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Recurrent Stroke Rates Are Higher Than Cardiac Events After Initial Stroke/TIA

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Introduction: Patients with ischemic stroke and TIA are at risk for recurrent ischemic cerebrovascular events as well as ischemic cardiac events. Understanding which of these adverse events is more likely to occur first is instructive for preventive therapy planning. Further, when using ICD-9 codes on claims data to identify subsequent ischemic events, the effects on event rates of using primary versus both primary and secondary diagnosis codes are unknown. **Methods**: Subjects for this analysis (n=1,923) were identified from a sample of hospital discharges from the Michigan Medicare population from January 1, 2001 - June 30, 2001 using administrative claims for ICD-9 codes corresponding to ischemic stroke/TIA. Medical record abstraction was conducted to collect history of stroke/TIA and demographics. Outcomes, including cardiac events (myocardial infarction (MI), percutaneous transluminal coronary angioplasty (PTCA), and coronary artery bypass grafting (CABG)) and ischemic strokes, were identified by administrative claims using ICD-9 codes for January 1, 2001 - June 30, 2003. Outcomes were identified using primary diagnosis only and using primary and secondary diagnoses. Comparison between cardiac and stroke event rates after an incident stroke/TIA were made using Kaplan Meier survival analysis. **Results**: Using primary and secondary diagnosis codes to identify outcomes, 172 had a cardiac event (62.8% MI, 7.6% CABG, 14.5% PTCA, 9.3% MI and PTCA, and 5.8% MI and CABG) and 239 had a stroke as their first event during the follow-up period. The rate of a cardiac event at 2 years was 10.6%, and for stroke was 14.6%. When only considering primary diagnosis codes, at 2 years there were 133 cardiac events and 182 strokes during the follow-up period. The corresponding rate of cardiac events at 2 years was 8.1%, while rate of stroke was 11%. **Conclusion**: Rates of stroke after initial stroke or TIA are higher than rates of cardiac events. The propensity after stroke/TIA to have the first recurrent ischemic event in the brain, rather than in the heart, has implications for prophylactic therapy selection. Stroke and cardiac events rates differ depending on whether primary or primary and secondary diagnosis codes are used to identify outcomes.

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Hypothyroidism and Risk of Stroke: Results From the National Health and Nutrition Examination Survey Follow-up Study

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BACKGROUND: Recently cardiovascular disease has been linked to deficiency of thyroid hormone. However, the long-term risk of stoke with hypothyroidism is unknown. We performed this study to evaluate the long-term risk of stroke, and type of stroke, with hypothyroidism and how this risk compares with that for persons with euthyroid status. **METHODS:** We used the 20-year follow-up data for 5034 adults aged 25 to 74 years who participated in the First National Health and Nutrition Examination Survey Follow-Up Study to determine the aforementioned risks. Hypothyroidism or hyperthyroidism was diagnosed by Resin T3 Uptake test and T4 assay. Incidence of stroke overall and incidence of ischemic stroke and intracerebral hemorrhage were determined from a review of hospital records and death certificates. Relative risk (RR) of stroke and stroke type in association with each category based on thyroid function was determined by Cox proportional hazards analysis after adjustment for potential confounding variables. **RESULTS:** A total of 5260 participants (mean age 48±14 years; 2360 men) were evaluated. Hypothyroidism was diagnosed in 855 (16%) participants. During the 20 year follow-up period, 255 strokes were observed of which 226 were ischemic stroke. After adjustment for differences in age, sex, serum cholesterol level, body mass index, diabetes mellitus, systolic blood pressure, and cigarette smoking, a significantly higher RR for all strokes was observed in participants with hypothyroidism (RR, 1,6; 95% confidence interval (CI), 1.2 to 2.2). The risk was significantly higher for ischemic stroke in persons with hypothyroidism (RR 1.6, 95% CI, 1.1–2.2). No association was observed between hyperthyroidism and stroke. **CONCLUSIONS:** Increased risks for stroke, and ischemic stroke, were observed in patients with hypothyroidism. Future clinical trials are required to evaluate whether thyroid hormone replacements can reduce the risk of stroke and alchemic stroke.

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Magnetic Resonance Imaging May Be a Useful Modality for Targeting "True" Ischemia in Stroke Prevention and a Surrogate Marker for Limiting Sample Size Requirement for a Trial

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Background and Objective: MRI has been a valuable tool as a surrogate marker for identifying new lesions in Multiple Sclerosis and has led to approval of new therapies. MRI could also be as useful in stroke prevention by identifying true ischemia with DWI abnormality and may reveal silent non-clinical events at follow up. We assessed the feasibility of using MRI at baseline and follow up as a surrogate for a minor stroke/TIA prevention trial. **Methods:** Patients with a TIA or minor stroke (NIHSS $<$ 4) presenting with hemiparesis or aphasia lasting $>$ 5 minutes within 12 hours from symptom onset were included. 3T MRI with DWI and FLAIR sequences were obtained at baseline and 1 month. Lesions were rated by a single neuroradiologist blind to clinical data. **Results:** Out of 108 patients, 71 had a DWI lesion at baseline, 12 (11.1%) had a new ischemic lesion detected by MRI at 1-month and 8 (11.3%) had growth of the baseline lesion. Of the 71 DWI lesions at baseline, 19 (26.8%) had a new MRI based ischemic lesion, and 12 (16.9%) had a stroke within the 30-day period. 1 out of 37 (2.7%) patients who were DWI negative at baseline had a new ischemic lesion and 1 (2.7%) had a stroke. Patients with a baseline DWI lesion were 5.7 times more likely to have a new lesion (95% CI: 1.0 to 42.7, p-value = 0.05) and 6.2 times more likely to have a stroke (95% CI: 1.0 to 46.2, p-value = 0.03). In planning a clinical trial, considering new ischemic DWI lesions as an outcome would require 2446 patients to demonstrate a 30% relative difference in treatment effect between 2 groups (alpha 5%, power 80%). Restricting the inclusion criteria to patients with a DWI lesion at baseline would reduce the sample size to 1622. **Conclusion:** MRI can be useful in acute stroke prevention trial design by limiting the sample size requirements. DWI lesion at baseline identifies true ischemia at much higher risk. Follow up MRI increases the yield of identifying new ischemia.

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Prehypertension Risk for Myocardial Infarction But Not Ischemic Stroke

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Background: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure identified a new category termed pre-hypertension. Our objective was to determine the long-term risk of cardiovascular diseases associated with pre-hypertension **Methods and Results:** We evaluated the association of pre-hypertension (120–139/80–89 mm Hg), and hypertension (greater than 140/or greater than 90 mm Hg) with the incidence of atherosclerotic brain infarction, all strokes, myocardial infarction and coronary artery disease. Framingham Study participants (n=5181) were pooled using repeated measures to follow-up period of 8–12 years. Cox proportional hazards analyses adjusting for age, gender, obesity, diabetes mellitus, and smoking status was used. **Results**: There were 11212 person-observations for ABI. Mean follow-up period was 9.9 ± 0.9 years. Pre-hypertension was not associated with an increased risk for atherosclerotic brain infarction (relative risk (RR) 2.1, 95% confidence interval (CI) 0.5 to 8.8). There were 12031 person-observations with a mean follow-up period of 9.8 ± 1.3 years for myocardial infarction. Pre-hypertension was significantly associated with an increased risk for myocardial infarction (RR 3.7, 95% CI 1.7 to 7.8). Pre-hypertension was also associated with an increased risk of coronary artery disease among the 11876 person-observations (RR 1.7, 95% CI 1.2 to 2.4). **Conclusions:** Based on data from the Framingham study, pre-hypertension appears to be associated with an increased risk of myocardial infarction and coronary artery disease but not stroke. Further studies are required to confirm the anticipated benefits of identifying and intervening in persons with pre-hypertension.

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Perceived Risk for Developing Stroke Among Older Adults

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Background and Purpose - Persons who accurately perceive their risk for stroke maybe more likely to engage in prevention practices to reduce their risk. The purpose of this study was to identify factors associated with perceived risk for stroke in older adults. **Methods and Materials -** In 2004, 800 adults aged 45 years and older in two rural counties participated in a telephone survey to assess their perceived risk for stroke. Respondents were also asked if they had a history of selected risk factors for stroke. **Results -** Overall, 39% of respondents perceived they were at risk for having a stroke. Respondents with diabetes (66% vs. 37%), high blood pressure (52% vs. 31%), high cholesterol (48% vs. 35%), a history of heart disease (60% vs. 37%), a history of stroke or TIA (66% vs. 37%), and current smokers (56% vs. 36%) were more likely to believe they were at risk for stroke compared to respondents without these characteristics. Respondents with atrial fibrillation (46%) and former smokers (34%) were no more likely to perceive themselves to be at risk for stroke compared to respondents without atrial fibrillation (38%), and non-smokers (36%). Perceived risk for stroke increased as the number of risk factors increased. However, 46% of respondents with three or more risk factors did not perceive themselves to be at risk. **Conclusions -** Many adults with multiple risk factors do not perceive themselves to be at risk for stroke. Clinical and public health efforts are needed to increase awareness of the risk for stroke.

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Endothelial Progenitor Cells During Acute Cerebrovascular Disease

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Background and Purpose: There is recent evidence to suggest that endothelial progenitor cells (EPCs), derived from bone marrow, may be associated with endothelial repair following ischemic injury in the cardiac and peripheral circulation. To date, there are no reports of clinical studies investigating the association of EPCs with cerebrovascular disease. **Objective:** To determine the effects of acute ischemic stroke on the levels of peripheral EPCs and to evaluate the effects of acute stroke on these cells over a subsequent period of 4 weeks. **Methods:** We recruited patients with acute ischemic stroke, transient ischemic attacks (TIAs) and controls without any history of cerebrovascular disease. All patients had assessment of vascular risk factors, full medical examination and blood drawn for measurement of EPCs. In patients with acute ischemic stroke, EPC levels were determined within 24 hours of the acute stroke, at 7 days and at 28 days. **Results:** Mean age was 63.4 years (SD 13.26). Of these eighty eight patients 56 (64%) were Male and 32 (36%) were Female. EPC count differed significantly (p = 0.001) between stroke patients (acute stroke mean 6.65; SD 8.48; stable stroke mean 10.72; SD 10.19) and control subjects (mean 24.24; SD 18.25) independent of age. The level of EPCs was significantly correlated with the Framingham Coronary Risk Score (FCRS) (r = -0.399;

p=0.001). Time-course studies from baseline to 7 and 28 days on the levels of EPCs in acute patients showed an increasing trend in their levels. **Conclusions:** Our results suggest that cerebrovascular disease is associated significantly with lower number of circulating EPCs compared to controls. The decrease in EPCs as is seen in acute ischemic stroke may be a possible mechanism to explain the increased risk of stroke and re-thrombosis immediately after a TIA or acute stroke.

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The Value of Cost-Effective Stroke Prevention Screening

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Introduction: A neurologist and a vascular surgeon have developed a new cost-effective means of stroke prevention screening (SPS). The purpose is to ferret out the immediate causes of the majority of strokes (carotid artery disease, atrial fibrillation and hypertension) that are asymptomatic in 80% of cases prior to the stroke so as to allow their proper management and prevention of strokes. In addition, the patient's lipid and cardiovascular disorders can be recognized and management initiated. The implementation of the SPS protocol in seniors in the Central Valley of California (CVC), at New York University (NYU), at Madigan Army Medical Center (MAMC) and by The American Vascular Association (AVA) is reported. **Method:** The stroke prevention screening protocol employed uses a quick carotid scan (QCS) for carotid artery disease, an EKG rhythm strip for atrial fibrillation, and a blood pressure determination. The protocol can be performed within 4 minutes and at a cost of $20/senior. The QCS is performed within 1 minute and uses either visualization of a significant lesion or of color shift connoting increased flow velocity on ultrasonic imaging as an indicator of carotid artery disease and need for a later full duplex examination. Sensitivity was 93% in our laboratory and 97% at NYU. **Results:** Seniors screened were 2,685 in the CVC, 610 at NYU, 458 at MAMC, and 7,971 by the AVA for a total of 11,724. The yield was 75.4% for carotid artery disease with 7.7% having possible >50% stenosis, 3.9% for atrial fibrillation, and 25.4% for unknown or inadequately managed hypertension. It is estimated that the carotid screenings alone prevented 58.6 strokes for an overall savings of $3,797,690. Screening 40 million Medicare recipients could potentially prevent over 200,000 of the 750,000 strokes occurring annually and save nearly 13 million dollars in health care costs. **Conclusions:** Stroke prevention screening can now be performed rapidly, accurately and cost effectively and can reduce stroke disability far more than treatment of strokes or rehabilitation. It is time to come together, implement SPS and find the means of ensuring expert management of the positive finds. SPS is a most important concept whose time has come and should be presented at our stroke meeting and fully discussed.

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Type of Migraine Aura Symptoms Determines Association With Ischemic Stroke: The Stroke Prevention in Young Women Study

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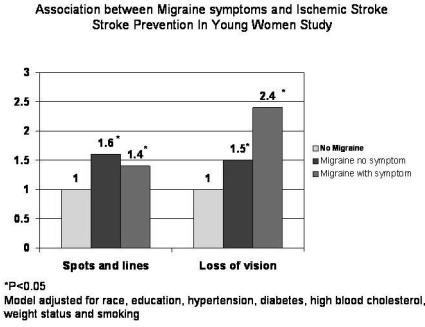
Background: While migraine headaches accompanied by aura have been associated with ischemic stroke, it is not clear which aura symptoms increase this likelihood. **Methods:** Data from the Stroke Prevention in Young Women Study (n=963), a population-based case control study among young women aged 15–49 years, were used to determine: whether migraine accompanied by visual loss versus the presence of lines and spots increased ischemic stroke likelihood. Logistic regression was used to assess these associations after adjusting for race, hypertension, high blood cholesterol, overweight, diabetes and smoking. Results: Stroke cases (n=542) were more likely to be hypertensive, diabetic, and smokers (all $p<0.05$). Women with migraine were more likely to be obese ($p<0.05$). Odds ratios for stroke risk compared to reference group without migraine are shown below. **Conclusions:** The type of aura symptoms influences stroke risk. Women with migraine accompanied by the presence of visual loss may be at substantially increased likelihood of stroke.



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Oral GpIIb/IIIa Inhibition Provides No Benefit Over Aspirin Alone in Preventing Ischemic Stroke/TIA After Acute Coronary Syndromes

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Background: The OPUS-TIMI 16 (Orbofiban in Patients with Unstable Coronary Syndromes) study, a multicenter, randomized, placebo-controlled trial, found that the oral GpIIB/IIIA inhibitor orbofiban increased mortality and failed to reduce major cardiovascular events (combined death, recurrent cardiac ischemia or stroke). We sought to determine whether orbofiban decreased risk of stroke alone. **Methods:** Inclusion criteria were cardiac ischemic discomfort at rest in association with ischemic EKG changes, positive cardiac markers, or (first 3,000 only) a history of prior cardiovascular disease, peripheral vascular disease, ischemic cerebrovascular disease, or diabetes mellitus; exclusion criteria included history of intracerebral hemorrhage (ICH) or need for long-term anticoagulation. Between 1997–98, 10,288 patients from 888 centers were randomized 1:1:1 to aspirin plus either placebo, orbofiban 50 mg bid, or orbofiban 50 mg bid for 30 days followed by 30 mg bid. We analyzed orbofiban treatment as one group because of similar clinical event rates. Cerebrovascular events were judged by clinical criteria, with brain imaging when available, and were adjudicated by two study neurologists blinded to treatment assignment. **Results:** The qualifying event was ST-elevation MI (STEMI) in 32%, non-STEMI in 23% and unstable angina in 45%. A prior history of ischemic stroke or TIA (IS+TIA) was present in 525 (5%). During 10 months of follow-up there were 150 (1.5%) patients with cerebrovascular events: 67 IS, 44 TIA, 14 ICH, and 25 events of uncertain type. The risk of IS+TIA and ICH was higher in the initial period (30-day IS+TIA rate 0.5%, subsequently 0.07%/month). Treatment with orbofiban did not reduce the risk of IS+TIA compared to placebo (adjusted HR 1.15, 95% CI 0.76–1.74, in a Cox proportional hazards model). There were 14 patients with ICH; 10 (71%) died, and 10 were taking orbofiban (HR 1.25, 95% CI 0.4–4.0). **Conclusions:** There is a low incidence of cerebrovascular events in the 10 months following acute coronary syndromes but the initial 30-day risk is higher. These results suggest that orbofiban, despite no excess risk of ICH, provides no benefit over aspirin alone in preventing IS+TIA after acute coronary syndromes.

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Predictors of Statin Use After Acute Ischemic Stroke in the STOPStroke Study

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Background: Statins reduce lipid levels, inflammation, stabilize atherosclerotic plaque, and increase vasodilation. Several studies have demonstrated a significant benefit of statins in preventing stroke. Thus appropriate implementation and successful maintenance of statin therapy are a priority for secondary stroke prevention. We sought to identify the factors associated with pre-stroke and post-stroke statin use and compliance at 6 months. **Methods:** We analyzed data on patients with acute (<24 hour) ischemic stroke who were prospectively enrolled in 'STOPStroke', an observational study evaluating the utility of CT/CTA in patients with suspected stroke. Clinical data, including a detailed medication history, was obtained through an interview and medical record review within 24 hours of admission, at discharge, and at 6 months. **Results:** We evaluated 341 patients (mean age 67.2, 52.1%male). Sixty-four (18.8%) of patients were taking a statin on admission. At discharge, 150 (44%) patients were taking a statin, including 68% initiated during the hospitalization. Discharge statin therapy was predicted by hypercholesterolemia ($p=0.01$) and pre-stroke statin use ($p=0.001$), but not age, gender, initial NIHSS, stroke mechanism, CAD, or vascular risk factors. Analysis of 6-month follow-up data (missing in 19%) showed that 110 subjects (76% of those discharged on a statin) remained compliant. Hypercholesterolemia ($p=0.009$) and large artery atherosclerosis ($p=0.02$) predicted statin use at 6 months. In-hospital initiation of statins ($p=0.0001$) and diabetes ($p=0.02$) were associated with discontinuation of statin therapy at 6 months. **Conclusion:** Hypercholesterolemia and the presence of large artery atherosclerosis predict in-hospital initiation of statins after ischemic stroke. A considerable proportion of patients (24%) started on a statin during the acute hospitalization do not remain on statins at 6 months. Further studies are needed to determine the reasons (e.g. adverse effects, patient non-compliance) for statin discontinuation in high-risk stroke populations such as diabetics.

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Physical Activity and Ischemic Stroke

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Background: Previous epidemiological studies have indicated that higher levels of physical activity is associated with lower risk of ischemic stroke. Most of the studies have used questionnaires that were age-neutral, however, most ischemic stroke events occur among elderly persons where physical activities may differ from that of younger age groups. Using a questionnaire specifically aimed at an elderly population may be better to assess the relation between physical activity and ischemic stroke occurrence. **Subjects and methods:** Patients admitted to hospitals covering the population of the central Copenhagen area, with ischemic stroke, were enrolled during the period August 12th, 2003 to April 1st, 2004. Community control subjects were selected among participants in the Copenhagen City Heart Study (CCHS) and matched to cases according to age, sex, and season. Physical activity was assessed using the Physical Activity Score for the Elderly (PASE) and the questionnaire used in the CCHS. Conditional logistic regression analyses were used in multivariate analyses. **Results:** A total of 133 case subjects and 301 control subjects were included in the study. For each 1 point increase in PASE score the odds ratio for ischemic stroke was 0.98 (0.98–0.99), equivalent to an odds ratio of 0.82 for each 10 points increase. There was no significant difference for men and women ($p = 0.60$). In analyses using the CCHS questionnaire there was no clear relation between level of reported physical activity and odds ratio for ischemic stroke. Univariate analyses suggested a U-shaped relationship whereas none of the results from multivariate analyses were significant. **Conclusions:** Using two unrelated questionnaires for assessing level of physical activity provided markedly different results. Whereas increasing PASE score was inversely, log-linearly, and significantly associated with odds ratios for ischemic stroke, using an age neutral questionnaire did not reveal a significant association. Age specific questionnaires is recommended for assessing the relation between physical activity and risk of stroke,

and the current results suggest that there is a dose-response relationship between physical activity and risk of ischemic stroke.

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Endarterectomy vs Angioplasty With or Without Stenting for Carotid Artery Stenosis: A Systematic Review

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Background - Carotid endarterectomy (CEA) is the standard strategy for stroke prevention in patients with carotid stenosis. Angioplasty with or without stenting (CAS) is an alternative procedure that may limit complications and decreased length of stay. **Objectives -** to determine if CAS is better than CEA for stroke prevention in patients eligible for either procedure. **Methods** - We searched MEDLINE and COCHRANE databases for relevant randomized or quasi-randomized clinical trials comparing CAS vs CEA. We included studies if valid endpoints such as stroke, death, and local complications were recorded. The analyses were performed using the fixed-effects model, and expressed as odds ratios with 95% confidence intervals. **Results** - Fifteen studies were included totaling 2774 patients (CEA =1431; CAS = 1343). The perioperative local complication rate was lower in the CAS (OR= 0.22 [0.14, 0.35]). Perioperative stroke, death, and stroke/death rates were higher in the same group (OR= 1.56 [1.07, 2.27], 1.09 [0.55, 2.14], and 1.64 [1.19, 2.28] respectively). Only four of the fifteen studies had long-term results that showed no significant differences in endpoints (OR=1.18 [0.76, 1.85]). **Conclusion** - At the present, the perioperative risk of stroke and death precludes the use of CAS in routine practice moreover, the long-term results are unknown.

Community/Risk Factors

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Silent Brain Infarcts and White Matter Lesions Were Associated With Subsequent Stroke and Vascular Death: Long-Term Prospective Study

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Background and purpose: Silent brain infarction and white matter lesions were frequently detected even in normal elderly subjects. We examined prospectively the association between these lesions and the risk of subsequent stroke or cause of death in neurologically normal adults. Methods: MRI scans were performed in 2,684 neurologically normal subjects without history of stroke (40 to 84 years; mean age, 58 years at entry) who received our health screening of the brain. We obtained information about their clinical stroke onset and death through a questionnaire which was sent to all subjects annually from 1992. Then, we confirmed detailed clinical information about stroke and death by telephone interview and inquiring to the hospital. Informed consent for this study was obtained from all subjects according to our institutional guideline. The silent brain infarction (SBI) was diagnosed by the findings as focal T2 hyperintensity lesions larger than 3 mm with correlative T1 hypointensity. Periventricular hyperintensity (PVH) and subcortical white matter lesions (SWML) were quantified on MRI at the first visit. Results: Average follow up period was 6.3 years. Stroke occurred in 103 subjects (3.8 %), and 93 subjects were dead during the follow-up. Incidence of clinical stroke was significantly higher in the subjects with SBI than in those without. SBI, PVH and SWML also increased the risk of stroke independently of other stroke risk factors (OR 3.6, 95% CI 2.2 - 5.8 for SBI, OR 2.3, CI 1.1 - 4.6 for PVH, OR 2.6, CI 1.3 - 5.3 for SWML, respectively). Regarding the cause of death, SBI and PVH significantly increased the risk of death (OR 1.9, CI 1.1 - 3.2 for SBI, OR 4.1, CI 2.0 - 8.5 for PVH, respectively). Cardiovascular diseases were significantly frequent on the cause of death in the subjects with SBI or white matter lesions. Conclusions: Silent brain infarcts and white matter lesions should be considered at high risk for clinical stroke and vascular death.

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Increased Levels of Serum High-Sensitivity C-Reactive Protein and Interleukin-6 Are Associated With Silent Brain Infarction

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Background and Purpose: Silent brain infarction (SBI) is frequently seen on MRI of patients with cardiovascular risk factors. Inflammatory processes have been shown to contribute to atherothrombotic vascular events. However, studies investigating the involvement of low-grade chronic inflammation in cerebral small vessel disease have been rare. We, therefore, conducted a prospective study to determine whether inflammatory markers are associated with SBI. **Methods:** Between April 2002 and December 2003, two hundred and five consecutive outpatients with no history of stroke, other cardiovascular events were enrolled in a prospective design. After excluding 11 patients having a clinically chronic or acute inflammatory disease, 194 (mean±SD age, 67.3±7.5 years; 101 women, 93 men) were analyzed in this study. Patients underwent brain MR imaging, carotid ultrasonography, and neuropsychological testing. We measured circulating levels of high sensitivity C-reactive protein (hsCRP) and interleukin-6 (IL-6) as inflammatory markers. Information on patient medical history, medication use, and smoking habit was obtained from clinical records and self-reports with investigator blinded to the MRI data. Relations between the prevalence of SBI on brain MRI and serum hsCRP and IL-6 levels were evaluated. **Results:** Mean serum hsCRP and IL-6 levels in patients with SBI was significantly higher than levels in patents without SBI (hsCRP: mean±SD [median], 0.33±0.86 [0.08] mg/dL Vs 0.08±1.60 [0.04] mg/dL; IL-6: mean±SD [median], 3.63±6.69 [1.89] pg/mL Vs 1.67±1.96 [1.20] pg/mL, respectively). After adjustment for cardiovascular risk factors and predisposing factors, hsCRP and IL-6 levels were shown to be significantly correlated with SBI (per SD hsCRP increase: OR, 1.51; 95%CI, 1.01 to 2.26; per SD IL-6 increase: OR, 1.88; 95%CI, 1.25 to 2.84). **Conclusions:** The present study showed that levels of circulating hsCRP and IL-6 are associated with SBI independently of traditional risk factors for cardiovascular disease. These associations suggest that inflammatory processes play important roles in cerebral small vessel disease.

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High LDL-3 Subfraction Levels as a Powerful Predictor of Silent Cerebrovascular Infarction in Patients With Essential Hypertension

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Background: Low-density lipoprotein (LDL) levels are considered to be associated with cerebrovascular disease. Recently, the lipid research has been focused on LDL subfraction as a new paradigm for cardiovascular risk factor. However, clinical significance of its measurement is still unknown. **Methods.** To investigate the relationship between LDL subfraction and cerebrovascular disease, we assessed LDL subfraction using newly developed HPLC-method and brain magnetic resonance imaging in 52 consecutive nondiabetic patients with middle-aged essential hypertension whose blood pressure was controlled under 140/90 mmHg with anti-hypertensive agents. Silent cerebrovascular damage was identified by the magnetic resonance imaging findings of lacunae. **Results.** Silent cerebrovascular damage was seen in 16 patients (31%). We evaluated the difference in LDL subfraction between 16 patients with silent cerebrovascular damage and 36 patients without silent cerebrovascular damage. The LDL-3 subfraction levels were higher in patients with silent cerebrovascular damage than those without it (8.0 ± 4.1% vs. 5.2 ± 2.3%; p = 0.003). Patients' characteristics including LDL levels (125 ± 18 mg/dl vs. 114 ± 27 mg/dl; p = 0.14) were similar between two groups. **Conclusions.** Our results firstly indicate that non-diabetic essential hypertension patients with silent cerebrovascular damage have higher LDL-3 subfraction levels. The LDL-3 subfraction levels may be a powerful predictor of silent cerebrovascular damage in patients with essential hypertension.

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Interaction Between Age, White Matter Disease, and the Presence of Microbleeds Among Patients With Cerebral Ischemia

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Introduction Hemosiderin deposits, detected on gradient echo magnetic resonance imaging sequences (GRE) are the result of microangiopathic processes affecting the cerebral circulation. These cerebral microbleeds (CMB) are more frequently found in ischemic stroke patients than in patients with peripheral artery disease or coronary artery disease. We evaluated why microbleeds developed in some, but not all, patients with TIA or stroke. Methods In 203 consecutively admitted TIA or stroke patients >50 years old undergoing GRE, we prospectively related CMB status to age, sex, cardiovascular risk factors, left ventricular hypertrophy on echocardiography, degree of white matter hyperintensity assessed with the Fazekas scale on FLAIR (WMD) and stroke subtype using TOAST criteria. Results Microbleeds were found in 50 TIA or stroke patients (24.6%). In univariate analysis, the presence of microbleeds was not related to age, sex, cardiovascular risk factors, left ventricular hypertrophy or stroke subtype. Microbleeds were more common with increasing degrees of WMD (p for trend<0.001). In multivariable analysis, increasing degrees of WMD (OR 25 for each 1-point increase in the Fazekas scale, p=0.009) and the interaction of age (per decade) and degree of WMD (OR 0.7, p=0.04) were independent predictors of microbleeds after adjustment for sex and hypertension. Conclusion White matter disease is a strong risk factor for the presence of microbleeds in TIA or stroke patients. In patients with white matter disease, microbleeds are more frequent when white matter disease occurs at a younger age.

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Elevated Homocysteine Is Associated With White Matter Disease: The Northern Manhattan Study

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BACKGROUND: Increasing evidence suggests elevated total homocysteine (tHcy) and other modifiable vascular risk factors are associated with white matter damage and may increase the risk of cognitive impairment and dementia. METHODS: The Northern Manhattan Study (NOMAS) is a population-based prospective cohort of 3,298 stroke-free subjects identified by random digit dialing. To date 202 had baseline fasting tHcy levels and follow up brain MRI scans with quantitative measures of white matter hyperintensities (WMH) and brain atrophy available. We used linear regression to examine the association between baseline vascular risk factors including elevated homocysteine and WMH volume adjusting for relevant covariates. RESULTS: Subjects (n=202, mean age 64.7; 54% women; 45% Hisp, 28% black, 23% white) had a mean WMH volume of 0.57% (median 0.3, range 0.04–3.7%) and a mean tHcy of 8.7 umol/L (median 8.3, range 3.1–20.0). Older age, hypertension, brain atrophy, and higher HDL cholesterol were associated with greater WMH volume, and renal function and B12 deficiency were associated with elevated tHcy in univariate analyses. In a linear regression model adjusting for age, creatinine, B12 deficiency, brain atrophy, HDL cholesterol, and hypertension, subjects with tHcy levels one SD above the mean (approx. 11.4 umol/L) had a greater volume of WMH compared to those with values below the mean (p=0.03). Hypertension (p=0.04), brain atrophy (p>0.001), and older age (p>0.001) were also independent predictors of increased WMH volume in the adjusted model. CONCLUSIONS: Elevated homocysteine and hypertension were independently associated with increased white matter hyperintensities in this multiethnic cohort. These data support the need for further work on the relationship between vascular risk

factors, WMH, and cognition as well as clinical trials to examine the effects of risk factor modification on these outcomes.

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Stroke Occurrence and Leukoaraiosis Are Independently Associated With Transition to Disability: The LADIS (Leukoaraiosis And DISability) Study

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Background: Preliminary results from this collaborative study indicate leukoaraiosis (LA) severity as a risk factor for transition to disability in the elderly. However, it is not clear whether stroke occurrence influences the effect of LA severity on determining this transition. **Objective:** To evaluate the independent effect of LA and stroke occurrence on the risk of transition to disability. **Methods:** The LADIS is a study involving 11 European centres, aimed at evaluating LA as independent determinant of disability in the elderly. Six-hundred-thirty-nine subjects (mean age 74.1 $\pm$ 5.0, M/F: 288/351) with different MRI-severity LA (mild, moderate, severe according to the Fazekas scale) and functionally autonomous (0 or 1 impaired item on Instrumental Activity of Daily Living - IADL scale) were assessed at baseline for demographics, vascular risk factors, comorbidities, cognitive, motor, and mood functions, and are being followed-up for 3 years with clinical and MRI studies. Transition to disability is defined as a variation on the IADL leading to impairment in more than one item. Functional status was also assessed by means of the Disability Assessment of Dementia (DAD) scale. **Results:** Out of the 639 subjects, 18 had a stroke (hemorrhagic or ischemic) during the first year of the study. Transition to disability occurred in 8 (44.4%) subjects with and in 73 (13.6%) subjects without new strokes (chi-square $P < 0.001$). Among subjects with new strokes, the rate of transition to disability increased along with increasing LA severity (0%, 50%, 55.5% in score 1, 2, and 3 respectively). Considering as dependent variable the transition to disability, a logistic regression analysis showed that severe LA (OR = 2.47, 95% CI = 1.34 - 4.55), stroke occurrence (OR = 4.09, 95% CI = 1.45 -11.54), age (OR =1.09, 95% CI = 1.04 -1.15) and basal DAD score (OR = 0.89, 95% CI = 0.85 - 0.94) were all predictors of transition. **Conclusions:** After the first year of follow-up, both stroke occurrence and baseline LA severity are independent predictors of transition to disability in the LADIS subject sample.

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Elevated Serum Interleukin-18 Levels Are Associated With Increased Carotid Intima-Media Thickness

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Background and Purpose: Interleukin (IL)-18 promotes atherosclerotic plaque growth and its circulating level can predict future coronary heart disease. However, it has not been established whether serum IL-18 levels are associated with severity of atherosclerosis. With the use of B-mode ultrasound, this study examines the relationships of serum IL-18, IL-6 and high sensitive CRP (hs-CRP) levels with the severity of atherosclerosis as assessed as carotid IMT. Methods: The study comprised 315 patients without histories of cardiovascular diseases (CVD). Severity of carotid atherosclerosis was evaluated as mean max-IMT, mean of the maximal wall thickness at 12 carotid segments. Serum IL-18, IL-6, and hs-CRP levels were determined in all patients. Results: Level of IL-18 was higher in men than in women, in patients with hypertension than in those not, and in patients with smoking history than in those not. Also, it was positively correlated with age, BMI, and triglycerides, and negatively with HDL cholesterol. Log-transformed IL-18, IL-6, and hs-CRP concentrations were positively correlated with carotid IMT ($r = 0.33$, 0.28, and 0.22, each $P < 0.001$, respectively). When controlling for traditional atherosclerotic risk factors and other inflammatory markers levels, only IL-18 levels were associated with IMT ($\beta = 0.20$, $P < 0.001$), whereas such an association disappeared for IL-6 and hs-CRP ($\beta = 0.06$ and 0.06, n.s.). Conclusion: Elevated serum IL-18 levels were independently associated with increased carotid IMT in individuals without histories of CVD, supporting the linkage between IL-18 and atherosclerosis.

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Increased Common Carotid Arterial Stiffness Is Independently Associated With Risk of Stroke

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Background and purpose: Aortic stiffness is an independent predictor of cardiovascular risk factors, cardiovascular and cerebrovascular mortality in patients with essential hypertension. There is little knowledge concerning the relation between the local stiffness of the common carotid arteries (CCA) and manifest cerebrovascular disease. Aim of the present cross-sectional study was to investigate the association of CCA stiffness with the risk of stroke and to determine whether this relationship was independent of conventional risk factors. **Methods:** A consecutive series of 193 acute first-ever stroke patients and of 106 age- and sex-matched control subjects underwent high-resolution B-mode carotid ultrasound examination (echo-tracking techniques). CCA distensibility, which is the inverse of stiffness, was measured as the change in diameter in systole relative to the diastolic diameter. Conventional cardiovascular risk factors as well as lipid-lowering and antihypertensive medications were documented. The ability of CCA distensibility to discriminate between stroke and control patients was evaluated by logistic regression analyses, followed by receiver operating characteristic (ROC) curve analyses. **Results:** CCA distensibility was significantly ($p=0.007$) lower in stroke (0.353 mm, 95%CI: 0.326–379) than in control (0.415 mm, 95%CI: 0.378–0.451) patients even after adjusting for blood pressure values (systolic, diastolic and pulse pressure), diastolic CCA diameter and height. Each 1-SD decrease in the CCA distensibilty increased the risk of stroke by 40.8% (OR: 1.408, 95%CI: 1.106–1.795, $p=0.006$); adjustment for cardiovascular risk factors slightly attenuated this relationship (OR: 1.410, 95%CI: 1.077–1.845, $p=0.012$). The area under the ROC curve for CCA distensibility predicting stroke patients was 0.592 (95%CI: 0.526–0.658). **Conclusion:** An increased CCA stiffness was associated with cerebrovascular disease even after adjustment for conventional cardiovascular risk factors. The causal interrelationship between the elastic properties of the CCA and the risk of stroke deserves further investigation by the use of longitudinal studies.

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Systolic Blood Pressure, LDL Cholesterol, and the Framingham Risk Score Are Better Predictors Than the Metabolic Syndrome of Carotid Intimal-Medial Thickness in Middle-Aged Adults: The Muscatine Study

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Background and Purpose: The Framingham risk score (FRS) and the metabolic syndrome as defined by NCEP III and WHO (MS-NCEP and MS-WHO) predict the risk of developing cardiovascular disease in older adults. Carotid intimal-medial thickness (IMT) has been used as a measure of the atherosclerotic process in younger adults and is predictive of stroke and myocardial infarction in older adults. We assessed the hypothesis that FRS, MS-NCEP, and MS-WHO would be more useful in predicting carotid IMT than would individual cardiovascular risk factors in a cohort of middle-aged adults. Methods: Using carotid ultrasound, the mean of the measurements of maximal carotid IMT at 12 locations was determined in a cohort of 306 men and 390 women aged 36 to 50 years living in Muscatine, Iowa. Anthropometric measurements, smoking status, blood pressure, fasting glucose, fasting insulin, and a fasting lipid profile were also obtained. Results: The mean FRS was 1.62, with 24% of the cohort having MS-NCEP and 18% having MS-WHO. Carotid IMT was more strongly correlated with the FRS (27%) than with either MS-NCEP (13%) or MS-WHO (10%). When all three scoring systems were included in a multivariable model, only the FRS was significant ($p<0.001$). Significant correlations with individual risk factors included systolic blood pressure (24%), LDL-cholesterol (21%), waist circumference (18%), HDL-cholesterol (-17%), smoking status (15%), fasting glucose (15%), and diastolic blood pressure (15%). In a multivariable model, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, smoking, and fasting glucose were significant. The FRS was not significant after adjusting for these risk factors. When predicting the upper quartile of carotid IMT, the area under the receiver operating characteristic curve based on FRS was 0.69, while it was 0.70 when based on systolic blood pressure and LDL-cholesterol combined. In conclusion, the Framingham risk score was more associated with carotid IMT in these middle-aged adults than was the metabolic syndrome using either the NCEP III or WHO definition, but carotid IMT could be predicted as well or better by using just two risk factors, systolic blood pressure and LDL-cholesterol.

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Common Carotid Intima-Media Thickness and the Risk of New Vascular Events in Patients With Manifest Atherosclerotic Disease

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Background: Common carotid intima-media thickness (CIMT) is an independent predictor of vascular events in the general population. Currently little is known on the relationship between IMT and new vascular events in patients who already have manifest arterial disease. We aimed to assess the strength of this relationship. **Methods:** The study was performed in the first consecutive 2473 patients with manifest vascular disease enrolled in the SMART-study (Second Manifestations of ARTerial disease), a cohort study among patients with manifest cardiovascular disease or cardiovascular risk factors. Common carotid IMT was measured at baseline. **Results:** Adjusted for age and sex, an increase in common CIMT of 0.2 mm was associated with the occurrence of all vascular events (hazard ratio (HR) 1.09; 95% confidence interval (95% CI) 1.01 - 1.17). Increasing carotid IMT was most strongly related to stroke incidence (HR 1.22; 95% CI 1.10 - 1.35). **Conclusion:** Common carotid intima-media thickness was associated with the occurrence of new vascular events, especially ischemic stroke, in patients with manifest arterial disease. These findings justify the use of IMT as surrogate endpoint in trials including patients with manifest vascular disease.

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Prediction of Asymptomatic Intracranial Cerebral Atherosclerosis

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Objective: This study is aimed to elucidate risk factors for intracranial cerebral atherosclerosis (ICAS), and develop models to predict ICAS before it becomes symptomatic. **Methods:** From February of 1999 to January of 2001, 1919 subjects were recruited, who visited the stroke prevention clinic and underwent transcranial Doppler (TCD). Those who had history of stroke, other illness to affect the results of TCD, or poor acoustic window, were excluded. ICAS was defined as abnormal findings on TCD compatible with ICAS. The association of ICAS with potential risk factors of atherosclerosis was investigated and ICAS prediction index (ICASPI) was developed based on those results. The validity of the index was examined by another set of 279 subjects who were recruited from June of 2002 to September of 2003. **Results:** Investigation of individual risk factors revealed that age, hypertension, diabetes mellitus, ischemic heart disease, C-reactive protein (CRP), LDL-cholesterol, and HDL-cholesterol were possible risk factors for ICAS. Modeling by multiple logistic regression analyses with backward elimination technique and likelihood ratio test showed that age, hypertension, diabetes mellitus, CRP, LDL-cholesterol, and HDL-cholesterol were statistically significant risk factors of ICAS. ICASPI was made based on those 6 risk factors. ICASPI showed linear correlation with ICAS ($p<0.001$ on Mantel-Haenszel Chi-square test). When ICASPI=0, ICAS was detected in 22.5%; when ICASPI=1, ICAS in 23.7%; when ICASPI=2, ICAS in 34.2%; when ICASPI=3, ICAS in 40.9%; and when ICASPI=4, ICAS in 52.2%; and when ICASPI=5, ICAS in 41.7%. In the second set of 279 subjects for validation of the index, ICASPI also showed statistically significant linear correlation with ICAS ($p=0.024$). **Conclusions:** This study shows that age, hypertension,

diabetes mellitus, LDL-cholesterol, HDL-cholesterol, and CRP are independent risk factors of asymptomatic ICAS and the prediction index based on those factors is valid to predict it.

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Thyroid Replacement Therapy Is a Risk Factor for Atrial Fibrillation in Stroke Patients

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Atrial fibrillation is an established risk factor for ischemic stroke. Subclinical hyperthyroidism may result from thyroid replacement therapy and has been associated with an increased risk for the development of atrial fibrillation. We sought to determine whether thyroid replacement therapy is a risk factor for atrial fibrillation in stroke patients. **Study Design**: Case-control study. **Methods**: Consecutive stroke patients with atrial fibrillation (cases) and without atrial fibrillation (controls) admitted to the Stanford Stroke Center between 1996 and 2004 were included. Data on age, gender, vascular risk factors, history of atrial fibrillation and/or atrial fibrillation on admission, and whether patients were taking thyroid replacement therapy, amiodarone, and warfarin at the time of admission were abstracted from hospital records by one investigator (NLV). We aimed to match each case by age and gender with two controls. **Results**: Thyroid replacement therapy was reported in 52/334 (15.6%) cases and 67/637 (10.5%) controls ($p=0.02$). More than 80% of thyroid replacement therapy users were female in both groups. In multivariate analysis, thyroid replacement therapy use was associated with an odds ratio of 1.65 (95% CI 1.05–2.59, $p=0.02$) with atrial fibrillation after adjusting for age, gender, hypertension, amiodarone use, and coronary artery disease. **Conclusion**: Thyroid replacement therapy may be an independent risk factor for atrial fibrillation in stroke patients.

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High Prevalence of *Chlamydia pneumoniae* Antibodies and Increased High-Sensitivity C-Reactive Protein in Patients With Vascular Dementia

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Background and Purpose: Chlamydia pneumoniae has been identified in atherosclerotic plaques of patients with cerebrovascular and cardiovascular disease. We studied relationships between Chlamydia pneumoniae infection, carotid atherosclerosis, and dyslipidemia in patients with vascular dementia (VaD), caused by stroke or small vessel disease, and Alzheimer's disease (AD). **Methods:** Presence of antibodies to Chlamydia pneumoniae (IgG and IgA), the serum concentrations of high-sensitivity C-reactive protein (hs-CRP) and atherogenic lipoproteins, and the carotid artery intima-media thickness (IMT) and plaques were determined in 31 patients with VaD, 61 patients with AD, and 32 age-matched controls without dementia. **Results:** Age, body mass index, systolic and diastolic blood pressures, and fasting plasma glucose, HbA_{1c}, HDL cholesterol, and apolipoproteins A-1, B, and E concentrations did not differ significantly among the three groups. However, the mean IMT and frequency of atherosclerotic plaques in the carotid arteries as well as the serum concentrations of LDL cholesterol, lipid peroxides, and lipoprotein(a) were significantly greater in VaD patients than in AD patients or nondemented controls. Hs-CRP concentrations and prevalence of Chlamydia pneumoniae IgG and IgA antibodies also were significantly higher in VaD patients than in AD patients and nondemented controls. Multiple logistic regression concerning VaD retained carotid IMT and plaques, IgG and IgA Chlamydia pneumoniae seropositivity, hs-CRP, LDL cholesterol, lipid peroxides, and lipoprotein(a) (Table). **Conclusions:** Our results suggest that carotid atherosclerosis, atherogenic lipoproteins, and Chlamydia pneumoniae infection (as documented by the IgG and IgA seropositivity together with increased hs-CRP) may be VaD risk factors.

TABLE. Multiple Logistic Regression Analysis of Risk Factors for VaD

	Odds Ratio	95% Confidence Intervals	P Value
Carotid IMT (1 mm or greater)	10.4	2.8–38.2	0.0003
Carotid plaque	8.3	2.0–33.8	0.0036
Chlamydia pneumoniae antibodies (IgG index > 1.1 and IgA index > 1.1)	3.3	1.0–10.5	0.0453
Hs-CRP (ng/mL)	1.0	1.0–1.0	0.0324
LDL cholesterol (mg/dL)	1.0	1.0–1.0	0.0204
Lipid peroxides (nmol/mL)	1.0	1.0–1.0	0.0042
Lipoprotein(a) (mg/dL)	1.0	1.0–1.1	0.3694

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The Role of Migraine in Acute Ischemic Stroke in Young Adults

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Objective: To investigate whether migraine could be a risk factors for the acute ischemic stroke in patients aging 16 to 44 years in a nested case-control study. **Patients and Methods:** For each patients admitted because of CT/MRI confirmed acute ischemic stroke (TIA excluded) was identified an age (± 1 year)- and gender-matched control subject selected among partners of non-vascular and non-migrainous outpatients. For either stroke and control subjects we recorded: history of at least 5 migraine attacks (either with and without aura according to the IHS criteria); usual risk factors for stroke; current utilization of contraceptive pill; current beverage of at least 2 glasses of wine per meals;current smoking of at least 5 cigarettes per day;blood pressure and cardiac rhythm. Data were matched with univariate analyses. Significant results were then entered into a logistic regression model to identify those data independently associated with stroke. **Results:** Two-hundred-thirty-eight stroke patients and an equal number of control subjects were included. Men were 117 and women were 121 in each group. Mean age of stroke patients was 35.4 years and of the control group 35.2 years. The persons suffering from migraine were 63 (26.5%) in the stroke group and 33 (13.9%) in the control group. That difference achieved statistical significance ($p = 0.0009$). Contraceptive pill utilization was not different between groups as for wine beverage and smoking habit. The logistic regression model retained migraine (Odds ratio 2.70, 95% confidence interval 1.66–4.41) together with hypertension (Odds ratio 9.10, 95% confidence interval 4.17–19.89) and any cardiopathy (Odds ratio 31.94, 95% confidence interval 4.15–238.73) as factors independently related to stroke. **Conclusions:** Migraine appears to be a relevant risk factor for the acute ischemic stroke in young people. In addition, the role of migraine in precipitating a stroke appears to be independent from the usual risk factors and from the consumption of wine, cigarettes and the contraceptive pill.

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C-Reactive Protein Predicts Further Ischemic Events in Transient Ischemic Attack Patients

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Background - There are many studies of clinical prognostic factors in patients with transient ischemic attack (TIA). Most of them have failed to identify parameters to predict vascular event appearance after the index TIA. We hypothesize that inclusion of a biological marker in the TIA study protocol might increase the prognostic value of classical risk factors. To test this, we have investigated the relationship between high sensitivity C-reactive protein (hsCRP) levels and the risk of new ischemic events in TIA patients. **Methods-** HsCRP levels were determined within the first 24 hours after the onset of clinical symptoms among 135 TIA patients. Stroke recurrence, or any vascular event was recorded at follow-up (446±294 days) **Results-** A total of 37 (27.4%) patients experienced an end-point event: 28 (20.74%) cerebral ischemic events, eight (6%) heart ischemic events, 4(3%) peripheral arterial disease, and eight (6%) vascular deaths. Cox proportional hazards multivariate analyses identify as independent predictor of stroke, age (HR 1.07, CI 1.01 to 1.13, $P=0.0171$), atherotrombotic etiology (HR 3.15, CI 1.28 to 7.75, $P=0.0123$) and hsCRP> 0.41 mg/dL (HR 2.46, CI 1.01 to 6.04, $P=0.0487$). Moreover, age (HR 1.05, CI 1.01 to 1.09, $P=0.0167$), atherotrombotic etiology (HR 3.93, CI 1.93 to 8.01, $P=0.0002$) and hsCRP> 0.41 mg/dL (HR 2.77, CI 1.32 to 5.81, $P=0.0073$) were independent predictors for any vascular event during the follow-up. **Conclusions-** HsCRP serum levels predict further new ischemic events during the follow-up. Routinely CRP measurement could be useful for identifying high risk TIA patients in order to plan aggressive prevention therapies and also silent vascular disease strategies diagnoses.

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Headache Syndromes in Patients With Unruptured Brain Arteriovenous Malformation

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Background: Only scant data are available on the frequency and type of headaches in patients with brain arteriovenous malformation (AVM), and their relation to morphological AVM characteristics has been insufficiently investigated. **Methods**: We analyzed data from 749 consecutive patients of the prospective Columbia AVM Databank. Patients were stratified into those with a history of headaches prior to AVM diagnosis and those with a negative headache history. Univariate and multivariate logistic regression models were used to test the effect of age, sex, AVM size (mm), location, venous drainage pattern, and presence of venous ectasia on a positive headache history in AVM patients. **Results**: Headaches occurred in 294 (40%) AVM patients; 108 (14%) had migraines (with and/or without aura), 67 (9%) had episodic or chronic tension type headache, 23 (3%) experienced thunderclap headache (unrelated to hemorrhage), and 96 (13%) remained unclassified. By univariate comparison, headaches occurred more frequently in women ($p<0.0001$) and were associated with large AVM size ($p=0.001$), lobar location ($p=0.0002$), borderzone AVM ($p<0.0001$), and venous ectasia ($p=0.0007$). The multivariate model confirmed the independent effect of female gender (OR 3.28, 95% CI 2.11–5.10), AVM size (OR 1.02, 95% CI 1.01–1.04), lobar AVM location (OR 2.19, 95% 1.18–4.05), and venous ectasia (OR 1.89, 95% CI 1.20–2.98). **Conclusion**: Our findings suggest an independent effect of female gender, AVM size, lobar AVM location and venous ectasia on the occurrence of headaches in partients with unruptured brain AVMs. In our cohort, the relative frequency of migraines is not different from the prevalence in the general population.

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Atherosclerotic Aortic Debris and Risk of Subsequent Stroke in Patients With Cerebral Ischemic Events: A Population-Based Study

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Background: Reports suggest that protruding atheromatous material in the thoracic aorta is an important cause of recurrent ischemic stroke. Methods: This historical cohort study included all 286 residents of Olmsted County, Minnesota, who had transesophageal echocardiography (TEE) within 60 days after their first TIA (n=90, 31.5%) or ischemic stroke (n=196, 68.5%) from 1993 to 1997. We used the Kaplan-Meier product-limit method and Cox proportional hazards regression analysis to estimate rates and identify predictors of subsequent ischemic stroke in these patients. Findings: Complex atherosclerotic aortic debris (CAAD) in the ascending and transverse segments of the arch was detected in 19 (6.6 %) patients. During 826 person-years of follow up, 3 patients with CAAD and 38 patients without CAAD had subsequent ischemic stroke. Estimated rates of subsequent ischemic stroke 4 years after first TIA or ischemic stroke were not significantly different for those with CAAD (15.8%, 95% CI 0–30.7%) and those

without CAAD (17.5%, 95% CI 11.9–22.7%, p=0.95). After adjusting for age, sex, and atherosclerosis other than in the thoracic aorta on TEE, CAAD was not a significant predictor of subsequent ischemic stroke (hazard ratio=0.76, 95% confidence interval 0.23–2.49, p=0.65). Interpretation: We found no evidence that CAAD is a risk factor for subsequent ischemic stroke in patients with first TIA or ischemic stroke in the general population.

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Elevated White Blood Count on Admission Independently Predicts Mortality Among Patients Hospitalized for Ischemic Stroke

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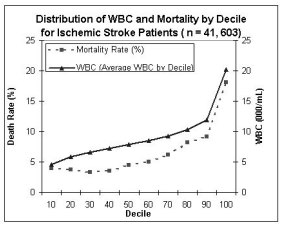
Objective: The relationship between WBC derangement on admission and mortality for ischemic stroke patients is an area of active study. Our objective is to depict the univariate and multivariate effect of abnormal WBC on mortality after accounting for demographics, acute pathophysiologic derangement, comorbidities, and type of stoke in a large patient population. **Methods:** Analysis included 44,102 (2,929 deaths) ischemic stroke admissions across 82 teaching and 145 non-teaching hospitals in the Atlas ™ (MediQual) database in 2000–01. Logistic regressions were used to control for age, laboratory values, vital signs, altered mental status, and comorbidities. ROC curve and Bootstrapping validated model fit. **Findings**: Overall, the median age was 76, 56% were women, and crude mortality was 6.6%. There was a significant correlation between elevated WBC and mortality (see chart below). There were 5,059 (12%) patients with elevated WBC between 10,900 and 14,100/ml and 3,119 (7%) patients with WBC > 14,100/ml. The risk adjusted odds ratios for the two elevated WBC groups were 1.3 (CI: 1.2–1.5) and1.8 (CI: 1.6–2.0) respectively. Other significant predictors ($p < .05$) included age, albumin < 2.7 g/dl, glucose > 135 mg/dl, pH arterial < 7.21 or > 7.48, PT INR > 1.1 or PT > 13 sec, creatinine > 3.0 mg/dl, systolic BP < 90 mm Hg, respiration < 10 or > 30 / min, altered mental status, metastatic cancer, and basil artery occlusion. The ROC for the model was .83. **Conclusions:** Elevated WBC on admission is an independent predictor of mortality for ischemic stroke patients. Research is needed to further understand the pathophysiologic mechanisms.



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Factors Influencing Short- and Long-Term Survival in the Copenhagen Stroke Study Cohort: A 10-Year Follow-up Study

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Survival after stroke was studied in the community-based Copenhagen Stroke Study (COST) over a 10-year period from 1992/1993 to 2002/2003. For the identification of independent determinants for survival admission stroke severity, age, gender and the cardiovascular risk factor profile was accounted for. Method and material: In a well-defined Copenhagen community all patients with stroke were seen on admission to hospital in the period March 1992 to October 1993. The stroke admission rate was 3.6/1000 inhabitants/year. On admission stroke severity was measured using the Scandinavian Stroke Scale (SSS, 0 - 58), stroke type was determined by CT-scan, and the presence of ischemic heart disease (IHD), hypertension, diabetes (DM), atrial fibrillation (AF) intermittent claudication, smoking, daily alcohol consumption and other disabling disease were examined and recorded in all. Date of death was obtained from the Danish Registry of Persons within a 10-year period following stroke. Independent predictors of death were identified using multivariate Cox regression. Results: In total 1152 patients with acute stroke were included. Mean age 74.2± 11 years, male/female 45%/55%, mean admission SSS-score 34±17. The one-year survival rate was 67.2%, the five-year survival rate was 37.2% and the ten-survival rate was 17.0%. Predictors of one-year mortality in the multivariate analysis was: Age Hazard Ratio (HR) 1.32 pr 10 years ↑ (p<0.001), stroke severity HR 0.65 pr 10 SSS points ↑ (p<0.0001), DM HR 1.49 (p<0.05) other disabling disease HR 1.50 (p<0.03). Predictors of 10-year mortality was: Age HR 1.60 pr 10 years ↑ (p<0.0001), female gender HR 0.69 (p<0.0001), stroke severity HR 0.79 pr 10 SSS points ↑ (p<0.0001), IHD HR 1.23 (p<0.05), former stroke HR 1.23 (p=0.05), DM HR 1.23 (p<0.02), AF HR 1.33 (p<0.02), smoking HR 1.18 (p<0.07), other disabling disease HR 1.44 (p<0.0005). Hypertension, type of stroke (hemorrhagic/ischemic), daily alcohol consumption and intermittent claudication were not significant predictors. Conclusion: Short-term survival is particularly determined by age and initial stroke severity. Long-term survival is also determined by gender, cardiovascular disease and diabetes. Hypertension per se was not a predictor of survival after stroke.

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Stroke Recurrence Rates Are Not Changing Over Time

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BACKGROUND: Previous population-based studies have shown that stroke recurrence rates after first ischemic stroke have not changed from 1950 to 1989. We hypothesized that advances in secondary stroke prevention in the 1990s would lead to decreased recurrence rates. We present the first population-based assessment of stroke recurrence rates over time since 1989. METHODS: We identified strokes from 7/93 to 6/94 and from 1/99 to 12/99 in the Greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS) region, a biracial population of 1.3 million. Strokes were found by screening ICD-9 stroke diagnosis codes of all inpatient, hospital-based and public health outpatient, and emergency department visits, as well as randomly selected private physician and nursing home records. All strokes were abstracted by study nurses, then reviewed by physicians. Among patients with first ischemic strokes, we identified both recurrent ischemic and hemorrhagic strokes during the one-year study periods, based on detailed review of initial hospitalization records and subsequent events with an ICD-9 stroke code. We estimated recurrence rates by Kaplan-Meier life-table analysis. RESULTS: There were 74 recurrent strokes (97% ischemic, 3% hemorrhagic) among 1,772 first ischemic strokes in 1993–94, and 75 recurrent strokes (89% ischemic, 11% hemorrhagic) among 1,815 first ischemic strokes in 1999. We found no statistically significant difference in recurrence rates in the GCNKSS population by comparing 1993–94 and 1999 (p=0.96). Our sample size provided 80% power to detect a 2% difference in estimated 365-day recurrence rates. CONCLUSIONS**:** Despite the emergence of several new secondary prevention strategies, we found no change in stroke recurrence rates between 1993–94 and 1999 within the same large population. Further studies characterizing the utilization of secondary stroke prevention methods within this population are needed.

Time from Initial Stroke	1993–94 Recurrence Rates (95% CI)	1999 Recurrence Rates (95% CI)
15 days	0.7%(0.5–0.9)	0.8%(0.6–1.0)
30 days	1.4%(1.1–1.7)	1.4%(1.3–1.7)
60 days	2.0%(1.7–2.3)	2.5%(2.1–2.9)
90 days	2.7%(2.3–3.1)	3.0%(2.6–3.4)
180 days	4.1%(3.6–4.6)	4.4%(3.9–4.9)
365 days	6.3%(5.5–7.1)	5.6%(4.9–6.3)

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Is Left Ventricular Hypertrophy a Predictor of Recurrent Vascular Events in African-American Stroke Patients?

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Background and Purpose: In population-based analyses such as the Framingham study, left ventricular hypertrophy (LVH) has been associated with an increased frequency of stroke. In Framingham, over a 36 year follow-up period, the risk of stroke was increased 4–7 fold in women and men with LVH at baseline. The influence of LVH on the risk for vascular events (stroke, MI, vascular death) in African Americans (AA) has been studied less, especially for recurrent stroke. We sought to assess the hypothesis that LVH would be a predictor of an increased vascular event rate in AA with a recent stroke. **Methods:** The African American Antiplatelet Stroke Prevention Study (AAASPS) database was used for this analysis. LVH was identified on the baseline ECG. 1809 patients with noncardioembolic stroke were enrolled in this secondary prevention study and followed for a two year period. Major vascular events during follow-up were recorded and we also analyzed whether pharmacologic treatment differed in patients with LVH. **Results:** The mean age of the patients was 61.3 years with 53.5% women. 399 patients (22.1%) had LVH on the baseline ECG. Among 193 patients with a recurrent stroke outcome event, 17.1% had LVH (p=0.08, Chi square analysis). There was no association between presence of LVH and MI or vascular death during the follow-up period. Patients with LVH had a higher baseline creatinine level (1.23 vs. 1.15 mg/dl, p=0.005). We did not identify any difference in use of various antihypertensive agents (such as ACE inhibitors) in patients with LVH, although patients with LVH were more likely to be treated with oral agents (p=0.05) or insulin (p=0.03) for diabetes. **Conclusions:** We did not identify a definite increase in the vascular event rate among AA stroke patients with LVH on the baseline ECG, although there was a trend for stroke alone. Patients with LVH had greater renal impairment and were more likely to be treated for diabetes, suggesting that LVH is a marker for overall vascular risk factor burden. Examination of larger cohorts in both primary and secondary prevention trials would be of interest to determine the overall clinical significance of LVH. Study supported by NIH/NINDS R01 NS 33430 to PBG

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Seven-Year Survival Trends of Stroke Patients: The Minnesota Stroke Survey

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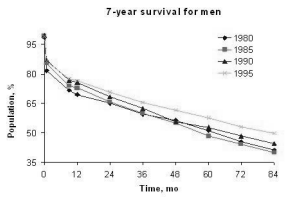
Background: With better medical care and hypertension detection and treatment, survival of stroke patients improved during the 1980s; however, little is known about recent trends. **Objective:** We hypothesize that 7-year survival will be greater among stroke patients in 1995 than in patients hospitalized in 1980, 1985, or 1990 and that definite stroke 28-day case-fatality rates decreased. **Methods:** Survival of hospitalized stroke was examined in the MN Stroke Survey (MSS), a population-based surveillance study conducted in 30–74 year old stroke patients during 1980, 1985, 1990, and 1995. All acute care hospitals in Minneapolis-St. Paul were surveyed. Hospital discharge codes were obtained and a 50% random sample of medical charts was abstracted by nurse abstractors. Diagnosis, CT scan, and vital status were obtained from the medical chart, and vital status after discharge was obtained from the MN Death Index. Strokes were validated using MSS stroke criteria. Sex-specific 28-day case fatality rates were determined. Age-adjusted, sex-specific 7-year survival curves were plotted for each survey year and examined to assess whether changes in stroke survival persisted after hospital discharge. **Results:** The 28-day case-fatality rates changed from 21.9% in 1980 to 11.2% in 1995 in men (p<0.01) and from 25% to 9.1% women (p<0.001). As shown below, the proportion of patients surviving 7-years was higher for men in 1995 (p<0.01), than any other

survey year. In women, survival followed the same pattern as in men, but was not different between survey years (p>0.05). **Conclusions:** These findings show that survival from stroke after hospital discharge improved substantially during the 1990's.



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Do Diabetic Patients Really Have Worse Outcomes After Acute Stroke Than Nondiabetics?

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Objectives: To analyse the differential features of diabetic acute stroke patients and its implications in stroke outcome. **Methods:** Observational study from the Stroke Data Bank of the Department of Neurology (1994–2003) with inclusion of consecutive ischemic and hemorrhagic stroke in-patients. Parameters analysed: risk factors, stroke subtype, severity at admission (Canadian Stroke Scale), length of hospital stay, in-hospital complications, mortality and functional state at discharge (modified Rankin Scale). TIA patients have been excluded from these last two parameters analysis. Descriptive and comparative analysis in patients with and without diabetes mellitus has been developed. **Results:** From 1994 to 2003, 4826 consecutive acute stroke patients were admitted in the department of Neurology, of whom1283 were diabetic. These patients with previous history of diabetes were older (70,98 vs 69,16% years old; p<0,001), had more rate of hypertension (70 vs 55,8%; p<0,001), peripheral vascular disease (9,1 vs 4,7%; p<0,001), dyslipemia (31,1 vs 22,3%; p<0,001) and previous stroke (18,1 vs 12%; p<0,001) than non-diabetic patients. Atherotrombotic (28 vs 17%; p<0,001) and lacunar infarction (24 vs 20,6%; p<0,01) were more frequent in diabetic patients. They also had more neurological complications as progressive stroke (4,5 vs 2,2%; p<0,001) and brain oedema (6,9 vs 5,2%; p<0,05) with no differences in systemic complications or in length of hospital stay. No differences with regards to stroke severity at admission neither than to stroke outcome at discharge were found. **Conclusions:** Previous history of diabetes mellitus is not associated by itself to more severity at admission neither than to a poor outcome in acute stroke patients. It is possible than the poor prognosis that has been traditionally attributed to diabetes could be due to the developing of hyperglycaemia in the acute phase of stroke, but we have not analysed this point. Further prospective studies are need in order to explore this possibility.

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Social Exclusion and Stroke Mortality

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In Sao Paulo, Brazil, stroke is responsible for one quarter of cardiovascular deaths among people aged 30 to 79 years-old (men=22.2%; women 27.0%). The burden of intracerebral hemorrhagic stroke is still higher when compared to ischemic stroke mainly among women. We hypothesized that this pattern could be explained by an unequal spatial distribution of stroke subtypes among neighborhoods due to social inequality, that is intracerebral hemorrhage death rates would be higher on the poorest areas. We applied the social exclusion score (an index that combine for every district, indicators as income, unemployment, years of school, and violence) as an index for social inequality. We compare age-adjusted mortality rates for stroke during the period of 1997–2003 among the 96 districts of the city grouped by quartiles of social exclusion score (I=lowest; II=mid-superior; III=mid-inferior; IV=highest). For all types of stroke, age-adjusted mortality rates for quartile I was for men 47.5 deaths for 100,000 inhabitants (95% Confidence Interval, 95%CI=41.1–53.8) and for women 33.8 deaths for 100,000 inhabitants (95% CI, 28.9–38.7). Considering quartile I as reference, the risk ratios for men living on districts classified in quartile II was equal to 1.48 (95%CI =1.42–1.55);for quartile III=1,62 (95%CI=1.55–1.72); for quartile IV=2.00 (95%CI =1.89–2.16) (P for trend <0.001). The risk ratios for women (quartile I as referent) living on districts classified in quartile II was equal to 1.40 (95%CI=1.35–1.46); III=1.70 (95%CI=1.62–1.82), IV=2,20; 95%CI =2.05–2.41). (P for trend <0.001) For cerebral infarction and intracerebral hemorrhage, the same patterns were observed for both genders. However, for subarachnoid hemorrhage (SAH) deaths rates this pattern was observed only for women. Concluding, social inequality does not explain the higher burden of intracerebral hemorrhagic stroke death rates.

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Trends in Stroke Subtypes: The Minnesota Stroke Survey

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Objective: We examine trends in stroke subtypes. We hypothesize an increase in the proportion of cardio-embolic strokes relative to other ischemic stroke subtypes. Possible mechanisms underlying such an increase are: 1. Improved survival after myocardial infarction (MI) due to new treatments for coronary artery disease 2. Increased use of cardio-diagnostic tests in ischemic stroke patients. Methods: We report on data from 1980, 1985, 1990 and 1995 Minnesota Stroke Surveys (MSS). The MSS is a population-based surveillance of hospitalized acute stroke cases (age 30 -74 years) in the Minneapolis-St.Paul area. Cases are identified by discharge codes and 50 % are sampled for abstraction. Cases are then validated as ischemic strokes and intraparenchymal (IP) hemorrhages by CT/MRI. Cases without scans are designated as undetermined. Ischemic strokes are further classified into those with and without cardio-embolic sources using the TOAST criteria for diagnosis of cardioembolism. Data were available on the following for all survey years. 1. atrial fibrillation/flutter 2. mitral stenosis 3. atrial myxoma or intra-cardiac clot 4. recent MI. Results: There were 212, 314, 363, and 432 validated ischemic stroke cases in survey years 1980, 1985, 1990 and 1995 respectively. Results are shown in the table. Conclusions: There is an overall increasing trend in the proportion of acute ischemic strokes with potential cardio-embolic sources (**). However, the proportion of ischemic stroke patients with a prior history of MI has remained stable (*). Hence, the increase in the proportion of ischemic strokes of presumed cardioembolic mechanism may be due to increased use of cardiodiagnostic tests in ischemic stroke patients rather than due to a shift in the population of patients.

Results - Minnesota Stroke Survey

Year	1980 N (%)	1985 N (%)	1990 N (%)	1995 N (%)
All strokes (includes undetermined)	382	419	435	489
Validated IP hemorrhages	45 (11.8)	49 (11.7)	49 (11.3)	49 (10)
Validated ischemic strokes	212 (55.5)	314 (74.9)	363 (83.4)	432 (88.3)
Ischemic strokes with prior MI history*	NA	57 (18.2)	76 (21)	78 (18.1)
The following refers to ischemic strokes				
–1.Atrial fibrillation/flutter	29 (13.7)	48 (15.3)	83 (22.9)	74 (17.1)
–2.Mitral stenosis	3 (1.4)	11 (3.5)	18 (5)	33 (7.6)
–3.Intracardiac thrombus/tumor	1 (0.5)	3 (1)	20 (5.5)	21 (4.9)
–4.MI within 8 weeks prior to stroke	18 (8.5)	20 (6.4)	41 (11.3)	24 (5.6)
Patients with any of 1–4 above**	44 (20.8)	71 (22.6)	117 (32.2)	118 (27.3)

* No significant trend; **Age adjusted proportions are significantly different, (p=0.0058).

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Perceptual, Social, and Behavioral Factors Are Associated With Delays in Seeking Medical Care in Patients With Symptoms of Acute Stroke

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Background and Purpose: Despite the availability of reperfusion therapy for treating acute ischemic stroke, most patients remain ineligible mainly due to late arrival to hospital. We hypothesized that perceptual, social, and behavioral factors affect delays in seeking help following symptom onset. Methods: During a 2-year period (2000–2002), 209 of 518 patients hospitalized in the Department of Neurology for ischemic stroke, who presented with stroke symptoms and fulfilled inclusion criteria were interviewed about their symptom experience, interpretation, and reaction, and brief personality assessments were performed in communicative patients. Odds ratios and 95% confidence intervals for risk of delay in seeking help for >3 hours (reaction time) were estimated. Following multivariate analyses, 7 variables associated with increased risk of delay and representing demographic, clinical, perceptual, social, and behavioral factors were included in an assessment of the effect of combined risk factors on delay. Results: Upon adjustment for demographic and clinical data, perceived severity and control of symptoms, contextual factors, symptom attribution, hesitation, advice of others, contact with ambulance, and high general anxiety, we found that beyond clinical variables, perceiving symptoms as not severe (2.38; 1.05–5.88), not being advised by others to seek help (5.55; 1.59–20), not contacting an ambulance (3.85; 1.59–10), and perceived control of symptoms (2.45; 1.08–5.71) were associated with delays in reaction time. When 7 factors predictive of delay (age < 70, male, NIHSS score < 5, non-sudden onset, perceived control of symptoms, not advised to seek help, and didn't contact an ambulance) were examined in combination, the proportion of patients delaying seeking help increased steadily with increasing numbers of factors:17%, 18%, 32%, 47%, 67%, and 94% for patients with 0–1, 2, 3, 4, 5, and 6–7 factors, respectively. Conclusion: Perceptual, social and behavioral factors contribute to delay in seeking medical care in acute ischemic stroke beyond demographic and clinical variables and, when combined, further increase the risk of delay. These findings may have important implications for designing programs to reduce delay in seeking help.

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National Healthline Responses to a Stroke Scenario: Implications for Early Intervention

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Objective: Acute stroke is a time dependent emergency where patients often present to the hospital outside of the therapeutic window for thrombolytic therapy. In order to determine the role that healthlines may have in promoting early access to therapy, this study evaluated patterns of healthline triage of potential stroke victims. **Methods:** Phone numbers of healthlines at 82 United States hospitals with active neurology residencies were acquired using the Internet. Each healthline was called and the operator was presented with a standardized, scripted stroke patient scenario. The operator was asked to choose one of four responses that could be given to the patient (wait for symptom resolution, contact a primary care physician (PCP), drive to a local urgent care center, call 911 for ambulance transport to a hospital). The operator was then asked to name common signs and symptoms of stroke. If the operator transferred the call, the process was repeated. **Results:** Forty-six healthlines participated, with 22% recommending the patient contact a PCP. The remaining 78% recommended EMS transport to local hospitals. Phone calls were transferred at least once in 18 cases, and 24% of the operators could not name one sign or symptom of stroke. **Conclusions:** Nearly a quarter of potential stroke victims were routed away from emergent treatment for the described

scenario. By diverting patients away from emergency therapy, patients are in jeopardy of falling out of the thrombolytic therapeutic window. Improved stroke education for healthline personnel may reduce time to presentation for many stroke patients.

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Healthcare Providers' Stroke Awareness

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Background - Several studies have suggested that healthcare providers often fail to follow established guidelines for stroke prevention. We sought to assess whether failure to adhere to guidelines was related to knowledge. **Methods** - The National Stroke Association sponsored a telephone survey of 504 primary healthcare providers between August and September 2002. Providers were sampled randomly from all regions of the U.S. All participants answered questions about management of 3 case vignettes and described their clinical practice and routine patient education. The chi-squared test was used to assess differences in appropriate and inappropriate responses between provider groups. **Results** - Respondents included 101 family/general practitioners, 101 internists, 100 obstetrician/ gynecologists (OB/GYN), 102 physician assistants (PA), and 100 nurse practitioners (NP). There were 195 (38.7%) women; average age was 47.4 ± 9.1 years (mean ± SD). Less than 50% stated that they review stroke risks and warning signs with patients as part of the annual exam. The three case vignettes focused on management of new onset atrial fibrillation (case 1), hypertension (case 2), and TIA (case 3) [Table]. Only 25% of OB/GYN, 43% of NP, and 55% of PA appropriately identified the need for anticoagulation in a patient with atrial fibrillation at high risk of stroke. Furthermore, 20% of NP and 26% of OB/GYN did not identify appropriate management of hypertension. The majority of providers (78 - 88%) treated TIA as an emergency. **Conclusions** - Several groups of primary care providers, including OB/GYN, PA, and NP, frequently failed to identify appropriate interventions for stroke prevention in case vignettes. Furthermore, many providers do not educate patients routinely on stroke risks and warning signs. Targeting certain groups of primary health care providers for educational campaigns could improve stroke prevention practices.

Table. Providers' responses for the three case vignettes on management of stroke prevention.

	FP/GP n =101 N	Internists n = 101 N	OB/GYN n = 100 N	PA n = 102 N	NP n = 100 N	Total n = 504 N (%)	Chi-squared p-value
[1]Case 1 (new onset atrial fibrillation):							
1) Appropriate: warfarin	80 21	86 15	25 75	56 46	43 57	290 (57.5)	<0.001
2) Inappropriate: other medications						214 (42.5)	
[2]Case 2 (hypertension):							
1) Appropriate: add any anti-hypertensives	94 7	97 4	75 26	93 8	80 20	439 (87.1)	<0.001
2) Inappropriate: no new medications/ don't know/ refer to other physician						65 (12.9)	
[3]Case 3 (acute TIA):							
1) To the nearest ER or stroke center	79 22	85 15	88 11	84 18 0	81 17 2	417 (82.7)	0.433
2) Same day clinic	0	1	1			83 (16.5)	
3) Next week clinic/ other						4 (0.8)	

FP/GP = family/general practitioners; OB/GYN = obstetrician/ gynecologists; PA = physician assistants; NP = nurse practitioners. **[1]Case 1**: 75 year-old woman presented 1 week after new onset atrial fibrillation which is rate-controlled. Her current medications include hydrochlorothiazide 50mg qd, metoprolol 25 mg bid. She is physically active and compliant. Which medications would you initiate as her primary care provider? **[2]Case 2:** The same patient from case 1 returned with blood pressure 155–175/90–95, and heart rate 70 - 90. Which medications would you initiate as her primary care provider? **[3]Case 3:** 72 year-old woman phones the clinic after having a 30-minute episode of difficulty speaking and right face and arm weakness. She is now normal. Her past medical history is unremarkable. What do you tell her?

Hemorrhage

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Novel Observations Regarding Acute Vasospasm and Influence of Race on Outcome After Subarachnoid Hemorrhage

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Introduction: Data on 3500 patients with aneurysmal subarachnoid hemorrhage (SAH) entered into 4 randomized trials conducted around the world between 1991 and 1997 were analyzed to ask questions about SAH. **Methods:** Uni- and multivariate statistical analyses were conducted to determine the effect of race and early vasospasm (EVSP) on admission angiography on SAH demographics and outcome. **Results:** Whites were significantly older than other races. Blacks more frequently had a history of hypertension and more commonly had elevated blood pressure on admission. Blacks and other minorities were more likely to have internal carotid aneurysms and whites were more likely to have posterior circulation aneurysms. In-hospital complications were not significantly different except for pulmonary edema, which was more common in whites. Outcome at 3 months was not significantly different between races. EVSP within 48 hours of SAH was diagnosed in 10% of patients and was significantly more likely in patients with poor neurological grade, history of SAH, intracerebral hematoma, larger aneurysm, thick SAH on CT and intraventricular hemorrhage. EVSP was not associated with delayed vasospasm but was associated with cerebral infarction and unfavorable outcome ($p<0.005$). There was a trend for patients with increasingly severe EVSP to have worsening outcome. **Conclusions:** Race was not a prognostic factor for outcome after aneurysmal SAH, suggesting that the higher SAH mortality previously observed in blacks is due to a higher incidence of SAH in blacks. Early vasospasm may be more important than previously thought as it was diagnosed in 10% of patients and was associated with cerebral infarction and poor outcome.

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NMDA Receptor Antagonist Memantine Promotes Functional Recovery in Rats With Experimental Intracerebral Hemorrhage

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Background: Intracerebral hemorrhage (ICH) is defined as the acute extravasation of blood into the brain parenchyma. It has been reported that in the early period of experimental hematoma, one of the main pathological factors in ICH, glutamate is highly accumulated in the hemisphere ipsilateral to the hematoma. The exact role of glutamate is not yet verified however, and there is no report about glutamate receptor suppression therapy in ICH. In this study, we attempted to suppress the glutamate injury with the NMDA receptor antagonist, memantine. **Methods:** Experimental ICH was induced by intrastriatal administration of bacterial collagenase in adult rats and memantine (20 mg/kg) was injected intravenously to each rat at 20 minutes after ICH induction and daily afterwards for 4 days. Modified limb placing test (MLPT) and elevated body swing test (EBST) were conducted to evaluate the behavioral recovery of the animals for 5 weeks. Also, by a spectrophotometric assay, the hematoma volume was estimated and immunohistochemistry with histological markers related to neuronal cell death (Bax, TUNEL, active caspase-3) was carried out at 3 days after ICH. **Results:** The memantine-treated rats showed markedly better functional performance on both two behavior tests (MLPT and EBST) from 1 week after ICH compared with the ICH-only group, and these effects persisted for up to 5 weeks. In the hemoglobin analysis, the hematoma volume of memantine group was decreased by 48 % compared to the ICH-only group at 3 days after ICH. In immunohistochemical analysis, the $TUNEL^+$, active $caspase\text{-}3^+$ and Bax^+ cells were less found in the perihematomal lesions ($p<0.01$) in the memantine-treated rats compared to ICH-only group. **Conclusions:** These findings suggest that the pathological progression in ICH may be associated with glutamate accumulation, thus memantine can be a potent drug in the treatment of ICH by suppressing glutamate-mediated excitotoxicity.

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Blood Transfusion Following Subarachnoid Hemorrhage Worsens Outcome

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Introduction: Blood is often liberally transfused to patients with subarachnoid hemorrhage (SAH) and cerebral vasospasm to improve oxygen delivery. Recently, it was reported that intraoperative blood transfusion worsened outcome in SAH. No adjustments were made for the severity of medical illness. We sought to determine the effect of blood transfusion on patient outcome adjusted for both neurological and medical severity. Methods: A retrospective analysis of 166 aneurysmal SAH patients admitted to the Neurological Intensive Care Unit between January 2000 and January 2004 was conducted documenting demographic data, Hunt-Hess score, Fisher grade, presence and severity of vasospasm by TCD sonography and Acute Physiology and Chronic Health Evaluation (APACHE II) score. The number of red cell transfusions and hemoglobin and hematocrit levels before and after transfusion were recorded. Outcome was determined at discharge using the Glasgow Outcome Score and Modified Rankin Scale (MRS). Statistical analysis was performed using univariate and multivariable logistic regression analyses. Results: On admission, the mean hemoglobin and hematocrit were 12.9Â±1.7 g/dl and 37.9Â±4.5%. The median admission Hunt-Hess score was 3 (25th, 75th quartiles 2,4). Ninety-six patients (57.8%) developed cerebral vasospasm. Eighty-one patients (48.7%) were transfused during their NICU stay an average of 2.7Â±1.8 units of red cells. Overall, 86 patients (51.2%) had a poor outcome defined as a MRS score ≥3. For patients with vasospasm, blood transfusion was independently associated with a worse outcome after adjustment for admission Hunt-Hess and APACHE II scores (Odd's Ratio 2.91, 95% CI 1.09–7.78). For those without vasospasm, transfusion had no effect on outcome (OR 0.81, 95% CI 0.10 - 6.49). Conclusion:Studies have shown that liberal transfusion strategies in critically ill patients worsen outcome. Blood transfusion after SAH also appeared to be independently associated with a worse outcome in patients with vasospasm when adjusted for neurological and medical severity. Further studies are needed to confirm this association, elucidate the underlying mechanisms, and determine the optimal transfusion threshold for patients with subarachnoid hemorrhage.

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Early Neurological Worsening and Prognosis of Intracerebral Hemorrhage

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Background: Spontaneous intracerebral hemorrhage (ICH) constitutes about 10–15% of all strokes and accounts for the highest mortality of all stroke types. Patients with a more favorable prognosis however have been poorly investigated so far. We therefore studied initial severity of neurological deficits, early neurological worsening and functional outcome in

patients not intubated nor comatose at admission. Methods: 446 consecutive patients from 11 Neurology departments with acute stroke units were prospectively documented on standardized case report forms. Stroke severity was assessed on the National Institutes of Health Stroke Scale (NIH-SS) at admission and 48–72 hours after admission. A predominantly central follow-up assessed functional outcome and death up to 120 days after admission. Results: 66 patients were admitted intubated or in comatose state. These patients had a mortality of 45.5% until 72 hours and 71.2% until 120 days after admission. Of 380 patients not intubated nor comatose at admission, 21 patients (5.5%) had died and 55 patients (14.5%) presented worsening of key neurological functions 72 hours after admission. Initial score on the NIH-SS, extent of hemorrhage, and ventricular bleeding were identified as independent predictors for worsening of key neurological functions or death. At follow-up, 60 patients (15.8%) had died and 120 patients (31.6%) had regained functional independence (Barthel Index $\geq$ 95). Age and the NIH-SS total score were identified as independent predictors for reaching functional independence. The resulting model was very similar to a recently validated prognostic model for acute ischemic stroke[1] and had a higher accuracy than the treating physicians' prognosis made within the first 72 hours after admission. Conclusion: Independent predictors for 120-day functional outcome following ICH in non-comatose patients are identical to ischemic stroke with very similar B-weights. In non-comatose patients, the NIH-SS total score at admission might be a more reliable predictor of functional outcome than other indicators of initial stroke severity. [1]Stroke 2004;35;158–162

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PKC and Rho Activation in an In Vitro Model of Cerebral Vasospasm After Subarachnoid Hemorrhage: Role of Bilirubin Oxidation Products

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Delayed cerebral vasospasm (CV) remains a major cause of death & impaired neurological recovery after subarachnoid hemorrhage (SAH). Despite intensive research efforts, the etiology is not yet known. *In vivo* models have implicated PKC & rho activation in arteries, but the method of inducing CV *in vivo* has been criticized. Our *in vitro* model uses human CSF from patients with CV after SAH & porcine carotid artery (PCA) smooth muscle. The aim of this study was to assess the activation of the PKC isoforms α & δ, & Rho in our *in vitro* model. The effects of purified bilirubin oxidation products (BOXes), which we have proposed to be the causative molecule in CSF_V were also examined. Understanding the etiology of CV will allow development of effective prophylactic treatments. SAH CSF was classified as CSF_V or CSF_C, based on whether JO_2 of PCA was stimulated above (V) or below (C) 0.4 μMol O_2/min/g dry wt by a 1:200 dilution of CSF. Tissue was exposed to 1:1 CSF_C, CSF_V or 1:100 BOXes for either 20 minutes, or 3 hours. Membrane & cytosol (M & C) fractions were subjected to SDS-PAGE & western blot analysis for PKC α & δ and Rho. Their activation was determined by the proportion of signal detected in the M:C fractions, quantified using ImageQuant software. Rho was activated at both time points in tissue treated with CSF_V. PKC-δ was activated at 20 min, but not 3 hrs, whereas PKC-α activation was only seen at 3 hrs. CSF_V only (not CSF_C) elicited these effects. BOXes activated all three proteins at both time points. These data show that PKC isoforms α and δ are activated in a time-dependent manner, δ at initiation of contraction, & α during tension maintenance. Rho activation suggests an involvement of phosphatase inhibition, which would contribute to the maintenance of tension. BOXes may be involved in all these intracellular events. *This research supported by NIH RO1 HL67186*

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Promoter Polymorphisms in Interleukin 6 and Interleukin 10 Are Associated With Cardiac Injury and Dysfunction After Subarachnoid Hemorrhage

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Previous studies of patients with subarachnoid hemorrhage (SAH) have found an association between elevated levels of inflammatory cytokines (ICs) such as interleukin-6 (IL-6) and the development of cerebral vasospasm. Elevated levels of ICs have also been found in patients with congestive heart failure and myocarditis. Single nucleotide polymorphisms (SNPs) in the promoters of the genes encoding IL-6 (174G>C) and the counter-inflammatory cytokine interleukin-10 (IL-10, 1082G>A) have been shown to modulate levels of ICs in patients hospitalized for coronary bypass surgery and pneumonia. The objective of this study was to test the hypothesis that IC promoter SNPs are associated with an increased risk of cardiac injury (troponin release) and dysfunction (reduced left ventricular ejection fraction [LVEF]) after SAH. Methods: This was a prospective cohort study of 167 patients admitted with aneurysmal SAH. The subjects were enrolled as soon as possible after admission, a blood sample was obtained for genotyping and measurement of cardiac troponin I (cTi), and an echocardiogram was performed. The cTi measurement and echo were repeated 2 and 5 days after enrollment. After DNA extraction, genotyping for the IL-6 174G>C and the IL-10 1082G>A SNPs was performed using a commercially available methodology (fluorescence polarization template-directed incorporation, Perkin-Elmer). For analysis purposes, a cTi level > 1.0 mcg/L on any of the three measurements was considered to be abnormal. The LVEF was treated as a continuous variable, using the lowest value from the three measurements. The relationships between the genotypes and the cardiac outcomes were quantified using Fisher's exact and Wilcoxon ranksum tests. Results: See table Conclusions: SNPs in the gene promoters encoding IL10 and IL6 are associated with cardiac injury and dysfunction, respectively, after SAH. These findings suggest a possible role of elevated levels of inflammatory cytokines in the genesis of neurocardiogenic injury.

Inflammatory Cytokine SNPs & Cardiac Outcomes

	IL-6 174G>C Genotype				IL-10 1082G>A Genotype			
	GG (N=71)	GC (N=65)	CC (N=17)	P	AA (N=62)	AG (N=77)	GG (N=28)	P
cTi > 1.0	15%	9%	18%	NS	5%	16%	18%	0.046 (AG/GG vs. AA)
Mean LVEF ± SD	61±11	65±10	57±10	0.032 (GG/GC vs. CC)	63±10	62±10	61±13	NS

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Early Electrocardiographic Morphologic Changes and Prediction of Delayed Cerebral Ischemia, Stroke, and High Troponin Level Among Aneurysmal Subarachnoid Hemorrhage Patients

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Introduction. An ECG is routinely done in most of our aSAH patients during the first 24 hours after hospital admission. Early ECG morphologic changes may be seen after aSAH. We performed a systematic assessment of these changes in the 12-lead ECG of patients suffering of aSAH, and studied their predictive value on several outcome variables. **Methods.** We analyzed the ECG's of 442 patients with aSAH during the first 24hrs of admission enrolled in the Columbia-University SAH-Outcomes-Project, between 10/1996–10/2002. Association of early abnormal ECG changes (ST abnormalities, QT-c prolongation, BBB, pathologic Q-wave, LAE, RAE, and LVH patterns) and prediction of Delayed Cerebral Ischemia (DCI), stroke secondary to vasospasm, high cardiac Troponin-I level (cTI$\geq$10μg/L), and adverse outcome by the modified Rankin Scale (mRS$\geq$2) by day 14 or at discharge from the index admission, were analyzed using forward conditional logistic regression models. **Results.** Morphologic abnormalities where seen in the ECG of 76% of patients during the first 24 hrs of the index-admission (mean=1.58±2.2 days). The most frequent abnormality was prolonged QTc$\geq$0.55 sec (34.4%). The combined QT-c/ST abnormality variable interacted with Hunt & Hess score in the prediction of DCI (exp-=3.14, p=0.002) and stroke from vasospasm (exp-=2.67, p=0.001). ST-depression $\geq$1mm in at least two leads (exp-=1.331, p=0.013) and pathologic Q-wave (exp-=1.427, p=0.028) were independent predictors of high cTI level ($\geq$10μg/L). All models were adjusted for aSAH severity (Hunt & Hess score). **Conclusions.** These data suggest that early ST segment and QT-c interval abnormalities occur early and among an important proportion of aSAH patients (43%). There is a significant effect of HH score in the predictive value of early QT-c and ST abnormalities for DCI and stroke from vasospasm. Early significant ST depressions and pathologic Q-waves in more than two leads predict a high cTI leak, which may be associated with cardiac dysfunction. Our early ECG morphologic changes had no clear prediction of functional outcome at 14 days using the mRS. Future research in early cardiac electrophysiological changes and cardiac dysfunction after aSAH is needed.

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Using Automated Clinical Data on Admission to Predict Mortality Among Patients Hospitalized for Hemorrhagic Stroke

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Context: Research models predicting stroke mortality have not been widely adopted due to the high cost of chart abstraction. A cost effective clinical model is crucial for large scale implementations of quantitative decision support. **Objectives:** To develop and validate a predictive model using automated laboratory data (LAB) for acute conditions and Uniform Billing data for demographics, discharge status, and comorbidities. The significance of vital signs (VS) and Altered Mental Status (AMS), that were not automated, was also analyzed. **Methods:** A model was derived from 2780 (611 deaths) hemorrhagic stroke admissions across 18 teaching and 26 non-teaching hospitals that exported LAB data to Atlas™ (MediQual) in 2000–01. Multiple cuts on admission LAB and VS were crafted per change-point methods. Age, LAB, comorbidities (identified by 6th digit ICD-9 coding), VS, & AMS were entered into logistic regressions. ROC curve assessed model fit and Bootstrapping validated the model internally. Manually abstracted data (n = 11080, 2517 deaths) from 180 hospitals validated the model externally. Hosmer-Lemeshow Chi^2 assessed calibration. Results are presented as odds ratios & 95% confidence intervals. **Findings**: Median age was 74. Crude mortality was 23%. Significant predictors included age, glucose > 174 mg/dl (1.7, 1.5–1.9), WBC >14.4 k/ml (1.5, 1.3–1.7), platelets < 89 k/ml (3.6, 2.7–4.7), pH arterial > 7.52 (1.6, 1.3–2.0), pCO2 arterial > 50 mm Hg (2.8, 2.1–3.8), creatinine > 1.7 mg/dl (2.7, 1.7–4.3), cancer (2.0, 1.4–2.8), subarachnoid or intracerebral hemorrhage (2.7, 2.4–3.0), systolic BP >190 mm Hg (1.7, 1.5–1.9), respiration > 30 / min (2.0, 1.3–2.9), temperature <96°F (2.0, 1.7–2.3), and severe AMS (12.5, 10.8–14.6). The ROCs for the derivative and validation models were .91 and .89 respectively, with excellent calibrations. **Conclusions:** LAB provides objective precise measures of acute pathophysiologic conditions. Variables indicating hyperglycemia, leukocytosis, thrombopenia, acidosis/alkalosis, and renal dysfunction constitute high risk. Cancer and hemorrhage site are also significant. VS & AMS add significant predictive power to the model and should be automated. Based mainly on automated data, this model is cost effective to implement.

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Perimesencephalic Subarachnoid Hemorrhage: A Population-Based Study

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Background: Nonaneurysmal perimesencephalic subarachnoid hemorrhage (PMSAH) appears to have an etiology and natural history distinct from aneurysmal rupture. Referral-based studies suggest that approximately 15% of SAH patients have no discernable cause of bleeding, but the incidence of PMSAH is unknown. We describe the first population-based study of PMSAH, with presentation of incidence rates and patient demographics. **Methods:** All patients age $\geq$ 20 hospitalized with first-ever, nontraumatic SAH in the Greater Cincinnati/Northern Kentucky metropolitan area were identified from 5/98–7/01 and 8/02–4/04. Traumatic and iatrogenic SAH were excluded. SAH associated with anticoagulation was included. PMSAH was defined as hemorrhage restricted to the suprasellar cistern and/or cisterns surrounding the brainstem (with scant blood allowed in the ventricles) and a negative cerebral angiogram. Incidence rates were age, race, and sex adjusted to the 2000 US population as appropriate. **Results:** There were 421 SAHs identified. Cases in Asian-Americans (2) were excluded, leaving 419 SAHs (316 white, 103 black) for analysis. Of 419 SAHs, 72 did not have angiograms. Among the remaining 347 cases, 283 had aneurysm rupture, 36 had nonaneurysmal hemorrhage not of the PMSAH pattern, and 28 had PMSAH. Among PMSAH cases, mean age was 49, 43% were women, 25% were black, 28% were hypertensive, and 32% were smokers. Annual incidence rates of PMSAH are presented in the table. **Conclusions:** PMSAH represents 5–10% of all SAH, and occurs with an annual incidence of approximately 0.6/100,000 persons ages $\geq$ 20. PMSAH, unlike aneurysmal SAH, is not more common in women. This may reflect differences in risk factors for PMSAH and aneurysmal SAH.

	All SAH Cases	SAH Incidence* (95% CI)	PMSAH Cases	PMSAH Incidence* (95% CI)
Total	419	8.9 (8.1–9.8)	28	0.6 (0.4–0.8)
Black	103	15.5 (12.4–18.5)	7	1.2 (0.3–2.0)
White	316	7.9 (7.0–8.8)	21	0.5 (0.3–0.8)
Men	121	5.6 (4.6–6.7)	16	0.7 (0.4–1.1)
Women	298	11.7 (10.3–13.0)	12	0.5 (0.2–0.7)

*Per 100,000 persons $\geq$ 20, age, race, and sex adjusted to the 2000 US population as appropriate.

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MMP-2 and -9 Activity Is Induced by Aβ Via Jnk Activation in Murine Cerebral Endothelial Cells

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Cerebral amyloid angiopathy (CAA), the accumulation of amyloid around cerebral vessels, is a frequent finding in the elderly with or without dementia. Spontaneous intracerebral hemorrhage (ICH) is the most recognized complication of CAA, yet little is known about the molecular mechanisms leading to CAA-related ICH. We have recently found that the amyloid-beta peptide (Aβ) induced the expression of MMP-9 in cerebral endothelial cells (CECs), and that MMP-9 immunoreactivity was present in amyloid-laden vessels in APPsw (tg2576) mice. To study intracellular mechanisms regulating MMP expression, we examined upstream pathways altered by Aβ in CECs. Aβ activated the stress kinase, c-Jun N-terminal kinase (JNK), in parallel with an increase in the phosphorylation of its substrate, the transcription factor, c-Jun. These changes were detected prior to Aβ-induced increases in MMP-2 and -9. Furthermore, Aβ increased AP-1 DNA binding, consisting of the c-Jun-c-Fos dimer (as determined by supershift assay). As AP-1 consensus sequences are found in the promoter region of the *mmp2* and *mmp9* gene, pharmacological disruption of AP-1 DNA binding with curcumin attenuated Aβ-induced MMP-2 and -9 expression, both at the RNA and protein level. Moreover, suppression of JNK activity using antisense oligonucleotides resulted in a decrease in c-Jun phosphorylation, and a decrease in Aβ-induced MMP-2 and -9 expression. Finally, JNK antisense oligonucleotides also decreased Aβ-induced extracellular matrix degrading activity, as demonstrated by cell invasion assay. These results suggest that Aβ activates JNK, resulting in c-Jun phosphorylation, AP-1 DNA binding, increased transcription of MMP-2 and MMP-9, and ultimately extracellular matrix degradation by CECs. We raise the possibility that these intracellular cascades may participate in vascular basement membrane breakdown and CAA-induced ICH.

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Cortico-Subcortical Distribution of Silent Microbleeds Is Different Between Hypertension and Cerebral Amyloid Angiopathy

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Background and Purpose: Silent microbleeds (SMBs) are mainly caused by advanced hypertension (AHT) or cerebral amyloid angiopathy (CAA), but the distributions of SMBs are quite different according to the causative diseases: SMBs are located diffusely in the whole brain area in AHT patients, but exclusively in cortico-subcortical area in CAA patients. We hypothesized that distribution of these SMBs may be different between AHT and CAA even in the cortico-subcortical area. **Methods:** A consecutive series of patients with intracerebral hemorrhage underwent brain MRI including gradient-echo sequences from Jan 1999 to Dec 2003 (n = 226). Out of the subjects, we selected typical AHT and CAA patients as follows: AHT group, 1) history of hypertension > 5 years, 2) symptomatic hemorrhage in putamen, thalamus or pons; CAA group, 1) symptomatic cortico-subcortical hemorrhage only, 2) consistent with "probable CAA" of Boston CAA Criteria. Patients with $\leq$ 5 cortico-subcortical SMBs were excluded from this study. The lesions were counted and localized by consensus of 2 stroke neurologists blinded to clinical information. **Results:** A total of 52 hemispheres (AHT group, n = 32; CAA group, n = 20) were analyzed. Number of SMBs was much higher in CAA group (47.6 $\pm$ 56.8, total 952 lesions) than in AHT group (17.4 $\pm$ 27.4, total 557 lesions; $p = 0.01$). The SMBs showed a significant predilection for the temporo-occipital lobes in AHT group, but for the parietal lobe in CAA group (Table). The most involved vascular territory was middle cerebral artery territory in both groups, but the lesion number in anterior cerebral artery territory was relatively high in CAA group. **Conclusions:** These data suggest that AHT and CAA may show different topographical distribution of SMB even in cortico-subcortical area. Our results should be helpful to differential diagnosis of early stage patients with isolated cortico-subcortical SMBs.

Analysis of silent microbleeds distribution

		AHT (n = 32)	CAA (n = 20)
Anatomical	Frontal	2.0 $\pm$ 3.4	5.4 $\pm$ 9.0
	Parietal	2.8 $\pm$ 6.4	20.8 $\pm$ 28.3
	Temporo-insular	7.7 $\pm$ 12.7	11.0 $\pm$ 12.7
	Occipital	5.0 $\pm$ 8.0	10.6 $\pm$ 15.4
Vascular	Anterior cerebral artery	1.4 $\pm$ 3.3	10.0 $\pm$ 12.6
	Middle cerebral artery	7.3 $\pm$ 14.8	23.7 $\pm$ 29.6
	Posterior cerebral artery	7.0 $\pm$ 11.6	13.2 $\pm$ 17.4
	Anterior choroidal artery	0.3 $\pm$ 0.7	0.3 $\pm$ 0.6
	Medullary branch	1.4 $\pm$ 1.5	1.5 $\pm$ 2.0

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Brain Atrophy and Long-Term Neurological Deficits After Experimental Intracerebral Hemorrhage: The Role of Iron

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Background: The long-term effects of intracerebral hemorrhage (ICH) on brain damage are poorly understood. Recent evidence suggests that some ICH-induced brain injury results from the products of hemoglobin degradation including iron. The present study examines the role of iron in brain atrophy and neurological deficits following ICH. Methods: Male Sprague-Dawley rats (n=42) received either infusion of 100μl autologous whole blood or insertion of a needle into the right caudate. Hematoxylin and eosin staining were used for histological examination. Iron levels and ferritin immunoreactivity were also examined. Deferoxamine (100 mg/kg, i.p. starting at 2 hrs after ICH, every 12 hrs for 7 days) was used as an iron chelator. Over the period of the experiment, the rats underwent behavioral testing (forelimb placing, forelimb use asymmetry and corner turn tests). Results: Brain atrophy in the caudate with prolonged neurological deficits occurred after ICH. There was significant caudate atrophy at 4 weeks (percentage of the contralateral caudate: 78.3$\pm$6.9% vs. 98.1$\pm$ 2.8% in the sham control, n=4, $p<0.05$) with enlargement of the ipsilateral lateral ventricle (percentage of the contralateral lateral ventricle: 296$\pm$184% vs. 130$\pm$47% in the sham control, n=4, $p<0.05$). Between 8 and 12 weeks, the ipsilateral caudate area was ~70 % of contralateral. Although partial functional recovery happened with time, residual neurological deficits were detectible at three months. Both iron accumulation and ferritin upregulation were present in the ipsilateral caudate. Deferoxamine reduced brain atrophy (caudate: 93$\pm$6% vs. 79$\pm$6% in the vehicle group, n=6, $p<0.05$; ventricle enlargement: 127$\pm$28% vs. 300$\pm$181% in the vehicle group, n=6, $p<0.05$) and improved behavioral outcomes ($P<0.05$). Conclusions: ICH results in an accumulation of iron in the brain that is not cleared within three months, which contributes to brain tissue loss and neurological deficits after ICH. Iron chelation may be a useful therapy for ICH patients.

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Burden of Silent Microbleeds Is Associated With Volume of Symptomatic Lobar Hemorrhage

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Background and Purpose: Silent microbleeds (SMBs) are frequently observed in patients with intracerebral hemorrhage (ICH), which is related to blood brain barrier (BBB) disruption of lipohyalinized arterioles. Based on previous observation of the relationship between BBB disruption and ICH volume, we hypothesized that presence or burden of these SMBs may be associated with increased volume of symptomatic ICH. **Methods:** Acute ICH patients with their first CT scanned within 2 days of onset and gradient-echo MRI in 7 days were included. Patients with pontine or cerebellar hemorrhages were excluded from this study. The ICH volume was measured on baseline CT scans using the ABC/2 method, and SMBs were counted and localized on gradient-echo MRI. Supratentorial location was divided into lobar area and deep gray matter (putamen and thalamus), and we classified the degrees of SMBs or ICH volume as 4-grade system using quartiles. Image analysis was by consensus of 2 stroke neurologists blinded to clinical information and CT-MRI pairings. To test associations between SMB and ICH volume, we used student *t*-test and Spearman correlation coefficient. **Results:** Analysis of 140 consecutive patients with ICH was performed. SMBs were found in 93 patients (66.4%) and the counted numbers ranged from 0 to 97. SMB group had increasing tendency of ICH volume (17.5 $\pm$ 16.9; non-SMB group, 14.8 $\pm$ 13.4), but there was no statistical significance ($p = 0.31$). However, in the patients with lobar hemorrhage (n = 39), the ICH volume increased more than 2-fold in SMB group (n = 24; 30.1 $\pm$ 18.7), compared with non-SMB group (n = 15; 13.9 $\pm$ 8.3; $p < 0.01$). There was also a significant correlation between the SMB burden and the degree of ICH volume ($r = 0.41$, $p = 0.01$). **Conclusions:** These data indicate increased volume of lobar hemorrhage in patients with SMBs in lobar area. We hypothesize that the SMB may reflect the degree of BBB disruption at least in the patients with lobar hemorrhage.