

# Stroke

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## **Aspirin for Stroke Prevention Taken in the Evening? \* Response:**

Ildikó Kriszbacher, Miklós Koppán, József Bódis, Hon-Kan Yip, Shun-Sheng Chen  
and Mien-Cheng Chen

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# Letters to the Editor

Stroke welcomes Letters to the Editor and will publish them, if suitable, as space permits. They should not exceed 750 words (including references) and may be subject to editing or abridgment. Please submit letters in duplicate, typed double-spaced. Include a fax number for the corresponding author and a completed copyright transfer agreement form (published in every issue).

## ACE and Subarachnoid Hemorrhage: Strategies for Genetics of Stroke

To the Editor:

I thank Slowik et al for their article investigating the angiotensin-converting enzyme (ACE) insertion/deletion (I/D) polymorphism in subarachnoid hemorrhage (SAH).<sup>1</sup> I wish to comment on several aspects of this article related to the design of genetic association studies for complex disorders such as SAH, which are important in interpreting their findings. It is impressive to note the high odds ratios achieved, however this study was less than half the size of the one it aimed to confirm.<sup>2</sup> The populations of the 2 studies were of European origin and the allele frequencies were also similar. Using calculations previously described<sup>3</sup> and the data from Keramatipour et al,<sup>2</sup> an estimated sample size of 600 subjects is required to show the presence of an association of ACE I/D with SAH with 80% power. It is surprising that Slowik et al achieved twice as high an odds ratio with half the sample size. The small sample size of this study could have resulted in a type 1 error.

ACE I/D polymorphism has been extensively studied in several disorders with conflicting results. Interestingly, Zhu et al showed that the I/D polymorphism is not functional and its association with elevated plasma ACE levels is secondary to a linkage disequilibrium (LD) effect.<sup>4</sup> We recently showed this to be the case for the association of the I/D polymorphism with essential hypertension as well.<sup>5,6</sup> To verify the effect of a gene it is important to genotype several single nucleotide polymorphisms (SNPs) across the gene, study the structure of the haplotype block and look for associations with the haplotypes, which considerably increases the power of a case-control study. Moreover, improvised study designs such as sib pair and TDT-trios are formidable tools for teasing out the genetic architecture of complex disorders. Elaborate algorithms exploring the combinatorial effects of SNPs in several candidate genes across the genome have recently become available and can add power to the analysis.<sup>7</sup> Using novel study designs entire pathways, such as the renin-angiotensin system (RAS), can be explored in complex disorders such as SAH. This is important as some components of RAS increase angiotensin II formation whereas others decrease it.<sup>8</sup> It is also worthy to collect details of disease characteristics which may serve as covariates in subsequent allele, genotype and haplotype analysis. The study design can be enhanced by including intermediate phenotypes in the study.<sup>9</sup> Recently, genome-wide SNP analysis using microarrays has brought linkage analysis for complex disorders within the realm of reality,<sup>10</sup> provided suitable pedigrees are available.

Without such elaborate efforts it will be difficult to meaningfully interpret results of genetic association studies for complex disorders. Studies of human polymorphisms had a modest presence in 1980 with just over 100 publications. After the explosive entry of ACE I/D in 1992<sup>11</sup> and ApoE  $\epsilon$ -4 in 1993<sup>12</sup> in the complex disease arena, there was an exponential rise in the studies of human polymorphisms, most being association studies. Approximately 3500 such studies are now published annually in indexed journals. Making sense of such a large number of studies, several presenting contradictory findings, is a colossal task. Unless well-determined guidelines are followed, and robust study designs and appro-

priate sample sizes are used, many resources will go to waste. Also, a majority of the genome will remain unexplored in most disorders, and only a few loci will be investigated repeatedly with no additional information gained. It is important that we realize the significance of well-planned genetic association studies aimed at stroke and associated complex disorders. In light of this, the National Institutes of Health funded Siblings with Ischemic Stroke Study is much appreciated.<sup>13</sup> Additionally, a Stroke Consortium could be made which would allow the use of DNA and other resources to investigators on approval of a proposal in a similar fashion as the Framingham Heart Study.<sup>14</sup> We must act before it is too late.

Mohammad Saeed, MD

Department of Biological and Biomedical Sciences  
Aga Khan University  
Karachi, Pakistan

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### Response:

We thank Dr Saeed for his letter emphasizing a very important aspect concerning the design of genetic studies, ie the calculation of the power of a study and the number of patients included in the control and case groups needed to provide replicable results. Interestingly, while analyzing the studies that assess the significance of different polymorphisms in a variety of stroke etiologies, which have been published in *Stroke* during the last five years, we found that this aspect of methodology was addressed only in a few cases. In general, the previous authors published in *Stroke* calculated the required number of cases and controls to achieve the power of 80% ( $P=0.05$ ). This was based on allele or genotype frequencies in the populations to achieve a given minimum odds ratios,<sup>1</sup> relative risk by allele,<sup>2</sup> or the proportion of the studied alleles in cases and controls.<sup>3</sup> Other journals, such as *Neurology*<sup>4</sup> and *Human Genetics*<sup>5</sup> have already published the guidelines for genetic association studies in humans. We feel it would be reasonable to prepare such guidelines for publication in *Stroke*. The information regarding the power of a study should be provided, in a uniform fashion, within the methodology section of all articles related to this topic.

A very important aspect in the design of genetic association studies (or any clinical study, for that matter) is the ability to generate significant and replicable results while keeping within budget constraints. It is well known that the population frequency of the II genotype, and not I allele, of the angiotensin-converting enzyme (*ACE*) gene is approximately 25% (23.7% in English patients<sup>6</sup> and 23.4% in our controls<sup>7</sup>). Bearing this in mind, we calculated that having 90 patients with aneurysmal subarachnoid hemorrhage and 128 controls, we would be able to obtain statistically significant differences between the groups if the odds ratio was  $>2.5$ , assuming the study's achievable power to be 80%, and  $P=0.05$ . In our study, type I error (probability of rejecting true  $H_0$  hypothesis) was 0.00001, which is very low.

It is commonly known that *ACE* gene insertion/deletion polymorphism, because it is an intronic marker, may be functionally neutral, but may be in linkage disequilibrium with other (functional) mutations within *ACE* or another gene.<sup>8</sup> The genetic association studies, such as we performed, generally answer the question as to whether the target allele or genotype remain risk factors for the disease, but they do not answer the question, does the causal relationship exist between them? We can only speculate therefore whether such a causal relationship exists. We have already planned to expand our studies of the *ACE* gene, examining several single nucleotide polymorphisms across the gene, and calculating association with haplotype(s). We agree with Dr Saeed that introducing genome-wide single nucleotide polymorphism analysis using microarrays is an approach that will ultimately enable study of complex disease mechanisms in greater detail.

**Agnieszka Slowik, MD**  
**Anna Borratynska, MD**  
**Joanna Pera, MD**  
**Tomasz Dziedzic, MD**  
**Andrzej Szczudlik, MD**  
*Department of Neurology*  
*Jagiellonian University*  
*Krakow, Poland*

**Agnieszka Kieltyka, MSc**  
*Department of Epidemiology and Preventive Medicine*  
*Jagiellonian University*  
*Krakow, Poland*

**Denise A. Figlewicz, PhD**  
*Department of Neurology*  
*University of Michigan*  
*Ann Arbor, Michigan*

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## Is Perimesencephalic Nonaneurysmal Hemorrhage of Venous Origin?

To the Editor:

We read with great interest the article by van der Schaaf and colleagues<sup>1</sup> in the July 2004 issue of *Stroke* in which the authors sought to assess the contribution of venous drainage patterns in the etiology of perimesencephalic hemorrhage (PMH). PMH, defined by a negative 4-vessel angiographic study as bleeding in the cisterns around the midbrain, is associated with an excellent outcome.<sup>2</sup> Using computed tomography angiography, van der Schaaf and colleagues found that patients with PMH had primitive venous drainage directly into dural sinuses instead of via the vein of Galen, as with patients having aneurysmal subarachnoid hemorrhage. They also observed that the side of the PMH related to the side of the primitive drainage. They concluded that these results support the venous origin of PMH. Although van der Schaaf and colleagues found differences in the venous drainage of these patients, they neglected to present direct evidence showing that primitive venous drainage led to hemorrhage around the midbrain. They speculated that direct venous pressure from the dural sinus might cause the rupture of the perimesencephalic veins. However, their speculation is not substantiated because other cerebral veins with direct connection to the dural sinus never rupture under normal circumstances. Moreover, if this variation of venous drainage were a cause of bleeding, it would have a high chance of rebleeding in the follow-up because venous drainage is not easily changed.

We would like to bring to the authors' attention our study of PMH<sup>3</sup> in which small bulges on the basilar artery were found in 2 patients by 3D rotational angiography. These lesions were thought to be intramural hematomas due to arterial dissection and to be responsible for the hemorrhage in each case. This finding matches the distribution of the hematomas, and the spontaneous healing of the dissection could explain the absence of rebleeding. The small bulges showed spontaneous resolution, but they were too small to be detected by computed tomography angiography, such as that employed by van der Schaaf and colleagues. Therefore, we would like to emphasize that some of the PMH were of arterial origin. Nonetheless, the study by van der Schaaf and colleagues, which focuses on venous drainage, provides an

important contribution to the literature. We congratulate the authors on their careful observations.

**Yuji Matsumaru, MD, PhD**  
**Kiyoyuki Yanaka, MD, PhD**  
**Akira Matsumura, MD, PhD**  
*Department of Neurosurgery*  
*Institute of Clinical Medicine*  
*University of Tsukuba*  
*Tsukuba, Ibaraki, Japan*

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### **Venous Drainage in Perimesencephalic Hemorrhage: Is Perimesencephalic Nonaneurysmal Hemorrhage of Venous Origin?**

#### **Response:**

We appreciate the interest of Dr Matsumaru and colleagues in our article on the venous drainage patterns in the etiology of perimesencephalic hemorrhage (PMH).<sup>1</sup>

Dr Matsumaru focuses our attention on their observation in 2 patients with a perimesencephalic pattern of hemorrhage, who had small bulges on the basilar artery that disappeared on follow-up imaging. These bulges were supposed to be intramural hematomas due to arterial dissection, and were not visible on standard DSA but only on the 3-D angiography.<sup>2</sup> The authors emphasized that some of the patients with a PMH might have had an arterial origin.

We are aware that in patients with a perimesencephalic pattern of hemorrhage, the cause is of arterial (vertebrobasilar) origin in 5% of the cases.<sup>3</sup> We also agree that an abnormal venous drainage is not the definitive cause in all patients with a PMH. However in patients with a unilateral primitive variant, the blood was always found on the side of the primitive drainage, which suggests a relation between the primitive venous variant and the bleeding. Four patients in our series had a “normal” venous drainage system in both hemispheres. We cannot substantiate the suggestion that in these 4 patients the PMH was caused by bleeding from small intramural hematomas. None of these patients underwent DSA.<sup>4</sup> Three of these 4 patients were scanned on a single-slice CTA scanner; the resolution of this scanner does allow the detection of such small bulges. The fourth patient, however, was scanned on a multislice CT scanner. Multislice (MS) CTA provides a high resolution and small vascular details can be detected.<sup>5</sup> In this patient we reviewed the CTA using multiplanar reconstruction in 3 directions and maximum intensity projection, but we did not find any irregularity on the vessel wall of the basilar artery.

Dr Matsumaru and coauthors also mention that other cerebral veins with direct connection to the dural sinus never rupture under normal circumstances and therefore think that our speculation that direct venous pressure from the dural sinus might cause rupture of the perimesencephalic veins is not substantiated. The authors also point out that if this variation in venous drainage were a cause of bleeding, it would have a high chance of rebleeding because the venous system is not easily changed.

We would like to emphasize that primitive variants lack fusion of the 3 primitive veins during the embryologic development of

the Galenic system.<sup>6</sup> This deficiency of anastomosis might make these vessels more prone to rupture due to sudden increase in venous pressure. Even though other veins do connect directly to the dural sinuses, the perimesencephalic fine venous network is usually protected from sudden pressure changes by the drainage from the basal vein of Rosenthal through the Galenic system into the straight sinus. It is possible that a more direct connection to a dural sinus makes this network more vulnerable to pressure changes. Some of the primitive veins cross the tentorial margin, which might lead to torsion or friction and therefore make these primitive variants even more prone to rupture. We speculate that the spontaneous healing of the venous system by fibrous tissue firms the vessel wall of the vein on its weakest point, thereby preventing it from rerupture.

Arterial dissections are a frequent cause of the hemorrhage in patients with subarachnoid hemorrhage, but without an aneurysm on angiography.<sup>7</sup> In most patients with subarachnoid hemorrhage from intracranial dissections, the pattern of hemorrhage is not confined to the perimesencephalic cisterns, but comparable to an aneurysmal pattern of hemorrhage.<sup>7</sup> Moreover, intracranial dissections leading to a subarachnoid hemorrhage have a 30% risk of rebleeding.<sup>8</sup> These characteristics are unlike those from PMH, and we do not think that arterial dissections are a frequent cause of PMH. The relatively benign symptoms at onset, the clinical course without rebleeding or secondary ischemia, and the localized pattern of hemorrhage favor a venous source in the majority of these patients. The observation of Dr Matsumaru et al offers an interesting vision in the etiology of PMH, which may hold true for some patients with a perimesencephalic pattern of hemorrhage. The higher resolution of the MS CT scanners and 3D angiography will provide more insight on this finding in the future.

**I.C. van der Schaaf, MD**  
**B.K. Velthuis, MD**

*Department of Radiology*  
*University Medical Center Utrecht*  
*Utrecht, The Netherlands*

**A. Gouw, MSc**  
**G.J.E. Rinkel, MD**

*Department of Neurology*  
*University Medical Center Utrecht*  
*Utrecht, The Netherlands*

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## Contrast Ultrasound Techniques in the Detection and Quantification of Patent Foramen Ovale: Myth Versus Reality

To the Editor:

I read with great interest the study of Anzola et al. The authors declared contrast-enhanced transcranial Doppler (ce-TCD) as the ideal tool to follow up patients after interventional device closure.<sup>1</sup>

Data show a high correlation between ce-TCD and contrast enhanced transesophageal echocardiography (cTEE) which is the current "gold standard" for detection of a right-to-left shunt through a patent foramen ovale (PFO), although there is a highly reported interobserver and intraobserver variability of the latter.<sup>2</sup> Furthermore, there are major methodological limitations of these techniques that need to be addressed.

The numbers of microbubbles reaching the brain can be quantified by ce-TCD, however the therapeutic impact of this information is unknown. There is no prospective study (neither by ce-TCD nor by cTEE) demonstrating that the amount of contrast shunting has any relevance for the outcome of these patients.<sup>2,3</sup> We have previously shown that the amount of contrast shunting does not correlate with the size of the PFO measured by 2-dimensional TEE or invasively by balloon sizing.<sup>4</sup>

Devuyst and colleagues reported that the amount of right-to-left contrast shunting through a PFO measured by ce-TCD mainly depends on strain rate and duration of the Valsalva maneuver.<sup>5</sup> As Anzola et al did not perform the ce-TCD follow up under these controlled conditions, 2 contrast studies may lead to different results in the same patient even if the PFO would not have been closed.

It has been shown previously that ce-TCD with saline contrast can remain positive, even without difference in the intensity, after complete occlusion of anatomical arteriovenous malformations.<sup>6</sup>

According to recent findings one must accept that there is no rigid diagnostic time window for differentiation between interatrial and intrapulmonary shunts.<sup>7–10</sup> And there is evidence that physiological arteriovenous intrapulmonary shunts do exist in most healthy humans.<sup>11</sup> As we know so far, shunting through this dynamic vascular network is influenced on a variety of patient dependent and methodological reasons like cardiac output, blood pressure, or drugs.<sup>11–13</sup>

Before and after PFO-closure we recommend, irrespective of the results of a ce-TCD, to perform a TEE examination, as it provides direct anatomic information regarding the site and nature of the shunt and regarding the device to exclude a thrombus formation.<sup>14</sup>

**Herwig W. Schuchlenz, MD**  
Graz-West Hospital  
Graz, Austria

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### Response:

Dr Schuchlenz's letter seems to put a special emphasis on the lack of specificity of contrast-enhanced transcranial Doppler (ce-TCD) in differentiating the source of a right-to-left shunt (RLS), namely patent foramen ovale (PFO) versus pulmonary fistulas. In our opinion, however, instead of showing limitation, this is an argument in favor of transcranial Doppler (TCD) as an ideal tool for screening and follow-up purposes inasmuch as paradoxical embolism is suspected responsible for otherwise cryptogenic strokes. It is commonly recognized that TCD detects more RLSs than transesophageal echocardiography (TEE), not only because TEE may miss pulmonary fistulas but also because even in cases of PFO, the patient may be unable to perform a Valsalva strain valid enough to divert bubbles from the right to the left atrium across the PFO.<sup>1</sup> This raises some doubt on the concept of TEE as the gold standard for PFO detection.

There are at least 2 studies that have shown a relationship between the amount of RLS as assessed with TCD and stroke occurrence or relapse.<sup>2,3</sup>

The ce-TCD test was always performed in controlled conditions following the recommendations of the Consensus of Venice<sup>4</sup> and the strength of Valsalva was regulated so as to obtain a reduction of at least 20% of the spectral amplitude. For these reasons we believe that the bubble load assessed in the middle cerebral arteries at follow-up testing truly reflected the degree of residual shunt.<sup>5</sup>

The fact that TCD (and TEE) remain positive after apparently successful embolization of a pulmonary arteriovenous malformation (AVM) in a patient with Rendu-Osler disease, as is reported in Yeung et al<sup>6</sup> is not surprising for at least 2 reasons. First, the embolization of a macroscopic pulmonary AVM may not abolish the local RLS. Second, Rendu-Osler disease entails the presence of multiple microscopic AVMs that can escape angiography but nonetheless bring about a cumulatively significant RLS.

Physiological intrapulmonary shunts are activated after prolonged strenuous exercise<sup>7</sup> whereas ce-TCD requires a simple Valsalva strain for a few seconds.

None of the patients in our series was under the effect of drugs likely to affect intrapulmonary shunts.<sup>8,9</sup>

Our policy is to perform TEE after TCD demonstrates RLS to confirm the intracardiac site before PFO closure and to repeat it postprocedurally only in those patients in whom TCD has shown a significant residual shunt or in those who relapse after successful closure. Routine use of TEE to detect thrombus formation in the left atrium does not seem justified in asymptomatic patients given the very low absolute incidence of thrombus formation with the more recent devices.<sup>10</sup>

**G.P. Anzola, MD**

**E. Morandi, MD**

*Service of Neurology  
S. Orsola Hospital FBF  
Brescia, Italy*

**F. Casilli, MD**

**E. Onorato, MD, FSCAI**

*Department of Cardiology  
Humanitas Gavazzeni Clinic  
Bergamo, Italy*

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## White Matter Hyperintensities: Pearls and Pitfalls in Interpretation of MRI Abnormalities

To the Editor:

Atwood et al acknowledge that the pathophysiology of white matter hyperintensities (WMH) is uncertain and underscore the possibility of ischemic etiology, especially in the elderly.<sup>1</sup> These authors regard WMH as an excellent marker of brain aging and emphasize their heritability in patients with negative correlation with cerebrovascular brain injury.

WMH are neither age-specific nor generally heritable, having been found in both sexes in hypertensive encephalopathy, puer-

peral eclampsia, migraine, and therapy with cyclosporin, interferon- $\alpha$ , and tacrolimus.<sup>2,3</sup> Kruit and coworkers found WMH in MRI only in women migraine patients,<sup>2</sup> which likely reflects an investigational artifact. Atwood et al did not exclude hypertensive and migraine patients from their analysis, which prominently confounds their interpretation of WMH as indicative of brain aging.

An important pathophysiological clue to the nature of WMH is offered by the characteristic difference in the distribution of infarcts and deep WMH in migraine patients. Predominantly posterior circulation territory (PCT) migrainous infarcts in contrast to anterior circulation infarcts in embolic or atherosclerotic thrombotic strokes in general are likely related to rheological factors. Anatomical vulnerability of the posterior cerebral artery renders it particularly susceptible to vasospastic influences in migraine patients.<sup>4</sup> The rare occurrence of neuroanatomically nonlateralizing—in relation to headache or aura—PCT infarcts in younger migraine sufferers might represent an uncommon complication of an adaptive vasospasm that rarely reduces perfusion critically in a particularly labile region.<sup>4</sup>

Diffuse nonlateralizing distribution of deep WMH unaffected by triptan use<sup>2</sup> indicates that WMH do not reflect the outcome of vasospastic ischemia. Also, local changes during migraine attacks, eg, excessive neuronal activation or excitotoxicity,<sup>2</sup> should logically manifest lateralizing WMH. Deep WMH, in contrast to infarcts, likely resolve totally along with resolution of symptoms and signs after treatment of hypertension or withdrawal (or reduction of dose) of immunosuppressive agents.<sup>3</sup> Vasogenic cerebral edema probably underlies WMH in hypertensive encephalopathy; breakdown of the blood–brain barrier has been shown in human and in rat models.<sup>3</sup> Attack-related, inconsistently-lateralized, and prolonged (>48 hours) hyperperfusion prevails in the cerebral cortex, thalamus, and basal ganglia in migraine.<sup>5</sup> In direct contrast to infarcts, WMH probably result from intense but self-limited cerebral hyperperfusion. I propose that WMH are markers of transient breakdown of the blood–brain barrier rather than aging.

The heritability of WMH volumes is an intriguing feature.<sup>1</sup> The decline in heritability estimates after age 60<sup>1</sup> indicates the nongenetic nature of this observation. Another indicator of the nongenetic nature of WMH is the absence of correlation with aging in women despite higher heritability. Migraine is more prevalent in women than in men, from approximately age 14.<sup>6</sup> Breakdown of the aging-marker hypothesis for WMH in women may relate to migraine headaches. Finally, heritability of WMH may relate more to heritability of hypertension or migraine or both. In the absence of any link to cerebrovascular disease, the menopause probably has no independent bearing on WMH. Spontaneous resolution likely underlies significantly smaller WMH volumes at younger age, especially in women,<sup>1</sup> in which cohort the highest prevalence of migraine can be expected. These authors also hope to establish a genetic link between WMH and silent brain infarctions.<sup>1</sup> Unless the resolution or otherwise of WMH is established prospectively, it is premature to link this MRI finding with cerebrovascular ischemic disease. Cross-sectional studies of WMH cannot establish vascular-related genetic influences, as has been suggested.<sup>1</sup> Assumption of the genetic model for WMH<sup>1</sup> is probably incorrect.

**Vinod K. Gupta, MD**

*Dubai Police Medical Services  
Dubai, United Arab Emirates*

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### Response:

In his letter to the editor, Dr Gupta argues that white matter hyperintensities (WMH) are neither age-specific nor heritable. As evidence in support of this argument, he expands on an already lengthy list of causes for WMH in order to underscore the nonspecific nature of these phenomena. He then focuses on the distribution of WMH in migraine patients to support his hypothesis that WMH represent transient breakdown of the blood–brain barrier rather than the aging process per se. Finally, Dr Gupta concludes that our data do not support the heritability of WMH.

In response to his observations that WMH should be considered nonspecific, we agree completely. Many diseases lead to WMH. We must note, however, that most of the causes identified by Dr Gupta are extremely rare in a community-based population such as the Framingham Heart Study, suggesting that the overall influence of these diseases is likely to be extremely low. Regarding his hypothesis that WMH reflect a breakdown of the blood–brain barrier, there is ample evidence to support this, particularly in multiple sclerosis; but again, the prevalence of this disease in a healthy population is so low as to be negligible, and all known subjects with multiple sclerosis or other neurological diseases affecting white matter were systematically excluded. Dr Gupta does note that transient breakdown of the blood–brain barrier may be common to migraine, but this would not explain our findings as migraine declines in prevalence with advancing age. In addition, we note that age-related increases in WMH volume are one of the most consistent findings in studies that limit analysis to extremely healthy individuals.<sup>1–4</sup> From these data, we conclude that age, in fact, does relate to WMH volumes for the general population. In the manuscript, however, we do caution that age-related cardiovascular diseases such as systolic hypertension are also likely to contribute to the extent of WMH,<sup>5</sup> leading us to suggest that WMH may serve as a phenotypic marker for both aging and disease.

Dr Gupta also argues that our data do not conclusively show heritability of WMH. As evidence for this, he notes the decline in heritability after age 60. He further concludes that our data state that there is no correlation with age and WMH among women. Regarding the decline in heritability seen with advancing aging, it is important to understand that this was a family-based study. With advancing age, individuals are less likely to have informative family members to estimate heritability, leading to the possibility of spurious findings such as that seen with the oldest woman of this study. In fact, other than this anomaly, the heritability estimates were remarkably consistent at about 0.60 across both age and gender differences. Dr Gupta's second argument for heritability reflects an apparent misunderstanding of the data. Age was not a significant *covariate* for the heritability estimates in women, but the correlation between age and WMH was high ( $r=0.50$ ) and nearly identical for men and women.

We appreciate Dr Gupta's critical review of our manuscript, but continue to believe that WMH lesions are strongly heritable. We also continue to believe that this heritability probably reflects both the processes of aging and concurrent disease and hope that WMH will serve as a new phenotype to explore the genetics of both processes.<sup>6</sup>

**Charles DeCarli, MD**

*Alzheimer's Disease Center and Imaging of Dementia and Aging Laboratory  
Department of Neurology and Center for Neuroscience  
University of California at Davis  
Sacramento, California*

**Larry D. Atwood, PhD**

**Philip A. Wolf, MD**  
*Department of Neurology  
Boston University  
Boston, Massachusetts*

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## Nicotinamide Attenuates Focal Ischemic Brain Injury: Meta-Analysis or Mechanism of Protection

*To the Editor:*

We read with great interest the recent article by Macleod et al.<sup>1</sup> They have shown a highly significant neuroprotective effect of nicotinamide on experimental stroke using the technique of systematic review or meta-analysis. The message is clear, and we believe this approach is useful and fairly robust in terms of statistical power. However, I would like to point out a possible pitfall of their overview. Nicotinamide, vitamin B3, is the precursor of nicotinamide adenine dinucleotide (NAD<sup>+</sup>), and it may act as a poly(ADP-ribose) polymerase (PARP) inhibitor. When ischemia-induced DNA strand breakage is too extensive, the overactivation of PARP may lead to intracellular NAD<sup>+</sup> depletion and subsequent secondary energy failure (ie, ATP depletion).<sup>2</sup> ATP levels can be dramatically increased following ischemia-reperfusion by nicotinamide.<sup>3</sup> This scenario is generally accepted to explain the neuroprotective action of nicotinamide. However, it is also well known that high doses of nicotinamide (250 mg/kg in our case<sup>4</sup>) increase regional cerebral blood flow, and many studies have ignored cerebral blood flow. Therefore, we cannot jump into a conclusion that nicotinamide is a pure neuroprotectant independent of vasodilative action. If one does not consider divergent mechanisms of the beneficial effects of a candidate drug, such a promising drug based on animal experiments may fail to work under clinical settings, even though pooling of animal data reveals undoubtedly obvious neuroprotection.



**Hiroshi Yao, MD**  
**Fumiko Sadanaga-Akiyoshi, MD**  
**Setsuro Ibayashi, MD**  
**Mitsuo Iida, MD**

*Department of Medicine and Clinical Sciences  
 Graduate School of Medical Sciences  
 Fukuoka, Japan*

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#### **Response:**

The comments of Yao and colleagues serve to further illustrate the potential uses of systematic review and meta-analysis in the context of the interpretation of data from animal studies in stroke.

Studies in focal cerebral ischemia may report measurement of cerebral blood flow (CBF). In most cases, they find no significant differences between control and treated groups, and use this to infer that any protective effect seen is not a consequence of changes in CBF. However, power calculations for such comparisons are seldom if ever reported; it may be that a true difference in CBF is missed because studies are underpowered for this comparison (ie, there is a type II or “false negative” error).

Analyses such as ours can illuminate the impact of study quality and study design on the estimate of efficacy. Equally, where data are available the same technique could be used to give a more precise estimate of the effect of a drug on CBF. This would reduce the probability of a type II error, and thereby reduce the risk that protection due to an effect on CBF might be incorrectly attributed to some other drug property.

It is likely that systematic review and meta-analysis can provide further insights both into the limits to the efficacy of individual drugs and into more generic determinants of outcome in experimental stroke. We are currently developing an international collaborative approach to establish priorities for future research and to develop a standard set of methodologies which might be used.

**Malcolm Macleod, MRCP, PhD**  
*Division of Molecular and Clinical Medicine  
 University of Edinburgh  
 Edinburgh, Scotland, UK*

**Tori O'Collins, BSc**  
**David Howells, PhD**  
**Geoff Donnan, MD**  
*National Stroke Research Institute  
 Melbourne, Australia*

### **Intravenous Magnesium for Neuroprotection in Acute Stroke: Clinical Hope Versus Basic Neuropharmacology**

#### *To the Editor:*

Saver and colleagues investigated the neuroprotective effect of early magnesium infusion in ischemic or hemorrhagic stroke in the field; three quarters of the infarct cohort were treated within 2 hours of onset, and nearly one-third within 1 hour of onset.<sup>1</sup> Dramatic early and good results were reported in the early (42%

of <2-hour infarct patients) and 90-day global functional outcomes (69% of all patients and 75% of <2 hour infarct patients), respectively. These authors recommend large-scale trials with field initiation of magnesium for early neuroprotection in stroke.

An essential prerequisite for any pharmacological agent to offer significant brain neuronal protection during strokes is its ability to freely cross the blood–brain barrier (BBB). Transport of magnesium from blood to cerebrospinal fluid across BBB is limited in normal humans; intravenous administration of magnesium sulfate does not increase cerebrospinal fluid magnesium concentration.<sup>2</sup> Orally or intravenously administered magnesium sulfate cannot affect brain neuronal function.<sup>3</sup> Acute stroke is a hemodynamically highly labile clinical condition and impressive functional outcomes with magnesium supplementation should be viewed critically and cautiously.

The adaptive nature of hypomagnesemia, seen in a wide variety of clinical conditions and circumstances, including hospitalization and diabetes mellitus, is not generally appreciated.<sup>4,5,6</sup> Magnesium impairs cardiac pump function, a physiological limitation to rapid therapeutic supplementation in acute myocardial infarction or congestive heart failure.<sup>5</sup> With a mean patient age of 74 years (range 44 to 92 years) in this trial,<sup>1</sup> the negative inotropic effect of magnesium infusion<sup>5</sup> can significantly impair cardiac output and cranial perfusion pressure in this presbycardiac cohort. Informed consent from potential patients for clinical trials involving magnesium supplementation must include pharmacokinetic information about magnesium and BBB. Absence of serious side effects<sup>1</sup> does not by itself support use of any neuroprotective agent. No large-scale trial of magnesium supplementation in stroke, in the field or in the hospital, should be envisaged without presenting this facet of magnesium pharmacology to the approving institutional review board.

**Vinod K. Gupta, MD**  
*Dubai Police Medical Services  
 Dubai, United Arab Emirates*

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### **Intravenous Magnesium for Neuroprotection in Acute Stroke: Neuropharmacology Supports Clinical Hope**

#### **Response:**

We thank Dr Gupta for his interest in our study, but we strongly disagree with his assessment of the pertinent literature. In fact, the basic neuropharmacology of magnesium sulfate provides substantial support for clinical stroke trials in humans.

Several studies show that magnesium does cross the blood–brain barrier, in both animals and in humans.<sup>1</sup> Brain magnesium concentrations are regulated by active blood–brain barrier transport.<sup>2,3</sup> Cerebrospinal fluid magnesium concentration increases by 20% to 25% in response to doubling of the serum concentration, and peaks around 4 hours after parenteral administration.<sup>3–5</sup> While this overall increase in cerebrospinal fluid magnesium concentration is modest, magnesium concentration is selectively substantially increased in regions of pathology, including focal ischemia and seizures.<sup>6,7</sup>



It is also well known that the mild negative inotropic effect of magnesium sulfate is offset by its lowering of peripheral vascular resistance, resulting in no clinically substantial impairment in cardiac pump function.<sup>8,9</sup> Several physiological studies suggest that magnesium increases cardiac output.<sup>10,11</sup> Even in patients experiencing active myocardial ischemia, magnesium sulfate showed only a very small increase in the incidence of cardiogenic shock or congestive heart failure in the large ISIS-4 trial,<sup>12</sup> and no adverse effect on cardiac pump function was reported in the more recent MAGIC clinical trial.<sup>13</sup> Most saliently, among stroke patients in the phase 3 IMAGES trial, there was no excess of cardiac events related to administration of magnesium sulfate.<sup>14</sup>

In addition, magnesium sulfate is a potent cerebral vasodilator, in part due to calcium channel antagonism at vascular smooth muscle cells and possibly effects on myosin-binding proteins that regulate contraction.<sup>15,16</sup> Consequently, magnesium sulfate typically increases, rather than decreases, cerebral perfusion.<sup>17–19</sup>

Magnesium sulfate has been demonstrated to reduce infarct volume in multiple animal models of stroke, has numerous identified beneficial neuroprotective and vascular effects, is already known to be efficacious in treating in humans a condition characterized by altered cerebral blood flow (eclampsia), and has shown a potential signal of efficacy when administered early after stroke onset (within 3 hour subgroup) in a randomized clinical trial.<sup>14</sup> Further trials of magnesium sulfate in early time epochs in acute stroke are well-supported by preclinical and clinical neuropharmacology.<sup>20</sup>

Jeffrey L. Saver, MD

Chelsea Kidwell, MD

Marc Eckstein, MD

Sidney Starkman, MD

for the FAST-MAG Pilot Trial Investigators

Department of Neurology,

UCLA Stroke Center

University of California, Los Angeles

Los Angeles, Calif

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## Surgery Versus Stenting: How Medical Device Makers Influence Patient Care

To the Editor:

A recent *Wall Street Journal* article<sup>1</sup> highlighted the unfortunate tactics of medical device makers (Medtronic Inc of Minneapolis, in this instance) that influence scientific research by financial incentives to medical consultants who are investigators, aggressive marketing, and ultimately legal action.

The above article describes the controversial issues surrounding stent graft repairs of abdominal aortic aneurysms. It caused me to recall another equally disturbing debate that exists regarding the most efficacious treatment of carotid stenosis: carotid endarterectomy (CEA) versus carotid artery stenting (CAS). In a presentation at the November 2002 American Heart Association meeting in Chicago, Illinois, Dr Jay Yadav from the Cleveland Clinic reported the initial results of carotid stenting and angioplasty with protection (filters used to trap debris inside the carotid artery after the plaque is disrupted with a balloon or stent) in patients at high risk for endarterectomy (SAPPHIRE Study). The 30-day major adverse clinical event rate (stroke, myocardial infarction, death) was 5.8% for CAS with protection and 12.6% for CEA.

In a review by the Performance Improvement Committee at HCA Wesley Medical Center, an affiliate hospital of the University of Kansas at Wichita, published in the *Physicians Bulletin*, 530 CEAs throughout a 24-month period beginning January 1998 were reviewed.<sup>2</sup> These procedures were performed on patients admitted with the primary diagnosis of carotid stenosis who underwent CEA. All CEAs were performed by 4 vascular and 8 cardiothoracic surgeons. Included were many high-risk patients similar to those used in the SAPPHIRE Study: patients with severe heart disease, emphysema, dialysis-dependent renal failure, restenosis after previous endarterectomy, and patients with prior neck irradiation. Same-stay stroke occurred in 1 patient and same-stay mortality (due to myocardial infarction) occurred in another patient.

Carotid endarterectomy has been one of the most extensively scrutinized operations of our time.

- 90% of patients can undergo operation with preoperative ultrasound only without arteriography
- 90% do not require intensive care monitoring

- 90% require hospital stay of 24 hours or less
- the vast majority require no postoperative restrictions
- arterial complications as a result of arteriography (such as aneurysm formation) are not pertinent to CEA
- charges are less than that of stent procedures
- recurrent stenosis rates are less than 10%
- combined risk of stroke and death in multiple reports is less than 3%

The main danger of CAS is distal embolization with resultant stroke. Many patients without clinical stroke have demonstrated embolic debris after CAS if studied by various diagnostic modalities. The majority of patients with significant carotid stenosis demonstrate plaque hemorrhage, which is prone to embolize spontaneously without manipulation with a wire or catheter. Surgeons have much better means of reducing embolic complications with complete control of arterial blood flow during operation as opposed to stenting procedures.

With more than 150 000 CEAs performed in the United States annually, medical device companies have a huge financial interest in this procedure. Consequently, patients who typically would have CEA are shifted to stenting. Hospital cost for each stent alone is approximately \$1500 or more, and some patients require more than one stent. In addition, these procedures necessitate multiple guide wires, catheters, balloon angioplasty catheters and protection devices, produced by the same companies who produce the stents.

The September 2003 edition of *Endovascular Today* devoted a section to an update on CAS.<sup>3-6</sup> Three of 4 clinical authors were chief medical editors of the journal and the other author was on the Editorial Advisory Board. Of these 4 authors, three are consultants to medical device companies (Cordis, Medtronic, and Guidant).

Are the reported results of CAS truly unbiased? Many of the leading investigators are paid consultants of medical device manufacturers. As a specialist in vascular disease, and specifically a vascular surgeon, I perform CEAs. I also perform stent procedures in most peripheral arteries where indicated and stent graft repairs of abdominal aortic aneurysms. These procedures are effective and offer patients potentially less morbid alternatives to open operations. On the other hand, CAS offers little advantage over CEA, a minimally invasive procedure itself. Theoretically, if one considers the pathology being treated and the sensitivity of brain tissue to a lack of blood supply, CAS is difficult to justify. If it is truly safer, I will perform the procedure like others in my specialty. Nonetheless, in such a potentially high-risk area, the public deserves meticulous analysis by unbiased investigators who have no financial tie to the results.

Alex D. Ammar, MD

Department of Surgery

University of Kansas School of Medicine  
Wichita, Kansas

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### Aspirin for Stroke Prevention Taken in the Evening?

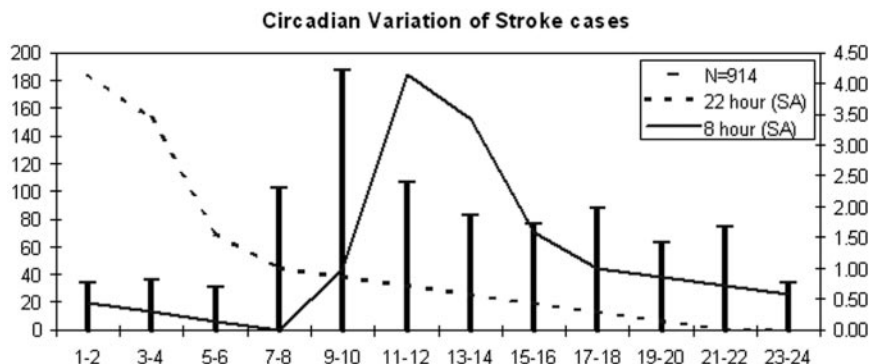
To the Editor:

We read the article by Yip et al<sup>1</sup> with great interest, in which they demonstrated that platelet activation significantly increases in acute ischemic stroke and substantially decreases thereafter. The lesser long-term pharmacodynamic potency of aspirin relative to clopidogrel raises the prospect of the need for more effective antiplatelet agents or a synergistic combination therapy for stroke prevention in the future.<sup>1</sup> Their results are very impressive and raise some ideas, particularly associated with the prevention's procedures.

According to World Health Organization data, in 1996 4.6 million people in the world died because of cerebrovascular manifestation of atherothrombosis.<sup>2</sup> In Hungary, nearly 18 000 people suffer stroke every year, half of whom die within a year. In cases of both cardiovascular and cerebrovascular diseases the significant decrease of morbidity/mortality can only be achieved by increasing the effect of prevention. A major form of secondary prevention is the administration of drugs inhibiting the aggregation of platelets.

Aspirin is one of the most common, useful, and inexpensive tools for prevention. The effect of aspirin on platelets is irreversible lasting for the duration of the platelet's life span ( $\approx 10$  days). Aspirin-mediated inhibition of platelet function occurs within 60 minutes of ingestion.<sup>3</sup>

The incidence of stroke assessed by onset of clinical symptoms exhibits a marked circadian variation with a peak period during the morning. Stroke usually occurs unexpectedly and more frequently in early morning hours (between 5 to 12 PM; see Figure) when the aggregability of thrombocytes is higher.<sup>4</sup>



Relation of plasma serum levels of salicylic acid and the daily distribution of the occurrence of acute ischemic stroke. Vertical bar graphs represent daily distribution of incidence of ischemic stroke.<sup>4</sup> Line diagrams show serum level of salicylic acid in  $\mu\text{g/mL}$  taken at 10:00 PM (dotted line) and at 8:00 AM (solid line). The maximum plasma concentration of salicylic acid occurs 3.5 to 4.0 hours after intake.<sup>5</sup> N=total number of patients involved in analysis, SA=salicylic acid.

Increased platelet aggregation in the morning and perhaps an upright posture may account at least in part for the observed circadian variation of the manifestation of stroke.

For prevention patients usually take aspirin in the morning. The treatment regimen is 1 tablet (100 mg) per day to be swallowed without chewing at least 30 minutes before breakfast. The relation of occurrence of stroke and the change of aspirin's plasma level taking in the morning is demonstrated in the Figure. It is obvious that highest plasma level of the drug occurs after the morning peak-incidence of the thromboembolic event, suggesting lower prophylactic effect of aspirin. Furthermore, this treatment regimen has its highest protective effect during the day, when, synergistically, normal physical activity exerts a protective action on thromboembolic processes. However, this method of daily aspirin administration has its lowest protective value against cardiovascular events during the night and early morning, when the lack of physical activity further augment the cascade of hemorheological events favoring platelet aggregation and subsequent ischemia. In contrast, highest plasma level of aspirin taken late evening (10:00 PM) would be reached prior to the peak-incidence of thromboembolic disorders. We are confident that this time shift in the administration of aspirin would fit better in the circadian scheme of the occurrence of stroke, thus resulting in a significantly more effective prevention. To prove the viability of this concept we propose to set up international, randomized, multicenter studies.

**Ildikó Kriszbacher, MSc**  
**Miklós Koppán, MD, PhD**  
**József Bódis, MD, DSc**  
*Institute of Nursing and Clinical Sciences*  
*Faculty of Health Sciences*  
*University of Pécs*  
*Pécs, Hungary*

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### Response:

Platelets play a key role in the pathogenesis of atherosclerosis and arterial thrombosis, which are the major contributors to the development of ischemic stroke and acute coronary syndrome.<sup>1–3</sup> Antiplatelet therapy is now a mainstay of primary and secondary prevention of death, myocardial infarction, and stroke in various categories of patients.<sup>4–6</sup> Previous studies have demonstrated the ischemic stroke to display a diurnal variation with a higher frequency in the early hours of the morning.<sup>7,8</sup> Although exactly why this circadian variation occurs remains uncertain, circadian variation of fibrinolysis, platelet aggregability, and arterial blood pressure, with their peak value in the morning, have been suggested to play a key role in this phenomenon.<sup>7–9</sup>

Given the safety, widespread availability, and minimal cost of aspirin therapy, aspirin is one of the most common antiplatelet agents for secondary prevention following an ischemic stroke.<sup>10</sup> Aspirin is rapidly absorbed in the upper gastrointestinal tract and results in a measurable inhibition of the platelet function within 60 minutes.<sup>11</sup> Additionally, a pharmacokinetic study has demonstrated that the peak serum level of aspirin is generally detected within 3.5 to 4.0 hours following ingestion.<sup>12</sup> While considering both the

circadian variation of a stroke and the particular pharmacodynamic effect of aspirin, Bodis and colleagues conjectured that taking aspirin in the morning after breakfast, as traditionally recommended, would offer a lower protective effect on recurrent stroke. They proposed that aspirin taken in the late evening, ie, around 10:00 PM, would benefit patients more than aspirin taken during the traditional administration time. To prove the viability of this hypothesis, they propose to set up international, randomized, multicenter studies.

We read with great interest regarding their hypothesis and opinion. However, 3 issues should be considered before conducting trials to test their hypothesis. First, if taking aspirin in the late evening could provide additional benefit than taking aspirin in the morning, a concern may arise over whether taking aspirin (100 mg) twice daily might be more protective to patients than daily administration. Second, owing to the benefits of aspirin in treating acute ischemic stroke,<sup>10</sup> acute coronary syndrome,<sup>3</sup> and in the secondary prevention for cardiovascular and cerebrovascular diseases,<sup>4</sup> numerous studies have attempted to evaluate aspirin as a primary prevention strategy.<sup>5,6,13</sup> While the results regarding the role of aspirin on the primary prevention of cardiovascular mortality remains inconsistent,<sup>4,13,14</sup> aspirin does not appear to significantly affect the primary prevention of a stroke.<sup>6,14</sup> These observations motivate the search for a more effective antiplatelet agent other than aspirin for primary stroke prevention in the future. Third, several randomized trials<sup>4,5,15</sup> have been conducted to determine the extent of reduction in terms of cardiovascular outcomes by different antiplatelet therapies in patients at risk of ischemic stroke. Clopidogrel, a new thienopyridine derivative that is chemically related to ticlopidine, blocks activation of platelets by selectively and irreversibly inhibiting the binding of adenosine diphosphate (ADP) to its receptor on platelets, subsequently inhibiting the ADP-dependent activation of the Gp IIb-IIIa complex, the major receptor for fibrinogen binding on platelet surface.<sup>5</sup> A related study has demonstrated that clopidogrel is more effective than aspirin in reducing the combined risk of ischemic stroke, myocardial infarction, or vascular death.<sup>5</sup> Our study<sup>16</sup> has provided basic evidence that clopidogrel is more potent than aspirin in suppressing platelet activation after ischemic stroke, and, therefore, further strengthens the conclusions of previous studies.<sup>4,5,15</sup> Although testing the hypothesis whether aspirin administered in late evening (at 10:00 PM) would offer greater benefit to patients would be more interesting, identifying a more effective antiplatelet agent for primary or secondary prevention of ischemic stroke would be more meaningful.

**Hon-Kan Yip, MD**  
**Shun-Sheng Chen, MD, PhD**  
**Mien-Cheng Chen, MD**  
*Department of Internal Medicine*  
*Chang Gung Memorial Hospital*  
*Kaohsiung Hsien, Taiwan, R.O.C.*

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## Predicting rtPA Associated ICH in Acute Stroke

To the Editor:

I read with interest the study by Trouillas et al from Lyon, France,<sup>1</sup> describing a plasma marker associated with parenchymal brain hemorrhage in patients treated with intravenous recombinant tissue plasminogen activator (rtPA) for acute stroke. Unusually high D-dimer levels measured at 2 hours after beginning rtPA were associated with increased risk of parenchymal hemorrhage within 24 hours. This is useful information that could be translated to patients treated elsewhere with a similar protocol. However, the currently adopted protocol for intravenous rtPA treatment of acute stroke in the United States and many other countries is according to the American Stroke Association (ASA)<sup>2</sup> and the American Academy of Neurology (AAN)<sup>3</sup> guidelines, and these guidelines differ in 2 important ways from the protocol used in Lyon. I would like to point out that because of these differences, the findings from Lyon may not translate to centers that follow the ASA/AAN guidelines.

First, the ASA/AAN guidelines do not recommend treatment beyond 3 hours after symptom onset, compared with up to 7 hours in Lyon. The mean delay to starting intravenous rtPA in Lyon was nearly 4 hours (based on a previous publication from that center),<sup>4</sup> which is approximately 90 minutes later than in the United States. This difference may be important as longer exposure to brain ischemia, with greater injury to the blood vessels and surrounding tissue, may predispose to hemorrhagic complications more than shorter exposure.

Second, the ASA/AAN guidelines advise against anticoagulation within 24 hours after rtPA treatment, compared with anticoagulation immediately after rtPA infusion in a considerable proportion of the patients in Lyon (exact proportion not stated). Anticoagulation is a well-established risk for parenchymal brain hemorrhage in multiple settings.

Thus, elevated D-dimer levels in acute stroke patients treated with intravenous rtPA according to the ASA/AAN guidelines may not be predictive of parenchymal hemorrhage, as they are in patients treated with the Lyon study protocol. It would be useful to validate the findings from Lyon in patients treated within the ASA/AAN guidelines.

Askiel Bruno, MD  
Department of Neurology  
Stroke Program  
Indiana University School of Medicine  
Indianapolis, Indiana

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## Response:

We have been interested by the constructive remarks of Dr Bruno, who points out the need of further studies on hemostasis in rtPA protocols using ASA/AAN guidelines, in order to confirm the predictive value of degradation factors. Some clarifications must, however, be given.

First, in our study,<sup>1</sup> we measured fibrin(ogen) degradation products (FDP), which involve fragments of fibrinogen and fibrin, while D-dimers originate exclusively from fibrin.<sup>2</sup> This postthrombotic increase of FDP at 2 hours (early fibrinogen degradation coagulopathy) was correlated with a fibrinogen decrease, indicating an impact of rtPA, at least partial, on circulating fibrinogen. It may be possible that D-dimers, which have a different biological significance, would not be predictive of early parenchymal hematoma. However, this measurement is now included in our prospective hemostasis evaluation.

Second, the Lyon protocol<sup>3,4</sup> was designed in 1993, before the NINDS rtPA Study<sup>4</sup> was published. At that time, the dose of rtPA, the window of administration, and the anticoagulant regimens were not standardized. However, the dose chosen was remarkably similar to that of the NINDS study (0.8 mg/kg). After the publication of the NINDS study results, we decided to continue the trial up to 200 patients, because our protocol was the unique opportunity to know what gave a slightly lower rtPA dose with a longer infusion time (90 minutes), a wider time window (7 hours), and precise postthrombotic heparin regimens. In the cohort of 157 patients with hemostasis screening,<sup>1</sup> the rate of symptomatic hemorrhage (3.8%) was lower than in part 1 (6%) and in part 2 (7%) of the NINDS study.<sup>4</sup> Thus, the hemostasis disturbances that we described are not linked to a more intense hemorrhagic process.

Third, the postthrombotic FDP coagulopathy does not seem to be influenced by heparin. In our cohort, only 20.3% of patients had a regimen with immediate postthrombotic unfractionated heparin. In several myocardial infarction trials including immediate use of intravenous heparin, an early FDP increase took place and was demonstrated to be correlated with bleeding complications, general or cerebral.<sup>5–11</sup>

Thus, there is a chance that early fibrinogen degradation coagulopathy, predictive of early parenchymal hematomas, may be confirmed in rtPA protocols following the ASA/AAN guidelines, without heparin during the 24 first hours, as well as in intraarterial protocols like PROACT II using postthrombolytic heparin.<sup>12</sup> Another answer may be given by the FRALYSE study, ongoing in France: this randomized, assessment blinded study, compares arms with the NINDS and Lyon protocols, with hemostasis and clinical parameters.

**Paul Trouillas, MD, PhD**

**Laurent Derex, MD**

**Frédéric Philippeau, MD**

**Norbert Nighoghossian, MD**

**Jerome Honnorat, MD**

*Cerebrovascular Unit*

*Neurological Hospital*

*Lyon, France*

**Michel Hanss, MD**

**Patrick French, MD**

*Hemostasis Department*

*Cardiological Hospital*

*Lyon, France*

**Patrice Adeleine, PhD**

*Biostatistical Laboratory*

*Lyon, France*

**Marc Dechavanne, MD**

*Hemostasis Laboratory*

*Lyon, France*

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