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## Tissue Plasminogen Activator –7351C/T Polymorphism and Lacunar Stroke

To the Editor:

Jannes et al<sup>1</sup> 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,<sup>1</sup> and the TT genotype has been associated with significantly reduced vascular tPA release rates.<sup>2</sup>

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.<sup>3</sup> Previous studies have suggested different genetic associations in the 2 groups.<sup>4</sup>

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  $\geq 1.5$  cm in diameter, cortical infarction of any size, a potential cardioembolic source and large-vessel disease defined as carotid, vertebral or basilar intracranial artery stenosis  $\geq 50\%$  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.<sup>4</sup> 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 ABgarose 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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## 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.<sup>1</sup>

The current 2 studies of the tPA -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 likely of noncaucasoid 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.<sup>2</sup> These pathological subtypes are also likely to have different genetic determinants. The tPA -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 tPA -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.

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## 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.<sup>1</sup> 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),<sup>2</sup> 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.<sup>3,4</sup> 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 reinterpreted, 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.<sup>5</sup> 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.

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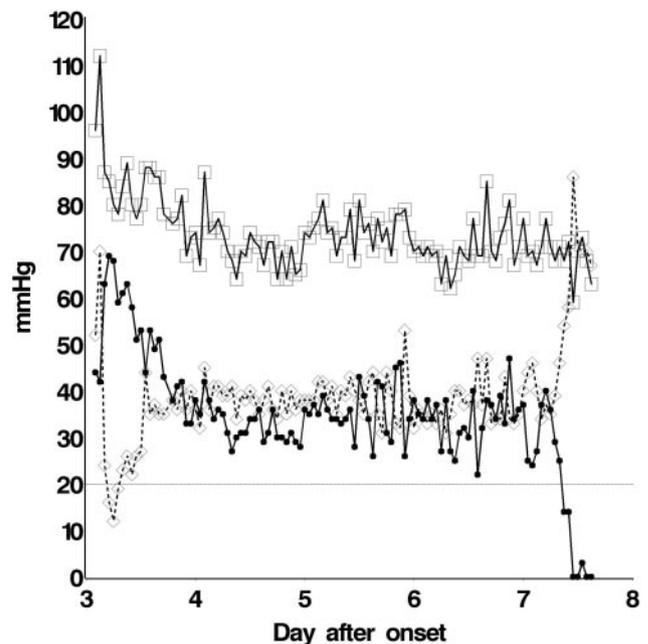
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## High Intracranial Pressure, Brain Herniation and Death in Cerebral Venous Thrombosis

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.<sup>1</sup> 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.



ICP (diamonds), mean arterial pressure (squares) and cerebral perfusion pressure (dots) are shown over a 5-day period. The horizontal reference line (gray) indicates the upper reference limit for the ICP (20 mm Hg).

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 pCO<sub>2</sub> 4.0 to 4.5 kPa and IV norepinephrine to main blood pressure) and anticoagulation with IV heparin were started. Because an ICP <20 mm Hg could not be maintained, paralysis and moderate 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 demescalated 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.<sup>1,2,3</sup> There are occasional reports of decompressive hemicraniectomy performed successfully in patients in whom medical treatment failed.<sup>4</sup> It 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).<sup>5</sup> 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.

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#### 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 sinus thrombosis.<sup>1</sup> 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.

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### 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.<sup>1</sup> 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 pathological 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 atherosclerotic plaques.<sup>2</sup> All plaques obtained during endarterectomy are characterized. In addition, patients fill in questionnaires

and undergo follow-up. Characterization of the atherosclerotic plaques pointed out that significant differences are observed between men and women. A study in 214 carotid endarterectomy plaques showed that male gender was associated with significantly higher fat content and significantly lower smooth muscle cell content.<sup>3</sup> These factors are generally considered to be associated with plaque destabilization and subsequent cardiovascular events.<sup>4</sup> More recently, a thrombectomy study in 211 patients experiencing acute myocardial infarction revealed that male sex was associated with more fresh thrombi while more organized plaque material was obtained in female patients.<sup>5</sup> 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.<sup>6</sup>

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.

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### Multilevel Educational Program for Emergency Medical Services

To the Editor:

I read with interest Wojner-Alexandrov and colleagues' article<sup>1</sup> 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.

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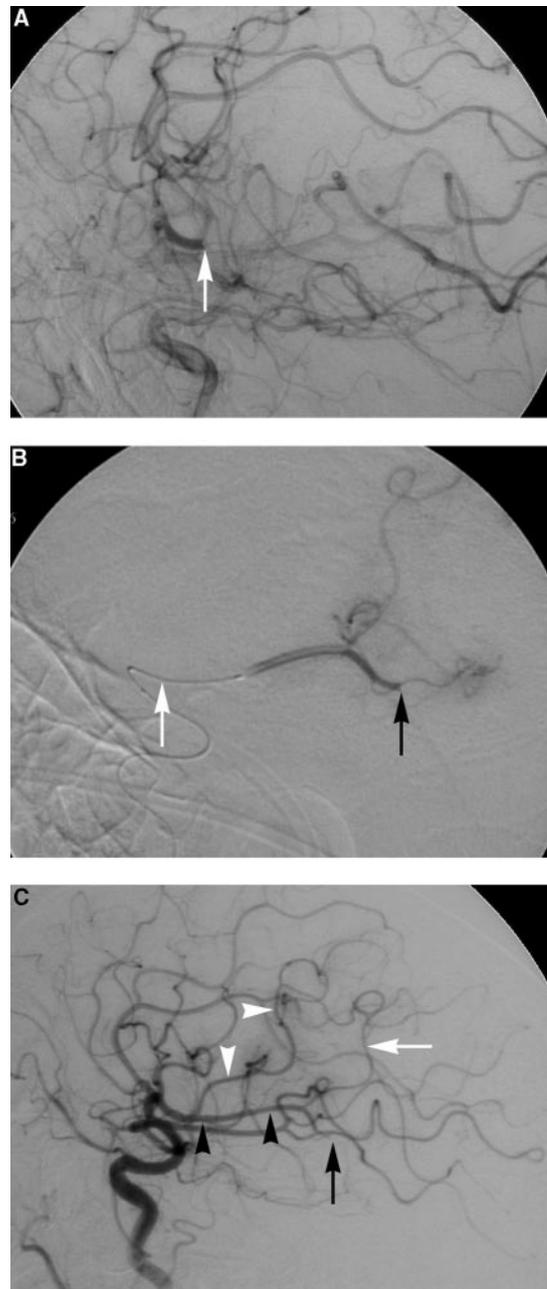
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### Deliberate Distal Displacement of a Middle Cerebral Artery Embolus as an Alternative Method to Treat a Thrombolytic-Resistant Clot

To the Editor:

Intra-arterial administration of fibrinolytic agents remains the primary endovascular option for patients with acute middle cerebral artery (MCA) thromboembolic disease.<sup>1,2</sup> However, the use of fibrinolytic agents is usually limited to a 3- to 6-hour window, is contraindicated in certain circumstances,<sup>3</sup> 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.<sup>4</sup> 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)



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 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).

performed  $\approx 3$  hours after onset revealed proximal occlusion of the superior division of the right MCA (M2 segment; Figure, A). 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.

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#### Response:

I enjoyed reading this report, and I congratulate the authors for their innovative approach. I would like to clarify 2 points concerning the Merci Retriever: (1) the Merci Retriever is indicated for proximal M2 occlusions, and (2) as of September 2005 and 13 months after FDA clearance, many neurointerven-

tionists have been trained in using the Merci Retriever, and it is now available in 180 hospitals in the US.

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### 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.<sup>1</sup> 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.

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#### 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  $2.5 \pm 0.19$ , and the mean INR of the 21 patients who experienced an ischemic event during follow-up was  $2.5 \pm 0.16$ , 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  $2.1 \pm 0.58$ , 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  $\geq 1.8$ . The last mean routine INR recorded before the event was  $2.34 \pm 0.56$ , 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  $2.5 \pm 0.7$ , 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  $\geq 1.8$  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.

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## 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 al<sup>1</sup> 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. Studies<sup>2,3</sup> 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 outcome might also be helpful to indicate the direction of statin research in aneurysmal subarachnoid hemorrhage in the future.

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### Response:

We would like to thank Dr Wong and Professor Poon for addressing the detrimental factors (immediate postoperative deficits, sepsis, and ventriculitis) which affected clinical outcome during the trial. Because immediate postoperative deficits and ventriculitis were closely associated with invasive neurosurgical procedures,<sup>1,2</sup> we believe that the imbalance between the pravastatin and placebo groups was a consequence of a relatively small sample size rather than any side effect of medication.

Although the severity of infection was not quantified, sepsis was more frequent in the pravastatin group.<sup>3</sup> However, the duration of noradrenaline use for sepsis-related hypotension seemed shorter in the pravastatin group (placebo versus pravastatin, 7.0±5.3. versus 3.7±3.2 days;  $P=0.07$ ) indicating a more rapid resolution of profound sepsis. These features did not raise major concern as to the potential for statin therapy to increase the incidence of significant sepsis. However, septic complications will need to be carefully scrutinized as part of a clinical phase III trial.

Our results also showed that acute pravastatin treatment reduced overall mortality in patients with subarachnoid hemorrhage.<sup>3</sup> The causes of the 8 deaths in the placebo group included 5 cases of cerebral infarction caused by vasospasm-related delayed ischemic deficits. None of the 2 deaths in the pravastatin group were related to vasospasm, and acute pravastatin therapy seemed to reduce vasospasm-related mortality (placebo versus pravastatin, 12.5% versus 0, log-rank test  $P=0.02$ ). However, there is little doubt in our minds that despite these encouraging findings, issues such as those raised in this discussion need to be addressed by conducting a large (Phase III) trial.

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## Morbidity and Mortality After Stroke—Eprosartan Compared With Nitrendipine for Secondary Prevention: Principal Results of a Prospective Randomized Controlled Study (MOSES)

To the Editor:

We read with interest the results of the MOSES trial published in the June issue of *Stroke*.<sup>1</sup> In this article, Schrader et al showed that among hypertensive patients with ischemic stroke(s) or transient ischemic attack(s) (TIAs) randomized to either eprosartan or nitrendipine, patients in the eprosartan group were less

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.

TIA's 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 TIA's (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.<sup>2,3,4</sup> 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?<sup>5</sup>

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

*To the Editor:*

The MOSES study<sup>1</sup> 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-analysis<sup>2</sup> 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 that of 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 Strandberg<sup>3</sup> 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 dihydropyridines<sup>4</sup> and by AT1-blockers,<sup>5</sup> 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.<sup>6†</sup>

AT2-mediated protection against cerebral ischemia has now been formally evidenced in experimental models. The group of Unger et al<sup>7</sup> showed that intracerebroventricular preadministration of irbesartan 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-

†The reality of greater stimulation of systemic angiotensin II with a sartan when compared with a DHP has been documented by a double blind cross over study in 18 hypertensive patients since angiotensin II levels were  $2.02 \pm 0.3$  ng/ml with amlodipine and  $2.96 \pm 0.33$  with valsartan ( $P < 0.05$ ) (Jan Struck et al. *J Hypertension*. 2002;20:1143–1149).

deleted mice with wild mice because for the same middle cerebral artery occlusion, the ischemic area was larger and the neurological deficit more severe in the AT2 gene-deleted mice. Furthermore, 10 day pretreatment with valsartan significantly reduced mortality, neurological deficit and ischemic area, and this protective effect was significantly weaker in the AT2-KO mice than in wild-type mice, evidencing the involvement of AT2-receptor in the protective effect of valsartan.<sup>8</sup>

In spite of this well established AT2-mediated cerebroprotective mechanism, it may be premature to promote eprosartan as the first choice treatment for secondary stroke prevention, all the more because its comparator nitrendipine was validated in primary<sup>9,10</sup> but not in secondary stroke prevention. To prevent stroke recurrence in patients with or without hypertension, only indapamide alone in PATS trial<sup>11</sup> and indamide+perindopril in PROGRESS trial<sup>12</sup> have been validated. Because the latter combination therapy decreased stroke recurrence risk by 43%, whereas indamide alone decreased it only by 29%, the combination therapy "indapamide+perindopril" should now be considered as the gold standard of secondary stroke prevention. Therefore, to establish which bitherapy is the most efficient in secondary stroke prevention, we propose that in association with indapamide (or another thiazide), eprosartan (or another sartan) be compared with perindopril (or ramipril which decreased stroke risk by 32% in HOPE trial,<sup>13</sup> whereas perindopril alone in PROGRESS nonsignificantly decreased stroke recurrence only by 5%).

Given that about two thirds of hypertensive patients need >1 drug to control BP, the identification of the most stroke-protective bitherapy is of primary public health importance.

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## 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.<sup>1</sup> 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<sup>2</sup> 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 Trial<sup>3</sup> sought to test for

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

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### Response:

Fournier et al and Boulanger et al have asked some interesting questions that have been discussed by the MOSES authors as well:

Boulanger et al argue that transient ischemic attacks (TIAs) are from a patient's perspective not as clinically relevant as a stroke because a TIA is not disabling. This is true, but TIAs are strong predictors of stroke, which has been shown again by van Wijk et al recently.<sup>1</sup> Therefore, TIAs are of clinical importance, and it had been predefined by MOSES-study protocol to include TIA in end point analysis. TIAs lead to hospitalization and further diagnostic procedures and therefore have economical impact. TIAs have been evaluated—as all end points—by blinded end-point committee in both treatment arms in the same way. The accuracy of a diagnosis of TIA may not be as good as for stroke. Because nearly all patients with TIA in Germany are hospitalized, the diagnosis has been assessed by neurologists as well in the majority of patients. Additionally, members of the end-point committee were neurologists and cardiologists. We agree that one of the key questions is how the eprosartan-based antihypertensive regimen, with or without combinations, compares to the combination of an angiotensin-converting enzyme inhibitor and diuretic, defined by the PROGRESS study, but final conclusions are difficult unless there will be results of a study comparing these alternatives in the future. Till these data are available some convincing results from experimental studies showing cerebroprotective effects of ARB should be considered.<sup>2,3,4</sup> Subgroup analysis of clinical large scale trials could add

some more information to answer the question how to treat hypertension after stroke.

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.

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### MOSES Raises Questions

To the Editor:

The MOSES trial confirms both the safety and efficacy of eprosartan in hypertensive patients with cerebrovascular disease.<sup>1</sup> The authors' conclusion that eprosartan provides "vascular protective effects" above that of nitrendipine, however, is not

substantiated by the data. Mortality was not different (57 eprosartan versus 52 nitrendipine;  $P=0.725$ ), nor was the first occurrence of a cerebrovascular event (80 eprosartan versus 89 nitrendipine;  $P=0.42$ ). Eprosartan did reduce total cerebrovascular events (102 versus 134;  $P=0.026$ ) but did not result in improvement in either functional or cognitive parameters. Perhaps this is a reflection that nondisabling TIAs rather than stroke drove the benefit. Furthermore, the apparent benefit with eprosartan may have been spurious because a single patient, presumably on nitrendipine, had multiple events.

The cardiovascular end points in MOSES take on a more intriguing significance considering the results of the VALUE trial, which compared the same 2 classes of drugs. In VALUE, the ARB valsartan was associated with a 19% ( $P=0.02$ ) increase in myocardial infarction (MI) compared with the calcium channel blocker (CCB) amlodipine. A highly controversial editorial addressed the increased MI rate in VALUE, suggesting that ARB as a class may not only lack vascular protection, but may possibly result in increased MI.<sup>2</sup> This hypothesis continues to be debated,<sup>3</sup> and despite the ongoing analysis of the data,<sup>4,5</sup> some have already concluded that an ARB may not have the same “vascular protection” of an angiotensin converting enzyme inhibitor (ACEI).<sup>6</sup>

Eprosartan, although reducing first time cardiovascular events (CV; 60 versus 84;  $P=0.03$ ), did not reduce total cardiovascular events. Acute coronary syndrome rates tended to be lower with eprosartan, which is encouraging, but the benefit with eprosartan on cardiovascular end points appears to be primarily related to a reduction in congestive heart failure (CHF). The reduction in CHF with eprosartan, surprisingly, did not correlate with a reduction in mortality. Considering the criterion for diagnosing CHF in MOSES was not reported, one has to wonder whether peripheral edema alone, a common side effect with CCB secondary to vasodilatation, led to an increase in the diagnosis of CHF in the nitrendipine patients. This, of course, would be erroneous in the absence of other symptoms or signs of CHF requiring treatment.

How should the results of MOSES influence clinical practice? Should ARB or CCB be first-line therapy in the hypertensive patient after cerebrovascular accident? Upwards of 64% of the patients in MOSES had a very strong indication for an ACEI because their premorbid diagnosis included coronary artery disease or diabetes mellitus.<sup>7</sup> Current guidelines<sup>8</sup> strongly recommend all patients with coronary artery disease receive ACEI independent of hypertension because of their unique “vascular protective” effects, the benefit which is above that of lowering blood pressure alone.<sup>9</sup> Many patients with cerebrovascular disease have concomitant coronary artery disease, which even in the absence of symptoms, will statistically lead to the demise of the patient. Thus, ACEI can reasonably be viewed as the “preferred” cardio-protective agent for a MOSES patient. And finally, a MOSES patient requires aggressive intervention of all vascular risk factors. Only 32% of the hyperlipidemic patients in MOSES received a statin. This suggests a real opportunity for dramatically improving the prognosis of a MOSES patient with a more judicious prescribing of statins.

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### 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.<sup>1</sup> These results could not be supported by the MOSES data.<sup>2</sup> In this study, the number of acute coronary syndrome in the eprosartan group was even less than in the nitrendipine group (39 versus 48; but 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 heart failure.

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).

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## Embolus Detection and Differentiation Using Multifrequency Transcranial Doppler

To the Editor:

In their article on the detection and discrimination of cerebral microemboli using dual-frequency transcranial Doppler (TCD), Markus and Punter write that this method is not accurate enough for use in clinical or research studies.<sup>1</sup> Furthermore, that “It is possible that further refinement of the dual-frequency approach may improve discrimination.” They unfortunately are not aware that further refinement of this method has in fact been carried out since our original description of the first multifrequency TCD in 2002.<sup>2</sup>

In our original description of multifrequency TCD using in vitro and limited in vivo data, we recognized 3 potential problems when using this method to differentiate cerebral microemboli.<sup>3,4</sup> Firstly, that small variations in the Doppler background signal and changes in reflected Doppler power measurements attributable to beam distortion could affect sensitivity when detecting small solid microemboli. We proposed therefore a horizontal lower dEBR (reflected ultrasound power at 2.5-MHz compared with that at 2.0-MHz) detection limit for small solid microemboli of  $-0.83$  dB. However, if the dEBR was within 0.2 dB of this limit (ie, between  $-0.63$  and  $-0.83$  dB), it was classified as uncertain solid. Subsequent clinical experience showed, however, that this dEBR detection limit sometimes had problems detecting small solid microemboli, such as those which can be present in patients with carotid stenosis. This clinical experience enabled us to improve sensitivity for solid microemboli without influencing specificity by changing lower dEBR detection limit from a horizontal line at  $-0.83$  dB to a dEBR detection limit with a slight slope of  $y = -0.1$ ,  $x = -0.12$  dB, where  $y = \text{dEBR}$  and  $x = 2.0$  MHz EBR.<sup>2</sup>

Markus and Punter did not use this refined lower dEBR for the detection of solid microemboli in their carotid stenosis patients, which can explain why many of the solid microemboli were not correctly classified in their study.

The second problem which we described in our original description of multifrequency TCD was resonance caused by very small gas bubbles ( $<3 \mu\text{m}$ ;  $<8$  dB). This was first apparent when ultrasound contrast was injected into the circulation but was subsequently observed in all clinical situations where air may be introduced into the circulation. Very small gas bubbles which resonate at 2.5-MHz ultrasound frequency will give a larger Doppler power measurement attributable to resonance and be incorrectly classified as solid. This is because embolus differentiation is based on the

principle that solid microemboli normally reflect more ultrasound at 2.5-MHz frequency compared with 2.0-MHz, whereas the opposite is the case for gaseous microemboli. Multifrequency TCD can therefore not correctly differentiate very small microbubbles where there is a possibility of resonance effects. This potential error can be reduced by using multifrequency TCD to discriminate only those emboli which cause a Doppler signal enhancement ie, embolus-blood-ratio (EBR) of  $>28$  dB/ms simultaneously in both 2.0-MHz and 2.5-MHz channels.<sup>2</sup>

These limits were not used by Markus and Punter which can explain why some of the microbubbles which were introduced into their patent foramen ovale (PFO) patients were wrongly classified as solid. This can especially be the case for  $\approx 4\%$  of the gaseous emboli shown in their plot.<sup>1</sup> These emboli gave a Doppler power increase at 2.0 MHz of 5 to 7 dB which corresponds to bubble sizes  $<3 \mu\text{m}$ .

It is also impossible to exclude the possibility that very small blood clots were introduced during their experiments in these patients even though they tried to avoid this by flushing the intravenous cannula.

The third problem which we acknowledged in our original publications was the fact that multifrequency TCD cannot accurately count all of the emboli when several emboli enter the sample volume at the same time. This is especially relevant when air bubbles are introduced into the cerebral circulation as is the case when an agitated air and saline solution is introduced into PFO patients.

Markus and Punter<sup>1</sup> also assessed a simple intensity threshold at 2.0 MHz to differentiate solid and gaseous microemboli. This detection threshold is only appropriate for their very special data set where  $\approx 88\%$  of their solid microemboli gave a reflected Doppler power at 2.0 MHz of  $<13$  dB, whereas  $\approx 88\%$  of the gaseous gave a reflected Doppler power at 2.0 MHz of  $>13$  dB. This is normally not the case in routine clinical situations when gaseous and solid emboli are present.

In conclusion, we completely agree with Markus and Punter that it is extremely important to have a TCD method which can differentiate between solid and gaseous cerebral microemboli if we are going to understand the clinical significance of these events.

We feel that the multifrequency TCD method has considerable potential and our subsequent clinical experience with this method in the past 3 years has allowed us to further increase its clinical accuracy in different patient groups. Our revised criteria have been described previously in *Stroke*<sup>2</sup> and in this letter, but to our knowledge have not been incorporated into any commercially available multifrequency TCD. These refinements can, however, be very easily made on the multifrequency instrumentation used by Markus and Punter.<sup>1</sup> They should now use a clinically more representative set of data to assess the accuracy of multifrequency criteria for embolus differentiation and, if necessary, propose further refinements which may help toward achieving the important goal of embolus differentiation.

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**Response:**

In our article<sup>1</sup> 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 1. No. of Embolic Signals in Each Classification**

	ES in Original Analysis	ES in New Analysis		
		1st Revision ≥7db at Both Frequencies	2nd Revision $y = -0.1$ , $x = -0.12$	Combined Revision
Carotid stenosis subjects				
Definite solid	65	54	73	64
Possible solid	8	3	13	8
Definite gaseous	60	31	51	20
Possible gaseous	12	8	8	5
Total emboli	145	96	145	97
Patent foramen ovale subjects				
Definite solid	20	18	70	68
Possible solid	3	2	15	14
Definite gaseous	624	547	535	453
Possible gaseous	1	1	28	28
Total emboli	648	568	648	563
	793	664	793	660

**TABLE 2. Sensitivities and Specificities for Solid and Gaseous Emboli Using the Different Data Analysis Approaches**

Classification Criteria	Solid Emboli		Gaseous Emboli	
	Sensitivity	Specificity	Sensitivity	Specificity
Original analyses				
All ES	50.3	94.2	96.5	50.3
Only ES of >7 dB AT 2.0 MHz	48.4	97.4	97.9	48.4
Only ES classified as definite	44.8	96.91	96.3	58.6
1st suggestion revision				
Only ES of >7 db at both frequencies	59.4	96.5	96.5	59.4
Only ES of >7 db at both frequencies and definite ES	63.5	96.5	96.5	63.5
2nd suggested revision				
All ES $y = -0.1$ , $x = -0.12$	59.3	86.9	86.9	59.3
Definite ES $y = -0.1$ , $x = -0.12$	50.3	82.6	82.6	50.3
Both suggested revisions				
Combined revision all ES	74.2	85.4	85.4	74.2
Combined revision only definite ES	66.0	87.9	87.9	66.0

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.<sup>2</sup> 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.

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1. Markus HS, Punter M. Can Transcranial Doppler Discriminate Between Solid and Gaseous Microemboli? Assessment of a Dual-Frequency Transducer System. *Stroke*. 2005;36:1731–1734.
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### EmboDop: Insufficient Automatic Microemboli Identification

To the Editor:

We read with great interest the recent article by Drs Markus and Punter<sup>1</sup> on the assessment of the EmboDop ultrasound system. Independent evaluation of this device was overdue.

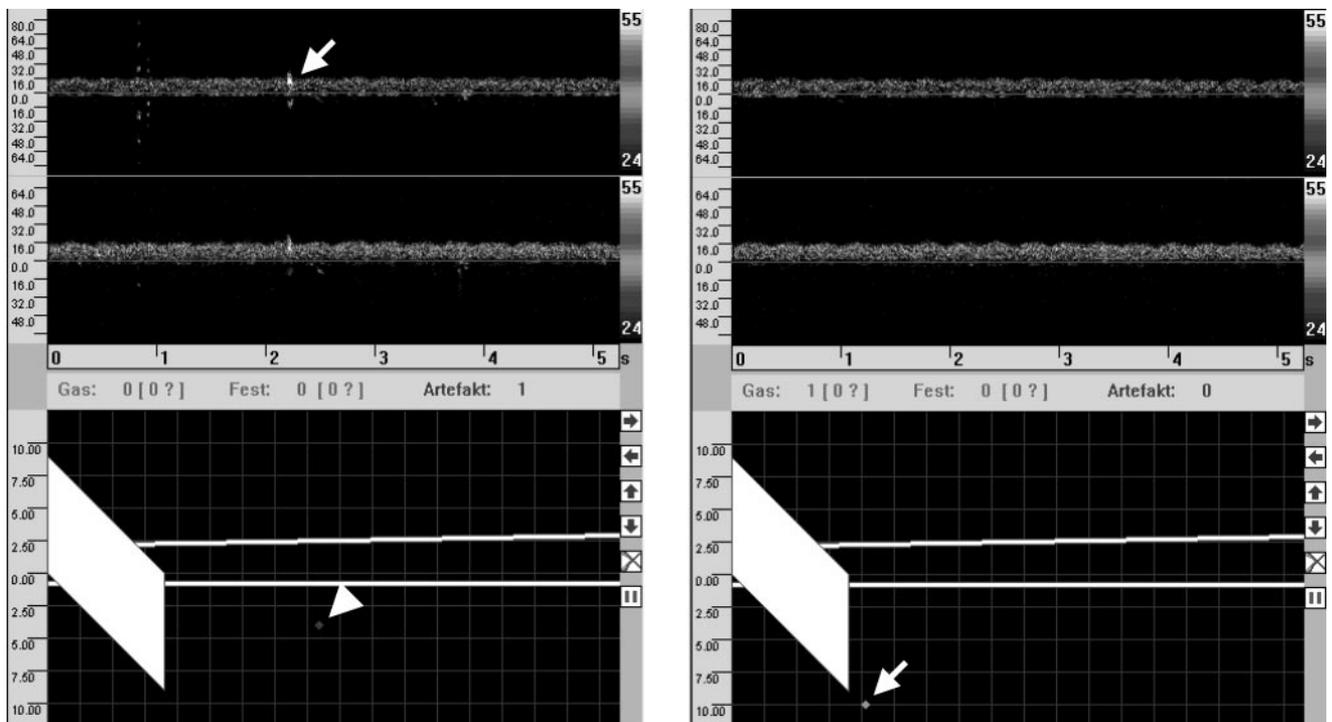
### Summary of the No. of Correctly Identified MES and the No. of False-Negative and False-Positive Findings as Provided by the EmboDop System

	Observer: Embolus Detected	Observer: No Embolus Detected	
EmboDop:			
Embolus detected	748 (correctly identified)	718 (false positive)	Σ: 1466
EmboDop:			
No embolus detected	508 (false negative)		Σ: 1256

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.<sup>2</sup> 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.



The figure shows representative Doppler frequency spectra of 2 patients during extracorporeal 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.

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.

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## Gender and Carotid Artery Stenosis

To the Editor:

The recent study by Dick et al<sup>1</sup> 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.<sup>2</sup> 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.

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## 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.

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

To the Editor:

Wolff et al<sup>1</sup> 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 hyperhomocystinemia,<sup>2</sup> which, in turn, is associated with accelerated progression of atherosclerosis<sup>3</sup> and, thereby, carotid artery intima-media thickening. Pregnancy is potentially a cause of folate deficiency.<sup>4</sup> 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.<sup>5</sup> 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.

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## Carotid Endarterectomy Versus Stenting: An International Perspective

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."<sup>1</sup>

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.<sup>2</sup> 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.<sup>3,4</sup> 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.<sup>5,6</sup> 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.<sup>7</sup> 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.

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### Response:

We wish to thank the authors for their response to our recently published commentary on carotid artery stenting (CAS).<sup>1</sup> 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.

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

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