To the Editor:

We read with great interest the study by Sztriha et al evaluating the early clinical outcome in a large sample of unprotected carotid artery stenting procedures. Although randomized studies comparing endovascular treatment with endarterectomy are showing encouraging results in favor of the endovascular approach, and cerebrovascular complications can occur during and in the early period after the procedure. Whereas intraprocedural complications may be caused by carotid plaque embolization and then they may be affected by the expertise of the physicians performing the procedures and by the development in endovascular technologies such as the use of protection devices, the etiopathogenesis of the cerebrovascular symptoms occurring after the end of the procedure may be unclear.

Sztriha et al observed cerebrovascular complications in 14 of 245 (5.4%) consecutive patients included in their study; most of these (9/14 [64.3%]) occurred after the procedure and involved the vascular territory of the carotid artery undergone to stenting (8/9 [88.9%]), but neither restenosis nor reperfusion damage was present. Also, Qureshi et al reported periprocedural cerebrovascular complications in 14 of 111 (13%) patients and mostly (71.4%) after the procedure. Can the passage of atherosclerotic material through the stent mesh explain postprocedural embolization?

We observed the case of a 73-year-old women treated with stenting for symptomatic 80% right internal carotid artery stenosis proven by selective angiography according to North American Symptomatic Carotid Endarterectomy Trial criteria. The intracranial angiogram obtained by selective injection of right internal carotid artery showed a moderate stenosis in the right pericallosal artery (Figure). Transcranial Doppler evaluation showed low mean flow velocity (38 cm/s) in the right carotid siphon and blood flow inversion in the right anterior cerebral artery precommunicating tract. A self-expanding stent (Carotid Wallstent monorail, Boston Scientific) was deployed inside the carotid artery and a residual stenosis degree <30% was obtained. The next day, the patient experienced sudden motor impairment in the distal segment of her left leg without other neurological deficits. Carotid duplex scanner examination excluded restenosis and transcranial Doppler showed normal mean flow velocity (62 cm/s) on the right carotid siphon and normal blood flow direction with normal mean flow velocity values (54 cm/s) in the right anterior cerebral artery precommunicating tract. Moreover, transcranial Doppler monitoring prolonged for 60 minutes on the right middle cerebral artery showed no microembolic event. Cranial MR diffusion-weighted image performed 12 hours after the onset of symptoms revealed an area of recent ischemia in the right frontotemporal cortex located in the vascular territory of the stenosed pericallosal artery (Figure).

This case shows that the postprocedural complication was likely caused by the intracranial hemodynamic changes after cerebral reperfusion. Particularly, the increase of blood flow velocity in the intracranial right carotid artery territory after recanalization could determine the detachment of embolic debris from the pericallosal artery stenosis leading to the frontal medial infarction. Therefore, we suggest that the presence of intracranial stenoses distal to cervical arteries stenoses should be considered during selection of candidates to endovascular treatment because they might be represent a harbinger of postprocedural cerebral ischemic complications.

Giovanni Orlandi, MD
Simone Gallerini, MD
Mirco Cosottini, MD
Luigi Murri, MD

From Department of Neuroscience
University of Pisa
Pisa, Italy

Response:

We thank Dr. Orlandi and his colleagues for their interesting and valuable comments. They suggest that postprocedural neurological complications following carotid artery stenting may be caused by the detachment of embolic debris from stenosed intracranial arteries in consequence of an increased blood flow.

The presence of an intracranial atherosclerotic lesion ipsilateral to an extracranial symptomatic carotid stenosis predicts a higher risk of stroke in medically treated patients. Carotid endarterectomy is of benefit in such patients. Cerebral microembolization, as detected by transcranial Doppler monitoring of the ipsilateral middle cerebral artery, may often be demonstrated following the completion of carotid endarterectomy. Predilatation, stent deployment, and postdilatation have been associated with microembolic signals during carotid stenting. The release of microemboli, however, may continue after the procedure, and may depend on the characteristics of the individual stent types.

We agree that embolization from the pericallosal artery may well have been a possible cause of stroke in the case presented by Orlandi et al. However, since sporadic embolization from the carotid artery may not be detected during a 60-minute Doppler monitoring of the middle cerebral artery, a control cerebral angiogram might have been helpful in demonstrating a change in the morphology of the intracranial stenosis, which would have implied the stenotic segment as a source of embolization. It is well known that postprocedural hypertension, a common phenomenon following carotid stenting, may result in significant hyperfusion in poststenotic arteries, possibly leading to hemodynamic strokes. We did not observe any intracranial stenoses in those of our patients who subsequently deteriorated neurologically, and we suggest that these complications were related to embolization from the stented carotid arteries.

We fully agree with Orlandi et al that the presence of intracranial stenoses distal to cervical arteries should be considered during the selection of patients for endovascular treatment, although this also...
Sex-Based Differences in Response to Recombinant Tissue Plasminogen Activator in Acute Ischemic Stroke

To the Editor:

In their pooled analysis article on gender differences in response to tissue plasminogen activator therapy, the authors conclude that tissue plasminogen activator was not significantly effective in male stroke patients (3-month favorable stroke outcome rate of 38.5% for treated patients versus 36.7% for placebo patients; P=0.52). However, that particular conclusion is only scientifically valid if the male placebo patients had the same baseline likelihood of a spontaneous stroke recovery as the male treated patients. Considering that the male placebo group’s favorable response rate was 36.7%, compared with 25% for the placebo patients in the 91- to 180-minute arm of the NINDS trial, it is questionable whether the treated and placebo male pooled analysis groups were balanced at baseline.

To substantiate the scientific validity of their conclusion, the authors should provide a stratified analysis in addition to a pooled (unstratified) analysis to verify that there was no significant imbalance in baseline stroke severity between the male treated and male placebo patients in their pooled analysis.

Jeffrey Mann, MD
Salt Lake City, Utah


In Vitro Models for Assessing Transcranial Ultrasound-Enhanced Thrombolysis

To the Editor:

Contrary to the promising results of recent clinical studies, Pfaffenberger et al conclude from in vitro data that diagnostic ultrasound (US) is not suitable for transcranial enhancement of tissue plasminogen activator (tPA) thrombolysis. Their contention is based on surprising control data showing significant clot lysis without tPA and plasminogen and relatively modest increases in clot dissolution with tPA. Interestingly, their reported clot weight loss of 21.8% after 1 hour of incubation in saline alone is much higher than that which they recently reported in another journal using the same methods (2.8%±1.8% and 11.0%±3.8%6). Likewise, the effect of tPA alone (27.4%) also differs with earlier results of 19.9%±4.3% and 22.7%±9.0%. These discrepancies seem important, because a 19.9% effect of tPA alone would have been lower than combined US and recombinant tPA through the skull (26.2%), thus encouraging the authors to positively assess transcranial US thrombolysis.

Because clot dissolution is dependent on the amount of plasminogen present and the amount of tPA available for activation of the plasminogen, little clot lysis should occur during the first 60 minutes of incubation in saline, with or without tPA. To study our hypothesis, we used experimental conditions similar to those of Pfaffenberger et al.
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present in the surrounding medium, ultrasound also enhances the entry of plasminogen into clots, resulting in more rapid generation of plasmin. If plasminogen is added. Pfaffenberger et al use an in vitro model that does not adequately differ, depending on its importance on lysis rate in the specific model for ultrasound-enhanced thrombolysis. The contribution of each mechanism will thus likely depend on the specific experimental conditions.

tPA inactivates some of the plasmin generated, resulting in a lower d-dimer level. This is because a high concentration of rtPA, plasminogen activation occurs more rapidly, but the maximal plasmin activity is not greater than at the lower rtPA concentration. This is because a high concentration of tPA inactivates some of the plasmin generated, resulting in a lower degree of clot dissolution.

In vitro models are useful for studying different mechanisms of US-enhanced thrombolysis. The contribution of each mechanism will differ, depending on its importance on lysis rate in the specific model used. Pfaffenberger et al use an in vitro model that does not adequately support the study of either physiological tPA lysis or US enhancement of thrombolysis. Ultrasound is known to facilitate the entry of tPA into clots, resulting in more rapid generation of plasmin. If plasminogen is present in the surrounding medium, ultrasound also enhances the entry of plasminogen, resulting in high plasmin activity within the clot and more rapid clot dissolution. Without addition of plasminogen, in vitro tPA lysis of human clot in saline shows no significant activity after 1 hour of incubation. Therefore, clot weight losses of 20% to 30% cannot be explained by proteolytic degradation and do not constitute meaningful data for questioning the merits of recent clinical trials providing evidence for US enhancement of tPA thrombolysis in stroke patients.

### D-dimer Antigen and Clot Weight Loss After Incubation With Saline and rtPA

<table>
<thead>
<tr>
<th>Clot Weight Loss After 24 Hours, %</th>
<th>D-dimer Antigen Released Within 1 Hour, μg</th>
<th>D-dimer Antigen Released Within 24 Hours, μg</th>
<th>Estimated Clot Weight Loss During 1 Hour According to D-dimer Antigen Released, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline (n=6) 0.15±7.76</td>
<td>1.43±0.17</td>
<td>14.79±2.79</td>
<td>0.01</td>
</tr>
<tr>
<td>rtPA, 8.62 μg/mL (n=6) 19.82±9.37</td>
<td>16.1±5.5</td>
<td>699.8±88.6</td>
<td>0.46</td>
</tr>
<tr>
<td>rtPA, 86.2 μg/mL (n=6) 12.28±10.26</td>
<td>37.9±24.3</td>
<td>504.9±122.1</td>
<td>0.92</td>
</tr>
</tbody>
</table>

rtPA indicates recombinant tissue plasminogen activator.


Response:

In answer to Dr Meairs’ letter concerning transcranial in vitro models for ultrasound-enhanced thrombolysis, we emphasize that the reason for varying control groups in 3 published studies by our group is a completely different sonication set-up reflecting the diverse study aims (schematic descriptions of the respective set-ups are shown as figures in 2 studies). The sonication methods were therefore not the same, as stated, and resulted in different control levels.

The authors of the letter produced whole blood clots to evaluate clot lysis. As described in their letter, clots should be weighed after 1 hour and 24 hours. However, as shown in a Table, the crucial parameter of clot weight after 1 hour of treatment was not measured, but only estimated according to D-dimer levels. Because of the high standard deviation up to nearly 100%, this method seems to be unreliable. In addition, a more accurate time response curve would have been helpful to get a better understanding of the presented data for 2 reasons. First, clots after 1 hour revealed a weight loss of 0.46%, but after 24 hours the weight loss was 19.82%, which is about 43 times higher. This is somehow curious. Second, why are high concentrations of recombinant tissue plasminogen activator more effective after 1-hour treatment but less effective after 24-hour treatment when compared with low recombinant tissue plasminogen activator concentrations? The authors state that this actually interesting effect is caused by inactivation of some of the generated plasmin at high recombinant tissue plasminogen activator levels. However, they do not provide the reader with any reference to support this notion.

As stated by the authors, ultrasound is known to facilitate the entry of tissue plasminogen activator into clots, which was demonstrated by our group recently, resulting in more rapid generation of plasmin. Plasminogen is present within the whole blood clot, as demonstrated in the same study by immunostaining. We agree with the authors that long-term treatment of in vitro clots, for instance, over 24 hours, would benefit from plasminogen substitution, but more relevant short-term effects are also mediated by locally present plasminogen.

However, as demonstrated in several studies, lysis rates of older clots are significantly reduced even if plasminogen is added. It might be because of the fact that internal plasminogen is then already consumed. The authors further state that ultrasound enhances the entry of plasminogen into the clot when added to the surrounding medium. This of course would be an important point, but again there is no reference given confirming this information.

In conclusion, we think that our study does not constrain the importance and significance of a recently published multicenter trial. As discussed in the article, in vitro data cannot entirely explain in vivo outcomes for stated reasons. However, we believe that information gained from our data might be useful for further designs of basic studies or even in vivo trials in this field.
Letters to the Editor

Stefan Pfaffenberger, MD
Walter S. Speidl, MD
Johann Wojta, PhD
Michael Gottsau-Wolf, MD
Department of Internal Medicine II
University of Vienna
Waehringer Guertel, Austria

To the Editor:

We read with interest the article by Dimopoulou1 on hypothalamicamished by means of GH provocative testing because for the age-related normal values provided by Aimaretti et al, determined with the Pantec assay. Therefore, it can be assumed that a different assay was used for measuring IGF-I by Dimopoulou et al. In fact, the IGF-I ranges given by Dimopoulou et al coincide with the normal ranges published on the Nichols Web site for the Nichols Advantage assay. Should the authors have used this assay, they should also have used the age-specific reference values by Brabant et al, because every assay requires a sufficiently large normative database to allow interpretation of results and these normative data cannot be extrapolated between assay methods.

In consideration of the age peak of aneurysmal SAH between 40 and 60 years, the criterion of IGF-I 2 standard deviations less than normal is not sufficient for predicting GHD in these patients, and a number of SAH patients with IGF-I levels normal for this age group might be erroneously not diagnosed as GH-deficient and vice versa.

In fact, in our patient group of 40 patients tested with the insulin tolerance test at least 1 year after aneurysmal SAH, only 1 patient with severe GHD (defined as peak GH value <3 μg/L in the insulin tolerance test) had an IGF-I level <2 SD below normal and in 3 of these GHD-deficient patients IGF-I was well within the normal range.

In summary, we feel diagnosis of GHD in SAH patients should be established by means of GH provocative testing because for the reasons stated. IGF-I measurement lacks sufficient specificity and sensitivity to establish or rule out GHD in these patients.

Ilonka Kreitschmann-Andermahr
Joachim M. Gilsbach
Department of Neurosurgery
University Hospital Aachen
Aachen, Germany


Response:

We thank Drs Kreitschmann-Andermahr and Gilsbach for their comments about our article.1 They raised the question of whether low insulin-like growth factor (IGF-)I concentrations are a reliable indicator of growth hormone deficiency (GHD). We agree that the best way to diagnose GHD is by provocative stimulation, with insulin tolerance test (ITT) representing the gold standard.2 However, ITT has potential risks and there is some concern about its safety in patients with a previous cerebrovascular insult. Therefore, we used IGF-I levels to screen for changes of the GH axis. Low IGF-I levels can be considered indicative of GHD if malnutrition, liver failure, poorly controlled diabetes mellitus, and uremia are ruled out,3 and this was the case in our study population.

Drs Kreitschmann-Andermahr and Gilsbach state that we failed to acknowledge from the quoted article by Aimaretti et al4 that IGF-I measurements are of diagnostic value only for patients younger than age 40 years because older patients with GHD may have IGF-I levels within the age-related normal range. However, in our study, only low IGF-I levels were considered as indicating GHD.

Diagnosing Growth Hormone Deficiency After Aneurysmal Subarachnoid Hemorrhage

To the Editor:

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Ilonka Kreitschmann-Andermahr
Joachim M. Gilsbach
Department of Neurosurgery
University Hospital Aachen
Aachen, Germany


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Drs Kreitschmann-Andermahr and Gilsbach correctly identified the use of the Nichols Advantage assay in our study, and we agree that the reference range reported by the manufacturers may have some impact on the interpretation of our data. A reanalysis on the basis of the age-related normative data given by Brabant et al demonstrated that all 11 patients, considered to have GHD, had IGF-I concentrations well below — 2 standard deviations for their age. This is consistent with our previous finding of IGF-I levels compatible with GHD in a substantial (albeit lower than previously reported) proportion of our patients.

The issue of what is the best way to diagnose adult GHD is controversial. Currently, provocative stimulation is the best way. However, when treating patients with GHD, GH doses are titrated so that IGF-I is kept in the age-related normal range. This is an inconsistent conundrum because IGF-I can be normal to begin with, and yet that is the goal of therapy. Thus, although a low IGF-I has a lower diagnostic yield, it may be of more clinical relevance when considering treatment of GHD. This seems to be also appreciated by Drs Kreitschmann-Andermahr and Gilsbach; in their extensive study, they considered low GH responses to ITT as indicating true GHD when IGF-I levels were below — 1 SD. To summarize, in the future, IGF-I levels will be increasingly considered as a criterion for decision-making in GHD patients. At present, Drs Kreitschmann-Andermahr’s and Gilsbach’s study and our study have contributed to bring into light the fact that neuroendocrine dysfunction is a neglected adverse outcome of subarachnoid hemorrhage that may possibly have a negative impact on patients’ lives.

Ioanna Dimopoulou, MD
Department of Critical Care Medicine
Evangelismos Hospital
National & Kapodistrian University of Athens
Athens, Greece

Stylianos Tzagarakis, MD PhD
Department of Endocrinology and Metabolism
Athens Polyclinic
Athens, Greece


Modern Therapeutic Approaches in the Rehabilitation of Walking Ability After Stroke
To the Editor:
Recently, the report by Yan et al about the impact of functional electrical stimulation (FES) on walking ability of stroke patients attracted our attention. The authors found that 15 sessions of FES (quadriceps, hamstring, tibialis anterior, and medial gastrocnemius muscle) applied to acute stroke patients combined with standard rehabilitation improved the walking ability. The study design meets the criteria of a high standard of scientific work.

Unfortunately, the authors chose as the standard rehabilitation approach the Bobath, or neurodevelopmental, facilitation approach. Particularly in the therapy of the lower extremities of stroke patients, this method has been shown to be less effective than other approaches. Hesse et al compared a treadmill training with the Bobath approach using an A-B-A study design. Both biomechanical parameters and functional assessment scores improved only during the treadmill training but not during the Bobath therapy. In a study by Pohl et al, the treadmill velocity was increased within each session, an approach that considerably enhances the therapeutic effect. Therefore, modern therapeutic strategies in the rehabilitation of stroke patients should include a task-specific training and shaping elements, ie, increasing the demand of performance in parallel with the improvement of performance. The neurodevelopmental facilitation approach widely ignores these standards. The study by Yan et al only shows that FES as a kind of repetitive movement training is superior to an approach that is known to be of minor effectiveness. It has not been shown that FES is more effective than modern task-specific approaches like the treadmill training. Considering the high technological expenditure, on the basis of these data it remains doubtful whether FES can be recommended as therapeutic tool.

Hartwig Woldag, MD
NRZ Leipzig
University Leipzig
Bennonitz, Germany


Response:
Dr H. Woldag questioned our choice of neurodevelopmental facilitation (Bobath) approach as the standard rehabilitation. He rightly noted that it has been shown to be less effective than treadmill training. The reality in Hong Kong is that neurodevelopmental approach is commonly used in hospitals. This is true also in Europe, where a survey showed that Bobath was the preferred approach by 67% of respondents. From an ethical standpoint, patients should not be withdrawn from their standard rehabilitation.

Another important point is that when patients cannot walk, treadmill training is not feasible. Our patients were studied during the acute stage, 9.2 ± 4.1 days after stroke. In contrast, Hees et al and Pohl et al examined their patients 176.8 days and 114.6 days after stroke, respectively. They found that treadmill training with partial body weight support, or with treadmill speed progressively adjusted, was more effective than Bobath approach or conventional gait training. However, all the chronic stroke patients recruited by Pohl et al could walk 10 m with (35%) or without (65%) walking aid. In contrast, only 12% (or 5) of our 41 patients with acute stroke could walk with a quadraped. Hence, only passive modalities/approaches such as functional electrical stimulation (FES) would be feasible.

Quite aside from the reality of patients’ flaccid status during the acute stage that made neuromuscular stimulation rather than treadmill training feasible, there were 2 other considerations. The first one related to concept-driven treatment approach. As presented in our article, repetitive execution of similar movements of the limbs have been identified as crucial for motor recovery in stroke subjects. In fact, using positron emission tomography, similar brain activation patterns had been observed in these subjects during either active or passive movements. We hypothesized that FES, which generated gait-simulated leg movements plus related cutaneous and proprio-
ceptive inputs, would be important in “reminding” subjects of how to walk during the acute stage. Therefore, we investigated whether FES plus standard rehabilitation (SR) was more effective than SR alone with placebo stimulation or alone in promoting the recovery of motor function and functional mobility during acute stroke. That was what we found from week 2 or 3 onward during the 3-week treatment. Even at week 8 after stroke, 84.6% of the patients receiving FES plus SR were still able to walk when compared with 60.0% and 46.2% of those receiving, respectively, placebo stimulation with SR or SR alone. Given statistically significant between-group differences (P<0.05), Dr Woldag’s statement that “it remains doubtful whether FES can be recommended as therapeutic tool” is not substantiated, at least for the patients we studied during the acute stage.

The second consideration is cost-effectiveness. When patients cannot walk, helping them with passive walking movements requires expert knowledge and skill that could be quite expensive in many countries. The cost for 2 dual-channel Respond Select stimulators and program timer is US $2352 and $64, respectively. Including technician time, the total cost of our homemade FES unit comes to $2600. This unit could be used to treat 14 patients per day (at 30 minutes per patient) for 3 weeks, or 242.6 patients per year. Presuming a lifetime usage of 5 years, 1 unit could treat 1213 patients. Therefore, the cost per patient comes to only US $2.1, in addition to minimal therapist time for the 3-week treatment. When the outcome is that 84.6% of the patients could return home, which is almost double the 46.2% of those receiving SR alone, adding FES to the SR should be considered very cost-effective to the health care system.

Christina W.Y. Hui-Chan, PhD
Department of Rehabilitation Sciences
the Hong Kong Polytechnic University
Hung Hun, Kowloon
Hong Kong (SAR), China

Oral Anticoagulation in Secondary Prevention After Cerebral Ischemia of Arterial Origin

Letter to the Editor:
We react to the article by Amarenco and Donnan1 in which they discuss stroke prevention strategies after publication of the MATCH trial. In our opinion, they rush to conclusions about the value of oral anticoagulants in the secondary prevention after noncardioembolic stroke.

SPIRIT2 did not show that oral anticoagulants were inferior to aspirin in terms of efficacy and net benefit to prevent stroke and death in patients with a noncardioembolic stroke, as stated by the authors. SPIRIT was designed to compare the efficacy and benefit of oral anticoagulants with those of aspirin, but the trial was stopped early because of an excessively high incidence of major bleeding complications in the anticoagulation group. The only conclusion that can be drawn from this trial is that oral anticoagulants with an aimed INR of 3.0 to 4.5 are not as safe as aspirin in patients with a noncardioembolic stroke. The limited number of patients in the trial and the short follow-up do not allow conclusions on the efficacy in preventing stroke; the 95% confidence interval for ischemic events ranged from a 40% benefit for anticoagulants to a 43% benefit for aspirin. From SPIRIT and WARSS,3 together it may be inferred that anticoagulation is not the therapy of choice if its target INR is either high (SPIRIT: 3.0 to 4.5, average 3.3) or low (WARSS: 1.4 to 2.8, average 2.0). However, this leaves an intermediate target (2.0 to 3.0) for which no efficacy data in the prevention of stroke are known. Observational data suggest that this intermediate target is the optimum in the benefit–risk balance of oral anticoagulation for patients with noncardioembolic stroke.4

The European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT)5 aims to fill this gap by comparing oral anticoagulants with an aimed INR of 2.0 to 3.0 with aspirin in the secondary prevention after noncardioembolic stroke. Only after completion of this trial can definite conclusions on the efficacy of oral anticoagulants be drawn.

P.H.A. Halkes, MD for the ESPRIT Study Group
Department of Neurology
University Medical Center Utrecht
Utrecht, the Netherlands

Postprocedural Emboli in Carotid Artery Stenting: Where Do They Come From?
Giovanni Orlandi, Simone Gallerini, Mirco Cosottini and Luigi Murri

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