Sex Hormones and Carotid Atherosclerosis in the Metabolic Syndrome

To the Editor:

We read with great interest the recent article by Dr Iglseder et al1 dealing with sex differences in early carotid atherosclerosis in the metabolic syndrome. The results of their study demonstrated that extent of plaques and carotid artery intima-media thickness parameters were significantly higher in subjects with the metabolic syndrome. In addition, it was demonstrated that in women, blood glucose and triglyceride levels showed the strongest association with intima-media thickness of the carotid artery, whereas in men high-density lipoprotein ranked first. The authors proposed that the effect of the metabolic syndrome on early atherosclerosis is more pronounced in women, and that the impact of the components of the metabolic syndrome on the carotid artery injury differs between men and women.

Evidence indicates that vascular endothelial function is markedly influenced by estrogen and is improved by hormone replacement therapy in postmenopausal women.2 In an in vitro study presented earlier, we demonstrated that 17β-estradiol increased membrane fluidity (a reciprocal value of membrane microviscosity) of erythrocytes and improved the rigidity of cell membranes in postmenopausal women via a nitric oxide– and cGMP-dependent mechanism.3 In a separate series of experiments, we showed that hormone replacement therapy restored the membrane microviscosity in elderly women with a concomitant increase in plasma nitric oxide metabolite level.4 These findings suggest that because abnormalities in membrane microviscosity could cause a disturbance in the rheological behavior and the microcirculation, estrogen deficiency might be involved in the pathogenesis of vascular complications in elderly women. Recently, the role of estrogen in male physiology has also become evident, and normal physiological estrogen, which is converted from testosterone by aromatase, may confer cardiovascular benefits for elderly men.5 In this context, we speculate that changes in sex hormones might modify the course of cardiovascular diseases in both men and women. Iemolo et al6 demonstrated that women had greater carotid artery stenosis compared with men. Although the authors described that the majority of women in the population were in the postmenopausal state, we would like to know the endogenous sex hormone status in both men and women in the present study. Because insulin resistance might be strongly linked to estrogen concentration,7 further studies should be performed to assess more precisely the relationship between sex hormones and vascular complications in the metabolic syndrome.

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Do Normal d-Dimer Levels Reliably Exclude Cerebral Sinus Thrombosis? A Solution of Problems?

To the Editor:

We thank Dr Kosinski et al1 for their fine work on d-dimers in cerebral sinus thrombosis (CST) which confirms earlier results from Switzerland by Lalive et al.2 CST often offers a chameleon of symptoms ranging from headache to focal neurologic deficits and thus causes diagnostic difficulties. Both studies suggest that normal levels could reliably rule out CST in patients with symptoms lasting no longer than 2 weeks. In contrast to the high sensitivity stood the rather low positive predictive value (55.7% in Kosinski’s study). We also have to bear in mind that patients with pregnancy or malignancy (among other causes of elevated levels) were excluded in this study representing a group with elevated d-dimer levels and a higher risk of developing CST. In addition, all patients were primarily seen by neurologists. Back in everyday practice, the positive predictive value appears to be lower. Since the Stroke publication in December 2004, patients were transferred to us in most cases with “classic” headache-like migraine or tension headache but (unfortunately) in connection with elevated d-dimers. None of them showed further clinical signs of CST, but elevated d-dimers prompted further investigations in some of them, mainly MRI or contrast computer tomography. None of them showed a pathologic finding responsible for the symptoms. This illustrates that the studies on one hand helped to exclude CST and on the other hand caused further expensive and time-consuming examinations. In earlier days, no further investigations would have been performed.

Thus, we should not forget that multiple reasons can cause elevated d-dimer levels, and the positive predictive value for sinus thrombosis should even be lower than reported.

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Response:

We thank Vatankhah et al for their comment because they are addressing a common problem regarding the use of diagnostic tools with a primarily high negative but poor positive predictive value. If such a test is used rather broadly and in an unselected patient population as if it were a screening test it may indeed lead to confusion and prove useless.

In fact, the difficulty of false-positive results using d-dimers has been studied quite extensively in the more frequent situation of patients suspected of other thromboembolic diseases, such as deep venous thrombosis or pulmonary embolism. Although broadly used in these patients, the positive predictive value of d-dimers is rather low, in most studies even lower than it was in our study on patients suspected of having cerebral sinus thrombosis (CST). To overcome this problem many studies suggest the combination of d-dimers with the use of clinical prediction rules, such as the Wells score.1 Following these clinical predictions, Linkins et al2 even suggest the use of different d-dimer cut-off values with a relatively high d-dimer cut-off point (lower sensitivity and higher specificity) in patients with a low clinical pretest probability. For patients suspected of having CST, however, no such pretest probability scoring exists, and because of its rarity it is very unlikely that a similar approach will ever be examined in a proper study for CST.

Thus, so far neither from our3 nor from any other study can we conclude that the use of d-dimers as a routine test in all headache patients coming to emergency wards can be recommended. d-dimers should only be used for exclusion in patients suspected by a neurologist to have CST. Patients with “classic” headache-like migraine, as Vatankhah et al stated, who happen to have CST. To the Editor:

mischaracterize our prior study2 as demonstrating “that women, treated with intravenous tPA within 6 hours of stroke onset had better functional outcome after 90 days compared with men.” Although our study did find that women had a greater treatment-effect with tPA than men, this was because placebo-treated women had worse outcomes than placebo-treated men, whereas tPA-treated women had similar outcomes to tPA-treated men. This is consistent with large registries of tPA-treated patients showing similar outcomes between men and women,3 and also with large general stroke registries (ie, primarily untreated patients) showing worse outcomes for women.4,5

Thus, greater benefit with tPA for 1 group does not necessarily imply better outcomes for that group. Making this distinction clear emphasizes the need for using placebo-controlled data to look at factors that influence treatment-effect because the differential impact of tPA on functional outcome between the genders would not be found if only tPA-treated patients are analyzed. The distinction is also important when considering mechanisms because the treatment-interaction we described requires (at least) two gender-specific effects to be at play. An explanation is needed not only for the enhanced treatment-effect of tPA among women, but also for the worse outcome in untreated women compared with men. Although higher tPA-related recanalization rates might be a potential explanation for the former observation, it cannot explain the latter observation.

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Gender Differences in tPA-Related Arterial Recanalization

To the Editor:

We were very interested in the results of the study by Savitz et al,1 which showed dramatic differences in the rates of recanalization between men and women in a small sample of tPA-treated patients from their institution. However, in this article, they mischaracterize our prior study2 as demonstrating “that women,


Response:

We appreciate the comments of Drs Kent and Hill. In their article, Kent et al2 found that women receiving recombinant tissue plasminogen activator (rtPA) were significantly more likely than those receiving placebo to have a near-normal functional outcome, defined as mRS ≤ 1 at 90 days, as opposed to men where there was no overall difference between placebo- and rtPA-treated patients. They report “women were significantly more likely to benefit from rtPA compared with men.” Our statement that “women treated with IV rtPA within 6 hours of stroke onset had better functional outcome after 90 days compared with men” is therefore not inconsistent with their own reporting. Perhaps, it would have been more accurate to state that rtPA-treated women achieved better functional outcomes at 90 days compared with placebo controls, in contrast to men who did not benefit from rtPA compared with their placebo counterparts. Because women achieve a better treatment effect from
Magnesium for Delayed Cerebral Ischemia in Aneurysmal Subarachnoid Hemorrhage: Time for a Paradigm Shift?

To the Editor:

The Magnesium Sulphate in Aneurysmal Subarachnoid Hemorrhage (MASH) study group investigated continuous intravenous magnesium sulfate infusion from days 4 to 14 after subarachnoid hemorrhage (SAH); the clinical outcome of recanalization of delayed cerebral ischemia (DCI) remains, however, uncertain.1 It is generally believed that magnesium supplementation reverses vasospasm and offers neuroprotection to ischemic brain tissues. Although the cardiovascular utility of magnesium supplementation is limited to hypomagnesemia-related arrhythmias,2 a consensus opinion currently, eclampsia appears pathogenetically similar to hypertensive encephalopathy with forced dilatation of cerebral vessels, hyperperfusion, and cerebral edema (rather than a primary neuronal defect),3 which effects are likely to be further worsened by administration of magnesium sulfate. Sustained infusion of magnesium over 24 hours in a cohort with potential blood-brain barrier disruption produced total and ionized cerebrospinal fluid (CSF) marginals increases in total and ionized cerebrospinal fluid (CSF) such as inhibition of excitatory amino acids, blockade of sodium and potassium channels, or local measures at the level of the CSF to manage the stimulus for cerebral vasospasm indeed lies in the CSF, regional variations in CSF magnesium concentration,4 a finding in accord with previous investigations in humans. Regulation of cerebrospinal fluid [Mg2+] is largely maintained following acute brain injury and limits the brain bioavailability of MgSO4.5,6 With this pharmacokinetic limitation of magnesium supplementation, mechanisms such as inhibition of excitatory amino acids, blockade of N-methyl-D-aspartate-glutamate receptor, and DNA stabilization become largely academic. In general, the scientific basis for magnesium supplementation in humans remains questioned.

The adaptive nature of hypomagnesemia in a wide variety of clinical circumstances, including the general population, hospitalized patients, hypertension, migraine, premenstrual syndrome, pancreatitis, extensive burns, and other diverse conditions, has not been appreciated.2,7–9 Occurrence of hypomagnesemia in >50% of patients with SAH1 does not indicate that SAH-associated vasospasm is a direct consequence of magnesium depletion. Also, magnesium is a naturally occurring calcium antagonist. Consequently, in the face of a life-threatening situation such as SAH, hypomagnesemia would optimize functioning of a host of calcium-dependent physiological processes to preserve the organism, including cardiac output and other cardiovascular reflexes. In a holistic sense, hypomagnesemia seems to promote survival in life-threatening illnesses. Because clinical benefit of magnesium supplementation in this scenario would be difficult to establish, such an approach can prove infeasible. No difference has been seen in the incidence of either new focal neurological deficits or poor outcomes in other studies comparing magnesium sulfate therapy with placebo.1

The belief that reducing the occurrence of DCI will improve outcome remains unproven despite use of the vasodilator nimodipine; besides, DCI occurs in a sizable fraction of SAH patients managed with nimodipine and maintained normovolemic.1 Although it may seem paradoxical not to use vasodilators to prevent DCI in SAH, it may be useful to reexamine our belief that cerebral vasospasm in SAH can be usefully modified by systemic vasodilators. Because SAH-associated cerebral vasospasm is probably related to the presence of blood in the CSF, any systemically administered putative therapeutic agent must freely cross the blood-brain barrier. Even more importantly, if the stimulus for cerebral vasospasm indeed lies in the CSF, regional or local measures at the level of the CSF to manage the blood-related intracranial vasospasm might yield better results in the future.

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Trial Design in “Magnesium Sulphate in Aneurysmal Subarachnoid Hemorrhage: A Randomized Controlled Trial”

To the Editor:

We read with great interest the study by W.M. van den Bergh regarding the randomized controlled trial on Magnesium Sulfate in Aneurysmal Subarachnoid Hemorrhage1. In essence, it was a negative study using delayed cerebral ischemia (DCI) and poor outcome at three months from the data provided. The methodology raised concerns us. The author, for some unexplained reason, truncated the aspirin group’s case selection as well as data to carry out the analysis. As noted in the MASH group’s trial protocol published in the Internet Stroke Center, the way would be to double aspirin to the group that had aneurysm intervention within 4 days. If the aspirin group were actually excluded, the study population would be undoubtedly


focused on patients with delayed aneurysm treatment. The study used DCI as the primary outcome measure and used CT evidence of infarct.

Magnesium is thought to be neuroprotective and reverse cerebral vasospasm in animal models. Thus, it would be of interest to look at their clinical vasospasm data and blood flow study data as Transcranial Doppler USG and SPECT. It would certainly enlighten about the possible actions of magnesium. The other reasons for the above data would be that some patterns of CT infarct may not be related to cerebral vasospasm, and some infarct may actually be masked by edema or metallic artifact as quoted by Rabinstein et al.4

The outcome was made in 3 months. From our experience, some of the poor-grade subarachnoid hemorrhage patients would show progressive improvements beyond 3 months after the initial insult. We proposed to also assess the 1-year outcome for more definitive conclusions. Our group is currently in the midst of conducting a multicenter trial directly looking at the administration of Magnesium Sulfate in patients with aneurysmal subarachnoid hemorrhage, aiming for a total patient recruitment of 340. The interim analysis was presented in the ICP Meeting held in Hong Kong last August.4

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Response:

We thank the responders for their interest in our study. This trial was designed to study whether magnesium reduces the occurrence of delayed cerebral ischemia (DCI). It was not the aim of our study to clarify the proposed mechanism of action of magnesium in subarachnoid hemorrhage (SAH). After finding that magnesium reduces DCI, the next step is to study whether magnesium improves eventual outcome. For such a study, much larger numbers of patients are needed: based on the current data, at least 1200. We are currently embarking on such a trial.

Dr Gupta notes that the clinical outcome of reduction of DCI remains, however, uncertain. He provides extensive pharmacological reasoning why magnesium might be detrimental in many conditions including eclampsia. Reasoning will not always give a proper or right solution in medicine; the proof is in the eating of the pudding. Nimodipine was developed to reduce vasospasm. It works, but not through reducing vasospasm. With respect to eclampsia, there is ample clinical evidence regarding the beneficial effect of magnesium.

Dr Gupta raises the question whether the proposed mechanism of action of magnesium in SAH is correct given the limited brain bioavailability of peripherally administered magnesium sulfate in patients with acute brain injury. However, a study in neurosurgical patients showed that peripherally administered magnesium sulfate does lead to a significant increase in the CSF magnesium concentration.5

The suggestion that hypomagnesemia might be beneficial is in contradiction with our observations in 107 consecutive patients admitted within 48 hours after SAH, the adjusted hazard ratio of hypomagnesemia for DCI being 1.9; 95% CI 0.7 to 4.7, which is hardly compatible with a benefit of low magnesium levels.6 Rather, the results of that study suggest a causal relation between hypomagnesemia and the occurrence of DCI, although we also feel that it is more likely that hypomagnesemia is just part of a more complex pathophysiological mechanism.

Dr Gupta ends with remarking that we may have to reexamine our belief that cerebral vasospasm in SAH can be usefully modified by systemic vasodilators and that regional or local measures at the level of the CSF might yield better results to manage the blood-related vasospasm. We do not aim to treat vasospasm but to prevent and treat DCI. Because only 70% of patients with vasospasm develop DCI and 30% of the patients with DCI have no vasospasm,7 we feel that focusing on vasospasm may yield results that are clinically less relevant. This is the very reason why we do not have the Transcranial Doppler USG and SPECT data Dr Wong et al are asking for. Wong and others conclude that this was a negative study. This comment has to do with the general way of presenting the results of a clinical trial. We strongly believe that a clinical trial first and for all should be seen as a tool to quantify a treatment effect and to accompany this treatment effect with a measure of its precision. We consider emphasis on hypothesis testing less appropriate because this leads to an unnecessary dichotomy of trial results into “positive” and “negative,” whereas there is much more than that in a trial. Had the trial been twice as large, we would have reached statistical significance for all outcome measures even if the effect size would be the same. In that situation the responders undoubtedly would have classified the trial to be “positive”, with the same effect size. Hence, the problem is the precision of effect estimate. We fully acknowledge that the final word has not yet been said; for that reason we plan a second, larger trial. But to label our current trial as “negative” is too simplistic an approach. If we consider this phase II trial as “negative”, no further phase III trials would be performed. This implies that a safe and inexpensive treatment that very well may prove to be effective would not be further studied.

Further, Wong and others are concerned that the aspirin group has been excluded from our analyses on the effect of magnesium. Moreover, they worry that we focused on patients with delayed aneurysm treatment. Our trial assessed the effects of 2 different agents, magnesium and aspirin, by means of a factorial design, implying that patients were randomized twice (if eligible for each of the agents), once for magnesium versus placebo, and once for aspirin versus placebo. In our recent article, only the results of the magnesium part of the study were presented. We did not exclude the aspirin group, but at the time of publication the results for that part of the trial were still unknown. Patients allocated to aspirin, however, were equally distributed among the patients on magnesium or placebo-magnesium.

We agree that it can be difficult to distinguish ischemic cerebral lesions on brain CT from other causes of hypodense lesions. For that reason we also imbedded clinical information to be as accurate as possible about the origin of new hypodense lesions on brain CT, but we may have misjudged some of the lesions.

The experience from the authors that the outcome after SAH is still improving after 3 months is in line with our own finding.8 Further improvement after 3 months would probably dilute the difference between both groups; however, immedi-
ately returning home after discharge instead of first spending a couple of months in a rehabilitation facility is in our opinion a clinically relevant difference, even if the eventual results after 1 year or more are similar. Moreover, many SAH trials use a primary outcome at 3 months.

We are looking forward to the results of the clinical trial (iMASH) Dr. Wong and others are performing.

**Walter van den Bergh, MD**

**Gabriel Rinkel, MD, FAHA**

**Ale Algra, MD, FAHA**

On behalf of the MASH Study group


**Use of Phenytoin and Other Anticonvulsant Prophylaxis in Patients With Aneurysmal Subarachnoid Hemorrhage**

To the Editor:

We read with great interest the article by Naidech et al. The authors started from the abstract statement that “Phenytoin is routinely used for seizure prophylaxis after subarachnoid hemorrhage . . . .” and went on to investigate the possible harmful effects on cognitive and neurological outcome. After a study of 527 subarachnoid hemorrhage patients, the authors concluded that higher quartiles of phenytoin burden were associated with worse telephone interviews for cognitive status scores at hospital discharge (P<0.001) and at 3 months (P=0.003) as well as poor functional outcome at 14 days (P<0.001) but not at 3 months (P=0.09). The authors then suggested that exposure to phenytoin after subarachnoid hemorrhage should be minimized and argued for a prospective study of phenytoin in patients at high risk for seizures after subarachnoid hemorrhage.

We avoid using phenytoin as anticonvulsant prophylaxis in patients with aneurysmal subarachnoid hemorrhage in our center for another reason. Oral nimodipine is currently indicated in patients with aneurysmal subarachnoid hemorrhage to reduce the risk of poor outcome and secondary ischemia after aneurysmal subarachnoid hemorrhage. Nimodipine is metabolized via the cytochrome P450 3A4 system located in both the intestinal mucosa and in the liver. Drugs that are known to either inhibit or to induce this enzyme system may therefore alter the first pass metabolism or clearance of nimodipine. As recommended by the company information sheet (UK), nimotop tablets should not be administered concomitantly with drugs which induce the CYP 3A4 system, such as the antiepileptics phenytoin, phenobarbitone, and carbamazepine, because this markedly reduces the bioavailability of nimodipine and hence its efficacy.

In our institute, we elected to use sodium valproate as anticonvulsant prophylaxis in patients with aneurysmal subarachnoid hemorrhage if indicated. The above problem in drug pharmacokinetic was avoided, but sodium valproate was suggested to be related to quantitative thrombocytopenia and functional defects in platelet aggregation. That might be a theoretical problem for patients selected for craniotomy and clipping of aneurysm and rebleeding before aneurysmal occlusion, though we did not find the above problem clinically. We agreed with the authors that, with the low incidence of seizures after subarachnoid hemorrhage (with most occurring soon after ictus), anticonvulsant prophylaxis perhaps should be reserved for the patients at high risk for seizures, and selection of appropriate agent remained a challenge.

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3. Bayer Pharmaceuticals Corporation. Summary of characteristics: Nimotop 30mg tablets. Nimotop/Tablets (30 mg)/SMPC/Approved/UK/SmPC NimTab UK 005/3/DOC.


**Response:**

We thank Drs Wong and Poon for their thoughtful comments. We agree that increased metabolism of nimodipine might account for some, though probably not all, of the harmful effects on phenytoin after subarachnoid hemorrhage (SAH). They are not the only readers to suggest this thoughtful hypothesis.

We attempted to repeat our analysis for valproate, but did not have enough data. Some clinicians believe that any other par enteral anticonvulsant must be better than phenytoin, but there are no data to support this. It is possible that other anticonvulsants might prevent seizures with fewer adverse events, but this remains to be seen.

Patients without risk factors for seizures after SAH (Table 2: previous seizure, subdural hematoma, cerebral infarction, NIH Stroke Scale at least 10, etc) probably do not benefit from any anticonvulsant after SAH. For the remaining patients, the tradeoffs for prophylactic anticonvulsant use in SAH, with any agent, remain to be prospectively defined.

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Sex Hormones and Carotid Atherosclerosis in the Metabolic Syndrome
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