Cerebral Aneurysms

**AB-14455-99**


**Object.** Findings from previous multicenter clinical trials have suggested that tirilazad mesylate, a synthetic nonnaluronal 21-aminosteroid, might be effective in preventing delayed cerebral ischemia following subarachnoid hemorrhage (SAH). This beneficial effect, however, was greater in males than females, possibly because of gender-related pharmacokinetic differences. The authors sought to assess the effects of administering a larger dose of tirilazad in women with SAH.

**Methods.** To test the efficacy of a higher tirilazad mesylate dose in female patients, a prospective randomized, double-blind, vehicle-controlled trial was conducted at 56 neurosurgical centers in Europe, Australia, New Zealand, and South Africa. Eight hundred ninety patients were randomly assigned to receive either 15 mg/kg/day of tirilazad mesylate or a placebo containing the citrate vehicle. The two groups were similar in prognostic factors for delayed cerebral ischemia and overall outcome. High-dose tirilazad appeared to be well tolerated because no differences in the incidence of untoward medical events were noted between the two groups. Medical and surgical interventions were no different in the two treatment groups except for hyodynamic therapy (intentional hypervolemia, induced hypertension, and/or hemodilution), which was more often used in the placebo-treated group to counteract symptomatic vasospasm (24% of patients given placebo compared with 18% of patients given tirilazad, p = 0.02).

Mortality rates and overall outcome, assessed using the Glasgow Outcome Scale at 3 months post-SAH, were not different between the two groups, despite a significantly lower incidence of delayed cerebral ischemia in patients given tirilazad. Post hoc subgroup analysis by neurological grade also did not reveal significant differences in outcome, although a trend toward a lower mortality rate favoring the study drug was present in patients with neurological Grade IV and V at admission (32% compared with 37%). Symptomatic vasospasm occurred in 33.7% of the placebo-treated patients as opposed to 24.8% of the patients who were given tirilazad (p = 0.005). The severity of symptomatic vasospasm was also attenuated by administration of the study drug (severe symptomatic vasospasm was reported in 11% of the placebo-treated patients compared with 6% of patients in the tirilazad-treated group (p = 0.008). Clinical cerebral infarction from vasospasm was also reduced from 13% in the vehicle-treated group to 8% in the tirilazad-treated group (p < 0.04).

**Conclusions.** The authors conclude that high-dose tirilazad mesylate is well tolerated in women with aneurysmal SAH. Although a significant reduction in the incidence of symptomatic vasospasm was observed in the treatment group, the primary end point (mortality rate at 3 months post-SAH) was not affected by the study drug. The use of other potentially effective rescue therapies (that is, hypervolemia, hemodilution, and induced hypertension) to counteract vasospasm may have been responsible for these contrasting observations between the two groups.


**Object.** Endoglin, a transforming growth factor β-binding protein, is a glycoprotein expressed on the surface of human vascular endothelial cells. Mutations of this gene are responsible for hereditary hemorrhagic telangiectasia and are associated with sporadic intracerebral hemorrhage as a risk factor. The purpose of this study was to examine the polymorphism of this gene in patients with intracranial aneurysms.

**Methods.** The authors identified the mutations and insertion polymorphism around exon 7 of the endoglin gene in 82 patients with intracranial saccular aneurysms (aneurysm group) and 114 control volunteers (control group).

The abstracts in this section have been typeset for consistency with journal format but otherwise appear as in the original articles.
A 6-base insertion (GGGGGA) was found in intron 7 at 26 bases beyond the 3’ end of exon 7. The homozygous insertion of intron 7 of the gene was present in 20.7% of the aneurysm group compared with 6.1% of the control group ($\chi^2=9.837$, $p=0.0073$). The insertion allele frequency was significantly higher in the aneurysm group (67 [40.8%] of 164) than that in the control group (63 [27.6%] of 228) ($\chi^2=7.48$, $p=0.0062$). The most notable clinical characteristic of the 17 patients with homozygous insertion in the aneurysm group was the relatively high percentage of patients with hypertension and of those with multiple aneurysms.

**Conclusions.** The data provide evidence of an association between aneurysm development and a polymorphism at a genetic variant of *endoglin* in patients with these lesions.

AB-14458-99


**Objective:** To determine which unruptured cerebral aneurysms should be treated considering the risks, benefits, and costs. **Background:** Asymptomatic unruptured cerebral aneurysms are commonly treated by surgical clipping or endovascular coil embolization to prevent subarachnoid hemorrhage (SAH). **Methods:** We performed a cost-utility analysis comparing surgical clipping and endovascular coil embolization with no treatment for unruptured aneurysms. Eight clinical scenarios were defined based on aneurysm size, symptoms, and history of SAH from a different aneurysm. Health outcomes of a hypothetical cohort of 50-year-old women were modeled over the projected lifetime of the cohort. Costs were assessed from the societal perspective. We compared net quality-adjusted life years (QALYs) and cost per QALY of each therapy to no treatment. **Results:** For an asymptomatic unruptured aneurysm less than 10 mm in diameter in patients with no history of SAH from a different aneurysm, both procedures resulted in a net loss in QALYs, and confidence intervals (CI) were not compatible with a benefit from treatment (clipping, loss of 1.6 QALY [95% CI 1.1 to 2.1]; coiling, loss of 0.6 QALY [95% CI 0.2 to 0.8]). For larger aneurysms ($\geq10$ mm), those producing symptoms by compressing neighboring nerves and brain structures, or in patients with a history of SAH from a different aneurysm, treatment was cost-effective. Coiling appeared more effective and cost-effective than clipping but these differences depended on relatively uncertain model parameters. **Conclusions:** Treatment of small, asymptomatic, unruptured cerebral aneurysms in patients without a history of SAH worsens clinical outcomes, and thus is neither effective nor cost-effective. For aneurysms that are $\geq10$ mm or symptomatic, or in a patient with a history of SAH, treatment appears to be cost-effective.

AB-14459-99


**Purpose:** To determine which unruptured cerebral aneurysms should be treated considering the risks, benefits, and costs. **Background:** Asymptomatic unruptured cerebral aneurysms are commonly treated by surgical clipping or endovascular coil embolization to prevent subarachnoid hemorrhage (SAH). **Methods:** We performed a cost-utility analysis comparing surgical clipping and endovascular coil embolization with no treatment for unruptured aneurysms. Eight clinical scenarios were defined based on aneurysm size, symptoms, and history of SAH from a different aneurysm. Health outcomes of a hypothetical cohort of 50-year-old women were modeled over the projected lifetime of the cohort. Costs were assessed from the societal perspective. We compared net quality-adjusted life years (QALYs) and cost per QALY of each therapy to no treatment. **Results:** For an asymptomatic unruptured aneurysm less than 10 mm in diameter in patients with no history of SAH from a different aneurysm, both procedures resulted in a net loss in QALYs, and confidence intervals (CI) were not compatible with a benefit from treatment (clipping, loss of 1.6 QALY [95% CI 1.1 to 2.1]; coiling, loss of 0.6 QALY [95% CI 0.2 to 0.8]). For larger aneurysms ($\geq10$ mm), those producing symptoms by compressing neighboring nerves and brain structures, or in patients with a history of SAH from a different aneurysm, treatment was cost-effective. Coiling appeared more effective and cost-effective than clipping but these differences depended on relatively uncertain model parameters. **Conclusions:** Treatment of small, asymptomatic, unruptured cerebral aneurysms in patients without a history of SAH worsens clinical outcomes, and thus is neither effective nor cost-effective. For aneurysms that are $\geq10$ mm or symptomatic, or in a patient with a history of SAH, treatment appears to be cost-effective.

AB-14460-99


**Objectives:** To determine (1) the incidence of microalbuminuria in patients with recent ischemic stroke, (2) its relationship to risk factors for stroke, (3) its prevalence in the major subtypes of ischemic stroke, and (4) its potential for identifying patients at increased risk for recurrent stroke, myocardial infarction, or vascular death. **Design:** Prospective case-control study. **Setting:** Outpatient clinics at the medical centers affiliated with the Department of Veterans Affairs and Oregon Health Sciences University in Portland, Ore. **Patients:** A total of 186 older men and women (median age, 65 years) who were enrolled in a prospective study of risk factors for recurrent stroke, including 97 patients with recent (6–8 weeks) ischemic stroke, 51 with similar clinical risk factors for stroke, including 24 with a history of remote stroke or transient ischemic attack, and 38 community-dwelling volunteers. **Results:** Microalbuminuria was 3 times more prevalent in patients with recent stroke (29%) than in those with clinical risk factors for stroke (10%), and was undetectable in healthy elderly controls ($P<.001$). The presence of microalbuminuria in recent stroke as well as in the combined recent and remote stroke or transient ischemic attack group ($n=121$) was predicted by diabetes (odds ratio [OR], 8.4; 95% confidence interval [CI], 2.6–27.0; $P<.001$; serum albumin levels (OR, 0.12; 95% CI, 0.03–0.50; $P<.005$); age (OR, 1.1; 95% CI, 1.0–1.2; $P<.01$), and ischemic heart disease (OR, 3.9; 95% CI, 1.0–9.1; $P=0.05$). Among patients with recent stroke the prevalence of microalbuminuria did not differ among major ischemic stroke subtypes, ie, atheroembolic, 23%; cardioembolic, 30%; and lacunar, 33%. During a mean $\pm SD$ of 1.5 $\pm 0.9$ years of follow-up, 20% of patients with recent stroke, 14% with risk factors for stroke, and 0% of healthy elderly volunteers had vascular end points ($P<0.004$), with events being as frequent in patients with microalbuminuria (32%) as in patients with macroalbuminuria (33%). After controlling for major clinical risk factors, microalbuminuria remained an independently significant predictor of future stroke in the combined recent stroke and remote stroke or transient ischemic attack group (Cox proportional hazard ratio, 4.9; 95% CI, 1.4–17.6; $P<.01$). **Conclusions:** Microalbuminuria is a common finding in patients with cerebrovascular disease and is associated with increased risk for stroke even after correction for the presence of confounding clinical risk factors. This data suggest that microalbuminuria merits further examination as a potentially inexpensive and easily measured marker of increased risk for stroke.

AB-14461-99

We prospectively determined the frequency of vocal cord paresis (VCP) among first-ever acute ischemic stroke patients. Vocal cords were examined endoscopically within 48 h of stroke onset, at 1 week and 1 month. Of the 54 study patients, 64.8% had lacunar (group 1), 22.2% cortical/lobe subcortical (group 2), 9.3% lateral medulla (group 3) and 3.7% other brainstem (group 4) infarcts. VCP was found in 11 (20.4%): 11.4% of group 1, 16.4% of group 2, 100% of group 3 and 0% of group 4. VCP was contralateral to the brain lesion in groups 1 and 2, and ipsilateral in 80% of group 3. VCP was strongly correlated with dysphonia (p<0.0001) and resolved in 2/11 patients after 1 week and in 5/11 after 1 month. Our finding of VCP among acute ischemic stroke patients questions the belief that the nucleus ambiguous is invariably bilaterally innervated by supranuclear centers.

**AB-14462-99**

**Neurological Complications After Cardiopulmonary Bypass: An Update**

**Introduction:** Neurological complications are, at the present time, considered among the most important causes of morbidity and mortality after heart surgery. We evaluated their importance and risk factors.

**Patients and Methods:** We retrospectively reviewed 2,528 consecutive patients who underwent cardiopulmonary bypass in a single center. In each one, we attended to previous vascular risk factors, such as surgical and postoperative events. We considered four categories of neurologic outcome: (1) persistent neurological focal deficits, (2) stupor or coma, (3) temporary neurological focal deficits, and (4) seizures. We carried out univariate and multivariate statistical analysis, looking for predictors of adverse neurologic events.

**Results:** Neurological complications occurred in 76 patients (3%); 36 of them (47%) had persistent neurological focal deficits, 18 (24%) stupor or coma, 18 (24%) temporary neurological focal deficits, and 27 (36%) seizures. Twenty-two patients with cerebral adverse outcomes died (29%), the overall mortality among the 2,528 cases being 5%. Predictors of risk were aortic aneurysm and aortic valve surgery, advanced age, female sex, and the use of intra-aortic balloon pump. A longer hospitalization time was noticed among patients with neurological side effects.

**Discussion:** Neurological complications are common and serious after heart surgery, as we have noticed with this series, the largest up to now, according to our review of the literature. They increase perioperative mortality and hospitalization time. Neurological morbidity and risk factors in our study are similar to those previously published.

**AB-14463-99**

**Predicting Deterioration in Patients With Lobar Haemorrhages—**

**Objective:** To study the clinical course and determine predictors of deterioration in patients with lobar haemorrhages.

**Methods:** A comprehensive review of 61 consecutive patients with lobar haemorrhages was performed. Neurological deterioration was defined as (1) decrease in Glasgow coma sum score by 2 points, (2) new lobar haemorrhages was performed. Neurological deterioration was defined as (1) decrease in Glasgow coma sum score by 2 points, (2) new neurological deficit, or (3) clinical signs of brain herniation. A univariate logistic regression was performed and expressed in odds ratios.

**Results:** Sixteen of 61 (26%) patients with lobar haemorrhages deteriorated after admission. In a univariate analysis, only a Glasgow coma score <14 predicted deterioration (75% of deteriorators v 24% who did not deteriorate; p<0.0001). Initial CT characteristics predictive of deterioration included haemorrhage volume >60 ml (63% v 16%, p<0.0001), shift of the septum pellucidum (75% v 36%, p<0.01), effacement of the contralateral ambient cistern (33% v 0%, p<0.0001), and widening of the contralateral temporal horn (50% v 0%, p<0.0001). Patients presenting and deteriorating within 12 hours of ictus declined due to enlargement of the haemorrhage. Those who deteriorated more than 12 hours after initial neurological symptoms, showed increased mass effect secondary to oedema.

**Conclusion:** Patients with lobar haemorrhages presenting immediately after ictus are at risk for deterioration from enlargement of the haemorrhage and predictors of deterioration may be absent. Patients with large volume lobar haemorrhages presenting to the emergency department with decreased level of consciousness and shift on CT are at risk for further deterioration from worsening oedema. These patients require close observation and early aggressive management may be warranted.

**AB-14464-99**

**Potential Source of Cerebral Embolism in Migraine With Aura: A Transcranial Doppler Study—**

**Background:** The recently found association between patent foramen ovale (PFO) and transient global amnesia (TGA) has suggested that paradoxical microembolization in the terminal vertebrobasilar territory might underlie at least some TGA cases. Migraine with visual aura is another paroxysmal disturbance in which a sudden dysfunction of cortical areas fed by the terminal branches of the basal artery is believed to trigger the attack. Therefore we investigated the prevalence of PFO in a consecutive unselected cohort of migraine patients.

**Objective:** To investigate the prevalence of PFO in a consecutive unselected cohort of migraine patients to search for a possible mechanism for the reported association of migraine with stroke.

**Methods and Results:** A total of 113 patients, consecutively referred by the Headache Outpatient Clinic for migraine with aura (MA+, mean age 34±12 years) were compared with 53 patients with migraine without aura (MA−, mean age 36±13 years) and with 25 age-matched nonmigraine subjects (mean age 31±10 years) selected from the hospital staff. PFO was assessed with transcranial Doppler sonography with IV injection of agitated saline, a technique that is 90% sensitive and 100% specific. The prevalence of PFO was 48% (54/113) in MA+ patients, 23% (12/53) in MA− patients, and 20% (5/25) in control subjects. The difference between MA+ and MA− patients was significant (odds ratio [OR]=3.13, 95% confidence interval [CI]=1.41 to 7.04, χ²=9.52, p=0.002) as was the difference between MA+ patients and controls (OR=3.66, 95% CI=1.21 to 13.25, χ²=6.46, p=0.01), whereas MA− patients did not differ from controls (OR=1.17, 95% CI=0.32 to 4.45, χ²=0.07). MRI was negative in 22 MA+ and 8 MA− patients.

**Conclusions:** Patent of the foramen ovale is associated with migraine with aura but not with migraine without aura. The increased risk of stroke found in epidemiologic studies in patients with migraine with aura may be explained by an increased propensity to paradoxical cerebral embolism.

**Epidemiology**

**AB-14465-99**

**Risk Factors for Stroke in Type 2 Diabetes Mellitus—**

**Objective:** To investigate modifiable and nonmodifiable risk factors for stroke in type 2 diabetes mellitus.

**Patients and Methods:** A total of 3776 patients aged 25 to 65 years newly diagnosed as having type 2 diabetes mellitus without known cardiovascular or other serious disease were studied for a median of 7.9 years. An initial stepwise evaluation of risk factors was done in 2704 patients with all risk factors measured, with the final Cox model analysis being of 3776 patients who had complete data on the selected variables.

**Results:** Of 3776 patients, 99 (2.6%) had a stroke. Significant risk factors for stroke in a multivariate model were age (estimated hazard ratio [95% confidence interval], 4.78 [2.56–8.92] for ≥60 vs <50 years), male sex (1.63 [1.08–2.47]) vs female), hypertension (2.47
[1.64–3.74]) vs normotension), and in 3728 patients who had electrocardiography at study entry, atrial fibrillation (8.05 [3.52–18.44] vs sinus rhythm). Obesity, lack of exercise, smoking, poor glycemic control, hyperinsulinemia, dyslipidemia, and microalbuminuria were not significantly associated with stroke in the model.

Conclusion: In patients with type 2 diabetes, aggressive antihypertensive therapy and routine anticogulation therapy for atrial fibrillation may reduce the risk of stroke.

AB-14466-99

Background—Hyperhomocysteinemia has been identified as a potential risk factor for atherosclerosis. This study examined whether a modest elevation of plasma total homocysteine (tHcy) was an independent risk factor for increased carotid artery intimal-medial wall thickness (IMT) and focal plaque formation in a large, randomly selected community population. We also examined whether vitamin cofactors and the C677T genetic mutation of the methylenetetrahydrofolate reductase (MTHFR) enzyme were major contributors to elevated plasma tHcy and carotid vascular disease.

Methods and Results—In 1111 subjects (558 men, 553 women) 52±13 years old (mean±SD; range, 27 to 77 years) recruited from a random electoral roll survey, we measured fasting tHcy and performed bilateral carotid B-mode ultrasound. For the total population, mean tHcy was 12.1±4.0 μmol/L. Plasma tHcy levels were correlated with IMT (Spearman rank r = 0.31, P = 0.0001). After adjustment for age, sex, and other conventional risk factors, subjects in the highest versus the lowest quartile of tHcy had an odds ratio of 2.60 (95% CI, 1.51 to 4.45) for other conventional risk factors, subjects in the highest versus the lowest quartile of tHcy had an odds ratio of 2.60 (95% CI, 1.51 to 4.45) for increased IMT and 1.76 (95% CI, 1.10 to 2.82) for plaque. Serum and dietary folate levels and the C677T mutation in MTHFR were independent determinants of tHcy (all P = 0.0001). The mutant homoyzogotes (10% of the population) had higher mean tHcy than heterozygotes or those without the mutation (14.2 versus 12.3 versus 11.6 μmol/L, respectively, P = 0.0001). The inverse association of folate levels with tHcy was steeper in the mutant homoyzogotes. Despite this, the C677T MTHFR mutation was not independently predictive of increased carotid IMT or plaque formation.

Conclusions—Mild hyperhomocysteinemia is an independent risk factor for increased carotid artery wall thickness and plaque formation in a general population. Lower levels of dietary folate intake and the C677T mutation in MTHFR are important causes of mild hyperhomocysteinemia and may therefore contribute to vascular disease in the community.

AB-14467-99
Homocysteine and Risk of Cardiovascular Disease Among Post-menopausal Women—Ridker PM (Div of Cardiovascular Diseases, Brigham and Women’s Hospital, 75 Francis St, Boston, MA 02115), Manson JE, Buring JE, Shih J, Matias M, Hennekens CH—JAMA. 1999;281:1817–1821.

Context Individuals with elevated levels of homocysteine tend to have higher prevalence of cardiovascular disease. However, prospective studies of homocysteine are inconsistent and data among women are limited.

Objective To determine whether elevated homocysteine levels in healthy postmenopausal women predict risk of developing cardiovascular disease.

Design Prospective, nested case-control study with a mean 3-year follow-up.

Setting The Women’s Health Study, an ongoing US primary prevention trial initiated in 1993.

Participants From a total cohort of 28 263 postmenopausal women with no history of cardiovascular disease or cancer at baseline, 122 women who subsequently experienced cardiovascular events were defined as cases, and 244 age- and smoking status–matched women who remained free of disease during follow-up were defined as controls.

Main Outcome Measures Incidence of death due to cardiovascular disease, nonfatal myocardial infarction (MI), stroke, percutaneous transluminal coronary angioplasty, or coronary artery bypass graft by baseline homocysteine level.

Results Of the 122 cases, there were 85 events of MI or stroke and 37 coronary revascularizations. Case subjects had significantly higher baseline homocysteine levels than controls (14.1 vs 12.4 μmol/L; P = .02). Subjects with homocysteine levels in the highest quartile had a 2-fold increase in risk of any cardiovascular event (relative risk [RR], 2.0; 95% confidence interval [CI], 1.1–3.8). This effect was largely due to an excess of cases with high levels of homocysteine; the RR for those with homocysteine levels at or higher than the 95th percentile (20.7 μmol/L) was 2.6 (95% CI, 1.1–5.7). Risk estimates were independent of traditional risk factors and were greatest for the end points of MI and stroke (RR for those with baseline homocysteine levels in the top quartile, 2.2; 95% CI, 1.1–4.6). Self-reported multivitamin supplement use at study entry was associated with significantly reduced levels of homocysteine (P < .001). However, the association between increasing quartile of homocysteine level and risk of MI or stroke remained significant in analyses controlling for baseline multivitamin supplement use (P = .003 for trend), and subgroup analyses limited to women who were (P = .02 for trend) or were not (P = .04 for trend) taking multivitamin supplements.

Conclusions Among healthy postmenopausal US women, elevated levels of homocysteine moderately increased the risk of future cardiovascular disease. Whether lowering the homocysteine level reduces risk of cardiovascular events requires testing in randomized controlled trials.

AB-14468-99

Objective To determine the relative risk (RR) of intracerebral hemorrhage (ICH) among African Americans compared with that among whites. Methods: Data from the First National Health and Nutrition Examination Survey Epidemiologic Follow-up Study were used to determine the incidence of ICH (n=78) in 10,851 whites and 1,802 African Americans during a 20-year follow-up period. Cox proportional hazards analyses were used to determine the RR of ICH among African Americans compared with that among whites. Results: The estimated annual incidence of ICH was 50 per 100,000 among African Americans and 28 per 100,000 among whites. The age- and sex-adjusted RR for ICH among African Americans was 1.9 (95% confidence interval [CI], 1.1 to 3.2). With the addition of systolic blood pressure and educational attainment to the Cox proportional hazards model, the RR decreased to 1.6 (95% CI, 0.9 to 2.7). The adjustment for additional cerebrovascular disease risk factors did not change this risk estimate appreciably. Conclusions: Compared with whites, African Americans have a twofold increased risk for ICH. Most of this risk may be explained by differences in educational attainment and systolic blood pressure. Unless additional efforts are undertaken to reduce racial differences in the prevalence of stroke risk factors, mainly systolic blood pressure and socioeconomic status, the African American–white disparities in the risk for ICH will likely continue.

Experimental Pathology
AB-14469-99
Brain Injury After Cerebral Arterial Air Embolism in the Rabbit as Determined by Triphenyltetrazolium Staining—Hindman BJ
AB-14470-99

Background—The role of plasminogen system components in focal cerebral ischemic infarction (FCI) was studied in mice deficient in plasminogen (Plg

METHODS: We introduced ICH in three groups of anesthetized mongrel dogs, consisting of seven animals each, by autologous blood injection (5.5–7.5 ml) under arterial pressure in the deep white matter adjacent to the lateral ventricles. We evaluated the effect of iso- or osmolar doses (5.5 mOsM/kg) of intravenously administered mannitol (1 g/ml), 3% NaCl (5.3 ml/kg), or 23.4% NaCl (0.7 ml/kg) administered 2 hours after the introduction of hematoma, on the following: ICP, cerebral perfusion pressure, cerebral oxygen extraction and oxygen consumption, and regional cerebral blood flow in regions around and distant to the hematoma. All measurements were recorded at baseline, before treatment, and 15, 30, 60, and 120 minutes after treatment. We also evaluated

AB-14472-99

OBJECTIVE: Elevated intracranial pressure (ICP) is related to mortality after intracerebral hemorrhage (ICH). To develop effective strategies for the medical treatment of ICP in cases of ICH, we evaluated the therapeutic efficacy of mannitol and hypertonic saline in a canine model of ICH.

METHODS: We introduced ICH in three groups of anesthetized mongrel dogs, consisting of seven animals each, by autologous blood injection (5.5–7.5 ml) under arterial pressure in the deep white matter adjacent to the left basal ganglia. We evaluated the effect of iso-osmolar doses (5.5 mOsM/kg) of intravenously administered mannitol (1 g/ml), 3% NaCl (5.3 ml/kg), or 23.4% NaCl (0.7 ml/kg) administered 2 hours after the introduction of hematoma, on the following: ICP, cerebral perfusion pressure, cerebral oxygen extraction and oxygen consumption, and regional cerebral blood flow in regions around and distant to the hematoma. All measurements were recorded at baseline, before treatment, and 15, 30, 60, and 120 minutes after treatment. We also evaluated
the water content (wet/dry weight) and blood-brain barrier permeability (Evans blue method) in pathologically demarcated regions of brain.

RESULTS: There was an immediate reduction in ICP (mm Hg±standard error of the mean) in the 23.4% NaCl (27.6±4 to 11.0±2 mm Hg, P=0.001), 3% NaCl (23.7±3 to 14.7±2 mm Hg, P=0.009), and mannitol (25.6±3 to 15.9±4 mm Hg, P=0.02) groups. Compared with pretreatment values, ICP was significantly lower in both the 23.4% NaCl (12.3±2 mm Hg, P=0.002) and 3% NaCl (17.6±2 mm Hg, P=0.008) groups but not in the mannitol group (18.7±4 mm Hg, P=0.08) 15 minutes after the administration of treatment. There was a gradual rise in ICP observed in the 23.4% NaCl and mannitol groups with time. Only in the 3% NaCl group was the ICP significantly lower than the pretreatment value at 120 minutes (18.0±2 mm Hg, P=0.02). A significantly higher cerebral perfusion pressure (108.4±4 versus 79.6±10 mm Hg, P=0.048) and lower water content in the lesioned white matter (65.5±1% versus 67.9±1%, P=0.07) was observed 2 hours after treatment in animals receiving 3% NaCl compared with animals receiving mannitol. There were no significant differences observed in regional cerebral blood flow, oxygen extraction, or oxygen consumption at any time point among the three groups.

CONCLUSION: Hypertonic saline, in both 3 and 23.4% concentrations, is as effective as mannitol in the treatment of intracranial hypertension observed in association with ICH. Hypertonic saline may have a longer duration of action, particularly when used in 3% solution. None of three treatment regimens influence regional cerebral blood flow or cerebral metabolism.

Imaging

AB-14473-99

BACKGROUND AND PURPOSE: Patients with spontaneous intracerebral hemorrhage (ICH) frequently have small areas of signal loss on gradient-echo T2*-weighted MR images, which have been suggested to represent remnants of previous microbleeds. Our aim was to provide histopathologic support for this assumption and to clarify whether the presence and location of microbleeds were associated with microangiopathy.

METHODS: We performed MR imaging and correlative histopathologic examination in 11 formalin-fixed brains of patients who had died of an ICH (age range, 45–90 years).

RESULTS: Focal areas of signal loss on MR images were noted in seven brains. They were seen in a corticosubcortical location in six brains, in the basal ganglia/thalami in five, and infratentorially in three brains. Histopathologic examination showed focal hemosiderin deposition in 21 of 34 areas of MR signal loss. No other corresponding abnormalities were found; however, hemosiderin deposits were noted without MR signal changes in two brains. All specimens with MR foci of signal loss showed moderate to severe fibrohialnosis, and there was additional evidence of amyloid angiopathy in two of those brains.

CONCLUSION: Small areas of signal loss on gradient echo T2*-weighted images indicate previous extravasation of blood and are related to bleeding-prone microangiopathy of different origins.

AB-14474-99

Background: Diffusion-weighted MRI (DWI) represents a major advance in the early diagnosis of acute ischemic stroke. When abnormal in patients with stroke-like deficit, DWI usually establishes the presence and location of ischemic brain injury. However, this is not always the case. Objective: To investigate patients with stroke-like deficits occurring without DWI abnormalities in brain regions clinically suspected to be responsible. Methods: We identified 27 of 782 consecutive patients scanned when stroke-like neurologic deficits were still present and who had normal DWI in the brain region(s) clinically implicated. Based on all the clinical and radiologic data, we attempted to arrive at a pathophysiologic diagnosis in each. Results: Best final diagnosis was a stroke mimic in 37% and a cerebral ischemic event in 63%. Stroke mimics (10 patients) included migraine, seizures, functional disorder, transient global amnesia, and brain tumor. The remaining patients were considered to have had cerebral ischemic events: lacunar syndrome (7 patients; 3 with infarcts demonstrated subsequently) and hemispheric cortical syndrome (10 patients; 5 with TIA, 2 with prolonged reversible deficits, 3 with infarction on follow-up imaging). In each of the latter three patients, the regions destined to infarct showed decreased perfusion on the initial hemodynamically weighted MRI (HWI). Conclusions: Normal DWI in patients with stroke-like deficits should stimulate a search for nonsiechmic cause of symptoms. However, more than one-half of such patients have an ischemic cause as the best clinical diagnosis. Small brainstem lacunar infarctions may escape detection. Comitient HWI can identify some patients with brain ischemia that is symptomatic but not yet to the stage of causing DWI abnormality.
Neurosonology

**AB-14476-99**


Transcranial Doppler is routinely used to assess the cerebrovascular reactivity, despite scarce information on its reproducibility. We evaluated the reproducibility of cerebrovascular reactivity measurements by this method utilizing different vasodilatory and vasoconstrictor stimuli. The cerebrovascular reactivity was measured in 45 healthy volunteers during hypercapnia induced by inhalation of a mixture of 5% CO\textsubscript{2} and 95% O\textsubscript{2}, breath holding and rebreathing, and during hypocapnia induced by voluntary hyperventilation. Three sets of measurements were performed at times 0, 1, and 24 h to assess the within-observer short- and long-term reproducibility. The reproducibility was analyzed using the intraclass correlation coefficient. For the CO\textsubscript{2} inhalation method, a good short-term (r\textsubscript{L}=0.55; 95% CI=0.39–0.68) and a good long-term (r\textsubscript{L}=0.43; 95% CI=0.25–0.59) reproducibility was found. For the breath-holding method a good short-term agreement was found (r\textsubscript{L}=0.41; 95% CI=0.22–0.57), while the long-term reproducibility was poor (r\textsubscript{L}=0.17; 95% CI=−0.03–0.36). Rebreathing showed a fair (r\textsubscript{L}=0.31; 95% CI=0.11–0.48) short-term and a poor (r\textsubscript{L}=0.17; 95% CI=−0.03–0.36) long-term reproducibility. For voluntary hyperventilation, the short-term reproducibility was good (r\textsubscript{L}=0.53; 95% CI=0.36–0.66), and the long-term reproducibility was fair (r\textsubscript{L}=0.31; 95% CI=0.11–0.48). In our study, CO\textsubscript{2} inhalation and voluntary hyperventilation had the highest reproducibility and should be preferred when assessing cerebral vasoreactivity, especially in follow-up studies.

**AB-14477-99**


B-mode ultrasound may be used to measure the intima-media thickness (IMT) in subjects with a history of atherosclerosis. The variability between measurements depends on the subjective interpretation of ultrasonographers and readers. The two carotid arteries, subdivided in common (CCA), bulbous (BUL) and internal (ICA) of 10 men with proven coronary disease, were scanned twice by two ultrasonographers with a 1-week interval. The IMTs were measured off-line by two readers. The number of IMT measurements was 75 (94%) of 80 in the CCA, 61 (76%) of 80 in the BUL and 43 (54%) of 80 in the ICA segment. In the CCA segment, the agreement between readers (mean=0.02 mm; limits=−0.26 to +0.3 mm) and between visits for each reader separately (reader 1: mean=0.01 mm; limits=−0.33 to +0.35 mm and, reader 2: mean=0.04 mm; limits=−0.36 to +0.44 mm) was better than in the more distal segments. Therefore, it is concluded that IMT measurements are best performed in the CCA segment.

Pharmacology / Therapeutics

**AB-14478-99**

**Choosing Antithrombotic Therapy for Elderly Patients With Atrial Fibrillation Who Are at Risk for Falls**—Man-Son-Hing M (Geriatric Assessment Unit, Ottawa Hospital, 1053 Carling Ave, Ottawa, Ontario, Canada K1Y 4E9), Nichol G, Lau A, Laupacis A—*Arch Intern Med.* 1999;159:677–685.

**Objective:** To determine whether the risk of falling (with a possible increased chance of subdural hematoma) should influence the choice of antithrombotic therapy in elderly patients with atrial fibrillation.

Design: A Markov decision analytic model was used to determine the preferred treatment strategy (no antithrombotic therapy, long-term aspirin use, or long-term warfarin use) for patients with atrial fibrillation who are 65 years of age and older, are at risk for falling, and have no other contraindications to antithrombotic therapy. Input data were obtained by systematic review of MEDLINE. Outcomes were expressed as quality-adjusted life-years.

**Results:** For patients with average risks of stroke and falling, warfarin therapy was associated with 12.90 quality-adjusted life-years per patient; aspirin therapy, 11.17 quality-adjusted life-years; and no antithrombotic therapy, 10.15 quality-adjusted life-years. Sensitivity analysis demonstrated that, regardless of the patients’ age or baseline risk of stroke, the risk of falling was not an important factor in determining their optimal antithrombotic therapy.

**Conclusions:** For elderly patients with atrial fibrillation, the choice of optimal therapy to prevent stroke depends on many clinical factors, especially their baseline risk of stroke. However, patients’ propensity to fall is not an important factor in this decision.

**AB-14479-99**

**Preventing Stroke in Patients With Atrial Fibrillation**—Ezekowitz MD (Yale Clinical Trials Office, 47 College Pl, Suite 202, New Haven, CT 06511), Levine JA—*JAMA.* 1999;281:1830–1835.

**Context** Atrial fibrillation, a common disorder that affects nearly one sixth of the population aged 75 years and older, is a major risk factor for stroke.

**Objectives** To review and evaluate the evidence supporting the use of warfarin and/or aspirin for stroke prevention in patients with atrial fibrillation.

**Data Sources** Prospective, randomized trials of patients with atrial fibrillation evaluating either warfarin or aspirin or both, from MEDLINE from January 1, 1966, to February 23, 1999.

**Study Selection** Five primary prevention placebo-controlled studies, which had been formally pooled, 1 study evaluating secondary prevention of stroke, 1 study comparing warfarin with aspirin, and 3 studies of warfarin in combination with aspirin were identified.

**Data Synthesis** The risk of developing stroke is heterogeneous and increases with each decade above 65 years; history of high blood pressure, diabetes mellitus, previous transient ischemic attack, or stroke; poor ventricular function; and in women older than 75 years. For patients younger than 65 years, without risk factors, and not receiving antithrombotic therapy, the risk of stroke is 1%/y; those without risk factors between the ages of 65 and 75 years have a risk of 1.1%/y if taking warfarin and 1.4%/y if taking aspirin. For all other patients, stroke risk is reduced from an untreated rate of between 4.3%/y and more than 12%/y to a rate of 1.2%/y to 4%/y with warfarin use.

**Conclusion** The protection afforded by warfarin is most pronounced in patients at the highest risk for stroke, while aspirin treatment seems adequate in low-risk populations.

**Surgery**

**AB-14480-99**


**Background:** Randomized trials of carotid endarterectomy for high-grade stenosis have shown a benefit for surgery under the condition of low perioperative complication rates. Concerns have been expressed that the complication rates of carotid surgery are higher in everyday practice and may vary considerably between centers. We prospectively established the complication rate for carotid surgery in a single institution.

**Design:** Prospective 2-year study. All patients received pre- and postoperative neurological evaluation. Laboratory tests included pre- and
postoperative brain imaging, intracranial and neck vessel sonography, conventional angiography, magnetic resonance angiography, and intraoperative monitoring. Participants: 108 consecutive patients: 54 asymptomatic patients fulfilling the inclusion criteria of the European Carotid Surgery Trial (ECST) and 54 asymptomatic patients fulfilling the inclusion criteria of the North American Trial on Asymptomatic Stenoses (ACAS). Setting: Single academic center with a high volume of carotid endarterectomies (>50 per year). Participating center in ECST. Main Outcome Measures: Stroke or death as defined in the randomized trials.

**Results:** The overall complication rate was 8.3% (95% CI 4.1–15.6%). Complications were more frequent in patients with symptomatic stenosis (11.1%, CI 4.6–23.3%) than in asymptomatic cases (5.6%, CI 1.5–16.4%). Three patients died (2 strokes, 1 myocardial infarction). Disabled strokes were found in 2 patients (Rankin scale scores 3 and 4). Nondisabling strokes (Rankin scale score 1 and 2) occurred in 4 patients. The complication rates for symptomatic and asymptomatic patients were higher than the ones reported in the randomized trials, but 95% confidence intervals showed that the differences were not statistically significant. The point estimates of complication rates still supported a benefit of surgery for patients with symptomatic stenosis, but denied a positive effect of endarterectomy for patients with asymptomatic stenosis. **Conclusion:** In this center, a beneficial effect of carotid surgery for asymptomatic stenoses cannot be safely assumed.

**AB-14481-99**


**Purpose:** The results of intraoperative and early postoperative carotid color-flow duplex scanning (CFS) after endarterectomy were reviewed to determine whether any perioperative studies could be eliminated.

**Methods:** Patients undergoing carotid endarterectomy with intraoperative CFS between 1986 and 1997 were identified. Early postoperative CFS was performed between 1 day and 3 weeks postoperatively, then it was performed again at 6 months postoperatively.

**Results:** During the study period, 560 patients, 325 men and 235 women, underwent 621 carotid endarterectomies. A satisfactory intraoperative carotid CFS was completed in 611 (98.4%) patients. There were 20 (3.2%) vessels with a major defect that required revision for fronds or flaps (n=11), retained atheroma (n=5), low flow (n=2), high velocity or turbulence (n=1), or dissection (n=1). Another 146 vessels (23.5%) had minor defects, such as retained proximal atheromas or small (less than 3 mm) fronds, but were not revised. The remaining 445 vessels were normal. The first postoperative CFS was normal in all the revised carotids and in 138 (94.5%) vessels with minor intraoperative defects. At 6 months, recurrent stenosis (more than 75% area reduction) was identified in 1 of 18 revised carotids (5.5%), 4 of 138 vessels (2.9%) with minor defects, and 17 of 406 vessels (4.2%) that were normal intraoperatively. The incidence of recurrent stenosis was not significantly different in the three groups (P=.7).

**Conclusion:** Intraoperative CFS is useful because major unsuspected defects can be corrected immediately, thus avoiding potential neurologic morbidity. However, the postoperative day 1 CFS can be eliminated in most cases, because it does not provide any relevant clinical information.

**Items of Interest**

**Why Do We Have a Stroke Belt in the Southeastern United States? A Review of Unlikely and Uninvestigated Potential Causes**—Howard G (Bowman Gray/Baptist Hospital, Dept of Public Health Sciences, The Wake Forest Univ School of Medicine, Medical Center Blvd, Winston-Salem, NC 27157-1063)—**Am J Med Sci.** 1999;317:160–167.


**The Protective Effects of Estrogen on the Cardiovascular System**—Mendelsohn ME (Molecular Cardiology Research Institute, Tufts Univ School of Medicine, New England Medical Center, 750 Washington St, No. 80, Boston, MA 02111), Karas RH—**N Engl J Med.** 1999;340:1801–1811. © 1999 Massachusetts Medical Society.


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