Tissue Plasminogen Activator —7351C/T Polymorphism and Lacunar Stroke

To the Editor:

Jannes et al.1 reported that a polymorphism in the tissue plasminogen activator (tPA) gene (—7351C/T) was associated with ischemic stroke in an Australian population. Stratification for stroke subtype demonstrated an association with lacunar infarction (OR: 2.7; 95% CI, 1.1 to 6.7), but not with other stroke subtypes. The authors interpreted this result as providing evidence that fibrinolytic factors play an important role in maintaining small vessel patency. The polymorphism is located within the binding site for the transcription factor Sp1, in the enhancer region of the tPA gene,2 and the TT genotype has been associated with significantly reduced vascular tPA release rates.2

This association could give clues to the pathogenesis of lacunar stroke, but first replication in independent populations is important, particularly because the original association was found in a small sample size, with only 43 patients in the lacunar subgroup. Therefore, we attempted to replicate it in a prospectively collected group of patients with well-phenotyped lacunar stroke. In addition, we determined whether the polymorphism predisposed to 1 particular type of lacunar stroke. It has been suggested that patients with larger lacunar infarcts (isolated lacunar infarction [ILI]) without leukoaraiosis may have microatheroma at the origins and proximal portions of the perforating arteries. In contrast, patients with lacunar infarction and confluent leukoaraiosis (ischemic leukoaraiosis [ILA]) may have a diffuse arteriopathy affecting the smaller perforating vessels.3 Previous studies have suggested different genetic associations in the 2 groups.4

Three hundred and twelve consecutive white patients presenting with lacunar stroke attending participating stroke services were recruited. Lacunar stroke was defined as clinical lacunar syndrome with accompanying lesion on MRI or CT. All patients had brain imaging and imaging of the carotid arteries with duplex or MR angiography. Patients with subcortical lesion ≥1.5 cm in diameter, cortical infarction of any size, a potential cardiogenic source and large-vessel disease defined as carotid, vertebral or basilar intracranial artery stenosis ≥50% were excluded. Two hundred and twenty-six (72%) had MRI and 86 (28%) had CT. In the principal center consecutive patients with lacunar stroke were recruited regardless of the presence of leukoaraiosis. To increase the number of cases with ischemic leukoaraiosis, in 4 additional centers, consecutive patients with ischemic leukoaraiosis were recruited. Patients were divided into 2 groups: ILI (absent/mild leukoaraiosis) or ILA (moderate/severe leukoaraiosis) according to a previously validated method.4 Six hundred and twenty-six age- and sex-matched controls free of symptomatic cerebrovascular disease were recruited by sampling family doctor lists from the same geographic locations as the patients. The study protocol was approved by local research ethics committees and informed consent was obtained from all participants. Genotyping was performed blinded to subtype diagnosis and case/control status.

DNA was isolated from blood samples using a commercial kit (Nucleon), and a 366bp region of DNA surrounding the tPA —7351C/T polymorphism was amplified using PCR. Digestion with Ban II restriction endonuclease produced 1 of 2 characteristic sets of fragments, depending on the presence of a C or a T allele at the SNP. The restriction fragments were separated on a 2% Micro A agarose gel.

Results were obtained for 611 (98%) controls and 301 (96%) cases. The genotypes distribution was in Hardy-Weinberg equilibrium (P=0.051). There was no association between the TT genotype and lacunar stroke before or after adjustment for age, gender, hypertension, diabetes, and smoking (before adjustment OR: 0.761; P=0.206; 95% CI, 0.499 to 1.162; after adjustment OR: 1.343; P=0.187; 95% CI, 0.866 to 2.084). This was also true for both subtypes (ILI before adjustment OR: 0.796; P=0.433; 95% CI, 0.451 to 1.406; after adjustment OR: 1.141; P=0.666; 95% CI, 0.626 to 2.081; ILA OR: 1.347; P=0.280; 95% CI, 0.785 to 2.310; after adjustment OR: 1.413; P=0.234; 95% CI, 0.800 to 2.497).

In conclusion, this study does not support the tPA polymorphism being a risk factor for lacunar stroke. It is most likely that the original association was a false-positive attributable to small sample size.

Acknowledgments

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Christine A. Armstrong, MSc
Steve N. Bevan, PhD
Kelly T. Gormley, BSc
Hugh S. Markus, FRCP
Centre for Clinical Neuroscience
St George’s University of London
United Kingdom

Simon A. Koblar, PhD
Department of Medicine
The Queen Elizabeth Hospital
University of Adelaide
Australia


Response:

We thank Armstrong and colleagues for acknowledging the importance of the original study, which found a positive association between the tPA —7351 TT genotype and lacunar stroke in an Australian population. As we concluded in the article, this association was made after subgroup analysis and was thus interpreted as hypothesis generating. We agree that confirmation in a larger, well-designed study is critical. It is important to reiterate that the tPA —7351 C/T polymorphism possesses a plausible biological reason to cause cerebral lacunar infarction,
and it has been implicated in other arterial disease phenotypes, namely coronary artery disease.\textsuperscript{1}

The current 2 studies of the IPA \textasciitilde 7351 C/T polymorphism in cerebrovascular disease illustrate the conundrum of genetic association studies, namely conflicting results. Many times the conflicting results may arise from differences in study power or methodology. It should be remembered that the results from all such studies may only be interpreted as supporting or negating a null hypothesis and do not indicate causation in linking a genotype with a phenotype. We acknowledge that the present study has a larger sample size than the first study. However, there still exist a number of methodological concerns within the present study, which may call to question the authors’ conclusion.

First, the selection of controls should be representative of the general population from which the cases originate. It may be argued that the recruitment of controls using family doctor lists is not representative of the general population and could result in bias toward an unhealthy cohort with cardiovascular disease. In the past, many genetic association studies had controls obtained from Red Cross blood banks, but it is now recognized that this may significantly confound a study’s finding. We took this into consideration and designed the first study such that controls were recruited randomly from the electoral role of the Adelaide metropolitan area from where the stroke patients resided. We believe this to be a major strength of the original study.

Second, the ethnicity of controls in the present study was not reported, which raises the question of population stratification bias. This may be of particular relevance to the present study as a large number of residents in the greater London region are a large number of non-caucasoid origin.

Third, in the current study the classification of lacunar stroke into subtypes dependent on the presence or absence of leukoaraiosis is of questionable relevance. Histopathological studies have shown that lacunar stroke is caused by either proximal microatheroma or lipohyalinosis, 2 entities which are distinctly different to the hyaline arteriosclerosis that underpins leukoaraiosis.\textsuperscript{2} These pathological subtypes are also likely to have different genetic determinants. The IPA \textasciitilde 7351 C/T polymorphism is hypothesized to influence the risk of stroke by its effect on lysis of an occluding thrombus irrespective of the underlying vessel pathology.

Fourth, the current study also differed in methodology from the original study in that an adjustment for other important confounding influences was not considered. These possible confounders included medication usage, hyperlipidemia, and family history of cerebrovascular disease.

In sum, the conflicting results from these 2 studies investigating the association of IPA \textasciitilde 7351 C/T polymorphism in lacunar infarction emphasizes that further large-scale prospective studies are required to clarify this current paradox. We contend that both studies have methodological deficiencies and thus the hypothesis remains valid.

**Letters to the Editor**

**The Call for Multicenter Studies of Pediatric Stroke**

To the Editor:

We were pleased to see the call for large, collaborative studies of pediatric stroke by Dr. Zahuranec et al.\textsuperscript{1} The authors present population-based incidence data and power calculations detailing the overwhelming number of pediatric stroke cases needed to identify risk factors in case-control studies. As members of the on-going International Pediatric Stroke Study (IPSS), a multicenter prospective childhood ischemic stroke registry, we would like to thank the authors and the editors for highlighting the need for large multicenter studies in childhood stroke, and wish to elaborate on both the role for, and difficulties associated with, such studies.

We believe the most pressing issue in childhood stroke at this time is the identification of effective secondary stroke prevention measures. Outside of certain subgroups of high-risk children (eg, sickle cell disease or congenital heart disease), stroke is rare, and the development of strategies for primary stroke prevention that can be widely implemented is probably unrealistic. Recurrent stroke, however, occurs with alarming frequency (in up to 25\% of children within 2 years of an initial stroke, even with best medical management),\textsuperscript{3} and proven strategies for secondary stroke prevention are lacking. Pediatric neurologists must therefore manage children with stroke by extrapolating from adult studies, but given the vastly different etiologies in children versus adults, this strategy is clearly not adequate.

We cannot design rational randomized controlled trials (RCTs) for secondary stroke prevention in children until data regarding rates and predictors of recurrent stroke are available. The goals, then, of collaborative studies of childhood stroke must also include identifying these rates and predictors. However, as Dr. Zahuranec et al highlight, the challenges facing such studies are great.

The first challenge is simply identifying ischemic stroke in children. The poor awareness of pediatric stroke among pediatricians, poor sensitivity of early CT scanning, and wider differential diagnosis for focal deficits in children frequently delay this diagnosis. In the authors’ population-based study, ICD-9 code searches of hospital discharge and emergency department diagnoses identified 6 hemorrhagic strokes, but only 1 ischemic stroke. This ratio of hemorrhagic to ischemic stroke is much higher than the 1:1 ratio previously reported for children, and their incidence of ischemic stroke (0.6 per 100 000) is lower than prior reports.\textsuperscript{3,4} Although this may reflect the uniqueness of their population, it could also reflect difficulty identifying cases by ICD-9 codes. In our own experience with on-going population-based studies, we have been surprised by the low yield of stroke-related ICD-9 code searches compared with text-string searches of radiology databases. Common reasons for missed ICD-9 diagnosis include: (1) stroke diagnosis not being coded at discharge in a child with severe medical illnesses (eg, stroke in the setting of overwhelming sepsis, leukemia, a lupus flare, or cardiac surgery), (2) stroke diagnosed only after discharge when either additional neuroimaging is performed or an in-patient imaging study is reinterpretated, or (3) children with stroke diagnosed and managed only as out-patients (eg, occipital stroke presenting with minor visual deficits).

The second major challenge, as identified by the authors, is identifying sufficient pediatric stroke patients to achieve adequate power in a study. Depending on the prevalence of the risk
factor and its strength of association with stroke, they estimated that hundreds to thousands of cases are needed. We similarly estimated that—depending on stroke recurrence rates, the treatment agents used, and the specific population targeted—RCTs for secondary stroke prevention in children would require between 215 and 1600 subjects. Only large, well-coordinated multicenter efforts will ever be able to produce such numbers.

Although a population-based cohort study is the superior study design for analyzing risk factors for a first stroke, prospective pediatric stroke registries that are not population-based, such as the IPSS, should provide meaningful data on rates and predictors of stroke recurrence at those centers that will conduct the RCTs. Although limited in terms of generalizability (all subjects have been enrolled at academic tertiary-care centers), the IPSS offers the advantage of rapid enrollment through its web-based registry. Since its initiation in 2002, the IPSS has expanded from 9 to more than 60 centers spanning 17 countries with 76 co-investigators. Over 500 patients from 18 centers have been enrolled into the web-database (https://www.sickkids.on.ca/cstrokestudy). The IPSS has also facilitated the development of a network of investigators interested in childhood stroke, and willing to participate in future RCTs.

In conclusion, we agree that the time is ripe for large multicenter studies of childhood stroke with the ultimate goal of obtaining the evidence desperately needed to guide the management of these children.

Heather Fullerton, MD, MAS
University of California San Francisco
Departments of Neurology and Pediatrics
San Francisco, Calif

John K. Lynch, DO, MPH
National Institute of Neurological Disorders and Stroke
Neuroepidemiology Branch
Bethesda, Md

Gabrielle deVeber, MD, FRCPC(C), MHSc
The Hospital for Sick Children
Division of Neurology
Toronto, ON


High Intracranial Pressure, Brain Herniation and Death in Cerebral Venous Thrombosis

To the Editor:

Sir, the study by Canhao and colleagues made the important point that the most frequent cause of death in patients with cerebral venous thrombosis (CVT) is transtentorial herniation and that these patients may potentially have benefited from decompressive hemicraniectomy. We would like to corroborate this argument by providing evidence for a rise in intracranial pressure (ICP) preceding brain herniation and death in a patient with CVT.

A 29-year-old pregnant woman who presented with confusion and vomiting was admitted to a district general hospital. A right-sided weakness developed within 2 days. A CT brain scan showed a left temporal hemorrhage without mass effect. Her Glasgow Coma Scale score dropped to 8/15; she was intubated and transferred to the neurocritical care unit at the National Hospital. A repeat CT demonstrated worsening of the hemorrhage with obliteration of the 3rd and 4th ventricles, and the diagnosis of a CVT was confirmed by magnetic resonance venography. At this point, the left pupil became fixed. An ICP bolt was inserted (opening pressure 50 mm Hg; Figure). ICP targeted management (propofol, fentanyl, midazolam, ventilation to maintain a pCO2 4.0 to 4.5 kPa and IV norepinephrine to maintain mean arterial pressure >100 mm Hg) could not be maintained, paralysis and moderate hypothermia were initiated. Because an ICP <20 mm Hg could not be maintained, paralysis and severe hypothermia were initiated. Despite these measures ICP continued to rise. A treatment trial with thiopental to lower ICP failed. Both pupils became fixed and dilated on day 6 on ICU. Several intractable peaks of ICP (>60 mm Hg) were followed by development of diabetes insipidus necessitating treatment with desmopressin. At 8:00 AM on the 7th day, periods of ventricular tachycardia and fibrillation started to appear leading to severe hemodynamic compromise and elevated ICP. The clinical diagnosis of brain stem herniation was made and treatment was demedicalized after an informed discussion with the family took place.

Mortality in CVT has decreased over the last decades from 30% to 50% to ≈4.3% in the acute phase.1,2,3 There are occasional reports of decompressive hemicraniectomy performed successfully in patients in whom medical treatment failed.4 There is of note that all 3 patients in this report already showed signs of brain herniation at time of operation. The authors pointed out that indications for surgical intervention are almost completely lacking. The decision to proceed with surgery implies that treatment (heparin) needs to be discontinued. In an individual case this may be a difficult decision because of the arguably beneficial effect (small sample sizes and large confidence intervals).5 Furthermore, there is no guide toward the best timing for surgical...
intervention. Fixed and dilated pupils may be too late a sign and repeated brain imaging is logistically difficult in the critically ill patient. Continuous ICP and arterial blood pressure monitoring as performed in the present case provides important data at the bedside. There is a need to investigate whether decompressive hemicraniectomy would be of benefit in those patients in whom medical management of ICP fails.

Axel Petzold, MD, PhD
Martin Smith, FRCA
The National Hospital for Neurology and Neurosurgery
Tavistock Intensive Care Unit
London, United Kingdom


Response:
We thank Petzold et al for illustrating with this case report the results of our study, regarding the causes of death in patients with cerebral vein and sinuses thrombosis.1 Probably, the patient here presented could have been saved if decompressive craniectomy had been performed before fatal clinical deterioration occurred.

We consider that the next step for evaluating the role of this intervention should be to carry out an international registry including cerebral vein and sinus thrombosis patients submitted to decompressive craniectomy.

Patricia Canhão, MD
José M. Ferro, MD, PhD
Department of Neurosciences and Mental Health
Hospital Santa Maria
Lisbon, Portugal


Pathophysiology of Gender Difference in Prognosis of Asymptomatic Carotid Stenosis: Research and Future Implications

To the Editor:
With great interest we read the recent article by Dick et al reporting that gender is an independent predictor of major adverse cardiovascular events in patients conservatively treated for high-grade carotid stenosis. The authors discussed possible mechanisms that would explain the observed differences in outcome: eg, cardiovascular risk profile and carotid plaque burden are higher in men, and hormones could be protective for women. As appreciated by the authors, their study design did not allow inferences regarding a causal relationship between gender and outcome. Recently, we hypothesized that gender could be associated with the pathophysiological substrate of acute cardiovascular events: a thin cap fibroatheroma. To gain insight in atherosclerotic plaque characteristics among patient groups experiencing carotid artery stenosis, we constructed a biobank containing organized plaque material was obtained in female patients. The value of plaque markers to predict cardiovascular events from plaque phenotype is subject of an ongoing study. Consistent with our hypothesis is that plaque area, which the authors refer to as a predictor of vascular events, is found to be related with plaque phenotype.

Eventually, increasing insight in pathophysiology of the vulnerable atherosclerotic plaque and upcoming imaging technology may shift focus to plaque markers in the search for the patient at risk. The observation that risk factors for cardiovascular events, like gender, are associated with atherosclerotic plaque characteristics support this idea.

Willem E. Hellings, MD
Bart A.N. Verhoeven, MD
Frans L. Moll, MD, PhD
Department of Vascular Surgery
University Medical Center
Utrecht, The Netherlands

Theo van den Broek, MD
Gerard Pasterkamp, MD, PhD
Experimental Cardiology Laboratory
University Medical Center
Utrecht, The Netherlands


Multilevel Educational Program for Emergency Medical Services

To the Editor:
I read with interest Wojner-Alexandrov and colleagues’ article in the July issue of Stroke, evaluating a multilevel educational program designed to improve both paramedic and hospital performance, and raise community awareness, regarding acute stroke. The authors are to be applauded for this multidisciplinary...
approach; in particular, the inclusion of emergency medical services personnel reflects recognition of the key role that events before arrival at the hospital can play in the chain of events needed to provide optimal care for the acute stroke victim.

However, I disagree with their conclusion that this program may decrease the time from the onset of symptoms to arrival at the hospital. For the entire group of patients for whom this interval was documented, there was no statistical difference between the preintervention (mean 226 minutes, median 95 minutes) and the active-intervention phase (mean 358 minutes, median 89 minutes). Even excluding those patients who presented more than 24 hours after symptom onset, there was no improvement in the active-intervention phase ($P=0.054$). Only when examining the proportion who arrived within 120 minutes of symptom onset was there a clinically small (58% versus 62%) but statistically significant difference between groups.

Perhaps more importantly from my perspective as an emergency medical services medical director, the program found an improvement in the accuracy of paramedic diagnosis of stroke, but apparently at the expense of additional time in the field. The time paramedics spent on scene increased from 16.7 minutes to 18.2 minutes—again a clinically small but statistically significant increase. Perhaps as a result of diversion to more distant hospitals that were participating in the regional stroke system, transport times also increased from 15.6 to 17.9 minutes. Although these differences are small, it is important to minimize delays in the field in order to maximize the chances of completing transport and emergency department workup within the 3-hour window for the small proportion of stroke patients who are eligible for and may benefit from thrombolysis.

David C. Cone, MD
Division of EMS
Section of Emergency Medicine
Yale University School of Medicine
New Haven, Conn


Deliberate Distal Displacement of a Middle Cerebral Artery Embolus as an Alternative Method to Treat a Thrombolytic-Resistant Clot

To the Editor:

Intra-arterial administration of fibrinolytic agents remains the primary endovascular option for patients with acute middle cerebral artery (MCA) thromboembolic disease. However, the use of fibrinolytic agents is usually limited to a 3- to 6-hour window, is contraindicated in certain circumstances, and has little or no effect against some types of clots (organized or tissue emboli, for example). In addition, fibrinolytic agents are associated with a risk of hemorrhage both at the site of the ischemic lesion and in remote intracranial and extracranial locations. As a result of these constraints, mechanical treatment options have recently been developed, including thromboaspiration techniques and thrombectomy devices. We illustrate our experience in a patient with acute MCA ischemia, in whom a proximal MCA clot was purposefully advanced into a distal branch in order to limit the extent of tissue infarction.

Our patient was a 42-year-old HIV-positive man admitted for acute respiratory distress. He was intubated and a chest tube placed for pleural effusion. During the hospital stay, he developed a sudden change in mental status and a left hemiplegia. CT showed a hypodensity in the right MCA territory suggesting acute ischemia. Cerebral digital subtraction angiography (DSA) performed ~3 hours after onset revealed proximal occlusion of the superior division of the right MCA by an embolus (arrow). B, DSA, Superselective injection of the right MCA, lateral view, documenting the final location of the embolus after mechanical displacement (black arrow). Superselective administration of 11 mg of tPA did not produce further changes in the size or location of the embolus. The initial embolus position is indicated by a white arrow. C, DSA, right common carotid injection, lateral view, after embolus displacement, showing the recanalized segment of the superior division of the right MCA (black arrowheads) and the final embolus location (black arrow). The manipulation allowed to revascularize several MCA branches, including the rolandic artery (white arrowhead) and anterior parietal artery (white arrow).

42-year-old man with acute mental status alteration and left hemiplegia. A, DSA, right common carotid injection, lateral view, showing occlusion of the superior division of the right MCA by an embolus (arrow). B, DSA, Superselective injection of the right MCA, lateral view, documenting the final location of the embolus (black arrow). A 1.9-French microcatheter (Prowler 14, Cordis) was advanced at the contact of the clot. During attempted clot disruption with
a 0.014 guide wire (Transcend Ex, Cordis), slight forward motion of the thrombus was observed. Because the presence of a chest tube would limit the dose of tissue plasminogen activator (tPA) that could be safely administered, it was decided to try pushing the clot as far as possible in the MCA distribution using the guide wire. The clot could easily be advanced into the angular artery (Figure, B). This manipulation was followed by intra-arterial administration of 11 mg of tPA without detectable effect on the clot (Figure, C). The patient was able to move his left arm and legs immediately after he woke up from the procedure. His mental status improved gradually to baseline. Intravenous heparin was continued for 24 hours. The patient was discharged home 14 days after the procedure. His neurological examination at discharge only showed a mild left facial droop; the motor strength was 5/5 bilaterally.

Our case illustrates an unusual endovascular technique for acute stroke treatment, which might be useful in patients with absolute or relative contraindications to fibrinolytic agents, clots resistant to fibrinolysis, or clots not accessible to currently available thrombectomy devices. Our patient showed each of the constraints mentioned above: (1) the presence of a chest tube was a relative contraindication to fibrinolytic therapy, (2) the MCA clot ultimately proved resistant to the given dose of fibrinolytic agents, and (3) the location of the clot (proximal M2 segment) was unfavorable to a thrombectomy device such as the Merci (Concentric), which was not then available anyway. In our patient, mechanical distal advancement of the clot into a distal MCA branch resulted in near complete resolution of the clinical symptoms, despite the absence of effect of the fibrinolytic agents.

Mayumi Oka, MD
Philippe Gailloud, MD
Division of Interventional Neuroradiology
The Johns Hopkins Hospital
Baltimore, Md

Eric Aldrich, MD
Department of Neurology
The Johns Hopkins Hospital
Baltimore, MD


Anticoagulation Intensity and Stroke During Warfarin-Use in Atrial Fibrillation Patients
To the Editor:

The interesting study by Poli and colleagues examined risk factors for ischemic stroke during anticoagulation of atrial fibrillation patients. For the 21 patients with ischemic events, it would be of interest to know the mean of the last “routine” INR before the ischemic event and the mean of the INR recorded nearest to/at the time of stroke to compare with the means of INRs during total follow-up of these 21 patients and of the mean INR for 343 patients without ischemic events. These data may shed additional light on the potential contribution of anticoagulation intensity to ischemic events in this setting.

Robert G. Hart, MD
University of Texas Health Science Center
Department of Medicine (Neurology)
San Antonio, TX


Response:

We thank Dr Hart for his interest in our study and for his questions aiming at clarifying our data. The mean INR of the 343 patients without ischemic events was 2.5 ± 0.19, and the mean INR of the 21 patients who experienced an ischemic event during follow-up was 2.5 ± 0.16, a difference not statistically significant. The mean INR related to the ischemic event (obtained at the time of the event or during the preceding 8 days) was 2.1 ± 0.58, statistically lower in comparison to both the mean INR of this group and the mean INR of all the other patients (P = 0.002). Fifteen patients had the INR related to the event ≥ 1.8. The last mean routine INR recorded before the event was 2.34 ± 0.56, not different with respect to both the mean INR value in this group and the mean INR of all the other patients (P = 0.1).

To evaluate if the occurrence of ischemic events could be related to a long period of under-anticoagulation, we have calculated the mean INR of the 3 months preceding the event. It was 2.5 ± 0.7, a figure not different from the mean INR of all the patients.

In our opinion, these data confirm that the reduced INR related to the event is only one of the risk factors for the occurrence of ischemic complications during OAT. In fact, 15 out of 21 patients had an INR ≥ 1.8 at the time of the event. In addition, patients without ischemic events during OAT had been exposed to the risk of a poor anticoagulation for a time similar to patients with ischemic events. Actually, the time spent below the intended therapeutic range was not different between the 2 groups. Oral anticoagulant therapy has an intrinsic variability of response so that even an optimized management cannot avoid significant periods of time with INR < 2.

The use of this treatment on a growing population makes this goal more and more difficult to obtain, further underscoring the need for a specifically devoted management. Together with the continuous efforts to ameliorate the quality of anticoagulation, the identification of other risk factors could help to reduce adverse events in nonvalvular atrial fibrillation patients.
Is There an Interaction Between Pravastatin and Clinical Events Other Than Vasospasm in Patients With Aneurysmal Subarachnoid Hemorrhage?

To the Editor:

We would like to congratulate Tseng et al1 for the article titled “Effects of acute treatment with Pravastatin on cerebral vasospasm, autoregulation, and delayed ischemic deficits after aneurysmal subarachnoid hemorrhage: A phase II randomized placebo-controlled trial”. The authors hypothesized that statins might improve cerebral vasomotor activity through cholesterol-dependent and -independent mechanisms. They randomized aneurysmal subarachnoid hemorrhage patients (18 to 84 years of age) within 72 hours from the ictus to receive either oral pravastatin (40 mg) or placebo daily for up to 14 days. They were able to show a decrease in incidence of vasospasm, duration of severe vasospasm, duration of impaired autoregulation, incidence of vasospasm-related delayed ischemic deficits and mortality with pravastatin treatment impressively in this 80-patient study.

The authors’ center had a clipping to coiling ratio of 4 to 1 for patients with aneurysmal subarachnoid hemorrhage. The authors reported a ventriculitis rate of 30% in statin group versus 17.5% in the placebo group, an immediate postoperative deficit of 22.5% in statin group versus 7.5% in placebo group, as well as a sepsis rate of 27.5% in the statin group versus 15% in the placebo group. The events seemed to double in all 3 categories in the statin group though not reaching statistical significance in this 80-patient study. That raised the puzzle whether it would be related to use of statins or other unspecified factors. Studies2,3 had suggested that prior statin-use might be related to a lower in-hospital infection rate and a lower C-reactive protein level. Little is known about the acute effect on sepsis after initiating statins. Would it actually be more sepsis? Clarification of the clinical events above may provide information to suggest a possible similar, neutral, or contradictory effect on sepsis.

The authors noted a significant higher mortality rate of 20% in the placebo group versus 5% in the statin group. It would be of interest to know contributing causes of the mortality, whether it would be related to vasospasm or other events as sepsis or cardiovascular events. A secondary analysis to see a relationship between total and LDL cholesterol levels on presentation and clinical events above may provide information to suggest a possible similar, neutral, or contradictory effect on sepsis.

Ming-Yuan Tseng, MD, MPhil, MSc
Marek Czosnyka, PhD
Hugh Richards, PhD
John D. Pickard, FRCS, Mchir
Peter J. Kirkpatrick, FRCS(SN)
Department of Neurosurgery
Addenbrooke’s Hospital
University of Cambridge
United Kingdom

likely to reach a primary composite end point of total mortality and all cardiovascular/cerebrovascular events, with an incidence density ratio of 0.79. We are concerned about the clinical interpretation of the composite outcome.

TIAs were included in both the primary composite end point and secondary end points for all cerebrovascular events. From a patient’s perspective, a TIA is not as clinically relevant as a stroke because a TIA is not disabling. Most cerebrovascular events in the MOSES trial were TIAs (66 in the eprosartan group versus 92 in the nitrendipine group). Only 36 ischemic strokes/intracerebral hemorrhages were seen in the eprosartan group, whereas 42 similar events were noted in the nitrendipine group. Without TIA, the difference between both groups may become marginal for cerebrovascular events. Furthermore, the accuracy of a diagnosis of TIA may not be as good as for stroke, particularly for nonneurologists. The MOSES study involved patients from internal medicine and general medicine practices. Although a blinded end point committee evaluated all events, a bedside assessment by a neurologist was not required.

In the context of the ACCESS, LIFE and VALUE trials, the MOSES study argues in favor of angiotensin receptor blockers in hypertensive patients and stroke or TIA.2,3,4 However, the key question is how this regimen, with or without a diuretic, compares to the proven combination of an angiotensin-converting enzyme inhibitor and diuretic, defined by the PROGRESS study.5

Jean-Martin Boulanger, MD, FRCP
Michael D. Hill, MD, FRCP
For the Calgary Stroke Program
University of Calgary
Alberta, Canada

Does the MOSES Trial Establish Superiority of AT1-Receptor Blockers Over Dihydropyridine/Calcium Antagonists in Secondary Stroke Prevention?

To the Editor:
The MOSES study1 has unequivocally shown that in patients with a history of cerebrovascular events, a blood pressure (BP)—lowering treatment based on eprosartan is more protective against both cerebrovascular event recurrence and cardiac complications than a treatment based on nitrendipine. Of paramount importance is the fact that this superiority was documented with similar BP decrease in both treatment arms and no difference in baseline BP. Furthermore, BP was monitored not only by office BP but also by 24-hour ambulatory BP at baseline and after 12, 24 and 48 months of follow-up. The office BP-lowering effect of eprosartan was even slightly smaller (1.5 and 0.6 mm Hg for the systolic and diastolic BP, respectively), which formally excludes any BP bias. Can we therefore postulate that a specific BP-independent stroke preventive effect of eprosartan is the only possible explanation for this better cardiovascular protection compared with nitrendipine?

To answer this question, it is important to carefully look at the add-on therapy. Interestingly as pointed out by the authors, the add-on therapy was comparable with the exception of the use of angiotensin-converting enzyme inhibitors (ACEI) and dihydropyridine calcium channel blockers (CCBs). In the eprosartan arm, ACEIs were less frequently used (11.3% versus 21%), whereas CCBs were used twice as often (14.4% versus 7.5%) when compared with the nitrendipine arm. Could this difference in add-on therapy have influenced the outcomes, considering that monotherapy with randomized drugs was used only in 34% and 33% of both arms? To elucidate this issue the last BP-lowering treatment (BPLT) trialist collaboration meta-analysis6 should be recalled: it showed that myocardial infarction was equally prevented by ACEI and dihydropyridine (DHP) CCBs but that prevention of stroke was better with CCBs whereas heart failure was better with ACEIs (relative risk = 0.89 and 0.82, respectively). This suggests that the differences in use of ACEI and DHP between the 2 groups would increase the heart failure risk but decrease the cerebrovascular risk in the eprosartan group. Conceivably, therefore, the superiority of eprosartan in cardiovascular prevention may have been attenuated with this add-on therapy, whereas superiority of eprosartan in cerebrovascular protection was likely to be enhanced.

However, it is unlikely that the 25% greater stroke risk reduction by eprosartan could entirely be explained by the difference in DHP/ACEI use prevalence because the greater reduction of stroke with DHP compared with ACEI in the BPLT trialist collaboration meta-analysis was only 11%. Furthermore, the ACEI/CCB prescription differences between the 2 arms affected only 7% of the patients not on monotherapy (ie, about 5% of the whole population).

Therefore, we quite agree with the editorial by Strandberg3 that the greater BP-independent cerebroprotection with eprosartan is real and might be explained by greater stimulation of AT2-receptor than with nitrendipine. Indeed, renin secretion and therefore angiotensin II formation might be increased by both dihydropyridines4 and by AT1-blockers,5 but stimulation of renin secretion may be greater with AT1-blockers because of blunting the strong AT1-mediated angiotensin II negative feedback on renin secretion. Indeed, long acting dihydropyridines may stimulate renin only by activation of the sympathetic nervous system, and this latter is heterogeneous with the various DHP-CCB as documented in the recent comparison of lercanidipine with nifedipine-gastrointestinal therapeutic system.6,†

AT2-mediated protection against cerebral ischemia has now been formally evidenced in experimental models. The group of Unger et al7 showed that intracerebroventricular preadministration of ibrsartan decreased the neurological deficit induced in the rat by transient occlusion of the midcerebral artery and that this protection was cancelled by coadministration of an AT2-receptor-blocker which impeded the blockade of anoxia-induced neuronal apoptosis. This AT2-mediated-cerebroprotection has also been confirmed by the comparison of AT2-receptor gene-
MOSES: Superiority or Noninferiority?

To the Editor:

The MOSES Investigators conclude that for a similar level of blood pressure control eprosartan demonstrates a protective effect relative to nitrendipine in hypertensive patients with a history of stroke.1 What is the basis of this claim? No difference in mortality or disability (either cognitive or physical) was demonstrated. The claim appears to be based on a significant difference in the composite end point using the incidence density rather than a traditional survival analysis (Table 3). A Cox proportional hazards analysis is given in Table 4 but only for the components of the primary end point and not the primary end point itself. There is no evidence from this analysis that cerebrovascular events are different between the groups. Yet, the incidence density approach (Table 3), preferred by the authors, suggests that there is. Which are we to believe? We must surely be cautious in accepting a result if it depends on the type of analysis used to obtain it. It would be interesting to see the result of a traditional survival analysis (excluding recurrent events) on the primary end point.

A further point worthy of examination is the inclusion of transient ischemic attacks (TIA) and recurrent events in the composite primary end point. In a discussion of the validity of composite end points it has been suggested that the components of a composite end point should be of similar importance. Clearly, a TIA does not have the same importance as death or a disabling stroke. TIA contributed 67% of all cerebrovascular events and thus made a large contribution to the primary end point. The use of recurrent events in the primary end point is unorthodox and requires robust theoretical justification. Even the authors do not seem particularly convinced on this point stating that “The protocol appears to be appropriate . . . .”. A few subjects experiencing multiple events could have a disproportionate effect on the outcome and lead to spurious conclusions.

In summary, the claim of the superiority of eprosartan over nitrendipine is not supported by the data and analysis presented. Might the data support a conclusion of the noninferiority of eprosartan to nitrendipine? The INSIGHT Trial3 sought to test for volunteers. Inhibition of presor response to exogenous angiotensin I and II. Circulation. 1991;83:1333–1342.


the superiority of a calcium channel antagonist over a diuretic in hypertensive subjects with one additional risk factor (although not stroke) for cardiovascular events. This study also had a planned secondary noninferiority analysis if superiority was not demonstrated. The margin of inferiority (the maximum difference of no clinical relevance) was set at 2% for the absolute difference in event rates. If we strip out TIA and pulmonary embolism, the primary end point of the MOSES Trial is similar to that of INSIGHT (although ideally any remaining multiple events should also be removed). It would thus be reasonable to use the same margin of noninferiority. If we do this, the absolute event rates are 20.41% and 23.85% for eprosartan and nitrendipine, respectively, over the period of the trial. This gives a difference in absolute event rates (eprosartan–nitrendipine) of −3.44% with a 95% one-sided upper bound of 0.3%. Because this is <2% we can accept eprosartan as noninferior to nitrendipine in this patient population.

Acknowledgements

Conflicts of interest: The author has received educational support and lecturing honorarium from various pharmaceutical companies, including Solvay pharmaceuticals.

Andrew Owen, FRCP, PhD
Department of Cardiology
Kent and Canterbury Hospital
Kent, UK

Response:

Fournier et al discussed several interesting aspects of secondary prevention by different antihypertensive agents and compared the MOSES and PROGRESS study. These indirect comparisons between the studies are difficult because of different trial designs, baseline parameters and the comparison of active antihypertensive treatment versus placebo in PROGRESS and 2 active antihypertensive treatments in MOSES. We agree with the points raised by Fournier et al concerning the mechanism of action, but we were not able to discuss them in extension because of limited word count in the article. Clinical studies like MOSES or PROGRESS often lead to speculations about underlying mechanisms of the observed clinical effects, but overall clinical studies usually cannot sufficiently solve these interesting questions on mechanisms.

Joachim Schrader, MD
Stephan Lüders, MD
Anke Kulcschewski, MD
Frank Hammersen, MD
Department of Internal Medicine
St.-Josefs Hospital
Cloppenburg, Germany

Kerstin Plate
Institute for Hypertension and Cardiovascular Research
Cloppenburg, Germany

Jürgen Berger, PhD
Medical Biometry and Epidemiology
University Hospital Hamburg-Eppendorf
Germany

Walter Zidek, MD
Department of Nephrology
Charité Campus Benjamin Franklin
Berlin, Germany

Peter Dominiak, MD
Department of Pharmacology and Toxicology
University of Lübeck
Germany

Hans Christoph Diener, MD
Department of Neurology
University of Essen
Germany

for the MOSES Study Group


MOSES Raises Questions

To the Editor:

The MOSES trial confirms both the safety and efficacy of eprosartan in hypertensive patients with cerebrovascular disease. The authors’ conclusion that eprosartan provides “vascular protective effects” above that of nitrendipine, however, is not


Response:

Drs Strauss and Verma discussed several important aspects of the MOSES study results concerning the cardiovascular end points in comparison to other data, especially the increase of myocardial infarction in the valsartan group of the VALUE trial.1 These results could not be supported by the MOSES data.2 In this study, the number of acute coronary syndrome in the eprosartan group was even less than in the nitrendipine group (39 versus 48; not significant) showing at least the safety of treatment with eprosartan in patients with cerebrovascular disease. Drs Strauss and Verma wondered if the diagnosis of heart failure in the MOSES study could be attributable to peripheral edema alone. This question is of course of great importance because the significant difference in first occurrence of cardiovascular events was attributable to peripheral edema alone.

To accept the diagnosis of CHF, more information like hospital demission-letters, echocardiography, chest x-ray, hospitalization and concomitant medication had to be documented and considered by the end point committee. Because of the limited number of words in the original article these methods could not be described in detail.

The benefit for the eprosartan group in terms of reducing cerebral events was not driven by a single patient with multiple events. There was a higher number of patients with >1 event in the same category of end points (TIA, ischemic stroke, acute coronary syndrome, CHF) in the nitrendipine group (16 versus 24; eprosartan versus nitrendipine).

Joachim Schrader, MD
Stephan Lüders, MD
Anke Kulchewski, MD
Frank Hammersen, MD

Department of Internal Medicine
St. Joseds Hospital
Cloppenburg, Germany

Kerstin Plate
Institute for Hypertension and Cardiovascular Research
Cloppenburg, Germany

Jürgen Berger, PhD
Medical Biometry and Epidemiology
University Hospital Hamburg-Eppendorf
Germany


**Response:**

In our article we applied the default software settings recommended by the manufacturer of this commercially available system, resulting in a sensitivity and specificity for solid emboli of 50.3% and 94.2%, respectively. There was some improvement in specificity when considering only those embolic signals (ES) classified as definite and those with an intensity increase >7 db when insonated with the 2.0 MHz transducer (Table 2), but this was at the expense of sensitivity. The sensitivities were 44.8% and 48.4%, respectively, and specificities were 96.91% and 97.4%, respectively.

We are grateful to Russell and Brucher for their suggestions and have reanalyzed our dataset with the further refinements as they describe. Results of the revised categorization of ES are shown in Table 1 and the revised sensitivities and specificities in Table 2. Firstly, we excluded ES which were classified as <7 db intensity at either frequency. This resulted in an improvement in sensitivity to 59.4% for all solid and 96.5% for all gaseous emboli, and specificity to 96.5% and 59.4%, respectively. However, this was at the expense of exclusion of a significant number of ES: 49/145 (33.8%) of the ES in patients with carotid stenosis and 80/648 (12.3%) of those in the PFO group. There was further improvement in sensitivity for solid emboli to 63.6%, with no change in specificity, when only ES categorized as definite were considered; this resulted in an additional 8 possible solid ES being excluded.

We performed a second analysis using the suggested lower dEBR detection limit $y = -0.1$, $x = -0.12$. When considering all ES this resulted in increased sensitivity for solid emboli (59.3%) but

<table>
<thead>
<tr>
<th>TABLE 1. No. of Embolic Signals in Each Classification</th>
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<tbody>
<tr>
<td><strong>ES in New Analysis</strong></td>
</tr>
<tr>
<td>-----------------------</td>
</tr>
<tr>
<td><strong>ES in Original Analysis</strong></td>
</tr>
<tr>
<td><strong>Carotid stenosis subjects</strong></td>
</tr>
<tr>
<td>Definite solid</td>
</tr>
<tr>
<td>Possible solid</td>
</tr>
<tr>
<td>Definite gaseous</td>
</tr>
<tr>
<td>Possible gaseous</td>
</tr>
<tr>
<td>Total emboli</td>
</tr>
<tr>
<td><strong>Patent foramen ovale subjects</strong></td>
</tr>
<tr>
<td>Definite solid</td>
</tr>
<tr>
<td>Possible solid</td>
</tr>
<tr>
<td>Definite gaseous</td>
</tr>
<tr>
<td>Possible gaseous</td>
</tr>
<tr>
<td>Total emboli</td>
</tr>
<tr>
<td>793</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>TABLE 2. Sensitivities and Specificities for Solid and Gaseous Emboli Using the Different Data Analysis Approaches</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Classification Criteria</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Original analyses</strong></td>
</tr>
<tr>
<td>All ES</td>
</tr>
<tr>
<td>Only ES of &gt;7 dB AT 2.0 MHz</td>
</tr>
<tr>
<td>Only ES classified as definite</td>
</tr>
<tr>
<td><strong>1st suggestion revision</strong></td>
</tr>
<tr>
<td>Only ES of &gt;7 db at both frequencies</td>
</tr>
<tr>
<td>Only ES of &gt;7 db at both frequencies and definite ES</td>
</tr>
<tr>
<td><strong>2nd suggested revision</strong></td>
</tr>
<tr>
<td>All ES $y = -0.1$, $x = -0.12$</td>
</tr>
<tr>
<td>Definite ES $y = -0.1$, $x = -0.12$</td>
</tr>
<tr>
<td><strong>Both suggested revisions</strong></td>
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<tr>
<td>Combined revision all ES</td>
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<td>Combined revision only definite ES</td>
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</tbody>
</table>
reduced specificity (86.9%) and reduced sensitivity for gaseous emboli (86.9%).

Implementing both revisions together resulted in increased sensitivity for solid emboli (74.2%) but reduced specificity (85.4%) and reduced sensitivity for gaseous emboli (85.4%).

In conclusion, the refinements as suggested by Russell and Brucher do improve sensitivity for solid ES. However, this is at a moderate loss of specificity and an exclusion of approximately a third of solid ES. ES >7 dB at 2 Mz have been found to be independently predictive of stroke, and may be infrequent in patients with carotid stenosis with a median per hour of only 4 in those subjects in whom ES are present during an hours recording. Therefore, exclusion of a third of these ES will convert some ES positive individuals to ES negative; it remains to be determined what effect this would have on the predictive value of the technique.

Hugh S. Markus, FRCP
Martin Punter, MRCP
Centre for Clinical Neuroscience
St Georges University of London
London, UK


EmboDop: Insufficient Automatic Microemboli Identification

To the Editor:

We read with great interest the recent article by Drs Markus and Punter1 on the assessment of the EmboDop ultrasound system. Independent evaluation of this device was overdue.

The figure shows representative Doppler frequency spectra of 2 patients during extracorporal circulation. Left: The micro embolic signal (arrow) was clearly identified by the human observer but wrongly classified as an artifact by the EmboDop system (arrowhead). Right: The EmboDop system identified a (gaseous) embolus (arrow) that could not be found by the human observer.

<table>
<thead>
<tr>
<th>Observer:</th>
<th>Observer:</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Embolus detected</td>
<td>No Embolus detected</td>
</tr>
<tr>
<td>748</td>
<td>508</td>
</tr>
<tr>
<td>(correctly identified)</td>
<td>(false negative)</td>
</tr>
<tr>
<td>718</td>
<td>1256</td>
</tr>
<tr>
<td>(false positive)</td>
<td></td>
</tr>
<tr>
<td>Σ: 1466</td>
<td>Σ: 1256</td>
</tr>
</tbody>
</table>

Differentiation between gaseous and solid microemboli in vivo is of utmost importance and would provide exciting new insights to the pathophysiology of stroke. Although the principle of the dual-frequency technique appears striking, the reliability of discrimination reported in the recent article is disappointing. Our own experience with the EmboDop system unfortunately supports these observations.

We performed transcranial Doppler monitoring of the left middle cerebral artery in 22 patients during coronary artery bypass grafting (CABG) using the EmboDop device. Standard machine parameters were used during data recording and offline evaluation. Digital Doppler data were then reevaluated offline by an experienced investigator according to the consensus criteria published in 1998. The observer was blinded to the results of the automatic micro embolic signal (MES) detection. A subset of Doppler data was additionally evaluated by a second observer to determine interobserver reliability.

Interobserver agreement was acceptable; 92 of 96 MES (95.8%) were identified concordantly by both observers.
During cardiac surgery the experienced observer (gold standard) detected overall 1256 MES in 22 patients. Only 748 MES (59.6%) were correctly identified and classified as solid or gaseous; 508 MES (40.4%) were overlooked by the EmboDop equipment (false-negative). Furthermore, 718 (solid or gaseous) MES were identified by the machine that could not be verified by the human investigator (false-positive; Table).

The percentage of false-negative MES varied between 19.4% and 73.1% (mean 40.4%; SD=16.2%) among the 22 patients, indicating that this poor recall ratio is not related to individual patients. The Figure indicates that misdiagnoses did not only occur if MES appear in clusters, which might complicate correct identification. Unambiguous identification of microembolic signals and sufficient artifact rejection are basic requirements before a differentiation between solid and gaseous particles can be performed. In the present study, the EmboDop system as it stands now did not fulfill these requisites. This fact might in part explain and confirm the disappointing findings reported by Drs Markus and Punter.

Wolff et al1 used a multivariate analysis to assess the significance of confounding variables. The causes of folate deficiency include chronic disease, such as Celiac or Crohn disease and poor diet, and these variables were not included as confounders. The possibility of confounding variable is the multivariate analysis. A community-based study reported that the prevalence of severe carotid stenosis are at a higher risk of vascular events (mainly stroke) compared with women. I was surprised that the authors did not include atrial fibrillation as a potentially confounding variable in the multivariate analysis. A community-based study reported that the prevalence of atrial fibrillation is greater in men compared with women.2 Atrial fibrillation, compared with women, this may explain their in-stance that the authors did not include atrial fibrillation as a potentially

**Letters to the Editor**

**Gender and Carotid Artery Stenosis**

To the Editor:

The recent study by Dick et al1 suggests that male patients with a severe carotid stenosis are at a higher risk of vascular events (mainly stroke) compared with women. I was surprised that the authors did not include atrial fibrillation as a potentially confounding variable in the multivariate analysis. A community-based study reported that the prevalence of atrial fibrillation is greater in men compared with women.2 Atrial fibrillation is an important risk factor for stroke. If the cohort of men recruited for this study have a higher prevalence of atrial fibrillation, compared with women, this may explain their increased risk of vascular events.

**Response:**

We have read with interest the letter of Dr Epstein, and we agree that this limitation has to be considered. Unfortunately, we did not monitor patients for persistence or occurrence of atrial fibrillation during the study period, and as outlined by Dr Epstein, there may have been differences between the genders in the study population. However, looking at the huge frequencies of cardiovascular adverse events in males and females, it seems unlikely that the entire effect may be explained by the differences in atrial fibrillation, although admittedly we cannot rule out a confounding effect of atrial fibrillation.

**Relation of Parity With Common Carotid Intima-Media Thickness Among Women of the Study of Health in Pomerania**

To the Editor:

Wolff et al1 report that both multiparity and nulliparity are associated with increased carotid artery intima-media thickening. I propose that folate deficiency may account, in part, for this result. Folate deficiency is linked with hyperhomocysteinemia,2 which, in turn, is associated with accelerated progression of atherosclerosis3 and, thereby, carotid artery intima-media thickening. Pregnancy is potentially a cause of folate deficiency.4 Consequently, it is possible that multiparous women are at risk of prolonged folate deficiency; this may explain their susceptibility to the development of carotid artery intima-media thickening.

There may also be a link between folate deficiency and nulliparity. Folate is necessary for DNA and RNA synthesis, and folate deficiency may therefore theoretically lead to infertility. Moreover, there is an association between folate deficiency and spontaneous miscarriage.5 It is therefore possible that a high proportion of childless women may be folate deficient. If this assumption is correct, these women are also at risk of increased carotid artery intima-media thickening.

Wolff et al used a multivariate analysis to assess the significance of confounding variables. The causes of folate deficiency include chronic disease, such as Celiac or Crohn disease and poor diet, and these variables were not included as confounders. The possibility that a higher proportion of childless women included in this study suffer from an affliction leading to folate deficiency, compared with women with one or two children, cannot be ruled out. If folate deficiency partially accounts for the results reported by Wolff et al then this may prompt further research into the benefits of folate supplementation to certain subgroups of patients to prevent progression of atherosclerosis.

**Walsall Manor Hospital**

**Walsall, United Kingdom**


To the Editor:
With interest we read the comment of Hobson et al entitled “Carotid Artery Stenting and the Recruitment Challenges in a clinical trial.”

Although we completely share the concerns of the authors regarding slow recruitment into the CREST Trial, constantly growing use of carotid stenting in symptomatic patients outside of protocols, and the lack of evidence in this area, we cannot agree with the perception that it is mostly up to CREST to solve the problems.

The authors mention shortly that larger clinical trials “are currently underway in North America and Europe.” With reference 10 they cite the CAVATAS trial that finished recruitment long ago. They state that “recruitment into these trials will also be slow and the data may not be available for the next 2 to 3 years.”

As the principal investigators of 3 European Trials, we would like to update the organizers of CREST and the readers of Stroke in the field of what’s going on in the randomized symptomatic carotid endarterectomy versus stenting trials outside of North America. The early results of CAVATAS were published 3 years ago and the results of long-term follow-up were presented at this year’s European Stroke Conference and will be submitted for publication soon.

The next on-going trial is the International Carotid Stenting Study (ICSS), the follow-up to the CAVATAS trial. This trial includes North American centers in Canada as well as several European countries and Australia, and its study protocol has been recently published.3 Almost 600 patients are already included in this trial.

The second trial, which is also not cited in this article, is the French EVA 3S Trial. Its trial design and protocol amendment has also recently been published.3,4 Almost 500 patients are already included in this trial.

The third one is the SPACE Trial. The trial protocol of SPACE has also been published.5,6 It is not adequately referenced by mentioning a poster at the ASA Meeting 2 years ago. This trial is probably the most advanced trial, and termination of recruitment is expected in the next couple of months. Therefore, it will not take 3 years until data from this German-Austrian Trial are available.

By the way, it should be mentioned that the 3 European Trials have already agreed to perform a joint data analysis after completion and publication of all 3 trials.7 We hope we will also be able to include results from CREST in this meta-analysis. We wish our American colleagues a lot of success in improving the recruitment rates. We need much more data from all the trials before it will be clear which treatment is optimal for symptomatic carotid stenosis.

Werner Hacke, MD, PhD, FAHA, FESC
Department of Neurology
Ruprecht-Karls-University Heidelberg
Germany

Martin M. Brown, MD
University College London
ICSS Central Office
The National Hospital for Neurology and Neurosurgery
London, UK

Jean-Louis Mas, MD
Service de Neurologie
Unité Neuro-Vasculaire
Hôpital Sainte-Anne
Paris Cedex, France

Response:
We wish to thank the authors for their response to our recently published commentary on carotid artery stenting (CAS).2 Our intent was to stimulate clinicians in the United States and Canada to become more involved in the NINDS, NIH-sponsored CREST (Carotid Revascularization Endarterectomy versus Stenting) protocol. Although recruitment to CREST was described as slow, we are pleased to announce that randomization continues to accelerate following publication of the commentary and now exceeds 600 participants at our over 100 clinical sites.

We have great admiration for our European colleagues and their accomplishments in the field of CAS and will welcome the early publication of data from the SPACE Trial. Our brief commentary was not designed as a comprehensive review. Nonetheless, we regret the impression or the inadvertent failure to acknowledge all currently active trials.

We welcome the opportunity to agree with the authors that expanded use of CAS outside organized randomized clinical trials threatens rigorous study of potential alternatives to carotid endarterectomy. As noted in our commentary, “If we fail to achieve a study of adequate size, we will not produce convincing evidence of the value of carotid stenting in stroke prevention.” We also agree that ultimate joint analyses of the trial results will be desirable. Dr Hobson corresponded previously with Professor Brown recommending such an effort and expressing our willingness to cooperate in these activities.

The CREST investigators applaud the performance of clinical trials in North America and Europe to clarify the role of carotid endarterectomy and stenting in the management of extracranial carotid occlusive disease. We have no disagreement with our European colleagues on this crucial point.

Robert W. Hobson II
University of Medicine and Dentistry
New Jersey Medical School
Newark, NJ

Thomas G. Brott
Mayo Clinic
Jacksonville, FL

Gary S. Roubin
Lenox Hill Hospital
New York, NY

Frank L. Silver
Toronto Western Hospital
Toronto, ON, Canada


Does the MOSES Trial Establish Superiority of AT1-Receptor Blockers Over Dihydropyridine/Calcium Antagonists in Secondary Stroke Prevention?
Albert Fournier, Gabriel Choukroun, Santhi Samy Modeliar, Olivier Godefroy, Jean-Michel Achard, Jiguang Wang and Franz Messerli

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