Cerebral Aneurysms

AB-14187-98


Object. The authors sought to determine whether the increased pulsatility of aneurysms, compared with normal intracranial arteries, on color “power” transcranial Doppler (TCD) ultrasound was due to a true change in aneurysm size and whether aneurysm dimensions change with intracranial pressure (ICP).

Methods. The authors studied nine patients who had suffered recent subarachnoid hemorrhages complicated by hydrocephalus requiring intraventricular cerebrospinal fluid drainage, in whom the presence of an aneurysm was confirmed on angiographic examination. Color “power” TCD studies of the intracranial arteries and aneurysm were obtained through the temporal bone window before and after insertion of the ventricular drain and then at different known ICPs.

Of the nine patients studied, four were examined both before and after insertion of a ventricular drain. At high ICPs, aneurysms appeared very “pulsatile” and the maximum cross-sectional area was small, whereas at low ICPs, aneurysms appeared larger and were much less pulsatile. The normal arteries did not change significantly in terms of pulsatility or maximum cross-sectional area at different levels of ICP.

Conclusions. The change in aneurysm size visualized with the aid of color power TCD is likely to be real. Aneurysm dimensions vary with ICP levels: the lesions are larger and less pulsatile at low ICPs and smaller but more pulsatile at high ICPs.

AB-14188-98


OBJECTIVE: Cerebral angioplasty is being increasingly used for symptomatic vasospasm secondary to subarachnoid hemorrhage. We attempted to determine the safety and efficacy of angioplasty for refractory vasospasm. We also looked at the influence of timing of angioplasty on outcome.

METHODS: We retrospectively studied patients with subarachnoid hemorrhage who underwent angioplasty in our institution to determine the safety and the success rate achieved with this procedure. The study period extended from August 1993 until February 1997. Clinical and radiological data were collected, with emphasis on clinical improvement after angioplasty and its relationship with timing of intervention. Thirty-one patients with 43 aneurysms and one case of arteriovenous malformation were included. Their ages varied between 26 and 68 years, with an average age of 44 years. Five patients were assigned Hunt and Hess Grade IV, 15 were assigned Grade III, 7 were assigned Grade II, and 4 were assigned Grade I. All patients except two underwent angioplasty after aneurysm clipping or coiling.

RESULTS: Angioplasty was performed an average of 6.9 days after the occurrence of subarachnoid hemorrhage, with a range from 1 to 14 days. It was performed early (within 24 h) after refractory clinical deterioration in 21 patients. A total of 81 vessels were dilated. Three angioplasty-related complications occurred: two femoral hematomas and one retroperitoneal hematoma. Clinical improvement was dramatic after 12 procedures, moderate after 11 procedures, and minimal or nonexistent after 9 procedures. There was a clear tendency toward more significant improvement in patients with earlier angioplasty (<24 h from onset of neurological deficit) (P=0.0038). At discharge, 8 patients had achieved good recoveries (Glasgow Outcome Scale score of 1), 11 had moderate disabilities (Glasgow Outcome Scale score of 2), and 10 had severe disabilities (Glasgow Outcome Scale score of 3). Two deaths were encountered, and they were unrelated to angioplasty. Follow-up was obtained for 27 patients: 25 had good outcomes, 1 was moderately disabled, and 1 died. There was no significant correlation between interval and outcome.

CONCLUSION: Our results indicate that angioplasty is a safe and effective treatment for symptomatic vasospasm that is refractory to hyperosmotic hypervolemic therapy. When used early (<24 h), it leads to significant clinical improvement. However, the long-term outcome is good, even in cases of delayed angioplasty. The prevention of worsening of the cerebral ischemia and its extension to other territories may be the reason.

Clinical

AB-14189-98


The etiology of carotid abnormalities is both congenital than acquired. The aim of this study was to clarify the role of aging and atherosclerosis in the acquired cases, and the role of these abnormalities in hemodynamic alterations and neurologic symptoms.

Over a 1-year period the authors studied all the subjects undergoing carotid examination by continuous-wave and color-coded Doppler sonography at an Angiology Unit. They evaluated neurologic symptoms; risk factors for atherosclerosis; number, sites, and kinds of carotid abnormalities; atherosclerotic lesions; stenosis; hemodynamic alterations of the carotid; and other localizations of atherosclerotic diseases.

There were 469 subjects: 272 (58%) with abnormalities (group 1) and 197 (42%) without abnormalities (group 2). The total number of abnormalities was 479 (104 tortuositities, 262 kinkings, and 113 coilings). The abnormalities were more prevalent in the elderly (P<0.001) and in women (P<0.001). In group 1 they found significant prevalences of hyperlipemia (P<0.001), hypertension (P<0.01), chronic cigarette smoking (P<0.01), and ischemic heart disease (P<0.05).

Carotid atherosclerotic lesions were more prevalent in group 1 than in group 2 (P<0.001); among the patients with atherosclerotic carotid lesions, those in group 1 were older than those in group 2 (P<0.001). Tortuosity seemed to be associated with fewer hemodynamic alterations. The authors conclude that atherosclerosis, hypertension, and aging may play an important role in producing carotid abnormalities. The aging seemed more important than atherosclerosis.

Only a prospective study of patients with carotid abnormalities and no atherosclerotic lesion will clarify the role of hemodynamics and neurologic symptomatology.

AB-14190-98

Quantitative Analysis of Cerebral Vasculopathy in Patients With Fabry Disease—Crutchfield KE, Patronas NJ, Dambrosia JM, Frei KP,
AB-14193-98

Background: Limited information exists on the frequency, trends in occurrence, risk factors, mechanisms, and outcome of ischemic stroke associated with illicit drug use among young adults in a geographically defined population. Methods: We reviewed ischemic stroke in young adults (aged 15 to 44 years) in 46 regional hospitals for 1988 and 1991. We examined stroke mechanisms and outcome in patients with recent drug use. Results: Recent illicit drug use was noted in 5/422 (12.1%) stroke patients. Patients with drug use were more likely to have hypertension (p = 0.004), and smokers (p = 0.006), and were less likely to have hypertension (p = 0.004) or diabetes mellitus (p = 0.004). Drug use was the probable cause of stroke in 20 (4.7%) patients. Among 31 (7.3%) patients with drug use as a possible stroke mechanism, more likely diagnoses included cardioembolic stroke in 18, hematologic/collagen vascular in 6, nonatherosclerotic vasculopathy in 5, and atherosclerosis in 3. There was no difference in outcome between drug-associated and non-drug associated stroke. Conclusions: Recent illicit drug use occurs in 12.1% of young adult stroke patients. Drug-associated young adult stroke seems to relate to vascular mechanisms other than those related to hypertension or diabetes. Case-control studies are needed.

AB-14194-98

Anticardiolipin antibodies (aCL) are a risk factor for cerebral ischemia. In migraine, the association is controversial, with widely varying results in different small series. The controversy in part may be due to the inherent difficulty in distinguishing the transient focal neurologic events (TFNE) of migraine from TIA. To assess the frequency of aCL in migraine, we prospectively evaluated consecutive adults under 60 years of age with migraine without aura and with recent TFNE (<24-hour duration) clinically suggestive of either migraine with aura or TIA. We
concomitantly enrolled persons with no CNS disease. Each person was interviewed and had blood drawn for solid-phase ELISA with IgG and IgM aCL isotyping. Neuroradiologic studies were reviewed. Patients with TFNE were followed every 6 months for the duration of the 3-year study. The frequency of aCL positivity (IgG <20, IgG >40, IgM >7.5) for the 645 patients with TFNE (8.8, 3.1, 4.2%), the 518 persons in the TFNE subgroup with migraine with aura (8.9, 3.3, 4.1%), the 497 persons with migraine without aura (7.0, 2.0, 3.6%), and the 366 control subjects (9.3, 3.6, 3.9%) did not differ significantly between groups. In TFNE patients with elevated aCL titer, the association was positive with diabetes mellitus, TFNE duration <15 minutes, and diplopia and was negative with hemiparesis, tinnitus, and family history of stroke. Findings on imaging consistent with cerebral ischemia were more frequent in aCL-positive persons. The short-term risk of stroke was uniformly low. In young persons, aCL is not associated with migraine or with TFNE, although diabetes mellitus, negative family history of stroke, and brief duration of symptoms (including diplopia) may predict immunoreactivity. Imaging studies suggest an ischemic etiology of TFNE in this cohort.

**AB-14195-98**

**Cardiovascular Risk Factors in Relation to Cigarette Smoking: A Population-based Survey Among Asians in Singapore**—Hughes K (Dept of Community, Occupational and Family Medicine, Faculty of Medicine, National Univ of Singapore, 119260, Singapore), Choo M, Kuperan P, Ong C-N, Aw T-C—*Atherosclerosis*. 1998;137:253–258 © 1998 Elsevier Science Ireland Ltd.

To investigate how cigarette smoking increases the risk of cardiovascular disease, risk factors were compared between 166 cigarette smokers and 312 non-smokers, in a random sample of males (Chinese, Malays and Asian Indians) aged 30–69 years from the general population of Singapore. There was adjusted for age and ethnic group. The prevalence of hypertension was lower in cigarette smokers (15.2%) than non-smokers (21.9%), with the difference reduced by adjustment for body mass index (BMI). Smokers had: lower mean serum HDL-cholesterol (0.76 versus 0.81 mmol/l) and higher mean serum fasting triglyceride (1.92 versus 1.71 mmol/l), which will increase atherosclerosis; higher mean plasma fibrinogen (2.75 versus 2.67 g/l) and plasminogen activator inhibitor 1 (PAI-1) (24.9 versus 22.2 mg/ml), which will increase thrombosis; and lower mean plasma vitamin C (4.4 versus 6.4 mg/ml) and serum selenium (118 versus 123 μg/l), which may increase atherosclerosis. Adjustment for BMI slightly increased the differences for HDL-cholesterol, fasting triglyceride, fibrinogen and PAI-1, indicating that less generalised obesity among smokers reduces their increased cardiovascular disease risk. Smoking was not found to be related to: diabetes mellitus; serum total cholesterol. LDL-cholesterol, apolipoproteins A1 and B and lipoprotein(a); plasma factor VIIc and prothrombin fragment 1+2; and plasma vitamins A and E and serum ferritin. There was no evidence of increased insulin resistance in smokers, as measured by mean fasting serum insulin.

**AB-14196-98**


The aim of this study was to determine the incidence of first-ever TIA and the distribution of risk factors in those patients with TIA in Dijon. We performed a prospective population-based study in Dijon City with 135,000 inhabitants, from 1990 to 1994, using several case-collection sources. Over a 5-year period, we recorded 258 cases of first-ever TIA, giving a crude annual incidence rate of 38.68/100,000 for men and 32.70/100,000 for women. The mean age of first-ever TIA was higher in women (71.75 years) than in men (70.35 years). A CT scan was performed in 97% of the cases and silent lacunes were discovered in 17% of cases. In our 5-year study in Dijon of first-ever TIA, we found incidence rates similar to those of previous population-based studies. Our results also support the hypothesis that risk factors for TIA are similar to those for stroke.

**Experimental Pathology**

**AB-14197-98**


The goal of this study was to determine whether aurintricarboxylic acid (ATA), an endonuclease inhibitor known to inhibit apoptosis, could ameliorate cell damage in a gerbil model of transient ischemia. Transient ischemia was induced in gerbils by bilateral carotid artery occlusion for a period of 5 minutes. Four micrograms of ATA was administered intraventricularly 1 hour before ischemia, and the brains were assessed histologically 1 week later to quantitate cell loss in the vulnerable CA-1 subsector of the hippocampus. In a separate set of experiments, 4 μg of ATA was administered intraventricularly 1 hour before ischemia and the brains were assessed for evidence of DNA fragmentation by the TUNEL method. There was only a 16% cell loss compared with nonischemic controls in animals pretreated with ATA that was significantly less (p<0.05) than the 48% cell loss in animals pretreated with saline alone. TUNEL-positive cells were first evident at 3 days and were still present at 7 days subsequent to ischemia. Maximal staining occurred at 4 days. Pretreatment with ATA virtually eliminated TUNEL staining at 4 days. These results support the hypothesis that the delayed cell death secondary to transient ischemia is, in part, apoptotic. Furthermore, ATA afforded significant neuronal protection and prevented DNA fragmentation.

**AB-14198-98**


The beneficial effects of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) on coronary events have generally been attributed to their hypocholesterolemic properties. Mevalonate and other intermediates of cholesterol synthesis (isoprenoids) are necessary for cell proliferation and other important cell functions; thus effects other than cholesterol reduction may help to explain the antiatherosclerotic properties of statins. Recently we provided in vitro and in vivo evidence of decreased smooth-muscle cell (SMC) proliferation and migration by fluvastatin and simvastatin, but not by pravastatin, independent of plasma cholesterol reduction. The ability of fluvastatin to interfere with arterial SMC proliferation at therapeutic concentrations (0.1–1 μM) prompted us to investigate the pharmacologic activity of sera from 10 patients treated with fluvastatin, 40 mg once daily, on the proliferation of cultured human arterial myocytes. Pravastatin, 40 mg once daily, displays a lipid-lowering activity similar to that of fluvastatin without affecting SMC proliferation and was investigated as a control for assessing this non-lipid-related effect of fluvastatin. Fluvastatin and pravastatin, given for 6 days to patients with type IIA hypercholesterolemia, resulted in a similar decrease in low-density-lipoprotein (LDL) cholesterol. However, the addition of 15% whole-blood sera from patients treated with fluvastatin to the culture medium resulted in a 43% inhibition of cholesterol synthesis in SMCs (p<0.01) that mirrored the pharmacokinetic profile of fluvastatin. When SMC proliferation was investigated, a significant inhibition of cell growth (~30%; p<0.01) was detected with sera obtained 6 h after the last dose. No effect on SMC proliferation or cholesterol biosynthesis was observed when sera from patients treated with pravastatin were evaluated. These results suggest that statins exert a direct antiproliferative effect on the arterial wall,
beyond their effects on plasma lipids, which could prevent significant cardiovascular disease.

**AB-14199-98**


The cell volume is regulated not only by inorganic ions, but also by organic osmolytes, such as amino acids, methylamines, and polyhydric alcohols (polyols). Using proton nuclear magnetic resonance spectroscopy (1H-NMR), we measured the tissue concentrations of amino acids (alanine, aspartate, glutamate, glutamine, N-acetyl-aspartate (NAA), taurine), methylamines (glycerophosphorylcholine (GPC), creatine + phosphocreatine (total creatine, tCr)), and polyols (myo-inositol) in the rat brain after middle cerebral artery occlusion (incomplete focal ischemia) or after decapitation (complete global ischemia). The total osmolytes expressed as a sum of total amino acids, total methylamines, and total polyols were significantly decreased at 24 h of focal ischemia (58.7% of control value; *P*<0.0025) whereas they were not changed following decapitation. The water content was increased from control value of 77.9%—84.1% after focal ischemia (*P*<0.0001) but not after decapitation. These results suggest that the brain organic osmolytes are involved in the process of edema formation following focal cerebral ischemia. Further elucidation of the cellular mechanisms regulating these organic osmolytes in cerebral ischemia may promote greater understanding of the pathophysiology involved in the evolution of brain edema.

**AB-14200-98**


We compared gradient-echo (GRE), spin-echo (SE) and stimulated-echo (STE) echo-planar imaging sequences for perfusion-weighted imaging at different field strengths. Focal cerebral ischemia was induced by endovascular occlusion of the middle cerebral artery in eight rats. MR was performed at 4.7 T or 2.35 T. With each sequence, we acquired data sets before, during and after bolus injection of Gd-DTPA with a time resolution of 1.2 s per image. The perfusion-weighted images were assessed with regard to image quality, artefacts, signal-to-noise ratio (SNR), and signal-attenuation-to-noise ratio (ΔSNR) of the non-ischaemic tissue. Visual assessment showed GRE-EPI images acquired at 4.7 T to suffer from distortion due to susceptibility artefacts. Artefacts were less marked with the SE and STE series. The GRE-EPI sequence gave the highest SNR and ΔSNR. At 2.35 T, the SNR of the STE sequences was less than 3 and therefore did not allow construction of reliable signal-time curves. SE-EPI was best suited for perfusion-weighted imaging at high field strength thanks to its minimal distortion artefacts and high SNR. Using lower field strengths (2.35 T and less), susceptibility artefacts are reduced: GRE-EPI sequences are then best suited, because they have the highest SNR and T2* sensitivity.

**AB-14201-98**

MK 801 and Dexamethasone Reduce Both Tumor Necrosis Factor Levels and Infarct Volume After Focal Cerebral Ischemia in the Rat Brain—Bertorelli R (Schering-Plough Research Institute, San Raffaele Science Park, Via Olgettina, 58, 20132 Milan, Italy), Adami M, Di Santo E, Ghezzi P—*Neurosci Lett.* 1998;246:41–44. © 1998 Elsevier Science Ireland Ltd.

Focal cerebral ischemia in rats produces elevated levels of tumor necrosis factor (TNF) in the ischemic brain region. To better understand the modulation of TNF during brain ischemia processes we carried out studies in a model of permanent middle cerebral artery occlusion (MCAo) in the rat. In non-treated ischemic animals, the maximum expression of TNF was observed at 12 h (246.1±33 U/L) in the ischemic cortex and declined reaching near zero levels 24 h after MCAo. Given 10 min after MCAo, MK 801 (3 mg/kg, i.p.), a non-competitive NMDA receptor antagonist, exerted significant neuroprotection as measured by 47% reduction of total volume of infarction (*P*<0.01 vs. ischemic-control). At the high dose of 3 mg/kg i.p., dexamethasone (DEX), which is known to reduce brain edema, decreased infarct size by 50% (*P*<0.01 vs. ischemic-control). Both MK 801 and DEX reduced TNF production in the ipsilateral cortex of ischemic animals by 61 and 73%, respectively (*P*<0.01 vs. ischemic-control). The data indicate that TNF levels increase after brain infarction, whereas they are reduced by neuroprotective agents, such as MK 801 and DEX, which act on different cellular levels.

**Imaging**

**AB-14202-98**


**PURPOSE:** The aim of this study was to assess the changes over time of internal carotid artery (ICA) dissections by using helical CT.

**METHODS:** Twenty-seven patients with 30 angiographically proved ICA dissections were followed up with helical CT at 7 to 62 months (median, 24 months) after conventional angiography. CT scans, analyzed independently by two radiologists in a blinded fashion, were evaluated for the presence of mural thickening, aneurysmal formation, and arterial occlusion. In cases without persisting occlusion or aneurysm, we measured the external diameter of the ICA at its upper segment.

**RESULTS:** The interobserver agreement was good. Mild mural thickening was observed in four cases of 30 previously dissected ICAs. All stenotic and nearly occlusive dissections without an aneurysm (n=12) reverted to a normal or nearly normal diameter. Half the aneurysms resolved spontaneously (four of eight). Of the 10 occluded ICAs, nine were recanalized, but their external diameter was significantly smaller than that of normal carotid arteries, and a hypoplastic appearance was seen throughout the cervical segment of the ICA in three cases.

**CONCLUSION:** Most arterial lesions tend to improve or disappear spontaneously, but persisting ICA narrowing may be observed in the late course of occlusive-type dissections.

**AB-14203-98**


Impaired CBF autoregulation during vasospasm after aneurysmal subarachnoid hemorrhage (SAH) could reflect impaired capacity of distal vessels to dilate in response to reduced local perfusion pressure or simply indicate that the perfusion pressure distal to large arteries in spasm is so low that vessels are already maximally dilated. Autoregulatory vasodilation can be detected in vivo as an increase in the parenchymal cerebral blood volume (CBV). Regional CBV, CBF, and oxygen extraction fraction in regions with and without angiographic vasospasm obtained from 29 positron emission tomography studies performed after intracranial aneurysm rupture were compared with data from 19 normal volunteers and five patients with carotid artery occlusion. Regional CBF was reduced compared to normal in regions from SAH patients with and without vasospasm as well as with ipsilateral carotid occlusion (*P*<0.0001). Regional oxygen extraction fraction was higher during...
vasospasm and distal to carotid occlusion than both normal and SAH without vasospasm ($P < .0001$). Regional CBV was reduced compared to normal in regions with and without spasm, whereas it was increased ipsilateral to carotid occlusion ($P < .0001$). These findings of reduced parenchymal CBV during vasospasm under similar conditions of tissue hypoxia that produce increased CBV in patients with carotid occlusion provide evidence that parenchymal vessels distal to arteries with angiographic spasm after SAH do not show normal autoregulatory vasodilation.

**AB-14204-98**

**Objectives**—Clinical data and neuroradiological findings of 19 patients with 20 vertebral artery dissections were analysed to describe the features of time of flight magnetic resonance angiography (MRA) for the diagnosis and follow up of this vascular disorder.

**Methods**—All patients underwent a combined MRI and MRA protocol with 1.5 T scanners, using a three dimensional flow compensated gradient echo sequence for MRA. Duplex sonography was performed on all patients and selective angiography was available from 17 vertebral artery dissections.

**Results**—MRI showed ischaemic lesions of the brain in 18 of 19 patients (95%). In the acute and subacute stage, MRA detected signal abnormalities within the dissected vertebral artery in 94% (16/17) and MRI was specific for a dissection in 29% (5/17). Sensitivity of selective angiography was 100% and specificity was 35% (6/17). Combination of the results of both methods increased the specificity to 50%. Duplex sonography was sensitive in 75% (15/19), but lacked specific results. Follow up magnetic resonance in 16 patients showed recanalisation of the dissected vessel in 10 (63%), persistent occlusion in five (31%), and a dissecting aneurysm in one (6%) patient.

**Conclusions**—Magnetic resonance improves the triage for selective angiography and discloses complementary information for the diagnosis of vertebral artery dissection. If magnetic resonance identifies a double dissected vessel in 10 (63%), persistent occlusion in five (31%), and a dissecting aneurysm in one (6%) patient.

**Neurosonology**

**AB-14205-98**

This study prospectively compared the accuracy of published duplex ultrasonographic criteria for 70%–99% internal carotid artery (ICA) stenosis according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method to determine angiographic stenosis. From March 1, 1995 to December 1, 1995, all patients considered for carotid endarterectomy (CEA) were studied with carotid duplex ultrasound and carotid angiography within 1 month of the ultrasound study. Duplex measurements of ICA peak systolic velocity (PSV), end diastolic velocity (EDV), and ratio of the ICA to common carotid artery (CCA) PSVs were recorded. Degree of stenosis on angiography was determined using NASCET criteria. A MEDLINE search to identify duplex ultrasound criteria to predict NASCET defined 70%–99% ICA stenosis was carried out. In addition, the original University of Washington criteria for critical stenosis (>80%) was also examined. The accuracy of these criteria was determined with angiographic results and the positive predictive value (PPV) of each criterion were compared. Ninety-nine patients with 185 carotid bifurcations were available for comparison. The different duplex criteria for determining NASCET defined 70%–99% ICA stenosis were: ICA PSV $> 175$ cm/sec or PSV $< 40$ cm/sec, PSV $> 230$ cm/sec, ratio of ICA to CCA PSVs $> 4$, PSV $> 130$ cm/sec plus EDV $> 100$ cm/sec, and PSV $> 270$ cm/sec plus EDV $> 110$ cm/sec. When compared with angiography, the calculated PPVs for these criteria were 71% (73/103), 81% (71/88), 86% (67/78), 88% (62/70), and 90% (57/63), respectively. The University of Washington criteria for critical stenosis (PSV $> 125$ cm/sec plus EDV $> 135$ cm/sec) had the highest PPV at 91.6% (55/60). The University of Washington criteria for critical stenosis had the highest PPV to predict a 70%–99% angiographic stenosis.

**AB-14206-98**

The morbidity and cost of conventional angiography (CA) have focused recent efforts in cerebrovascular imaging upon the exclusive use of noninvasive techniques. Our purpose was to prospectively evaluate carotid magnetic resonance angiography (MRA) and to compare its accuracy with color-flow duplex (CFD). Fifty patients were prospectively evaluated with CA and MRA after clinical and CFD findings indicated the need for carotid angiography. CFD measurements of peak systolic velocity (PSV) and end-diastolic velocity (EDV) were made. MRA results were categorized as 0%–39%, 40%–59%, 60%–79%, or 80%–99% stenosis or occluded. Determination of percent carotid stenosis by CA was made as in the North American Symptomatic Carotid Endarterectomy Trial (NASCET). Using receiver operating characteristic (ROC) curves, the probability of correctly predicting a $\geq 60$% stenosis using various CFD thresholds and MRA was assessed. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) in determining $\geq 60$% stenosis were estimated. For MRA the sensitivity was 85% (95% Confidence Interval [CI] = 69%–94%), specificity 70% (CI = 56%–81%), PPV 68% (CI = 53%–80%), and NPV 86% (CI = 72%–94%). For CFD the sensitivity was 89% (CI = 74%–96%), specificity 93% (CI = 82%–98%), PPV 89% (CI = 74%–96%), and NPV 93% (CI = 82%–98%). When MRA and CFD results were concordant (n = 64), the sensitivity was 100% (CI = 89%–100%), specificity 95% (CI = 81%–99%), PPV 94% (CI = 77%–99%), and the NPV was 100% (CI = 92%–100%). The area under the ROC curve for CFD was 95%, compared to 83% for MRA (p = 0.0005). We conclude that the low specificity of MRA precludes its use as the definitive imaging modality for carotid stenosis. The 93% specificity of CFD alone warrants its consideration as a definitive carotid imaging study. By ROC curve analysis, CFD offers superior accuracy to MRA. Our data support noninvasive preoperative carotid imaging for detecting a threshold stenosis of $\geq 60$% whether CFD is used alone, or in combination with the selective use of MRA.

**Pharmacology / Therapeutics**

**AB-14207-98**

**Background**—Vitamin K deficiency may be associated with osteoporosis.

**Objective**—To assess the effects of warfarin on bone.

**Design**—Prospective observational study.

**Setting**—Four centers in the United States.

**Participants**—6201 elderly, postmenopausal women.
Measurements: Self-reported warfarin use, bone mineral density at the hip and the heel, hip bone loss over 2 years, and fractures during 3.5 years of follow-up. Analyses were adjusted for baseline differences, age, weight, and estrogen use.

Results: Compared with warfarin nonusers (n=6052), warfarin users (n=149) more frequently had poor health, involuntary weight loss, nonhaematide use, and frailty but had similar bone mineral density at the hip (difference, 1.6% [95% CI, −0.7% to 4.1%]) and heel (difference, 2.1% [CI, −1.6% to 5.6%]). Users and nonusers had similar rates of bone loss (1.1% and 0.8%; P=0.18) and fractures (relative hazard, 1.0 [CI, 0.60 to 1.7]).

Conclusion: In this population, warfarin use did not decrease bone mineral density or increase fracture rates.


The effects of estrogen on cardiovascular risk factors have been less well defined in men than in women. We measured lipid and lipoprotein concentrations, lipoprotein particle size distributions, lipoprotein (a), homocysteine, and markers of thrombosis and fibrinolysis in 22 healthy elderly men (age 74±3 years, mean ±S.D.) before and after 9 weeks of treatment with 0.5, 1 or 2 mg day of oral micronized 17β-estradiol, LDL-C (−6%), apo B (−9%), triglyceride (−5%), and homocysteine (−11%) concentrations decreased with estradiol, whereas HDL-C (+14%) increased. Intermediate-size VLDL subclass concentrations were lowered and LDL and HDL subclass levels altered in such a way of to cause average LDL and HDL particle size to increase. Lipoprotein (a) did not change. Fibrinogen (−13%) and plasminogen activator inhibitor-1 (PAI-1) concentrations (−26%) decreased, but there were no changes in thrombotic markers including thrombin-antithrombin III complex, prothrombin fragment 1.2, D-dimer, antithrombin activity, protein-C and S and von Willebrand factor antigen. Breast tenderness occurred in four men and heartburn in five but did not require discontinuation of treatment. We conclude that oral estrogen in men reduces homocysteine, fibrinogen, and PAI-1 concentrations and favorably influences VLDL, LDL and HDL subclass levels without increasing markers of thrombotic risk.


Background and Purpose: Lubeluzole is a benzothiazole derivative that has shown neuroprotective properties in different experimental models. This multicentre, double-blind, placebo-controlled trial was conducted to assess the safety and efficacy of lubeluzole in patients with an acute ischaemic stroke. Methods: Patients who presented with clinical signs and symptoms of acute cerebral hemispheric ischaemic stroke were randomised to intravenous therapy with placebo (n=360) or lubeluzole 7.5 mg over 1 h followed by 10 mg/day for up to 5 days (n=365). Treatment was initiated within 6 h of symptom onset. Mortality at 12 weeks was the primary end point. Secondary end points included neurological status (European Stroke Scale), functional outcome (Barthel Index), and disability level (Rankin Scale). The primary and secondary end points were all analysed using the protocol-defined Cochran-Mantel-Haenszel’s general association test. An additional analysis, the logistic regression approach, that included risk factors of age, baseline stroke severity and their interactions with treatment, was used to analyze outcome measures at 3 months. Results: In the total ischaemic stroke population, the overall mortality rate at 3 months was similar for lubeluzole (21.0%) and placebo (21.4%). The logistic regression model confirmed the effect of age on mortality risk, but showed that this was independent of treatment. Treatment benefit was related to stroke severity, as determined by the Clinical Global Impression rating, that is a pronounced clinically significant reduction in mortality was noted in the lubeluzole-treated patients for whom stroke severity was mild to moderate, but not in those for whom it was severe. This was found on the basis of a post hoc analysis not specified in the hypothesis. Lubeluzole did not increase morbidity among stroke survivors, as measured by the European Stroke Scale, Barthel Index and Rankin Scale. No safety concerns were seen with lubeluzole treatment. Conclusions: In the overall study population, treatment with intravenous lubeluzole within 6 h of the onset of ischaemic stroke did not affect mortality or clinical outcome. Among patients with mild to moderate ischaemic stroke, lubeluzole decreased mortality without increasing morbidity.


Background Our objective was to assess the risks and benefits of carotid endarterectomy, primarily in terms of stroke prevention, in patients with recently symptomatic carotid stenosis.

Methods This multicentre, randomised controlled trial enrolled 3024 patients. We enrolled men and women of any age, with some degree of carotid stenosis, who within the previous 6 months had had at least one transient or mild symptomatic ischaemic vascular event in the distribution of one or both carotid arteries. Between 1981 and 1994, we allocated 1811 (60%) patients to surgery and 1213 (40%) to control (surgery to be avoided for as long as possible). Follow-up was until the end of 1995 (mean 6.1 years), and the main analyses were by intention to treat.

Findings The overall outcome (major stroke or death) occurred in 669 (37.0%) surgery-group patients and 442 (36.5%) control-group patients. The risk of major stroke or death complicating surgery (7.0%) did not vary substantially with severity of stenosis. On the other hand, the risk of major ischaemic stroke ipsilateral to the unoperated symptomatic carotid artery increased with severity of stenosis, particularly above about 70–80% of the original luminal diameter, but only for 2–3 years after randomisation. On average, the immediate risk of surgery was worth trading off against the long-term risk of stroke without surgery when the stenosis was greater than about 80% diameter; the Kaplan-Meier estimate of the frequency of a major stroke or death at 3 years was 26.5% for the control group and 14.9% for the surgery group, an absolute benefit from surgery of 11.6%. However, consideration of variations in risk with age and sex modified this simple rule based on stenosis severity. We present a graphical procedure that should improve the selection of patients for surgery.

Interpretation Carotid endarterectomy is indicated for most patients with a recent non-disabling carotid-territory ischaemic event when the symptomatic stenosis is greater than about 80%. Age and sex should also be taken into account in decisions on whether to operate.


BACKGROUND: Anticoagulant-related hemorrhage occurs with an incidence of approximately 1%/patient-year in mechanical heart valve recipients. Intracranial hemorrhage poses a difficult clinical choice; continuing anticoagulation therapy may enlarge the volume of the hemorrhage, early reinstitution of anticoagulation therapy may predispose patients to recurrence, and reversal of anticoagulation therapy may place patients at risk for systemic embolization involving the brain. The risk of embolization may also be greater for patients with atrial
fibrillation, cage-ball valves in the mitral position, and reduced ventricular function. This dilemma exists because of a lack of data for a large series of patients.

METHODS: We reviewed the medical records and neuroimaging studies for a consecutive group of patients admitted with intracranial hemorrhage and mechanical heart valves. We reviewed neurological presenting data, cardiac risk factors for systemic embolization (atrial fibrillation, enlarged atrial chambers, reduced ventricular function, and the type and location of the metallic valve), and hospital management.

RESULTS: We studied 39 patients with intracranial hemorrhage and mechanical heart valves (median age, 69 yr). Four patients had experienced previous transient ischemic attacks or minor strokes. The time from valve replacement to intracranial hemorrhage ranged from 2 months to 19 years (median, 6 yr). The type of intracranial hemorrhage was acute subdural hematoma (n = 20), lobar hematoma (n = 10), subarachnoid hemorrhage (n = 4), cerebellar hematoma (n = 3), or basal ganglionic hematoma (n = 2). Thirteen patients died within 2 days of admission. All 26 surviving patients received fresh frozen plasma and vitamin K. Fifteen patients underwent evacuation of acute subdural hematoma, and in one patient an anterior communicating aneurysm was clipped. The duration of discontinuation of anticoagulation therapy varied from 2 days to 3 months (median, 8 d). None of the patients developed transient ischemic attacks, ischemic strokes, valve thrombosis, or systemic embolization. No recurrence of intracranial hemorrhaging was observed during hospitalization and reinstitution of anticoagulation or antplatelet agent administration.

CONCLUSION: Temporary interruption of anticoagulation therapy seems safe for patients with intracranial hemorrhage and mechanical heart valves but without previous evidence of systemic embolization. For most patients, discontinuation for 1 to 2 weeks should be sufficient to observe the evolution of a parenchymal hematoma, to clip or coil a ruptured aneurysm, or to evacuate an acute subdural hematoma.

Surgery

AB-14212-98

Background. A time-dependent decline in cerebral blood flow (CBF) has been reported in cardiac surgical patients despite stable pump flows and arterial carbon dioxide tension. Other studies have failed to support these hypothermic cardiopulmonary bypass (CPB) results, showing preservation of CBF during CPB. The purpose of the study was to define the influence of mildly hypothermic CPB duration on CBF.

Methods. Cerebral blood flow was measured using xenon-133 washout and alpha-stat blood gas management during nonpulsatile CPB. Cerebral blood flow measurements were made after the initiation of CPB and near the end of bypass during pump flows of 2.4 L·min⁻¹·m⁻². Results. Fifty-two coronary bypass patients were studied. The average time between CBF measurements was 54 ± 20 minutes (mean ± standard deviation), with a range of 10 to 100 minutes. Temperature and arterial carbon dioxide tension were controlled: (1) after the initiation of CPB, temperature was 35.5 ± 0.4°C and carbon dioxide tension was 37 ± 2.8 mm Hg; whereas near the end of bypass temperature was 35.6 ± 0.5°C and carbon dioxide tension was 36 ± 2.3 mm Hg. We found no correlation between CBF and time on CPB (p = 0.47; r = 0.10), in contrast to other studies suggesting that CPB duration may intrinsically affect CBF.

Conclusions. Our experimental results include the following: (1) during mildly hypothermic bypass, CBF does not decrease in relation to time and (2) cerebral flow-metabolism coupling is intact at 35°C.

AB-14213-98

Purpose: The EVEREST Trial was designed to determine whether the surgical technique influences the durability and complications of carotid endarterectomy (CEA). The current report focuses on the study design and preliminary results.

Methods: EVEREST is a randomized multicenter trial. A total of 1353 patients with carotid stenosis requiring surgical treatment were randomly assigned to receive standard (n = 675) or eversion (n = 678) CEA. Primary end points included carotid occlusion, major stroke, death, and restenosis rate.

Results: The rate of perioperative major stroke and death (1.3 for each study group) and the incidence of early carotid occlusion (0.6% for eversion vs 0.4% for standard) were similar. No significant differences were found between eversion and standard CEA with respect to incidence of perioperative transient ischemic accident, minor stroke, cranial nerve injuries, neck hematoma, myocardial infarction, or surgical defects as detected with intraoperative quality controls. Clamping time was significantly shorter for eversion CEA compared with patch standard procedures (31.7 ± 15.9 vs 34.5 ± 14.4 minutes, p = 0.02). A shunt was inserted in 11% of patients undergoing eversion CEAs and in 16% of patients undergoing standard procedures. Overall 30-day events occurred in 13.3% of the eversion group and in 11.4% of the standard group (p = 0.3). At a mean follow-up of 14.9 months (range, 1 to 38 months), 16 (2.4%) restenoses occurred in the eversion group and 28 (4.1%) occurred in the standard group (odds ratio, 0.56; 95% confidence interval, 0.3 to 1.1; p = 0.08).

Conclusion: The preliminary results of the EVEREST Trial suggest that eversion CEA is a safe and rapid procedure with low major complication rates. No significant differences in restenosis rates were observed between eversion and standard CEA at the available follow-up. Longer-term results are necessary to assess whether the eversion technique influences the durability of CEA.

AB-14214-98

OBJECTIVE: The aim of this study was to retrospectively analyze the reasons for the failure of radiosurgical treatment of cerebral arteriovenous malformations (AVMs).

METHODS: Seventeen cases of noncured AVMs were reviewed 3 years after radiosurgical treatment. Follow-up ranged from 33 to 54 months (mean, 44.3 mo). Lesion dimensions varied from 9 to 55 mm (mean, 29.2 mm). The lesions were located in critical or near-critical brain regions. Angiography was performed under Talairach’s stereotactic conditions. Two large AVMs bled 36 and 39 months after receiving irradiation, respectively. These two AVMs had been incompletely irradiated.

RESULTS: Retrospectively, in four cases (23.5%) we observed errors in determining AVM target shape and size because of inaccurate definition of the nidus and/or because of stereotangiographic incompleteness (absence of external carotid artery injections). In five large and/or irregularly shaped AVMs (29.4%), a strategy of partial volume irradiation had been used. In one patient (5.8%), we observed the recanalization of previously embolized AVMs. In another case (5.8%), the target had been partially missed. The AVMs in one case (5.8%) had been treated with an ineffective peripheral dose. In one (5.8%), the failure occurred
because of the lesion angio-architecture. In four cases (23.5%), no evident reasons for failure were determined.

CONCLUSION: The results of this study suggest the necessity of complete irradiation of the nidus. The strategy of partial volume irradiation might be avoided, even if it necessitates lowering the doses to treat large AVMs. Accuracy in the target determination is required, and complete stereoangiography is necessary.

AB-14215-98

OBJECTIVE: The goal of this study was to evaluate the pathological changes associated with radiation treatment (stereotactic radiosurgery or conventional irradiation) of angiographically occult vascular malformations (AOVMs).

METHODS: Eleven patients underwent surgical resection of an AOVM in the mesial temporal lobe, brain stem, thalamus, or basal ganglia after previous radiation treatment. The indications for surgery were recurrent symptomatic bleeding from the lesion in 10 patients and recurrent intractable seizures in 1 patient. Radiation was used as the initial therapy because the risk of surgical resection was deemed too high. Three patients received conventional radiation therapy of 3000 to 5400 rads at an outside institution. One patient received radiosurgery with the gamma knife at another institution using a dose of 15 Gy to the margin. The remaining 7 patients received stereotactic radiosurgery with a helium-ion particle beam. The dose range was from 18 to 26 Gy equivalents. The interval from radiation to surgical resection ranged from 1 to 10 years, with a mean of 3.5 years. These lesions were compared with 10 nonirradiated cavernous malformations.

RESULTS: One irradiated lesion was identified pathologically as a true arteriovenous malformation despite being angiographically occult. This lesion did not demonstrate significant changes in the vasculature but did have radiation necrosis of the surrounding brain 5 years after 25 Gy equivalents of helium-ion radiosurgery. Two other specimens were too small to identify the type of vascular malformation adequately. Of the remaining eight malformations identified as cavernous malformations, six showed a combination of marked fibrosis of the vascular channels, fibrinoid necrosis, and ferrugination. However, the fibrinoid necrosis was the only finding unique to the irradiated lesions compared with nonirradiated controls. All the irradiated lesions still had patent vascular channels; none were completely thrombosed.

CONCLUSION: Radiosurgery or conventional radiation therapy did not cause histologic vascular obliteration in intracranial AOVMs evaluated 1 to 10 years (mean 3.5 yr) after radiation delivery. It should be recognized that these patients are irradiation failures who may not be representative of all irradiated patients. However, recurrent bleeding from AOVMs may relate to poor radiation response in some patients.

AB-14216-98

PURPOSE: To evaluate the long-term results of irradiation alone or of embolization with or without irradiation in patients with dural carotid cavernous fistulas (DCCFs).

MATERIALS AND METHODS: Between 1984 and 1996, symptomatic DCCFs in 26 patients were treated by using irradiation alone (protocol 1, \( n = 12 \)) before April 1988 and by using embolization as an initial treatment (protocol 2, \( n = 14 \)) during and after April 1988. When angiography showed no improvement after embolization, irradiation was added (\( n = 6 \)). On the basis of drainage flow speed, DCCFs were classified as fast, medium, or slow.

RESULTS: With irradiation alone, all six patients with slow- to medium-type DCCFs had cure with a mean follow-up of 62 months. Four of six patients with fast-type DCCFs had cure or improvement, but the remaining two had no change. In the embolization group, irradiation was added in six patients with fast-type DCCFs. With a mean follow-up of 24 months, four of the six patients had cures, one had improvement, and one had no clinical change. Those who underwent protocol 2 had cures significantly earlier than those who underwent protocol 1 (\( P < .05 \)).

CONCLUSION: Conventional radiation therapy resulted in cure of DCCFs in nine (75%) of the 12 patients and in improvement of signs and symptoms in one (8%). Fast-type DCCFs may not always be improved. Radiation therapy may be useful in DCCFs after embolization.
Abstracts of Literature
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