Summary: A number of studies have linked chronic exposure to infectious agents such as *Helicobacter pylori*, *Chlamydia pneumoniae*, and herpes viruses to coronary artery disease and stroke (Wimmer MLJ, et al [Stroke 1996;27:2207-10] and Ridker PM et al [Circulation 1998;98: 2796-2799]) with atherosclerosis. It has been thought that chronic infections may lead to an inflammatory process through remote signaling of inflammatory mediators that ultimately begin the process of atherosclerosis. The authors postulate that it is more likely that an aggregate of infectious burden, rather than a single infection, would lead to such a proinflammatory state.

This study measured antibody titers to common infectious microorganisms (*Chlamydia pneumoniae*, *Helicobacter pylori*, cytomegalovirus, and herpes viruses 1 and 2) in community participants who were stroke free. A weighted index of infectious burden was then calculated based on Cox models derived from the association of each infection with stroke risk. Maximum carotid plaque thickness was then determined with high-resolution carotid artery duplex scanning. The association between infectious burden and maximum carotid plaque thickening after adjustment for other risk factors was determined using weighted least squares regression.

Serologic results for all five infectious organisms were available for 861 participants (mean age, 67.2 ± 9.6 years) in whom maximum carotid plaque thickness measurements were also available. The infectious burden index was a mean of 1.0 ± 0.35 (median, 1.08), and 52% of the participants had detectible plaque (mean, 0.90 ± 1.04 mm). Infectious burden was associated with maximum carotid plaque thickness (adjusted increase in maximum carotid plaque thickness 0.09 mm; 95% confidence interval, 0.03-0.15 mm per standard deviation increase of infectious burden).

Comment: An implication of the study is that infectious burden may be a modifiable risk of atherosclerosis and that measurement of carotid plaque thickness may provide a way to assess the effects of an anti-infective strategy. A weakness of the study is that serologic measurements of infection and carotid plaque thickness were determined at only a single time. Temporal relationships between carotid plaque thickness and infectious burden cannot be determined from these data. Another problem with the infectious etiology of atherosclerosis theory is that clinical trials of antibiotic therapy for infectious agents thought to be associated with atherosclerosis have not been shown to reduce vascular risk (O'Connor CM, et al [JAMA 2003;2901: 1459-66] and Cameron CP, et al [N Engl J Med 2005;352:1646-54]).

Limb-Shaking Transient Ischaemic Attacks in Patients With Internal Carotid Artery Occlusion: A Case-Control Study

Persoon S, Kappelle LJ, Klijn CJM. Brain 2010;133:915-22.

Conclusion: Transient ischemic attacks (TIAs) marked by limb-shaking are associated with high-grade carotid stenosis or internal carotid artery occlusion and can be recognized by short duration and precipitation by rising or exercise. They are also accompanied frequently by paresis and indicate an impaired hemodynamic state of the brain.

Summary: Case-reports have described limb-shaking as an unusual clinical feature of TIAs (Klijn CJ, et al [Neurology 2000; 55: 1806-12] and Firlik AD, et al [Neurosurgery 1996;39:607-11]). The limb-shaking characterizing these TIAs consists of brief, jerky, and coarse involuntary movements involving an arm or a leg and has been associated with high-grade stenosis or occlusion of the internal carotid artery (ICA). An unanswered question is whether patients with high-grade ICA stenosis or occlusion who have limb-shaking TIAs have a worse hemodynamic flow state than patients with ICA stenosis or occlusion who do not have limb-shaking TIAs. In this study the authors sought to describe clinical characteristics of limb-shaking in patients with TIAs or moderately disabling strokes associated with occlusion of the ICA. They also sought to investigate whether the hemodynamic state of the patients with limb-shaking is worse than in patients with symptomatic ICA occlusion without limb-shaking.

The authors studied 34 patients (82% men; mean age, 62 ± 7 years) who had limb-shaking associated with ICA occlusion and 68 age-matched and sex-matched controls who had hemispheric TIAs or minor disabling strokes and ICA occlusion but who did not have limb-shaking. They investigated collateral pathways using contrast angiograms and also studied carbon dioxide reactivity measured by transcranial Doppler imaging.

Limb-shaking TIAs were found to last <5 minutes and were often accompanied by paresis of the involved limb. Patients with limb-shaking TIAs compared with controls more frequently had symptoms precipitated by exercise or rising (odds ratio [OR], 14.2; 95% confidence interval [CI], 4.2-47.9). Patients with limb-shaking TIAs also more frequently had recurrent ischemic deficits after ICA occlusion before inclusion in this study (OR, 8.2; 95% CI, 2.3-29.3). Patients with limb-shaking TIA's also tended to have lower carbon dioxide reactivity (mean, 5% ± 16% vs 12% ± 17%; OR. 0.97 per 1% increase; 95% CI, 0.94-1.00). Patients with limb-shaking TIAs had a greater dependence on leptomeningeal collaterals (OR, 6.8; 95% CI, 2.0-22.7).

Comment: Limb shaking as a manifestation of a TIA is a relatively unknown to most vascular surgeons. Most of these patients have ICA occlusion; 10% of patients with ICA occlusion will have limb-shaking TIAs. Some of these patients, however, have high-grade ICA stenosis rather than occlusion and therefore are of interest to the peripheral vascular surgeon. It is important to note that this particular form of TIA is likely hemodynamic and not embolic. Patients with limb-shaking TIAs undergoing carotid endarterectomy therefore, perhaps, should be strongly considered for shunting during the performance of the endarterectomy when technically feasible.

New Ischemic Brain Lesions on MRI after Stenting or Endarterectomy for Symptomatic Carotid Stenosis: A Sub-Study of the International Carotid Stenting Study (ICSS)

Bonati LH, Jongen LM, Haller S, et al and the ICSS-MRI study group. Lancet Neurol 2010;9:353-62.

Conclusion: In a substudy of patients randomized in the International Carotid Stenting Study (ICSS) comparing carotid artery stenting with carotid endarterectomy for symptomatic carotid stenosis, patients randomized to the stenting group had three times more ischemic lesions found by post-treatment magnetic resonance imaging (MRI) diffusion-weighted imaging (DWI) than patients randomized to the endarterectomy group. Cerebral protection devices did not seem to be effective in preventing ischemic DWI lesions after stenting.

Summary: The ICSS randomized patients with symptomatic carotid artery stenosis to carotid stenting or carotid endarterectomy. Of the 50 centers that participated in the ICSS study, 7 took part in an MRI substudy, the results of which were reported in this article. In the MRI substudy, MRI was done 1 to 7 days before treatment (endarterectomy or stenting), at 1 to 3 days after treatment (post-treatment scan), and again at 27 to 33 days. The primary end point of this substudy was the presence of at least one new ischemic brain lesion on DWI on the post-treatment scan. Analysis was per protocol, and investigators who read the scans were blinded to whether the patient had received endarterectomy or carotid stenting.

The substudy comprised 231 patients (107 in the endarterectomy group and 124 in the stenting group). The detection of one new DWI lesion on post-treatment scans done a median of 1 day after treatment occurred more frequently in the stenting group (50% of the 124 patients) than in the endarterectomy group (17% of the 107 patients; odds ratio [OR], 5.21; 95% confidence interval [CI], 2.78-9.79; $P < .0001$). There were changes at 1 month on fluid-attenuated inversion recovery sequences in 28 of 86 patients (33%) in the stenting group and in 6 of 75 patients (8%) in the endarterectomy group, (adjusted OR, 5.93; 95% CI, 2.25-15.62; $P = .0003$). In centers with a policy of using cerebral protection devices, new DWI lesions were present after treatment in 37 of 51 patients (73%) in the stenting group and in 8 of 46 (17%) in the endarterectomy group (adjusted OR, 12.20; 95% CI, 4.53-32.84). In centers with a policy of using unprotected carotid artery stenting, new DWI lesions were present in 25 of 73 patients (34%) in the stenting group and in 10 of 61 patients (16%) in the endarterectomy group (adjusted OR, 2.70; 95% CI, 1.16-6.24; interaction $P = .019$). Subanalyses of age <71 years, sex, whether the qualifying event was a TIA or stroke, and whether there were DWI lesions present on the pretreatment scan all indicated higher rates of new DWI lesions after stenting compared with endarterectomy.

Comment: Previous nonrandomized studies have also suggested higher rates of ischemic lesions detected on DWI imaging after stenting compared with endarterectomy. A meta-analysis of these studies is presented in Fig 4 of this article and indicated the OR of new ischemic lesion after treatment was 6.71 (95% CI, 4.57-9.87) favoring endarterectomy. The authors' OR of 5.21 is very similar to that obtained from the meta-analysis. The clinical significance of DWI lesions in the long run is unknown but is postulated to eventually lead to cognitive decline and dementia (Pendlbury ST et al [Lancet Neurol 2009;8:1006-18]). Of particular interest is the apparent lack of protection against DWI lesions afforded by cerebral protection devices. One might postulate, given the relative ORs for DWI lesions with and without protection devices, that protection devices actually increase the risk of DWI lesions! There are a number of reasons why cerebral protection devices may have been ineffective in this study. For instance, all protection devices in this study were of the filter type, and conclusions about other types of devices cannot be made. Another possible conclusion is that cerebral protection during carotid artery stenting is another idea that seems like a good idea but does not hold up to proper scrutiny when one actually examines data collected by unbiased observers.

Patient Outcomes after Acute Pulmonary Embolism: A Pooled Survival Analysis of Different Adverse Events

Klok FA, Zondag W, van Kralingen KW, et al. Am J Resp Critical Care Med 2010;181:501-6.

Conclusion: Within 4 years of acute pulmonary embolism (PE), half the patients will have an additional serious adverse clinical event.

Summary: Most articles on acute PE focus on incidence and case fatality rates. There are little data on the long-term fate of the patients. This report, however, does provide a more long-term perspective of the fate of patients with PE. We know that death related to PE occurs in approximately

2% to 6% of patients with a hemodynamically stable PE and in >30% of patients with PE presenting with shock or hemodynamic instability (Chest 2002;121:877-905; Arch Intern Med 2004;164:92-96). About 25% of patients do not survive the first year after the diagnosis of PE, with most deaths relating to cancer or chronic heart disease rather than to PE itself (N Engl J Med 1992; 326:1240-1245). We also know that patients with PE are at risk for recurrent PE, chronic thromboembolic pulmonary hypertension, arterial cardiovascular events, and a new diagnosis of cancer (N Engl J Med 1998;338:1169-73; AMA 2005;293:2352-61). The goal of this study was to assess long-term risk for adverse events after PE.

The authors analyzed consecutive patients diagnosed with PE between January 2001 and July 2007. Patients were monitored until July 2008 for occurrence of adverse clinical events, defined as death, symptomatic or recurrent venous thromboembolism, cancer, arterial cardiovascular events, and chronic thromboembolic pulmonary hypertension. Statistical analysis included calculation of hazard ratios (HR) and 95% confidence intervals (CI) for individual end points and a combined end point with adjustments for confounders. There were 308 patients with unprovoked and 558 patients with provoked PE. An additional 334 patients without PE were also studied. Median follow-up was 3.3 years. Patients with unprovoked PE had a lower overall risk for death than patients with provoked PE (HR, 0.59; 95% CI, 0.43-0.82). However, they had a higher risk for non-malignancy-related death (HR, 1.8; 95% CI, 1.3-2.5), recurrent venous thromboembolism (HR, 2.1; 95% CI, 1.3-3.1), cancer (HR, 4.4; 95% CI, 2.0-10), cardiovascular events (HR, 2.6; 95% CI, 1.5-3.8), and chronic thromboembolic pulmonary hypertension (1.5% vs 0%). The fraction of patients with provoked and unprovoked PE without events after 1 year was 70%, decreased to <60% after 2 years, and was <50% after 4 years. In comparison, 85% of patients without PE were free of clinical events after 4 years.

Comment: These data are sobering. More than 70% of patients with PE will have had a major clinical event by 4 years after the PE. One is tempted to ascribe the late events to the initial occurrence of the PE, but clearly, a diagnosis of cancer as a late clinical event is not caused by the PE. Nevertheless, the high rate of late adverse events that are potentially related to the initial PE (recurrent PE, recurrent venous thromboembolism, and thromboembolic pulmonary hypertension) argues for better protocols for prevention of PE through individual risk stratification of at-risk patients.

Stenting versus Endarterectomy for Treatment of Carotid-Artery Stenosis

Brott TG, Hobson RW 2nd, Howard G, and the CREST Investigators. N Engl J Med 2010;363:11-23.

Conclusion: In patients with symptomatic or asymptomatic carotid stenosis, a composite outcome of stroke, myocardial infarction, or death does not differ between patients undergoing endarterectomy or those undergoing carotid artery stenting. During the periprocedural period, there is a higher risk of stroke with stenting and a higher risk of myocardial infarction with endarterectomy.

Summary: The authors randomly assigned patients with asymptomatic or symptomatic carotid artery stenosis to undergo carotid endarterectomy or carotid artery stenting. The primary end point was a composite end point of stroke, myocardial infarction, or death from any cause during the periprocedural period or any ipsilateral stroke ≤4 years after randomization. There were 2502 patients participating in the study, with a median follow-up of 2.5 years. There were no significant differences in the estimated 4-year rates of the primary end point between the stenting group and the endarterectomy group (7.2% and 6.8%, respectively; hazard ratio with stenting, 1.11; 95% confidence interval, 0.81-1.51; $P = .51$). The primary end point did not differ according to sex ($P = .34$) or symptomatic status ($P = .84$). The 4-year rate of stroke or death was 6.4% with stenting and 4.7% with endarterectomy (hazard ratio, 1.37; $P = .14$). Rates among asymptomatic patients were 4.5% and 2.7%, respectively (hazard ratio, 1.86; $P = .07$). There were differences in periprocedural rates of individual components of the end points between the stenting and endarterectomy group. Rates of death for stenting were 0.7% vs 0.3% for endarterectomy ($P = .18$). Rates of stroke were 4.1% for stenting vs 2.3% for endarterectomy ($P = .01$). Rates of myocardial infarction were 1.1% for stenting vs 2.3% for endarterectomy ($P = .03$). After the periprocedural period, incidences of ipsilateral stroke with stenting and with endarterectomy were both low (2% vs 2.4%, respectively; $P = .85$).

Comment: The CREST results are finally published. The question now is what do we do with them? The primary end point of the study, a combination of stroke, death, and myocardial infarction, did not differ between the stented and surgically treated patients ($P = .38$). This was secondary to a higher incidence of periprocedural myocardial infarction in the endarterectomy patients. Rates of stroke and death were higher in the stented group, both in the periprocedural period and out to 4 years (any stroke, $P = .01$; any periprocedural or postprocedural ipsilateral stroke, $P = .01$; any periprocedural stroke or death or postprocedural ipsilateral stroke; $P = .0.005$; Table 2 of the article). The results basically mirror those of other government-sponsored large randomized trials that favored endarterectomy over stenting for stroke prevention or failed to establish noninferiority of stenting (Ederle J, et al [Lancet 2010;375:985-97]; Mas J-L, et al [N Engl J Med 2006;355:1660-71]; and Ringleb PA, et al [Lancet 2006;368:1239-47]) Additional analysis in CREST indicated stroke had an adverse long-term outcome on quality of life, whereas perioperative myocardial infarction had no effect on quality of life measures. Overall it would seem the evidence favors endarterectomy over stenting, but this will surely continue to be debated.