shunt might have been avoided.

Finally, we believe it would have been interesting if the authors had further investigated independent predictors of postoperative neurological complications (eg, clamping times, hyperensive brunts, microemboli detected at TCD, contralateral occlusion, etc) through multivariate analysis.

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Multiple Regression Analysis of 5 Subjects With Versus 88 Subjects Without Neurological Complications

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>B</th>
<th>SE B</th>
<th>95% Confidence Interval</th>
<th>P</th>
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<tbody>
<tr>
<td>% Reduction of middle cerebral artery mean velocity</td>
<td>0.00401</td>
<td>0.00009</td>
<td>0.00205–0.00595</td>
<td>0.0001</td>
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<tr>
<td>Contralateral internal carotid</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>% Stenosis</td>
<td>0.00210</td>
<td>0.00005</td>
<td>0.00009–0.00320</td>
<td>0.0003</td>
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<tr>
<td>Number of emboli (dissection)</td>
<td>0.00219</td>
<td>0.00038</td>
<td>0.00081–0.00542</td>
<td>0.5686</td>
</tr>
<tr>
<td>Clamping duration, min</td>
<td>0.02794</td>
<td>0.00776</td>
<td>0.01251–0.04338</td>
<td>0.0005</td>
</tr>
<tr>
<td>Stump pressure, mm Hg</td>
<td>0.00008</td>
<td>0.00113</td>
<td>0.00177–0.00273</td>
<td>0.6768</td>
</tr>
<tr>
<td>Constant</td>
<td>−0.51457</td>
<td>0.11986</td>
<td>−0.75281–0.27632</td>
<td>0.0000</td>
</tr>
</tbody>
</table>
present in air bubbles is replaced by oxygen, and because oxygen bubbles have a shorter life span because of higher solubility in blood, the number of MES reaching the brain is reduced. Up to this point, we agree with the authors.

Kaps et al also performed a hyperbaric chamber experiment (n=1). Compared with the baseline condition (air respiration at atmospheric pressure), they noted a strong reduction in the number of MES when the patient inhaled 100% oxygen at an increased ambient pressure of 175 kPa, an intermediate reduction in the number of MES under inhalation of 100% oxygen at 250 kPa, and no reduction under breathing air at 250 kPa. In the discussion, they stated that the (negligible) increase in MES found in the latter condition agreed with the results observed for one patient in Spencer’s hyperbaric study,2 and could be explained by the increase of cavitation under hyperbaric conditions. On this point, we differ.

We twice performed a hyperbaric chamber experiment using the same sheep with a prosthetic heart valve (Medtronic Parallel) implanted in the mitral position. MES were measured for 30-minute periods in the right carotid artery, because the sheep’s thick temporal bone precluded ultrasonic examination of the cerebral vessels. With the sheep breathing air, we observed an increase in the number of MES recorded at 300 kPa (mean, 4.9 MES/min) compared with the number of MES recorded at 100 kPa (mean, 3.5 MES/min). Although this result agrees with that of both Kaps et al and Spencer, no increase in MES numbers was expected for the following reasons.

According to the oxygen saturation curve of hemoglobin, inhalation of 100% oxygen at increased ambient pressure will result in the saturation of the hemoglobin and hence a reduced solubility and increased life span of oxygen bubbles when compared with the situation of 100% oxygen at atmospheric pressure. This would explain why Kaps et al found an intermediate number of MES under inhalation of 100% oxygen at 250 kPa. Switching to respiration of air at increased ambient pressure results in the return of nitrogen in blood, and nitrogen-containing bubbles will be formed. Since nitrogen is less soluble than oxygen, this will result in the baseline number of MES, although these MES might be smaller in diameter.3

In addition, we disagree with Kaps et al with respect to the postulated increased effectivity of cavitation under hyperbaric conditions. It is well established that cavitation induced by prosthetic heart valves is a threshold phenomenon. When the pressure drop induced by valve closure has a sufficiently large amplitude to decrease the regional pressure to 0 kPa, valve closure will induce cavitation in blood near the point of impact.4 From the studies with air respiration at increased ambient pressure, we can deduce that the change from 0 to 300 kPa is a minor change when compared with pressure fluctuations induced by valve closure. We therefore anticipate that a further increase in ambient pressure will suppress rather than amplify cavitation.

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Response

We would like to thank Dr Bot and his colleagues for their letter, which has provided us with another opportunity to bring microembolic signals rising from artificial heart valves into focus. It is clear that we agree with the view that such signals are primarily due to the effects of gas bubbles. However, we could not quite comprehend the remaining statements that were made. What needed to be known was the nature of the microembolic signals which were being measured.

In this regard, the saturation of hemoglobin could not be considered to play any role at all. It was, in fact, the amount of physical dissolved gas being released by cavitation that acted as the only decisive factor in bringing about these effects.

Under normobaric conditions, when breathing air at standard room temperature and pressure, the largest component of physically released gas appearing in the blood is nitrogen. Under hyperbaric conditions, the quantity of gas released will increase in line with the increased partial pressures of the individual gases, as defined by the laws of Henry and Dalton. The increased ambient pressure has absolutely no effect on the magnitude of the cavitation, because liquids are noncompressible. As such, we could not agree with the view that “a further increase in ambient pressure will suppress rather than amplify cavitation.” The comments made concerning the unitary measure kPa are justified, and all units that were given in kPa must be corrected by a factor of 100.

Aside from that, it should be pointed out that the rate of microembolic signals due to cavitation is dependent on the design of the artificial valve; the position of the valve, of course; and the site at which the microembolic signals were recorded. In this respect, one can not make direct conclusions on the rate of microembolic signals arising from the aortic valve in experiments where the number of MES was measured.

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Contrast-Enhanced Transcranial Color-Coded Real-Time Sonography: A Reliable Tool for the Diagnosis of Middle Cerebral Artery Trunk Occlusion in Patients With Insufficient Temporal Bone Window

To the Editor:

Baumgartner et al recently reported on the diagnostic value of contrast-enhanced transcranial color-coded duplex sonography (CE-TCCS) in ischemic cerebrovascular disease. In this study, 33 patients with insufficient temporal insonation conditions (21 patients had ischemic stroke and 12 suffered from transient ischemic attack) were investigated after application of a galactose-based echo contrast agent. The presence of an insufficient temporal bone window was indicated when two sonographers
estimated that they were unable to evaluate the basal cerebral arteries by means of color and spectral Doppler imaging in unenhanced examinations. After application of a galactose-based echo contrast agent, 66% of the CE-TCCS examinations were considered conclusive. Cross-flow through the anterior and posterior communicating arteries due to extracranial occlusive disease could be demonstrated in 3 and 2 patients, respectively. No stenoses or occlusions of intracranial arteries could be visualized.

We would like to add our CE-TCCS experiences in severely affected stroke individuals with insufficient acoustic bone windows (IABW). 30 patients (17 women and 13 men; mean age, 75.2 [range, 59 to 86] years) with IABW and severe cerebrovascular event (European Stroke Scale score of <35 points) suggestive of middle cerebral artery (MCA) trunk occlusion were examined after injection of 9 ml of 400mg/ml echo-contrast agent (Leovist; Schering AG). The temporal bone window was considered absent if no vascular structure could be detected in unenhanced TCCS images. Occlusion of the MCA was diagnosed if the following criteria were met: (1) discontinuous or missing color-coded signal of the MCA main stem, (2) visualization of at least one other ipsilateral artery (anterior cerebral artery or posterior cerebral artery), and (3) identification of the MCA on the contralateral side. For comparison with CE-TCCS scans, at least one angiographic study (digital angiography, MR angiography, or spiral CT angiography) was performed within 12 hours after the onset of clinical symptoms. The ultrasonic examination was recorded on videotape and evaluated off-line by two experienced ultrasound investigators who were blinded to the results of angiographic studies. It was required that both investigators confirm the diagnosis. In 15 patients, both angiographic and CE-TCCS examinations demonstrated an occluded MCA main stem (Figure); in 13 individuals both diagnostic methods showed a patent vessel. In 2 cases (1 with and 1 without occlusion of the MCA main stem in angiography) it was not possible to make a definite diagnosis.

Temporal hyperostosis is known to be a major obstacle for successful transtemporal insonation of the basal cerebral arteries. Because of insufficient penetration of the ultrasound beam through the temporal bone, up to 35% of stroke patients cannot be successfully examined.2 It has been shown that CE-TCCS may overcome this anatomic hindrance in the majority of healthy individuals.3,4 Nevertheless, the clinical relevance of these findings in stroke patients has not previously been established. The study of Baumgartner et al1 shows for the first time that CE-TCCS allows the assessment of intracranial cross-flow and accurate depiction of most intracranial arteries in two thirds of the stroke patients with inconclusive unenhanced examinations. In accordance with Otis et al5 but in contrast to Baumgartner et al, we found conclusive CE-TCCS results in more than 90% of stroke patients with IABW. A likely reason for this disparity may be the application mode of the echo contrast agent. Compared with the short application period (10 to 15 seconds) in the study of Baumgartner et al, we injected the echo contrast agent over a period of at least 3 minutes. In this way improved signal enhancement was achieved by avoiding color artifacts (“blooming”) that may totally obscure ultrasound images during the first phase of echo contrast enhancement.

A, Axial unenhanced TCCS image demonstrating an insufficient acoustic temporal bone window without visualization of any intracranial vessel, (B indicates weak depiction of the brain stem); B, after application of echo contrast agent, the missing color-coded signal of the symptomatic middle (1), anterior (2), and posterior (3) cerebral arteries are clearly detectable; C, visualization of the contralateral MCA (4); and D, spiral CT angiography showing MCA trunk occlusion (arrow).
In the study of Baumgartner et al, no intracranial stenosis or occlusion was detected by CE-TCCS or angiography. This finding is most likely attributed to the fact that the incidence of MCA occlusions is low and that the disease may not be found in smaller series of unselected stroke patients. Nevertheless, a rapid and reliable diagnosis of MCA occlusion is of major importance, because immediate therapeutic interventions such as thrombolysis or decompressive surgery may improve the prognosis of this vascular syndrome. In this respect, our experiences in severely affected individuals show that CE-TCCS is an accurate and time-saving tool for the diagnosis of MCA trunk occlusion in patients with IABW. In conclusion, our findings clearly confirm the clinical value of transpulmonary echo contrast agents for improved diagnosis in stroke patients.

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Response

We have read with great interest the data and comments of Postert et al. It is important to note that these authors assessed intracranial hemodynamics with color Doppler imaging without making use of spectral Doppler sonography, which is different from our contrast-enhanced (CE) transcranial color-coded duplex sonography (TCCS) investigation and previous nonenhanced CE-TCCS studies. Reducing TCCS to color Doppler imaging has several limitations. (1) Especially in patients with inadequate temporal windows, color Doppler imaging parameters are set to obtain the best possible sensitivity for detecting signals by use of the lowest emission frequency, the highest emission energy, and the largest color Doppler gate. Together with the color-blooming artifact induced by the echo contrast agent, these measures reduce the spatial resolution of color Doppler imaging that is already inferior to B-mode imaging. Thus, the reliable identification of intracranial arteries without the additional use of spectral Doppler may become impossible. (2) A deep middle cerebral vein that drains toward the insula and the basal vein of Rosenthal provides color Doppler signals showing the same flow directions as the middle and posterior cerebral arteries, respectively. Consequently, it is very difficult to distinguish venous flow from slow arterial flow without the use of spectral Doppler sonography. (3) In the case of color Doppler suspicion of a nonoccluded cerebral artery, this technique is not adequate for evaluating the presence of a stenosis. The presence of high velocities or aliasing on the color Doppler scale may also represent increased velocities due to increased flow that may occur in collaterals and arteries feeding arteriovenous malformations. Furthermore, color Doppler cannot distinguish aliasing from reversed flow that may occur in the presence of turbulence.

Postert et al reported conclusive CE-TCCS studies in 93% of their patients compared with 66% in our series. These authors assumed that the different detection rates were related to differences in contrast medium administration: we injected within 10 to 15 seconds one or more boluses of 2.0 g, whereas they infused 3.6 g over a period of at least 3 minutes; identical concentrations of 400 mg/mL Levovist were used in both studies. We agree with Postert et al that the slower administration of the echo contrast agent may reduce color artifacts and extend the duration of diagnostically useful Doppler signals. However, we disagree with their assumption that color artifacts shortened the duration of diagnostically useful Doppler signals and were the reason for the higher rate of inconclusive CE-TCCS investigations in our series. First, color blooming can be avoided simply by reducing the color Doppler gain. The echo contrast agent and its concentration and the ultrasonic emission frequencies (2 MHz) and energies (the upper limit is given by the Federal Drug Administration) were identical in both CE-TCCS studies. Thus, we assume that both CE-TCCS studies differed in the definitions of conclusive transtemporal CE-TCCS investigations that were given by distinctive study goals and in patient selection. We examined patients with ischemic strokes located in the hemisphere underlying a temporal bone with an insufficient acoustic window. Consequently, we appreciated the presence of a conclusive study when CE color and spectral Doppler sonography enabled evaluation of the presence or absence of stenoses and occlusions in the middle, posterior, and anterior cerebral arteries and of cross-flow through the circle of Willis. Conversely, Postert et al insonated patients with acute ischemic stroke to investigate whether the MCA was occluded. Accordingly, they used less severe criteria for defining conclusive CE-TCCS investigations of the ipsilateral hemisphere, because only color Doppler depiction (or onedepiction, in case of occlusion) of the middle, anterior, or posterior cerebral artery was needed. It is likely that differences in selection of patients with insufficient temporal acoustic windows were the other cause of the lower number of conclusive CE-TCCS studies in our series. In our study, CE-TCCS detected the contralateral MCA in 25% of cases (8 of 32 patients), whereas Postert et al visualized by definition the contralateral MCA in 93% of their cases. We have reviewed our videotapes and found that by using the color Doppler criterion of Postert et al, the contralateral MCA would have been detected in 28% of cases, which suggests that our patients had more CE-TCCS refractory temporal ultrasonic windows. The fact that the patient populations were on average aged 70 to 75 years in both studies but were 70% female gender in our series compared with 57% in that of Postert et al underlines this assumption, because ultrasound attenuation caused by the tem-
poral bone increases with age and is substantial in elderly women.12

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