A Systemic Review of the Risk Factors for Cervical Artery Dissection

To the Editor:

We read with interest the review by Rubinstein et al1 on risk factors for cervical artery dissection. In a case-control study, we had analyzed the role of recent infection on cervical artery dissection.2 This study was referenced by the authors; however, our main findings were not correctly cited by the authors. In univariate analyses, recent infection and high-social status were significantly more common, and smoking was significantly less common in patients with cervical artery dissection (CAD) than in patients with cerebral ischemia of other origin. In conditional logistic regression analysis, infection within 1 week (odds ratio, 2.87; 95% CI, 1.18 to 7.00) and high-social status (odds ratio, 6.54; 95% CI, 1.88 to 22.7) remained significantly associated with CAD. Because coughing, sneezing, and vomiting that often occur during infection could explain the association between CAD and acute infectious disease, we systematically assessed the frequency of these mechanical factors. Recent cough, sneezing, and vomiting tended to be reported more often by CAD patients (60.5%) than by control patients (41.4%; P=0.06). In multivariate analysis, infection within 1 week, (odds ratio, 2.42; 95% CI, 1.01 to 5.8; P=0.046) but not cough, sneezing, or vomiting (odds ratio, 1.60; 95% CI, 0.67 to 3.8; P=0.29), was associated with CAD. This indicates that mechanical factors during infection do not explain the association between CAD and infections.

Therefore, the data given by Rubinstein et al1 in the abstract and the text regarding infection are not correct and require revision together with conclusions in their review. From our study and the results by Guillou et al,3 so far recent infection has to be regarded as a risk factor for cervical artery dissection. Furthermore, high-socioeconomic status may be another factor that is associated with the risk of CAD, although this certainly requires additional investigations.

Rubinstein et al1 mentioned the possibility of a selection bias in our study. Our case-control study2 was not part of a population-based register; however, it was based on consecutive patients in both groups. Given the fact that almost all of the younger patients with cerebral ischemia in the catchment area are treated in the University Center, the risk of selection bias can be rated as very low. In summary, 2 well-performed case-control studies found an independent association between recent infection and CAD that was not explained by factors such as mechanical stress to cervical arteries.2,3

Armin J. Grau, MD, PhD
Florian Buggle, MD
Department of Neurology
Klinikum der Stadt Ludwigshafen a.Rh. Bremerstr
Ludwigshafen, Germany

Response:

We would like to thank Drs Grau and Buggle for their interest in our article. They raise 2 important issues.

Their first objection may have to do with clarity of the text. We are not suggesting that the weak association refers to the relationship between dissection and the mechanical factors associated with infection, such as coughing, sneezing, or vomiting, but rather, the association between infection and dissection, even when these mechanical stressors are controlled for. Therefore, our article also agrees with the authors that recent infection may be an important risk factor, which is an association noted by others. However, this association may not be very strong. High socioeconomic status may also be an important risk factor and perhaps a subject for additional study; however, we did not identify any case-control studies that have confirmed this relationship.

Regarding the second point, case-control studies are notoriously sensitive to selection bias. Our objection was not whether patients were selectively identified (ie, consecutive), but rather that the control group chosen (ie, cerebral ischemia) may be inappropriate. Quite simply, controls must be a representative sample of the study base and must have an equal chance to develop the target disease as the cases. If not, it is a case of comparing apples with oranges. The mechanism of cerebral ischemia is quite clearly different from dissection, and we suggest that the risk factors may also differ (eg, “vascular risk factors”), which is why we proposed that healthy subjects might be a more suitable control. Otherwise, this may result in a potential overestimation of risk.

Note: This article was originally published online as a “systematic review.” However, this was a typographic error and should have read, “a systematic review.”

Sidney M. Rubinstein
Saskia Peerdeman
Maurits van Tulder
Scott Haldeman
Institute for Research in Extramural Medicine
(EEMGO Institute)
VU University Medical Centre
Amsterdam, The Netherlands

Transcranial Doppler and Carotid Artery Disease Strokes: More Than Just Risk Stratification

To the Editor:

Two important studies addressing the role of transcranial Doppler ultrasound (TCD) microemboli detection and stroke prevention have been published recently.1,2 Markus and MacKinnon1 studied 200 patients within 3 months of a focal neurological event. Their study demonstrated that the presence of microembolic signals detected during 1 hour of TCD monitoring was an independent predictor of future stroke and transient ischemic attack (TIA). Two major implications were proposed, first that TCD emboli detection could be useful for risk stratification in patients with carotid stenosis and, second, that the technique could be used to assess the efficacy of antithrombotic therapy. In the recently published Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial,2 dual antiplatelet therapy (aspirin plus clopidogrel) resulted in more effective control of microembolic signals than single antiplatelet therapy (aspirin alone). There was an associated reduction in the subsequent prevalence of TIAs and strokes.

Similar conclusions were drawn by the authors of both studies, in particular those patients with recent symptoms and emboli should be operated on urgently “wherever possible.” However, a recent systematic review of the risks of carotid endarterectomy in relation to both the clinical indication for and timing of surgery has shown that urgent carotid surgery carries a much higher risk (19.2%; 95% CI, 10.7 to 27.8) than elective surgery (odds ratio, 3.9; 95% CI, 2.7 to 5.7; P<0.001; 13 studies).3

Immediately after a TIA or stroke, there is a rise in TCD-detected microembolic signals. Those patients who continue to embolize are at greater risk of an additional neurological event.4 Recurrent or crescendo TIA patients represent a particularly high-risk group. It is possible to stop both emboli and additional symptoms in these patients with TCD-directed IV antiplatelet agents, with the dose being incrementally increased until the microemboli cease. Consequently, it is possible to influence the timing of surgical intervention, allowing patients to undergo carotid endarterectomy safely on the next elective list,5 avoiding the risks associated with urgent or emergency surgery3 or the necessity of the clinical indication for and timing of surgery, and the technique of surgery, allowing patients to undergo carotid endarterectomy safely on the next elective list,6 avoiding the risks associated with urgent or emergency surgery3 or the risks associated with delay6 in patients whose microemboli persist despite oral antiplatelet therapy.1,2,4

In the study by Markus and MacKinnon,1 the time between index event and assessment was considerably >72 hours in most of the subjects examined. This leads to the conclusion that some reported strokes could have been prevented. We believe that earlier assessment would show a stronger beneficial influence of TCD-directed antithrombotic therapy followed by surgery when necessary. Microemboli are surrogate markers for the risk of future embolic events. The pharmacological efficacy of therapeutic interventions can now be assessed rapidly, noninvasively, and inexpensively. TCD emboli detection appears to offer an important advance enabling the optimal integration of both medical therapy and the timing of surgery, and the technique should be more widely available.

Kyle T.S. Pattinson, BM, FRCA
Nuffield Department of Anaesthetics
University of Oxford, John Radcliffe Hospital
Oxford, United Kingdom

Christopher H.E. Imray, MB, BS, FRCS
Coventry and Warwickshire County Vascular Unit
University Hospitals Coventry and Warwickshire NHS Trust
Coventry, United Kingdom


Response:
Like Pattinson and Imray, we agree that Doppler embolic signal detection shows great promise in identifying patients with symptomatic carotid stenosis at high risk of early recurrent stroke. This group of patients may well benefit from more aggressive antiplatelet therapy. It is also possible that the use of the technique, combined with more aggressive antiplatelet therapy to reduce embolization in active embolizers, could allow carotid endarterectomy to be delayed in some patients.

However, based on considerable current evidence, patients with stable symptomatic carotid stenosis should be operated on as soon as possible. It has been clearly shown from analysis from the ECST and NASCET trials that the stroke risk in the first 2 weeks is very high.1 The metaanalysis that the authors quote showed no difference in the odds of stroke and death after early carotid endarterectomy for established stroke compared with late surgery.3 The excess risk was only seen in the smaller group of patients with unstable symptoms, ie, progressing stroke or crescendo transient ischemic attacks (TIAs). Therefore, in the majority of patients with a single ischemic TIA, or stroke with small infarct, current evidence suggests that carotid endarterectomy should be performed as soon as possible. In the more unstable patient with progressing symptoms, crescendo TIAs, or a large infarct, transcranial Doppler may well be useful in guiding treatment to allow stabilization before elective surgery. It may also be useful in guiding treatment in patients with stable symptoms and TIA or minor stroke in the many units worldwide where endarterectomy cannot be performed immediately as a result of logistic and resource issues.

In addition, before recommending its widespread implementation, some caution is required. Ideally, it should be shown in a large clinical study that this approach, when implemented on a widespread clinical scale, does allow stroke to be prevented. This will depend not only on the ability of embolic signals to predict stroke, as we have recently demonstrated, but also on the ability of clinical units to reliably implement the technique, including evaluation for embolic signals in real time. Current research studies, such as the 2 cited by Pattinson and Imray,4,3 have used assessment of the presence of embolic signals at a later date by a single experienced observer on data stored on digital audiotapes.

Hugh S. Markus, FRCP
St. George’s Hospital Medical School
London, UK

Andrew MacKinnon, MRCP
St. George’s University of London
London, UK


Use of Quantitative Magnetic Resonance Angiography to Stratify Stroke Risk in Symptomatic Vertebrobasilar Disease

To the Editor:
The recent article by Amin-Hanjani and coworkers1 was interesting, but we believe that there are several flaws in their algorithmic approach. The authors erroneously conclude that distal blood flow reduction, especially in the basilar artery as demonstrated by phase contrast-quantified MRA (QMRA) and

surrogate marker presence of distal atherosclerotic stenosis >50%, effectively allows stratification of patients with symptomatic vertebral basilar disease (VBD) into surgical and nonsurgical groups. We believe this is erroneous for several reasons. Weintraub and Khoury previously reported that neck angulation, ie, hyperextension and rotational movements, induced mechanical compression of the proximal vertebral artery producing significant hemodynamic changes. By using QMRA, low flow, occlusion, and reversed flow were identified in a significant number of patients. Additionally, hypoplastic vertebral arteries were noted in 25% of the cohort, which was also statistically associated with higher incidence of postural circulation stroke. Thus, symptomatic VBD can be significantly induced by neck positioning, yet this issue was never addressed in their algorithm. Of particular interest is that basilar artery flow reduction occurred in one third (33%) of the hypoplastic vertebral artery cohort compared with less than 20% of the nonhypoplastic vertebral artery cohort. The issue of hypoplastic vertebral arteries was not addressed by the authors. Sturzenegger and Newell feel that even a reversal of flow in the basilar artery is “irrelevant” provided that the perfusion pressure is sufficient.

It is also well known that atherosclerotic plaques by themselves may be an epiphenomena, and thus using this as a surrogate marker may be potentially erroneous.

There are many common causes leading to symptomatic VBD not addressed by the authors that would be of particular interest. It would be informative to know how many patients were female, how many had beauty parlor shampooing in the hyperextended position previous to diagnosis, as well as other significant factors of recent infection, performance of yoga, or neck exercises or chiropractic, and so on.

These comments are meant to be instructive in developing an effective flow algorithm of the entire vertebral basilar system. Risk stratification needs to be accurate and hopefully safe. The authors noted that 2 patients experienced stroke in the surgical cohort.

Michael I. Weintraub, MD
New York Medical College
Neurology and Internal Medicine
Valhalla, NY

Andre Khoury, MD
Phelps Memorial Department of Radiology
Sleepy Hollow, NY


Response:

We thank Drs Weintraub and Khoury for their interest and comments on our recent publication. To clarify, distal blood flow was the basis for our management algorithm. The presence of >50% stenocclusive symptomatic vertebrobasilar disease (VBD) was not a surrogate marker for stratification within this algorithm as the authors imply, but merely a description of the patient cohort studied with this algorithm. We examined this particular cohort of patients because they represent the population demonstrated to be at high risk of stroke and also most often referred and considered for intervention.

In regard to the hemodynamic changes that may occur with changes in neck position, we certainly agree, and it is well documented, that there are patients who develop vertebrobasilar insufficiency (VBI) as a result of mechanical compression.

However, this population is not the patient cohort that formed the basis for the application of our algorithm. We do feel that the use of our algorithm may well extend to such patients, although we have not tested this in the appropriate population of patients with VBI induced by neck positioning or angulation. Measuring distal flow with the head positioned in the posture that tends to aggravate symptoms would certainly be a worthwhile prospective application of the algorithm. Documentation that low distal flow develops under those circumstances would be compelling evidence of mechanical compression as the underlying etiology.

The authors’ comment that the issue of hypoplastic vertebral arteries is not addressed is incorrect and reflects a misunderstanding of the underlying premise of our algorithm. Distal flow reflects the status of the proximal vessels. As such, the presence or absence of a hypoplastic artery and its consequences will be reflected in the distal flow measurement.

In regard to the comment that “there are many common causes to symptomatic VBD,” we would point out that this should more accurately read “there are many common causes to VBI”; symptomatic VBD in our publication is defined as symptoms in the setting of >50% atherosclerotic stenoocclusive disease and therefore does not have “many common causes.” As noted here, our article sought to address risk stratification in symptomatic VBD. We believe that risk stratification for patients with other causes of VBI will also be attainable with a flow-based algorithm and are hopeful that future work by ourselves and others will expand the use of flow-based clinical decision-making.

Sepideh Amin-Hanjani, MD
Fady T. Charbel, MD
University of Illinois at Chicago
Chicago, Ill


Should We Distinguish Between Periventricular and Deep White Matter Hyperintensities?

To the Editor:

The recent article by DeCarli et al addresses a somewhat neglected aspect of white matter hyperintensities (WMH), the significance of their anatomical location. The authors argue that the commonly accepted categorization into deep (DWMH) and periventricular (PVWMH) WMH is arbitrary, because the 2 are very highly correlated, and a spatial analysis does not reveal distinct populations. We think that this conclusion is premature, because the categorization depends on a number of factors. The first limitation of their analysis is that they examined individuals in their 70s who presented to a specialty clinic, suggesting that the white matter lesions in their sample were at an advanced
stage. If an analogy is drawn from cerebral atrophy in dementia, regional differences in atrophy that are present in the different subtypes of dementia become less prominent in the later stages. In our study of WMH in middle age (60 to 64 years), the correlation of DWMH and PVWMH was much lower \((r=0.621; P<0.001; n=477)\), accounting for <40% of the variance.\(^6\) It is possible that the 2 subtypes of WMH have different but converging trajectories, possibly because of overlapping but not identical risk factors and pathogenesis. Neuropathological differences between DWMH and PVWMH have been reported,\(^3\) which suggest that whereas cerebral ischemia is a common etiological factor, other mechanisms may be differentially involved. In our study, hypertension was a risk factor for both, but diastolic blood pressure \((BP)\) correlated significantly with DWMH, whereas both systolic and diastolic BP were correlated with PVWMH.\(^4\) Homocysteine was a determinant of DWMH but not PVWMH,\(^5\) but lung capacity was more strongly related to PVWMH.\(^6\)

The functional significance of the 2 subtypes is also likely to be different. In an earlier study involving stroke patients,\(^7\) we showed that although DWMH accounted for only one third of the total WMH volume, with the other two thirds being PVWMH, it had a stronger relationship with cortical perfusion. Our recent analysis of data from 397 community-based middle-aged individuals suggests that DWMH have a significant relationship with cortical atrophy \((r=0.15; P=0.003)\) and ventricular dilatation \((r=0.18, P<0.0005)\), but PVWMH do not \((r=0.06, P=0.21); r=0.03, P=0.56\) respectively.\(^8\) There are also demonstrated differences in the effect of DWMH or PVWMH on cognitive function, motor function,\(^9\) and emotions.\(^10\)

Therefore, we support the continuing distinction between DWMH and PVWMH, at least for research. In fact, additional anatomical categorization into lobar and arterial territorial regions may be relevant for some purposes. To lump all of the WMH into 1 category will hamper our understanding of their pathogenesis and functional relevance.

**Perninder Sachdev, MD, PhD, FRANZCP**

**Wei Wen, PhD**

**School of Psychiatry**

**University of New South Wales and Neuropsychiatric Institute**

**Prince of Wales Hospital**

**Sydney, Australia**

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**Response:**

We appreciate the keen observations of Drs Sachdev and Wen regarding the importance of anatomical distributions of abnormal white matter hyperintensities (WMH) as seen on MRI. In fact, we agree with Drs Sachdev and Wen that the location of WMH is important, but we continue to believe that current categorical definitions of subcortical versus deep white matter are probably inadequate, because they do not have clear biological correlates. For example, the superior longitudinal fasciculus, an anatomically discrete white matter bundle, traverses both periventricular and deep white matter locations. Evolving image mapping methods such as our own\(^1\) and that of Drs Sachdev and Wen\(^2\) offer the unique opportunities for an "unbiased" analysis of the anatomical distribution of WMH throughout the brain, offering the potential for better correlation with anatomically valid white matter structures. Unfortunately, appropriate statistical methods have yet to be developed for this approach. In this regard, we are developing new statistical methods that will take into account the location of WMH relative to important biological and anatomical structures and enable more sophisticated spatial analysis.

The authors raised a second issue related to study differences in subject selection. We have previously shown that total WMH volume is strongly associated with age, and age-related differences increase more dramatically with age after 60 years.\(^3\) As Drs Sachdev and Wen\(^2\) note, the distribution of WMH may also vary with subject age. For example, younger individuals are more likely to have limited WMH abutting the ventricular system with scattered, punctate WMH throughout subcortical white matter. As we suggest, WMH may "coalesce" or merge with periventricular WMH as total WMH burden increases,\(^1\) which could explain differences in relationships shown by Drs Sachdev and Wen\(^2\) and ourselves. Underlying disease will also affect the distribution of WMH. For example, WMH may be more common in the frontal areas of individuals with depression\(^4\) or involve gray matter structures in stroke. Whereas age-related or disease-related differences among various studies may explain some of the differences in reported relationships between WMH location and behavior, we continue to believe that advances in our understanding of the etiology and seminology of WMH will be best served by developing new methods that enable accurate anatomical representation of white matter tracts.

**Charles DeCarli, MD**

**Department of Neurology and Imaging of Dementia and Aging Laboratory**

**Center for Neuroscience**

**University of California at Davis**

**Davis, California**

**Danielle Harvey, PhD**

**Division of Biostatistics**

**Department of Epidemiology and Preventive Medicine**

**University of California at Davis**

**Davis, California**

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HMG-CoA Reductase Inhibitors Improve Acute Ischemic Stroke Outcome

To the Editor:

Dr. Moonis and colleagues are to be congratulated on an important study that provides further insight into the usefulness of statins in improving ischemic stroke outcome.1 However, I disagree with the premise of the first sentence of the introductory section of their article, which reads as follows: “Prospective studies have demonstrated that HMG-CoA reductase inhibitors (statins) reduce stroke recurrence by 20% to 25%.”2,3 Indeed, there is little basis for drawing this conclusion from the studies cited to support this statement.

The Scandinavian Simvastatin Survival Study demonstrated that statin treatment reduced the risk of primary stroke in a cohort of patients with coronary disease and high low-density lipoprotein cholesterol.2 Furthermore, although a post hoc analysis, not prespecified, of subjects entered into the Heart Protection Study with a history of symptomatic ischemic cerebrovascular disease revealed a significant reduction in major vascular events in favor of simvastatin, there was no beneficial treatment effect for stroke prevention by the statin agent.4 As such, currently there remains no convincing data that statins are beneficial in reducing recurrent stroke. The ongoing SPARCL study will likely shed further light on this issue.5

Bruce Ovbiagele, MD
UCLA Stroke Center
Los Angeles, Calif


Response:

I want to thank the Dr. Bruce Ovbiagele for his thoughtful comments and his interest in our article.1 I agree that the data on risk reduction of recurrent ischemic stroke is largely based on studies in patients with coronary heart disease.2 Interestingly, the American Stroke Association still recommends using statins in patients with ischemic stroke with or without ischemic heart disease with the aim of secondary prevention. Space limitation and the fact that the objective of this research report was to assess the effects of statins on stroke outcome and not stroke recurrence did not allow room for a more detailed discussion on statins and risk reduction of recurrent ischemic stroke. Results of the SPARCL trial should be helpful in answering this question.3

Majaz Moonis, MD, MRCPI, DM
Department of Neurology
University of Massachusetts Medical School
Worcester, Mass


Is Neurointensive Care Really Optional for Comprehensive Stroke Care?

To the Editor:

Expertise matters. The recent recommendations for Comprehensive Stroke Centers (CSC) put forth by the Brain Attack Coalition (BAC) make this argument convincingly using consensus and medical evidence when available.3 This document represents a landmark in advancing the care of stroke patients and will likely have important policy implications for hospitals, administrators, and regulatory agencies in planning for identification, certification, and management of CSCs. Certainly, this has been the case for the certification of Primary Stroke Centers recently implemented by the Joint Commission on Accreditation of Healthcare Organizations.

Given the important implications of the CSC recommendations, it is unfortunate that the BAC has actually created recommendations that encourage less than comprehensive care for critically ill stroke patients, placing them at risk for less favorable outcomes. Specifically, the BAC has designated neuroscience intensive care units (NICU) and neurointensivists as optional components of a Comprehensive Stroke Center. Moreover, with no supporting evidence referenced, they have indicated that hiring a neurointensivist (and presumably developing an NICU) is likely associated with significant institutional cost. Some hospital administrators would likely see this as a BAC-sanctioned opportunity to reduce the availability of neurointensivists and NICUs (including specially trained neurocritical care nurses) because they will be perceived as costly and optional for certification. Thus, the BAC has created recommendations that may well have a real and potentially dangerous impact on stroke patients.

Why is this a bad idea? Several studies have shown that, in fact, neurointensivists and NICUs save lives and improve the outcome of stroke patients.2,3,4,5 Additionally, this usually comes with reduced length of stay and cost of care.3,4,5 Throughout the CSC recommendations, the BAC acknowledges the desirability of neurointensive care expertise and neuroscience critical care.

Ideally, every hospital that receives acute stroke patients will create the infrastructure to be certified as a Primary Stroke Center. Many fewer hospitals that are equipped to deal with the most complex cases will deserve CSC designation. We are sensitive to the concern that there may not currently be adequate numbers of neurointensivists to meet the CSC need. However, we feel that the bar should be set high for CSCs, and institutions pursuing this designation should not have the ability to sacrifice care for a mistaken expectation of cost savings. Recognizing that neurointensivists may include neurologists, neurosurgeons, anesthesiologists, internists, and pediatricians with special training...
in neurocritical care, there are more of us than you realize. The Neurocritical Care Society has over 500 members from 43 states and 24 countries and is growing rapidly.

We challenge the BAC to revise their recommendations to include neurointensive care expertise as mandatory for Comprehensive Stroke Centers. Failing to do so will likely undermine the goal of providing comprehensive care for the sickest and most complex stroke patients. Expertise matters. Our patients deserve it; so do yours.

J. Claude Hemphill III, MD
Thomas Bleck, MD
J. Ricardo Carhuapoma, MD
Cherylee Chang, MD
Michael Diringer, MD
Romergrkyo Geocadin, MD
Stephan Mayer, MD
Owen Samuels, MD
Paul Vespa, MD

on behalf of the
Neurocritical Care Society
Minneapolis, Minn


Should We Distinguish Between Periventricular and Deep White Matter Hyperintensities?
Perminder Sachdev and Wei Wen

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