Stroke Mimics in a Prehospital Stroke Treatment Trial

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Background: As stroke is a time-urgent neuroemergency, start of treatment by paramedics in the field as soon as possible after symptom onset offers the greatest prospect of success for neuroprotective therapeutic agents. However, stroke patients represent only 2-3% of all field transports, and among patients with neurologic complaints encountered by paramedics, nonstroke causes are 10 times more common than stroke. To avoid exposing an untoward proportion of nonstroke patients to active agents, field treatment clinical trials and eventual clinical practice require a high rate of diagnostic accuracy. We evaluated the success of the stroke screening prehospital stroke identification procedures in the NIH Field Administration of Stroke Therapy - Magnesium (FAST-MAG) phase 3 trial, and the etiologies and clinical features of stroke mimics (SM). Methods: FAST-MAG is a randomized, double-blind, placebo-controlled trial of Magnesium Sulfate administered by paramedics to individuals with suspected stroke within 2 hours after symptom onset. We use a 2 step patient identification procedure: 1) Los Angeles Prehospital Stroke Screen (LAPSS) used by paramedics to identify potential patients, 2) Paramedics then call the central study neurologist from the scene by cellphone to give a brief report. The neurologist speaks to the patient or family member and performs a brief (15-90 second) stroke-focused history. The neurologist then renders a diagnosis of likely stroke. Prelaunch sample size assumptions projected a 5% rate of SM patient entry into the trial.

Results: This analysis was performed on the first 567 enrolled patients. Average time from last known well to start of study drug was 35 +/- 52 minutes. Final diagnosis 3 months after the event was acute ischemic stroke (AIS) in 411 (72.5%), intracranial hemorrhage (ICH) in 136 (24%), and SM in 20 (3.5%). Final diagnoses of SM were seizures (6 patients), 30%, intracranial neoplasms (6 patients, including 1 with seizures), anxiety (2 patients), migraine (2 patients), metabolic abnormalities (1 patient with hypoglycemia, another with hyponatremia), urosepsis (1 case), and 3 had other conditions. The hyponatremia patient had a seizure. On average, compared to patients with final diagnosis of AIS or ICH, SM patients were younger (64 +/- 13 versus 70 +/- 13 years, p < 0.06), had lower systolic blood pressure (SBP 141 versus 159 mm Hg, p = 0.012) and milder neurological deficits on presentation (NIHSS 5.8 versus 9.3, p < 0.009). Frequency of cardiovascular risk factors was similar between stroke and SM, except for diabetes (17.2 versus 35%, respectively, p < 0.012) and milder neurological deficits on presentation (NIHSS 5.6 versus 9.3, 139 mm Hg, p < 0.012) and milder neurological deficits on presentation (NIHSS 5.6 versus 9.3).

Conclusions: Combined LAPSS and neurologist phone screening enables patient enrollment hyperacutely in prehospital neuroprotective acute stroke trials with low, acceptable rates of SM entry. SM should be considered when patients are young, have normal SBP and have mild neurological deficits.

Major Cerebrovascular and Cardiovascular Events After Emergency Department Discharge for Dizziness or Vertigo

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Background: Dizziness and vertigo are common reasons for Emergency Department (ED) visits, but uncertainty about the underlying etiology is common at discharge. Given the potential that serious cerebrovascular and cardiovascular etiologies could be missed, we studied the frequency and timing of subsequent adverse vascular outcomes for ED patients who are discharged home with a primary diagnosis of dizziness or vertigo. Methods: We identified a cohort of all patients with an ED discharge diagnosis of dizziness or vertigo between January 1, 2005 and June 30, 2005 using encounter data from the California Office of Statewide Health Planning and Development. Inclusion criteria were in-state residence, age > 18, valid social security number and demographic information, disposition to home, and absence of primary outcomes at presentation. Using probabilistic record linkage and validated methods for determining outcomes, we identified the first hospitalization or death for cerebrovascular events (acute ischemic stroke and intracerebral hemorrhage), cardiovascular events (acute myocardial infarction, unstable angina and ventricular arrhythmia), and major vascular events (cerebrovascular and cardiovascular events) for 6 months after ED discharge. Data were analyzed using survival analysis. Results: Among 31,078 patients discharged with dizziness or vertigo diagnoses, mean age was 56.3 years and 63.1% were women. During 15,193 person-years of follow-up, there were 276 adverse vascular events, representing a 6-month cumulative risk of 0.88% (95% CI 0.79-1.00%). There were 198 strokes and 96 major cardiovascular events representing cumulative risks of 0.61% (0.53-0.70%) and 0.31% (0.25-0.37%) respectively (see Figure). Although the rate of vascular events was similar throughout the study period, the monthly stroke risk was higher in the first month compared to subsequent months (0.29% vs. 0.06%). Conclusions: ED patients who are discharged home with a primary diagnosis of dizziness or vertigo have a low rate of subsequent hospitalization and death from major vascular events overall, with a stroke attributable to the event occurring in only about 1 in 500 patients in the following month. Reassurance and more cost-effective evaluation may be indicated for the majority of these patients.
National Access to Primary Stroke Centers (PSC) and Impact of Using Air Ambulances to Improve Patient Access to PSCs

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Background: One significant barrier to the only available stroke treatment (tPA) is lack of access to acute specialized stroke care. Our objectives were to determine population access to certified Primary Stroke Centers (PSCs) in the US, identify gaps in coverage, & to describe the potential incremental increase in population access to stroke care using the existing complement of US air ambulances if pre-hospital triage to stroke centers was permitted nationwide. Methods: A list of the Joint Commission (JCI) certified PSCs, including location, was obtained from TJC, & population data was obtained via the US Census Bureau. Population data were analyzed at the block group level. Driving distances, ambulance driving speeds, & prehospital times were estimated using validated models & adjusted for population density. The location of the 546 existing national air ambulance depots was obtained from the Atlas & Database of Air Medical Services. Access was determined by summing the population that could reach a PSC within specified time intervals & was aggregated by block group, state, region, & for the entire country. Results: Fewer than 1 in 4 Americans (22.3%) has access to a PSC within 30 minutes. Currently, less than 1/2 (43.2%) have access within 45 minutes, & just over 1/2 (55.4%) have access within 60 minutes. If EMS were to cross state lines, the percent with 30, 45 & 60 minute access would increase only minimally to 22.6%, 44.2%, & 57.2%, leaving over 135 million Americans without 60 minute access to a PSC. The addition of air ambulances to existing ground ambulances increased access from 22% to 26% for 30 minutes, 43% to 66% for 45 minutes, & from 55% to 79% for 60 minutes. The combination of pre-hospital regionalization & air ambulance transport of acute stroke patients would reduce the 135.7 million Americans without 60 minute access to a PSC by half, to 62.9 million.

Conclusions: Only about half of the US population has timely access to a certified PSC. Using air ambulances to triage patients with ischemic stroke to PSC increases the US population with prompt access to stroke care. This effect is most evident in rural states & for patients with long pre-hospital transport times. There are implications for the ongoing design of the US stroke system. Regionalization of acute stroke care needs to be addressed at both state & national levels.

Age-Based Eligibility for and Treatment with rt-PA: A Population-based Estimate

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Intra: Previously, we reported that 8% of ischemic stroke patients were eligible for rt-PA within our population in 1993/94. However, rates of eligibility for rt-PA by age have never been presented. We hypothesized that as age increases, eligibility for rt-PA will decrease due to co-morbidities. We also hypothesized that the disparity between those eligible and those treated will be the greatest among the oldest patients. Methods: All adult ischemic stroke cases in 2005 among residents of the 5-county-Greater Cincinnati/Northern Kentucky (GCNK) region (population 1.3 million) were ascertained at all local hospitals via ICD-9 codes 430-438 and were then physician verified. Patients who had emergency department arrival times > 3 hrs from symptom onset and/or had one or more of the standard rt-PA exclusion criteria as published in national guidelines were considered ineligible for rt-PA. Only patients residing in the study area were included in this analysis (transfers from outside counties excluded). Treatment with rt-PA in this region is exclusively given by the GCNK Stroke Team. Eligibility and treatment rates were calculated and stratified by age decade. Chi-square and logistic regression were used for statistical analysis. Results: There were 1830 ischemic stroke events presenting to an emergency department in the population, of which 148 (8.1%) were eligible for rt-PA. The percentage of patients eligible for rt-PA actually increased with increasing age (p for trend = 0.02), see Table for age-specific eligibility and treatment rates. A total of 78 patients (4.3%) were treated with rt-PA (6 of which were deemed ineligible, e.g., unexpected changes in medical history, treatments beyond 3 hours). There was a non-significant trend for the relationship between age and treatment of eligible patients (p = 0.09). Specifically, treatment of eligible patients was most likely in those aged 55 to 74 years compared with both younger (18 to 54 years, p = 0.08) and older (>75 years, p = 0.06) patients. Investigation of the individual eligibility criteria found that older patients were more likely to be excluded for high INR (p = 0.002), and younger patients for milder stroke (p < 0.0001). Discussion Contrary to our hypothesis, the eligibility for rt-PA significantly increased with increasing age of the ischemic stroke patient. Further detail regarding exclusions by age will be presented. We also found a non-significant trend towards higher rates of rt-PA treatment in those aged 55-74, compared to younger or older patients.

Adherence of Emergency Department Blood Pressure Management in Acute Ischemic Stroke to the AHA Guidelines: A Population-based Study

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Objectives: Blood pressure (BP) elevation is common in acute ischemic stroke (AIS). Severely elevated systolic blood pressure (SBP) is associated with increased risk of neurologic decline and poor outcome in AIS. The 2003 AHA guidelines for the management of blood pressure in AIS recommend anti-hypertensive therapy only if BP is greater than 220/120 mmHg, with a goal of reducing BP by 15 to 25% in the first 24 hours. Aggressive lowering of the SBP by more than 20 mmHg is associated with neurologic decline, increased infarct volume, and poor outcome. We hypothesized that AIS patients in the emergency department (ED) often receive anti-hypertensive therapy at BP below the recommended treatment threshold and that BP reduction greater than 20% occurs early in treated patients. Methods: The Greater Cincinnati/Northern Kentucky Stroke Study Periodically reviews every stroke case occurring in the region (est. pop. 1.3 million) during a given year. In 2005, AIS cases were ascertained at all 16 local hospitals by screening ICD-9 codes 430-438 and prospective screening of ED admission logs. BP was recorded at ED presentation as well as before and after treatment with anti-hypertensive drugs. If given. Hypertension was defined as SBP > 120/80 mmHg, based on the 2003 AHA AS guidelines, and hypotension was defined as SBP < 100 mmHg. Chi square tests and Mann-Whitney U-tests were used for comparisons. Results: There were 1797 AIS patients not treated with rt-PA presenting to an ED, median age was 72 years, 43.0% were male and...
24.7% were black. At presentation, 120 patients (6.7%) met criteria for treatment. There were 218 patients treated with anti-hypertensives, of whom 78 (34.9%) met treatment criteria on ED arrival and 72 (33.3%) met treatment criteria immediately after treatment. The proportion of blacks who were treated was hypertensive (18.6% vs 10.2%, p<0.001). Treated patients were younger than those who were not treated (median age 68 vs 73 years, p<0.001), and treated patients had greater stroke severity than patients who were not treated (median estimated NIHSS 4 v 3, p=0.032). Treatment was independent of sex. Median change in SBP was -25 mmHg (range -100 to 25 mmHg). The median percent change in SBP was -12.4% (range -49.2 to 10.2%) with more than 20% decreased by more than 20% in 117 treated patients (53.7%) and by more than 20% in 55 treated patients (25.2%). Three patients became hypotensive after treatment.

Conclusion: Treatment is often initiated at BP lower than recommended by AHA guidelines, and the rate of change of BP is frequently greater than recommended, although severe hypotension was rare. Further studies are warranted to determine what impact this may have on patient outcome.

7 Inter-rater Reliability of Transient Ischemic Attack Diagnosis in the Emergency Department

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Background: The diagnosis of TIA is challenging and has poor inter-rater reliability. Because of their high short-term risk of stroke, patients presenting to the emergency department (ED) with TIA require rapid identification, evaluation and treatment. The objective of this study was to determine the inter-rater reliability of physician diagnosis of TIA in 4 community-based EDs.

Methods: An ED-based observational cohort study of TIA patients presenting to 4 hospitals in Michigan was conducted over a 1-year period. A convenience sample of TIA cases were prospectively recruited and independently rated by 2 trained research staff. The case definition was based on the presence of transient focal neurological symptoms that lasted less than 24 hours. Using objective criteria an ED physician at each site reviewed the completed medical records and classified each case as a definite TIA (i.e., > 90% probability), Probable TIA (i.e., > 50%), Possible TIA (i.e., < 5%) or Not TIA (i.e., < 5%). Cases at all 4 sites were then independently reviewed by a neurologist using the same criteria. Inter-rater reliability was measured by the kappa (k) statistic with 95% confidence intervals (CI). Subsequently, consensus meetings were conducted between each ED physician and the neurologist to re-evaluate the complete medical record and, where necessary, re-code discrepant results. Results: A total of 366 cases were enrolled. Following the initial independent assessment, the overall inter-rater reliability between the ED physicians and the neurologist was poor (k = 0.38, CI 0.29-0.47) with an overall agreement of only 67%. The reliability for ruling-in TIA (i.e., definite TIA vs. all others (k = 0.46, CI 0.36-0.56) and for ruling-out TIA (i.e., Not TIA vs. all others (k = 0.15, CI 0.04-0.26) was also poor. Following the consensus meeting, the overall inter-rater reliability improved dramatically (k = 0.86, 0.81-0.91) with an overall agreement of 92%. Reliability was also excellent for ruling-out TIA (k = 0.86, CI 0.84-0.93) and ruling-out TIA (k = 0.98, CI 0.95-1.0). After the consensus meetings, 30 cases (8.2%) were determined not to be TIA. The most common reasons for classifying cases as not TIA were duration of symptoms lasted > 24 hours or a valid alternative diagnosis was identified. Other causes of discrepancies included confusion with the interpretation of the diagnostic criteria, and poor medical chart documentation.

Conclusion: The diagnosis of TIA in the ED is made difficult by the lack of data on the completed clinical course and diagnostic results. The initial inter-rater reliability of TIA diagnosis was poor, but improved substantially following a consensus meeting. These findings suggest that substantial misclassification errors can occur with the diagnosis of TIA in the ED, and that accurate diagnosis may be achieved only following review of the completed medical record including all diagnostic test results.

8 Testing the Mismatch Hypothesis in the Randomized EPITHET Data Set: The Effect of Treatment, Mismatch and Their Interaction on Infarct Growth

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Background and Purpose: The EPITHET trial tested whether intravenous tPA attenuated infarct growth in patients with perfusion-diffusion imaging (PWI-DWI) mismatch. The lack of significant infarct growth attenuation with tPA in mismatch patients may reflect a problem with the pre-specified mismatch definition rather than absence of a treatment effect. The mismatch hypothesis, that the presence of PWI-DWI mismatch predicts a differential response to treatment, could not be demonstrated in the EPITHET trial. The pre-specified mismatch definition was modified only 14% non mismatch patients, leaving mismatch vs. no mismatch comparisons underpowered. This may not have been the most statistically sensitive way of testing the mismatch hypothesis. Therefore, we re-analyzed the original EPITHET data using a continuous measure of mismatch rather than by dichotomy and assessed the interaction between mismatch and treatment, fundamental to the mismatch hypothesis.

Methods: We used the EPITHET perfusion Tmax maps and ROIs quantifying acute (DWI) and follow-up (Day 90 T2) MRI lesion volumes. Absolute infarct growth and absolute mismatch volumes were calculated. The Tmax definition used to define hyperperfusion was determined using ROC analysis against final infarction in patients with less than 50% reperfusion and no parenchymal hematoma (ECASS I/II and 2). An ANCOVA model was then used to examine the significance of mismatch, treatment and their interaction on infarct expansion using this Tmax definition in all patients with Day 90 T2 imaging and no PH. Results: The ROC analysis was performed in 15 and the ANCOVA model in 66 patients fulfilling the inclusion criteria above. The optimal Tmax for infarct prediction was Tmax=6 seconds (OR 4.3-6) with an average specificity of 89% and sensitivity of 91%. Using Tmax=6 seconds, the ANCOVA model (Residual %) yielded the following coefficients for the predictors of infarct expansion (CI, p-value): Mismatch: 0.45 [0.33-0.58], p<0.0001; Treatment: 4.2 [1.5-7.1], p=0.0067; Mismatch-Treatment interaction = -0.31 [-0.49-0.14], p=0.0006. Adjusting for baseline NIHSS and acute DWI size did not change the pattern of the significant terms. On average, 43% of the mismatch region progressed to infarction, but tPA treatment limited infarction to 14% (p<0.45-0.31) of the mismatch volume. Treatment, in the absence of mismatch did not significantly influence infarct growth. Conclusion: This analysis shows a significant effect of tPA treatment exclusively in the presence of a mismatch and supports the mismatch hypothesis. The model indicates that larger mismatches are more likely to identify patients with higher response to tPA in terms of growth attenuation. Limitations include that as infarct growth was not assessable in patients with PH or patients lost to follow up.

9 Delay and Dispersion of Collateral Perfusion Measured From Arterial Inflow and Venous Outflow Radially Alter MRI Definitions of Penumbra

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Background: Delay and dispersion are hallmarks of collateral flow in acute cerebral ischemia. The resulting alterations in arterial inflow and venous outflow functions (AIF and VOF) in the ischemic territory are not taken into account in standard calculated perfusion maps on CT and MRI, which may therefore be prone to error in defining true penumbra. We analyzed the impact of selecting AIF and VOF from collateral routes on the derivation of standard definitions of “penumbra” with dynamic contrast-enhanced perfusion MRI. Methods: MRI perfusion datasets were acquired in 76 consecutive cases of isolated proximal MCA occlusion in acute stroke verified by DSA. Four combinations of AIF and VOF from collaterals and normal arterial or venous sites were used prior to deconvolution to calculate multiparametric perfusion maps. Standard AIF/VOF sites included contralateral MCA and superior sagittal sinus (SS) whereas collateral-specific AIF/VOF used distal (collateral MCA and ipsilateral internal caudate veins). Volumetric measures of relative cerebral blood volume (rCBV), Tmax, and mean transit time (MTT) were compared for these AIF/VOF combinations in both cardioembolic and atherosclerotic cases. Results: Collateral (C) and (c)VOF both markedly varied across all cases in this series of isolated proximal MCA occlusion. CAF showed markedly delayed flow, extending into the late venous phase. cVOF demonstrated different degrees of delay and dispersion compared to the RSS. Use of CAF/cVOF did not result in rCBV differences when compared with normal AIF/VOF (p<NS). Unlike rCBV, MTT and Tmax volumes of penumbra based on standard thresholds radically differed when CAF/cVOF were used (p<0.01).

Areas of severe Tmax and MTT delay were similar, yet overall penumbral lesion volumes diminished. Such novel distinctions in Tmax volumes could not be achieved by standard approaches of varying thresholds in TMA definitions of penumbra due to inherent non-linearity of this parameter. Use of CAF/cVOF provided delay correction to visualize perfusion in areas not visualized with normal AIF/VOF. Delay and dispersion in both arterial and venous collateral routes vary across individuals. Use of CAF/cVOF provides delay correction and more restrictive definitions of ischemic penumbra that account for venous pooling.

10 Acute Perfusion and Diffusion Abnormalities Predict Early MRI Lesion Recurrence After Minor Stroke and TIA

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Background: Transient ischemic attack (TIA) and minor stroke is associated with early recurrence. Although clinical recurrence rates have been shown to be very high within 7 days of initial symptoms, there are no current studies in this time period. There is also a paucity of data regarding the prognostic value of perfusion-weighted imaging (PWI) in TIA and minor stroke patients. We conducted a prospective serial PWI and diffusion-weighted imaging (DWI) study...
to determine the rate of new radiological lesions in patients with TIA and minor stroke. We hypothesized that acute PWI deficits would be associated with the development of new DWI lesions in the early post-stroke period.

**Methods:** Patients (n=42) with TIA and minor stroke (NIH stroke scale score ≤3) underwent MRI at admission, and 1 week and 4 weeks after symptom onset. Acute PWI deficit and DWI lesion volumes were measured with planimetric techniques. Follow-up scans were examined for new DWI and Fluid Attenuated Inversion Recovery (FLAIR) lesions at days 7 and 30. **Results:** The median patient age was 72 (range 51-92). The median ABCD² score was 5 (range 1-8). The median time to initial mRI was 24.8 h (range 3.8-110.1). Acute DWI lesions were present in 22 patients (52%). New DWI lesions developed in 7/42 patients (17%) at 1 week and in another 3 (cumulative 24%) at 4 weeks. None of the patients with normal baseline DWI scans developed infarcts at any point during the study. Patients with new infarcts were significantly more likely to have baseline DWI lesions (χ² = 7.6, p = 0.009). Patients who developed new lesions at day 7 had significantly larger baseline DWI lesion volumes (16.3±8.1 ml) than those without new infarcts (1.9±3.8 ml; p = 0.003). Similarly, patients with new infarcts by day 30 had larger baseline DWI volumes (13.1±9.5 ml) than those without recurrent lesions (2.2±4.1 ml, p = 0.009). A total of 31 patients had baseline PWI and follow-up data. DWI lesion volumes (Tmax +2s) were larger in patients with recurrent lesions at 7 days (median 81.2 ml, range 9.9-99 ml) than those without new infarcts (median 0 ml, range 0-84 ml, p = 0.001). Patients with recurrent lesions were more likely to have baseline PWI deficits (χ² = 15.6, p = 0.0001). All new lesions at day 7 and 30 were within the areas affected by baseline PWI deficits. Logistic regression indicated that DWI lesion volume predicted the development of new lesions at day 7 (OR = 1.52 per ml [1.12, 2.07], p = 0.007). Regression also indicated that PWI deficit volume predicted recurrent lesions at day 7 (OR = 1.05 per ml [1.01, 1.08], p = 0.009). **Conclusions:** These results provide objective imaging-based evidence for very early recurrent events following TIA and minor stroke in a significant number of patients. These events are much more likely to occur in patients with larger DWI lesions and hyperperfused tissue, demonstrated with PWI.

**Early ADC Normalization Lags Tissue Reperfusion and Does Not Predict Tissue Survival**

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Although reversal of apparent diffusion coefficient (ADC) has been reported following thrombolysis in acute ischemic stroke, the temporal relationship between tissue reperfusion and ADC reversal is unclear. Moreover, ADC reversal and tissue status in the hyperacute phase of stroke has been understudied. Twenty-two patients were sequentially imaged with DWI and PWI at 2.9±0.9 hrs (tp1) and 6.3±0.3 hrs (tp2), and one month FLAIR (tp3) after stroke symptom onset, of which 17 patients received IVtPA at 1.8±0.5 hrs after onset. Mean transit time (MTT), ADC, and FLAIR images were aligned across different tps. ADC was defined as abnormal for values < (mean - 2*SD) and MTT was defined as abnormal for values > 4 seconds of the mean MTT of the contrastral hemisphere. Based on the characteristics of ADC at tp1 and MTT at tp1 and tp2, suggesting spontaneous reperfusion prior to tp1, (2) ROnon-repert defined regions with abnormal MTT on both tps and abnormal ADC at tp1, suggesting no reperfusion, and (3) ROnorm reflected regions with normal MTT on both tps and mild decrease ADC (70 - 75 ×10-5 mm2/s) at tp1. For ROnong (Fig, blue diamonds), ADC values increased substantially from tp1 to tp2 and correlated with time (r = 0.84, Spearman correlation, p = 0.0002). The ADC values in ROnong revert back close to normal value (pink line in Fig) at tp2. To further understand how the delayed ADC reversal may link to final outcome, the tissue survival rates for ROnong was calculated and found to be 48.6%. This is contrasted with ROnong-repert (Fg, red circles) with similar tp1 ADC and ROnorm (Fg, green circles) with similar tp2 ADC, which have tissue survival rates of 11.8% and 93.8%, respectively. Our results have demonstrated: 1) a time lag to ADC normalization after reperfusion occurs and (2) that the fate of repertursed tissue with slightly reduced ADC at 6 hours is very different depending on whether the ADC was initially abnormal. The latter finding suggests that a single ADC measurement does not fully reflect the cellular processes that distinguish reversible from irreversible ischemia.

**Clinical-Occlusion Mismatch Strongly Predicts Response to IV tPA and Long-term Outcome After Early and Delayed Recanalization**

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**Background:** Although the NIHSS score correlates well with the location of MCA occlusion, an efficient collateral blood supply may maintain perfusion in the penumbra area and ameliorate clinical deficit despite persistent occlusion, leading to a clinical-oclusion mismatch (COM). We aimed to investigate response to iv tPA and clinical outcome after early and delayed recanalization in patients with and without COM. **Patients and Methods:** We evaluated consecutively 546 acute strokes due to MCA occlusion treated with tPA < 3h. NIHSS score was performed at baseline and serially < 24h. Presence and location of MCA occlusion and recanalization was assessed with TCD at baseline, 6h and 12h of stroke onset. A ROC curve identified a NIHSS score >14 points (sensitivity 78%; specificity 83%) as the value that better discriminate the presence of a proximal MCA occlusion (pMCAO). Clinical-oclusion mismatch (COM) was defined as patients with pMCAO and a pre-treatment NIHSS score < 11 points (2 SD below the 14-point discriminative value). MRS score was used to assess outcome at 3 months. **Results:** A total 309 patients with pMCAO treated with iv tPA were included in the study. Median pre-treatment NIHSS score was 17 (IQR 6-24), 58 (19%) patients showed COM before treatment. COM patients were more frequently diabetics (34% vs 18%, p = 0.039) and less likely to show early ischemia on baseline CT (13% vs 26%, p = 0.006) than non-COM patients. 6-h recanalization rate was significantly higher in COM (n=40;69%) compared to non-COM (131;52%) (p = 0.008). Clinical fluctuations before recanalization were significantly (p = 0.035) more frequent in COM (32%) than non-COM (11%). Although the rate of delayed recanalization (6-12h) was comparable in both groups, COM was associated with a higher degree of 24-h clinical improvement (p = 0.034) after delayed recanalization. SICH rate was similar in both groups. Among 171 patients who recanalized < 6h , COM (OR 4.5 ; 95%CI 1.45-6.4) and age <65 (OR 3.1; 95%CI 1.14) were independent predictor of good outcome (mRS 0-2). Moreover, among delayed recanalizers (n=74), COM increased in 2-folds the likelihood of good outcome (mRS 0-2; 34% vs 18%, p = 0.002). **Conclusion:** Clinical-oclusion mismatch as a surrogate marker of an efficient collateral circulation strongly predicts good response to iv tPA and improved outcome after early and delayed recanalization.

**Oxygen Metabolic Index Predicts Gray Matter Infarction Better Than Apparent Diffusion Coefficient and Mean Transit Time During Hyper-Acute Ischemic Stroke**

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**Objectives** PBT studies have suggested that cerebral metabolic rate of oxygen utilization (CMR ogl) is a good time-independent predictor of viable tissue in acute ischemic stroke. We have developed a novel MRI approach to measure oxygen metabolic index (OMI), a parameter closely related to CMR ogl. In a cohort of acute ischemic stroke patients, we directly compared the ability of OMI, apparent diffusion coefficient (ADC), and mean transit time (MTT), measured at 3 and 6 hours after symptom onset, to predict brain tissue destined to die or remain alive at 1 month. **Methods** Nine acute ischemic stroke patients were imaged at 2 timepoints: 2.9-3.0 hours (tp1) and 6.3-3.0 hours (tp2) after onset. All patients received iv tPA prior to tp1. Dynamic susceptibility contrast was used to measure cerebral blood flow (CBF). An asymmetric spin echo sequence was used to calculate oxygen extraction fraction (OEF). OMI is the product of CBF and OEF. All measurements were normalized to the contralateral hemisphere. Co-registration and segmentation aligned timepoints and separated gray from white matter, respectively. 

Histograms were constructed to demonstrate the relative frequency of OMI (or ADC or MTT) values for tissue destined to die or survive on 1 month FLAIR. ROC analyses quantified the ability of the parameter to distinguish living and dead tissue. Areas under the ROC curves (AUC) for the 3 parameters were compared using Friedman nonparametric test for related samples and post-hoc Sign test. **Results** Representative 3-hour OMI, 3-hour ADC, 3-hour MTT, and 1 month FLAIR maps are shown for a patient with acute left MCA infarction (Fig.). Histograms show relative frequency of 3-hour OMI (or ADC or MTT) values for “dead” voxels at 1 month (red curve) and “alive” voxels at 1 month (green curve). For gray matter at tp1, mean AUCs for OMI, ADC, and MTT were 0.84, 0.75, and 0.80, respectively. (χ² = 9.6, p = 0.008; post-hoc pairwise comparisons for OMI vs ADC (p = 0.038), OMI vs MTT (p = 0.038), and ADC vs MTT (p = 0.122). For white matter at tp1 and for both gray and white matter at tp2, there were no significant differences between the AUCs of the 3 parameters. **Conclusions** Hyper-acute measures of OMI predicted gray matter death better than ADC and MTT, suggesting that OMI shows promise as a potential MR imaging approach to delineate the core of an evolving infarct.
Tissue Salvageability in the Penumbra Decreases Linearly With Increasing Tmax

Archana Purushotham, Maarten G Lansberg, Michael Miyash, Jean-Marc Olivot, Roland Bamm, Stephanie M Kemp, Gregory W Albers; Stanford Univ, Palo Alto, CA

Background: The region of perfusion-diffusion mismatch in acute stroke is thought to estimate the penumbra. Tmax is a measure that has been increasingly used to assess cerebral perfusion. Early reversal of Tmax lesions (reperfusion) is highly correlated with favorable clinical outcomes and attenuation of infarct growth. However, the relationship between the severity of Tmax delays and tissue salvageability is unclear. We sought to determine whether the degree of delay in Tmax correlates with the degree of prolongation of Tmax, and if there is a Tmax threshold beyond which tissue is destined to infarct even if reperfused.

Methods: The DEFUSE study treated 74 stroke patients with IV tPA between 3 and 6 hours after symptom onset. MRI was performed immediately before and 3 to 6 hours after treatment as well as at 30 days. For each patient, a Tmax map was created on 3D-DSPRINT images. Voxels in the mismatch region were grouped according to whether they reperfused or not. Voxels in the reperfusion and non-reperfusion groups were compared for the correlation between VOI Tmax values (19-21 sec), individual voxel level, even tissue with high Tmax values may be salvageable with reperfusion. This relationship is present both for voxels that reperfuse and those that do not reperfuse and these differences were amplified with increasing Tmax at the highest Tmax values (19-21 sec), >70% survival was observed with reperfusion. Conclusion: The more severe the Tmax perfusion deficit, the more likely it is that tissue in the mismatch region will go on to infarct. This relationship is present both for voxels that reperfused and those that did not. No Tmax threshold identified voxels that invariably went on to infarction. Thus, at the individual voxel level, even tissue with high Tmax values may be salvageable with reperfusion.

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Emergency Services Feedback: Closing the Loop Increasing Knowledge

Theresa L Hamm, Mercy Med Cntr, Des Moines, IA; Brian Helland, Clive Fire Dept, Clive, IA; Dan Keough, Mercy Med Cntr, Des Moines, IA

Background and Purpose: Pre-hospital Emergency Medical Service (EMS) providers are often the first line health care providers to assess and initiate treatment to stroke victims. A number of patients remain incorrectly identified. There is a variable range of utilization of EMS services by stroke victims, some published data suggesting 38-65%. Evidence suggests those patients correctly identified by EMS providers in the field correctly transported to a stroke center have a statistically higher rate of treatment and improved outcomes. We hypothesize education, relationship building, and feedback are key factors related to increasing volume of stroke victims presenting via EMS to a stroke center. Our goal is to increase the distribution of patients arriving via EMS services. Methods: A survey of regional EMS providers was conducted. Results indicated the need for increased interaction of EMS personnel with stroke team members for “real time” stroke education, interaction with Emergency Department personnel, and rapid report back to EMS by the stroke team regarding diagnosis and treatment. In response to survey results our stroke team instituted an immediate feedback strategy. A feedback tool was created to provide a 24 hour progress report on the patient to the transporting EMS team. In addition to the report, if appropriate, de-identified CT and MRI imaging is shared. This provides visual identification of vascular distribution, correlating with neurological assessment. Our stroke team members provide education during local EMS centers, offer free continuing education credits to facilitate the education process, and build relationships with providers. A community “mock stroke alert” was conducted with the assistance of a local EMS provider. This allowed for community, EMS, and ED stroke education to be completed in a single screening session, with all members of the local community. Results: A survey of regional EMS providers was conducted. Results indicated the need for increased interaction of EMS personnel with stroke team members for “real time” stroke education, interaction with Emergency Department personnel, and rapid report back to EMS by the stroke team regarding diagnosis and treatment. In response to survey results our stroke team instituted an immediate feedback strategy. A feedback tool was created to provide a 24 hour progress report on the patient to the transporting EMS team. In addition to the report, if appropriate, de-identified CT and MRI imaging is shared. This provides visual identification of vascular distribution, correlating with neurological assessment. Our stroke team members provide education during local EMS centers, offer free continuing education credits to facilitate the education process, and build relationships with providers. A community “mock stroke alert” was conducted with the assistance of a local EMS provider. This allowed for community, EMS, and ED stroke education to be completed in a single screening session, with all members of the local community. Results: A survey of regional EMS providers was conducted. Results indicated the need for increased interaction of EMS personnel with stroke team members for “real time” stroke education, interaction with Emergency Department personnel, and rapid report back to EMS by the stroke team regarding diagnosis and treatment. In response to survey results our stroke team instituted an immediate feedback strategy. A feedback tool was created to provide a 24 hour progress report on the patient to the transporting EMS team. In addition to the report, if appropriate, de-identified CT and MRI imaging is shared. This provides visual identification of vascular distribution, correlating with neurological assessment. Our stroke team members provide education during local EMS centers, offer free continuing education credits to facilitate the education process, and build relationships with providers. A community “mock stroke alert” was conducted with the assistance of a local EMS provider. This allowed for community, EMS, and ED stroke education to be completed in a single screening session, with all members of the local community.
strategies has resulted in a statistically significant increase in EMS transport of stroke victims from 47% to 68% (2-proportions test P-value = 0.002). Conclusions: Implementation of strategies including education, relationship building, and feedback has led to an increase in stroke victims arriving via EMS. This increase is multi-factorial, relating to evidence based practice, increased EMS provider satisfaction, and awareness of stroke as a 9-1-1 emergency, as evidenced by 65% of acute stroke victims presenting to our emergency department via EMS.

Maximizing Patient Care Through the Use of Interdisciplinary Team Meetings

Kelly Schuler, Branning Beverly, Nancy Boetmer, Kristen Krutke, Kelly Coddington, Victoria Joaquin, Blake Munson, Jean Rose-Denery, Bronson Sara, OSF St. Joseph Medical Ctr, Bloomington, IL

Background and Purpose: Lack of structured documentation and patient care coordination deficiencies resulted in fragmented provision of care. Processes were needed to meet the needs of the patient for coordination of care and assistance in the discharge planning related to all disciplines including: Physician, Nursing, Nutrition, Home Care, Social Service, Rehab, Activity, Pastoral Care, QRM, Palliative Care, and Neuro Science. A lack of centralized documentation for the Comprehensive Overview of each patients condition existed. A team integrated goal needed to be formulated. Method: Collaborative team meetings are held on individual patient care units 2-3 times weekly. An Interdisciplinary Team (IDT) template for documentation of team discussion/activities was developed using our methodology for positive communication (POM) framework. Components include: a) Situation- Patient diagnosis and Physician or Physicians on case. b) Background- Members/Disciplines present. a) Assessment- Reports from each discipline with the nursing information being given by the Patient Care Facilitator. A representative from each discipline gives a short concise report from their perspective. Recommendations: After discussion occurs, needs are identified and goals are generated by team collaboration resulting in a comprehensive measurable goal(s). Results: Work by the Stroke Team on using this IDT goal- setting format has led to use of this process for all patients and all diagnoses. Improvement in coordination of care; raised awareness of all aspects of each patients condition through the involvement of all the disciplines; providing a comprehensive picture of the patients condition for clinicians unable to participate in meetings; and demonstrated compliance with The Joint Commission standards for Primary Stroke Center Requirements as related to Discharge have been positive results of this endeavor. Conclusion: Coordination of Care for our individual patients is shown improved through the use of the standardized process. A lack of structured documentation for the full-scale mRS was available. A team integrated process as evidenced by improved Press Gainey scores related to "Nurses kept you informed, Physicians kept you informed, and Staff include you in decisions re: treatment" which are currently trending at the 99th percentile.

An Analysis of the Impact of Stroke Camp on Stroke Survivors and Caregivers

Maureen Mathews, OSF Healthcare, Peoria, IL; Marylee Nunley, Larry Schaer, None, Peoria, IL; Judith Beck, David Wang, Jan Jahnle, Arun Talkd; OSF Healthcare, Peoria, IL

Background: Depression, loneliness, and social isolation are common characteristics of survivors and caregivers following a stroke event. Stroke camp provides a unique opportunity to learn more about the daily lives of stroke survivors and their caregivers. Methods: Study approved by the community IRB. Survey of stroke victims from 47% to 68% (2-proportions test P-value = 0.002). Conclusions: A majority of acute intervention cases at our center are transfer patients. The development of a standardized process for communication is expected to result in improved consistency in patient care during transfer and has already enhanced relationships with referring hospitals and EMS crews.

Endpoint for Clinical Trials Involving Patients With Intracerebral Hemorrhage: Modified Rankin Scale as a Dichotomized or Ordinal Outcome

Jill Novitzke, Zeenat Qureshi Stroke Cntr, Univ of Minnesota, Minneapolis, MN; Yoko Y Palesch, Div of Biostatistics and Epidemiology, Med Univ of South Carolina, Charleston, SC; Renee Martin, Div of Biostatistics and Epidemiology, Med Univ of South Carolina, Charleston, SC; Adnan I Qureshi, Zeenat Qureshi Stroke Cntr, Univ of Minnesota, Minneapolis, MN; For ATACH Investigators

Background: A binary outcome based on modified Rankin scale (mRS) provides simplicity and straightforward clinical interpretation. Dichotomization of mRS introduces a compromise for the following reasons: dichotomous outcome analysis may decrease statistical power. Because of the drawbacks of dichotomization, shift analysis using the proportional odds model (POM) has recently gained attention. Shift analysis is particularly advantageous when treatments confer a relatively uniform, mild benefit to patients over a wide range of stroke severities. However, unlike dichotomized outcome analysis, POM requires that the assumption of proportionality of the odds ratios (ORs) is met and its use remains highly controversial in clinical trials in patients with intracerebral hemorrhage (ICH). Objective: To determine if the assumption of proportionality of the odds ratios are met in clinical studies evaluating outcomes in patients with ICH. Methods: We calculated the ORs by different cutoffs using data from clinical studies recruiting patients with ICH on scores where on the full-scale mRS were available. Results: A total of 4 clinical trials recruiting 1765 patients were analyzed. The results are shown in the Table. The variations in OR based on various cutoffs used within the same study suggested a high likelihood of the proportionality assumption not being met.

Table. Odds ratios by different mRS cutoffs in various trials involving patients with ICH

<table>
<thead>
<tr>
<th>mRS</th>
<th>FAST† (N=555)</th>
<th>ATACH (N=51)</th>
<th>GAIN (N=564)</th>
<th>CHANT (N=595)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cut point</td>
<td>OR</td>
<td>95%OR limit</td>
<td>OR</td>
<td>95%OR limit</td>
</tr>
<tr>
<td>0</td>
<td>0.80</td>
<td>0.32</td>
<td>2.01</td>
<td>0.69</td>
</tr>
<tr>
<td>1</td>
<td>0.84</td>
<td>0.55</td>
<td>1.27</td>
<td>2.57</td>
</tr>
<tr>
<td>2</td>
<td>0.94</td>
<td>0.66</td>
<td>1.33</td>
<td>2.62</td>
</tr>
<tr>
<td>3</td>
<td>0.78</td>
<td>0.56</td>
<td>1.09</td>
<td>2.67</td>
</tr>
<tr>
<td>4</td>
<td>0.72</td>
<td>0.49</td>
<td>1.06</td>
<td>1.64</td>
</tr>
<tr>
<td>5</td>
<td>0.84</td>
<td>0.55</td>
<td>1.27</td>
<td>1.56</td>
</tr>
</tbody>
</table>

†The FAST analysis is based upon comparison between placebo and 80µg/kg dose; ** ATACH analysis is based on comparison between patients with <60mmHg and <60 mmHg reduction in SBP at 6 h after treatment.

Conclusion: Dichotomization of mRS scores may be preferable as an endpoint in clinical trials recruiting patients with ICH primarily for simplicity (i.e., no need for model assumptions) and interpretability.
Optimal Definition of the Malignant Profile in the DEFUSE-EPITHET Pooled Database
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Background: The Malignant profile is an MRI pattern empirically defined during the DEFUSE study that predicts poor outcome following reperfusion. The aim of this study was to optimally define the Malignant profile using a statistical approach. Furthermore, we hypothesized that the Malignant profile would have greater accuracy for predicting poor outcome in patients who achieved reperfusion. Methods: Ischemic stroke patients from DEFUSE (a prospective cohort treated with intravenous IA) and EPITHET (a prospective randomized double blinded study of intravenous tPA versus placebo) treated in the 3-6 hour window from onset were pooled. To achieve uniform volumes, DWI and PWI data were reanalyzed using the RAPID automated software program. Reperfusion was defined as a reduction of at least 50% and 10mL of the PWI lesion volume defined by Tmax > 4 sec. Poor outcome was defined as a modified Rankin score of 5 or 6 at day 90. ROC analysis was used to select the optimal DWI and/or PWI threshold volumes that most accurately predicted poor outcome. We compared the accuracy of the optimal definition of the Malignant profile between patients who achieved reperfusion vs. non-reperfusers. Results: 117 patients met the eligibility criteria for this analysis, reperfusion occurred in 69 (59%). The optimal sensitivity/specificity for predicting poor outcome in patients with reperfusion was achieved using a PWI threshold of either 95 mL (Tmax > 8 sec) or 65 mL (Tmax > 10 sec). Both of these criteria identified 8 patients (12%) as having the Malignant profile and 6 of these (75%) had a poor outcome. Using only DWI alone, or combining DWI and PWI criteria, reduced the positive predictive value and did not improve specificity. Prediction of poor outcome in patients who did not reperfused was not as accurate; the >95 mL (Tmax > 8 sec) criterion identified 14 (29%) of the non-reperfusers as Malignant and 7 (5%) had poor outcome.

Table: Prediction of poor outcomes in patients with PWI volume > 95 mL (Tmax > 8 sec)

<table>
<thead>
<tr>
<th>PPV</th>
<th>NPV</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant profile with reperfusion</td>
<td>75%</td>
<td>93%</td>
<td>60%</td>
</tr>
<tr>
<td>Malignant profile, no reperfusion</td>
<td>50%</td>
<td>74%</td>
<td>44%</td>
</tr>
<tr>
<td>P value</td>
<td>0.380</td>
<td>0.011</td>
<td>0.420</td>
</tr>
</tbody>
</table>

Conclusion: Based on ROC analysis of the DEFUSE-EPITHET pooled database, the optimal definition of the Malignant profile is achieved using a PWI threshold of either 95 mL (Tmax > 6 sec) or 65 mL (Tmax > 10 sec). Poor outcome patients were detected among the reperfusion group with significantly greater specificity. These findings suggest that reperfusion may influence the prediction of patients with the Malignant profile and inclusion of these patients in clinical trials of reperfusion therapies may mask the beneficial effects of reperfusion.

Mass Thrombolysis: Final Results of the FRALYSE and FRALYSE-MRI Randomized Studies in a 7 Hour Window. A Comparison Between the NINDS Procedure and a Procedure With a Lower Dose and Longer Infusion
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Purpose The FRALYSE study was designed to increase the thrombolysis eligibility by a 0-7 hour window on a CT basis, and to test the potential superiority of the Lyon-FA Protocol (LFP) over the NINDS Protocol (NFP). Methods The FRALYSE clinical study was a randomized study in a 7 hour window concerning patients with acute cerebral infarcts involving 2 arms: (A) NINDS procedure (tPA infusion 60 minutes, 0.9mg/kg) ; and (B) LTP procedure (infusion 90 minutes, 0.8 mg. kg). The evaluation at 80 days was blinded. The primary endpoint was disability at 90 days. Five centers participated in the study: Lyon; Nice, Bourg, Nantes and Auch. The double-blind FRALYSE-MRI study included patients of the FRALYSE cohort, with a stroke MRI before thrombolysis and at a mean delay of 12 hours after thrombolysis. Results From 2001 to 2005, 373 patients have been included in FRALYSE-clinical and 65 in FRALYSE-MRI (median OTT: 230 min, median baseline NIHSS : 14). The proportion of patients after 3 hours was 85%. The overall security included a mortality of 8.4% and a symptomatic hemorrhagic rate of 4.3% as per SITS-MOST. The global excellent outcome rate (mRS 0,1) was 35.7 % (intention to treat and 36.2% in per protocol analysis. A late efficacy rebound of 39.4% mRS 0.1 was observed in patients treated between 4.5 and 7 hours. In the FRALYSE clinical analysis, there was no statistical difference between the proportion of mRS 0-1 patients in the NINDS (36.1%) and LTP (35.2%) groups, although there was a trend to a slight superiority of LTP in patients <30 and <3 hours. Interestingly, FRALYSE-MRI showed a significant superiority of the LTP procedure with a delayed mismatch volume decrease (p=0.04). Conclusion 1. “Mass thrombolysis” including systemically patients within 7 hours is safe and yields an honorable output of 36.2%. 2. This enlargement of the window multiples by 5 the eligibility and increases considerably the benefit to humanity performed by a neurovascular unit. If one compares the LTP cohort to the NINDS placebo group, there is a mean of 4.75 lives saved (mRS 0,1) in keeping the window from 3 to 7 hours. 3. The LTP procedure, which was designed before the NINDS, is clinically equivalent to NINDS, despite its superiority on MRI.

Acute Stroke Patients Treated With IV Ipa Based on “Time Last Seen Normal” Have Lower Rates of Hemorrhagic Transformation Than Patients With a Witnessed Symptom Onset
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The benefit of intravenous thrombolysis in the treatment of acute ischemic stroke is well established. However, there is a decrease in likelihood of improved outcomes and an increase in the incidence of hemorrhagic events. Current guidelines delay the commencement of therapy with any delay in the time window for treatment is traditionally based on witnessed symptom onset, although patients who are discovered with symptoms of stroke and were last seen to be in their usual state of health within the time window are typically considered candidates based on the “time last seen normal”. The study compared outcomes between patients treated with IV Ipa at designated stroke centres depending on whether or not symptom onset was witnessed. Methods - From the Registry of the Canadian Stroke Network, we identified all consecutive patients treated with IV Ipa for acute ischemic stroke at 11 provincial stroke centres (Ontario, Canada) who were with a witnessed symptom onset compared with those in whom the stroke onset was unwitnessed and were treated based on the “time last seen normal”. Results - Of 1562 ischemic stroke patients treated with IV Ipa between 2003 and 2008, the stroke onset was not witnessed in 211 patients (14%) who were treated based on “time last seen normal”. The time of symptom onset was witnessed in 1351 patients (86%). Of the two groups were identical in terms of demographics and vascular risk factors. Patients treated based on “time last seen normal” were also different in terms of severity of presenting symptoms, discharge modified Rankin score, or discharge destination. However, multivariate analysis revealed that patients treated with IV Ipa based on “time last seen normal” had a lower rate of hemorrhagic transformation than patients treated based on a witnessed symptom onset. This is in keeping with the likelihood that treatment based on “time last seen normal” over-estimates the time of symptom onset, and suggests that these patients are also more likely to experience a beneficial outcome, both within the traditional 3-4.5 hour time window, as well as within the extended 3-4.5 hour time window. These two distinct groups should be evaluated prospectively, particularly within the extended time window, in order to determine whether a difference in clinical outcome is observed.

Does Presence of Arterial Obstruction Influence the Treatment Effect of Intravenous Ipa Over Placebo in the 3-6 Hour Time Window?
Deidre A De Silva, National Neuroscience Institute, Singapore General Hosp Campus, Singapore, Singapore; Leonid Churilov, National Stroke Research Institute and The Univ of Melbourne, Melbourne, Australia; Jean M Olivot, Stanford Univ, Stanford, CA; Soren Christensen, Univ of Melbourne, Melbourne, Australia; Maarten G Lansberg, Michael Mlynash, Matus Straka, Stanford Univ, Stanford, CA; Bruce C Campbell, Univ of Melbourne, Melbourne, Australia; Roland Bammer, Gregory W Albers, Stanford Univ, Stanford, CA; Stephen M Davis, Univ of Melbourne, Melbourne, Australia; Geoffrey A Donnan, Florey Neuroscience Institute, Melbourne, Australia; on behalf of the EPITHET-DEFUSE Investigators

Background and Purpose: The aim of thrombolysis is reperfusion of salvageable tissue through arterial obstruction recanalization. Baseline arterial obstruction has been (DIAS III) utilized as a selection criterion for thrombolytic therapies. There is no published data from controlled studies comparing the treatment effect of thrombolitics over placebo therapy between patients with and without arterial obstruction. We hypothesized that the presence of arterial obstruction improves the treatment effect of IV Ipa over placebo in patients with arterial obstruction. Methods: We analyzed a pooled data of two studies which included 254 stroke patients treated in the 3-6 hour time window from the DEFUSE study (prospective cohort treated with IV Ipa) and EPITHET trial (prospective randomized controlled study of IV Ipa versus placebo). Baseline MRI imaging prior to treatment included mRAS and DWI. Follow-up imaging, performed at day 30 in DEFUSE and day 90 in EPITHET, included FLAIR or T2 imaging used to determine final lesion volume. Infarct growth was calculated as the difference between baseline DWI and final lesion volumes. Baseline arterial obstruction of large intracranial arteries (ICA, M1, M2 and PCA) was graded as complete occlusion, partial obstruction or normal flow. We performed a quartile range analysis to predict absolute growth to determine the influence of arterial obstruction on treatment effect of IV Ipa over placebo. Results: Among 72 patients with either complete occlusion or partial obstruction, median infarct growth was lower...
Results: ROC analyses were performed to select the PWI and/or DWI thresholds that optimally predict poor outcome. Poor outcome was defined as a modified Rankin score of 5-6 at day 90. ROC analyses performed between six to eight hours from symptom onset (“early” group) to those six to eight hours from onset (“late” group). Results: Currently, there are 546 patients in the early group and 123 in the late group. Median time to treatment was 4.0 hours in the early group and 6.8 in the late group. Revascularization (TICI ≥ 2b) occurred in 74% and 65% of early and late groups, respectively, though this difference did not reach statistical significance. Age and initial National Institute of Stroke Scale was not significantly different between comparison groups. In both groups, revascularization was associated with significantly higher rates of good outcomes in both the early and late cohorts. Ischemic stroke patients presenting six to eight hours from symptom onset should be considered for intra-arterial intervention.

### Large and Severe Baseline PWI Volumes Predict Poor Response to Intravenous tPA vs. Placebo in the Pooled DEFUSE-EPHET Database

**Background:** It is unclear if patients with large baseline DWI and/or PWI lesions benefit from IV tPA beyond 3 hours. We aimed to identify volume thresholds of baseline MRI lesions that predict poor outcome with IV tPA. **Methods:** We analysed a cohort of 175 ischemic stroke patients from the DEFUSE and EPHTHE database treated with IV tPA at 3-6 hours from symptom onset. Baseline PWI and DWI scans performed prior to treatment were analyzed using the Rapid automated software program. DWI lesions were determined by a combined relative DWI and absolute ADC threshold technique. PWI lesions were thresholded at >8, >8-10, and >125 mL. Poor outcome was defined as a modified Rankin score of 5-6 at day 90. ROC analyses were performed to select the PWI and/or DWI thresholds that optimally predict poor outcome.

**Results:** Among the 116 tPA patients and 46 placebo patients with technically adequate baseline scans, 28 (40%) and 16 (22%) had poor clinical outcome respectively. The most accurate Tmax threshold for prediction of poor outcome was >125mL. Among tPA patients with baseline PWI (Tmax >8 sec) volumes >90mL, poor outcome occurred in 71% (12/17). Using a higher threshold (>125mL), 89% (8/9) of tPA patients had poor outcome. PWI lesion volumes predicted poor outcomes with greater sensitivity, specificity and positive predictive value than DWI volumes. Adding optimal PWI thresholds to the IV tPA benefit model did not improve its performance. Among placebo patients, neither DWI nor PWI thresholds were able to accurately predict poor outcome in the placebo group.

### Intra-arterial Treatment of Ischemic Stroke Patients Six to Eight Hours From Symptom Onset: Preliminary Pooled Results of MERCI, Multi MERCI, and Merci Registry

**Baseline PWI (Tmax >8 sec) volume >125mL was a better predictor of poor outcome in the IVtPA vs placebo group (OR 16.0, 95% CI 4.1-67.3) than IV tPA alone (OR 4.1, 95% CI 1.3-13.2).** The odds ratio for poor outcome in patients with baseline PWI lesion volumes (Tmax >8 sec) >125 mL vs. >125mL in the IVtPA group was 34.8 (95%CI 4.1-329), significantly higher compared with the placebo group, OR 2.1 (95%CI 0.4-10.7), p = 0.029. 

**Conclusion:** Large baseline PWI (Tmax >8 sec) lesions >125mL strongly predict poor outcome in patients treated with IVtPA vs. placebo at 3-6 hours in the pooled DEFUSE-EPHET database. These data suggest that it is potentially harmful to treat patients with large and severe PWI lesions with IV tPA beyond 3 hours.

### Thrombolysis is Associated With Improved Outcome in Elderly Stroke Patients: A Non-randomized Comparison of Outcomes Amongst Patients From the Virtual International Stroke Trials Archive (VISTA)

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**Background:** Thrombolysis for acute ischemic stroke has proven benefits but randomised data in patients >80 years is limited, and use in the elderly is not approved in most countries. We have examined outcomes amongst patients enrolled in neuroprotection trials (1998-2007) who would not have been registered in SITS-MOST or described in thrombolysis trial reports. We compared outcomes between thrombolysed (T) and non-thrombolysed (C) patients after adjustment for stroke severity and age, and examined association of outcome with thrombolysis exposure. Method: We report dichotomised outcomes of functional independence (mRS 0-2) and mortality by 90 days; and overall distribution of modified Rankin Scale (mRS). We classified patients by age <80 versus >80 (young; elderly). Results are expressed as proportions with 95% confidence intervals (CI). Treatment effect across the mRS distribution was assessed by the Cochran-Mantel-Haenszel test adjusted for baseline NIHSS (NIH) and age, followed by proportional odds logistic regression analysis to estimate the odds ratio (OR).

**Results:** Data were available for 5817 patients, 1535 T and 4282 C. 20.5% were aged >80 years (mean ±SD 85.1 ±3.4). Baseline severity was higher amongst T than C (median NIHSS 14 vs 13, p<0.001). Treatment effect was significantly higher among elderly (p = 0.037). Among elderly, the rate of good outcomes was numerically higher, but did not reach statistical significance.

### Good Outcome and Mortality Rates in Early vs. Late, Revascularized and Non-Revascularized, Cohorts

<table>
<thead>
<tr>
<th>Revascularized</th>
<th>Non-Revascularized</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>90d Good Outcomes (mRS=0-2) Early (&lt;6hrs) Late(6-8hrs)</td>
<td>40.2% 32.5%</td>
<td>9.3% 9.3%</td>
</tr>
<tr>
<td>90d all-cause Mortality Early(&lt;6hrs) Late(6-8hrs)</td>
<td>30.5% 32.5%</td>
<td>55.0% 39.5%</td>
</tr>
</tbody>
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### Abstracts and presentations are embargoed for release at date and time of presentation or time of AHA/ASA news event. Information may not be released before then.
Transplantation of Human Neural Stem Cells Improves Axonal Plasticity and Attenuates Impairment of Axonal Transport in the Post-ischemic Microenvironment

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Introduction: Transplantation of human neural progenitor cells (hNPCs) has emerged as a promising new experimental treatment approach for stroke. However, questions regarding the mode of action of the grafted cells remain unresolved. A growing body of data proposes that hNPCs enhance endogenous repair mechanisms after stroke. Here we addressed the hypothesis that hNPCs improve axonal plasticity and transport in the post-ischemic brain.

Methods: Vehicle or hNPCs derived from fetal cortex were transplanted into the ischemic cortex of NIH Nude rats at 7 days after distal middle cerebral artery occlusion. Neurological recovery was assessed weekly using a battery of sensorimotor tests. 4 weeks after grafting, animals were injected with the anterograde axonal tracer biotinylated dextran amine into the contralesional cortex and sacrificed one week thereafter. The extent of axonal sprouting towards the lesioned cortex was quantified in different brain regions by confocal image analysis, and impairment of axonal transport was assessed by amniotic fluid precursor protein staining. To investigate putative mechanisms of axonal plasticity, a high-throughput in vitro assay based on co-culture of rat E14 cortical progenitor cells with hNPCs and immunodepletion of vascular endothelial growth factor (VEGF), thrombospondin (TSP)-1/2, SPARC, and Silt was used. Axonal transport function was assessed by live imaging of dextran-labeled vesicles in cultured rat cortical neurons using a microfluidic culture platform with hNPCs or vehicle added distal to the axonal compartment.

Results: Transplantation of hNPCs resulted in significantly improved behavioral recovery within 2 weeks compared to controls. Accordingly, tMNS-grafted rats showed increased transcallosal axonal rewiring to the ipsilesional cortex, striatum, and thalamus, as well as to the contralateral corticospinal tract at 5 weeks after transplantation. Neutralization of VEGF, TSP-1/2, and Silt, but not SPARC, partially abolished the response on behavioral recovery in vitro. Furthermore, impairment of axonal transport after stroke was significantly attenuated in hNPC-treated animals, exposure to hNPCs improved anterograde axonal transport in vitro. Conclusions: Our findings suggest that transplanted hNPCs significantly improve axonal rewiring on the contralateral side and anterograde axonal transport after stroke. Neutralization of VEGF, TSP-1/2, and Silt were identified to mediate the effects on axonal sprouting in vitro. Understanding how transplanted hNPCs influence the post-ischemic microenvironment might help us to improve cell transplantation approaches for stroke.

Treatment of Acute Stroke With Thymosin β4

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Background: Thymosin β4 (Tβ4) is a developmentally expressed 43-amino acid peptide that inhibits organization of the actin-cytoskeleton by sequestering of G-actin monomers enabling cells to migrate. Tβ4 is in phase II clinical testing for treatment of skin ulcers. We tested the hypothesis that Tβ4 improves functional neurological outcome in a rat model of embolic stroke.

Methods: Male Wistar rats (n=18) were subjected to embolic middle cerebral artery occlusion (MCAo). Tβ4 (Regenerex, Inc.) (6 mg/kg/ip) was administered 24 hours after MCAo and then every 3 days for 4 additional doses (n=9). Rats treated with saline were used as a control (n=9). The modified Neurological Severity Score (mNSS) and adenosine removal test (ART) were performed before MCAo and at various times for 7 weeks. The rats were sacrificed 56 days after MCAo and lesion volumes were measured. Immunostaining was performed with antibodies against Ng-2 (chondroitin sulfate proteoglycan), CNPase (2', 3'-cyclic nucleotide 3'-phosphodiesterase), bromodeoxyuridine (BrdU) and neurofilament-H (NF-H). Myelinated axons were identified with Bielschowsky/Luxol blue staining (B/L). Additionally, neural progenitor cells (NPC) were isolated from the subventricular zone (SVZ) of normal rats (n=3) or rats subjected to 7 day stroke (n=3). The effect of Tβ4 on gene expression in the NPCs was examined in vitro. Results: Ischemic rats treated with Tβ4 demonstrated a significant overall improvement (p<0.01) in the ART and the mNSS when compared to controls starting at 14 and 35 days, respectively, after MCAo and lasting for at least 56 days. Treatment with Tβ4 significantly (p<0.05) increased remyelination as evidenced by increased B/L staining and NF-H staining at the ischemic boundary region, which was associated with significant (p<0.005) augmentation of oligodendrocyte progenitor cells (NG2+ cells) and myelinating oligodendrocytes (CNPase+, cells) compared with the saline treatment. Lesion volumes showed no significant differences between the two groups. In vitro, incubation of normal NPCs with Tβ4 upregulated epidermal growth factor receptor (EGFR) and NG-2 expression by 2.4 and 2.1 fold, respectively. However, Tβ4 increased EGFR mRNA levels by 2.8 fold in normal NPCs and by 2.4 fold in NPC isolated from stroke rats. Conclusions: The present study suggests that Tβ4 improves neurological outcome after embolic stroke in rats. Axonal remodeling enhanced by Tβ4-increased oligodendrocyte progenitor cells and myelinating oligodendrocytes may contribute to the observed functional improvement. EGFR has been implicated in NPC migration and its upregulation by Tβ4 suggests that it is a candidate pathway for the effect of Tβ4 on oligodendrocyte.
results also suggest that, at least for cortical stimulation, basal ganglia and cingulate might be important to therapeutically enhancing motor gains in patients with chronic stroke.

Ischemic Stroke May Activate Bone Marrow Mononuclear Cells to Enhance Recovery After Stroke
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Background: Our recent studies suggest that intact bone marrow mononuclear cells (MNCs) compared to saline controls or inactivated MNCs reduce neurological deficits in animal models of stroke using various behavioral outcome measures. MNCs may promote recovery through trophic mechanisms. We addressed the hypothesis that ischemic stroke influences the cytokine elaboration and recovery effects of autologous MNCs. Methods: We quantified various anti-inflammatory, angiogenic, and trophic cytokines from MNCs derived from the bone marrow of the tibia in Long Evans rats (3 months old) 1 day before stroke and 1 day after stroke in the same animal. Acute ischemic stroke (AS) was induced by suture occlusion of the middle cerebral artery (MCA). Cytokines were analyzed by microtiter colorimetric enzyme linked immunosorbant (ELISA) assays from MNCs of pre-stroke and post-stroke animals (N=4–6). In separate experiments involving 3 groups of animals, Long Evans rats (3 months old) underwent MCA occlusion and 24 hrs later received an intra-carotid injection of saline (group 1) or autologous MNCs, prepared from the same animal, either 1 day before (group 2) or 1 day after stroke (group 3). All animals were randomized before surgery to the different groups and therefore received either pre-stroke autologous MNCs or post-stroke autologous MNCs or saline (N=6 in each group). The rats were followed on the cylinder test for 28 days after stroke in which ipsilateral paw contact during a full rear is quantified compared with the contralateral paw. Results: PDGF-1, GM-CSF, IGF-1, and IL-10 were increased in post-stroke MNCs compared with post-stroke MNCs, as shown in Table 1. Saline treated animals showed a preference for ipsilateral paw forelimb placement (0.6 ± 0.88). Compared with animals that received pre-stroke autologous MNCs, rats treated with post-stroke autologous MNCs showed greater improvement on the cylinder test at 28 days after stroke (0.4 ± 0.1 for ipsilateral paw contact compared with 0.2 ± 0.1; p<0.05). Conclusion: Autologous treatment from post-stroke MNCs appears to be a better source of cells than pre-stroke to enhance recovery after ischemic stroke. This may be explained by our finding that ischemic stroke modulates the cytokine profile of MNCs.

Cytokine concentrations

<table>
<thead>
<tr>
<th>No.</th>
<th>Cytokine</th>
<th>Pre-stroke</th>
<th>Post-stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PDGF</td>
<td>8 ± 0.5</td>
<td>18 ± 1 (S)</td>
</tr>
<tr>
<td>2</td>
<td>GM-CSF</td>
<td>3 ± 0.26</td>
<td>11 ± 0.51</td>
</tr>
<tr>
<td>3</td>
<td>IGF-1</td>
<td>1451 ± 235</td>
<td>23722 ± 450</td>
</tr>
<tr>
<td>4</td>
<td>IL-10</td>
<td>51 ± 3.5</td>
<td>90 ± 10.5</td>
</tr>
<tr>
<td>5</td>
<td>VEGF</td>
<td>426 ± 6.7</td>
<td>463 ± 7 (NS)</td>
</tr>
</tbody>
</table>

N.S: Not Significant; S: significant (p<0.05 comparing pre-stroke vs post-stroke). Data are presented as mean ± S.D. Values are presented as pg/ml.

This research has received full or partial funding support from the American Heart Association, National Center.

Daidzein Promotes Functional Recovery and Enhances Gliadirected Synaptogenesis in an Experimental Animal Model of Stroke
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Increasing evidence suggests that synaptic plasticity and remodeling occur weeks after stroke. Although CNS synaptogenesis has been viewed as an entirely neuronal event, astrocytes control the process through the regulation of cholesterol homeostasis. Daidzein, a major component of soy isoflavones, has been shown to promote axonal outgrowth and increase expression of the genes that are involved in cholesterol homeostasis. The present study investigates whether daidzein is neuroprotective and promotes functional recovery following stroke. C57B1/6 mice were subjected to 30 min transient middle cerebral artery occlusion and were treated daily with vehicle or daidzein (10 mg/kg, SC) for 7 days and then continually treated every other day up to 1 month. Assessment of acute infarct volume at 3 days or analysis of tissue volume that contains scar or non-injured remaining tissue in the ipsilateral side at 1 month post-ischemia revealed no differences between the groups. In spite of lack of neuroprotection, daidzein treated mice exhibited improved optokinetic tracking response, a sensitive integrated sensory/motor function, compared to vehicle treated mice (p<0.001, n=9–11). To seek a mechanism of action, transcriptional analysis for functionally regulated genes was performed. The expression of genes that are involved in synaptogenesis were determined. Daidzein selectively increased the expression of ATP binding cassette transporter G1 (ABC1G) gene that functions in cholesterol efflux in C6-D1A astrocyte cell line. In addition, treating mice with daidzein increased LXR, a transcription factor, at 3 days and its downstream target gene ABCG1 at 1 month in the ipsilateral side of the brain. This was accompanied by profound increases in synaptophysin (red) and PSD-95 (green) immunoreactivity inside of the scar tissue, indicating that daidzein promotes the structural formation of synapses (arrows in the figure). The study showed that daidzein-induced functional recovery is associated with gliadirected neuronal synaptogenesis and suggests that functional recovery may depend on the quality of repair and remodeling, not the size of infarct, of affected tissue.
patients were prospectively enrolled. All patients underwent at least one MRI. No adverse events occurred during MRI acquisition. Mean age was 62±17, 46% were female, and 70% had a history of hypertension. Median (IQR) GCS was 14 (10-15) and ICH volume 14 mL (5-38). Hematoma location was lobar in 45% and deep in 38%; 43% had associated IH. The final ICH diagnosis was hypertension or cerebral amyloid angiopathy in 56% of patients. After review of the MRI, the stroke neurologist changed the diagnostic category in 26%, diagnostic confidence in an additional 16%, and management in 15% of the patients. Within each of the nine diagnostic categories, the diagnostic yield of MRI was highest for establishing diagnoses of ICH secondary to ischemic stroke with hemorrhagic transformation (75%), vascular malformations (69%), and cerebral venous thrombosis (57%).

Conclusions: The results of this study demonstrate substantial additive clinical benefit of early routine MRI in patients with spontaneous ICH and/or NH.

Increase in Volume of Perihematomal Hyperintensity Exceeds Amount of Brain Swelling After Intracerebral Hemorrhage


Objective: To determine the effect of changes in perihematoma water content on brain volume over the first week after intracerebral hemorrhage (ICH). Background: Neuroradiographic studies have shown that the volume of perihematoma hyperintensity increases after ICH, but whether this leads to increased brain volume or is due to diffusion of serum beyond the confines of the original clot has not been established. Design/Methods: Fifteen patients aged 66±13 were studied with sequential MRI scans 0.9±0.5, 2.5±1.1, and 6.1±1.9 days after spontaneous supratentorial ICH. None received hyperosmolar therapy. Changes in hemispheric brain volume were assessed on the MPRAGE sequence using the Brain Boundary Shift Integral, a method that measures average intensity change in a boundary region-of-interest including all brain/CSF boundaries for the entire subjects brain. Clot volume and total lesion volume (clot + perihematoma hyperintensity) were outlined on each slice of each FLAIR (n=10) or TSE (n=9). Data were compared using t-tests. Results: Median clot volume was 14 cc (range 2-43) at baseline and decreased at scan 2 (11 cc, p=0.03) and scan 3 (10 cc, p=0.0001). Relative to scan 1, brain volume increased minimally at scan 2 (ipsilateral: 5.3±7.0 cc; contralateral: 3.9±6.5 cc) and returned toward baseline at scan 3 (ipsilateral: 1.7±6.0 cc; contralateral: -0.3±5.7 cc). Lesion volume increased at scan 2 (6.2±5.9 cc; p=0.004) and increased further at scan 3 (7.0±6.6 cc; p=0.001) due to an increase in perihematoma hyperintensity. Using contralateral hemisphere change to correct for hydration-associated volume change, ipsilateral hemisphere volume (ipsi corrected) increased 1.4 cc at scan 2 and 2.0 cc at scan 3. The change in lesion volume was 3.5 times that of the corrected ipsilateral hemisphere volume change.

Conclusion: Minimal brain swelling occurs bilaterally after ICH and returns to baseline within one week. The increase in ipsilateral hemisphere brain volume represents 27-28% of the increase in lesion volume, thus >70% of the increase in perihematoma hyperintensity may represent further diffusion of serum rather than a true increase in edema volume.

Practical Risk Stratification for the Presence of Underlying Vascular Lesions in Patients With Intracerebral Hemorrhage: The Secondary ICH Score

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Purpose: To develop a practical scoring system to stratify patients with intracerebral hemorrhage (ICH) according to their risk of an underlying vascular etiology. Materials and Methods: Utilizing a database of 623 ICH patients who were evaluated by multi-detector CT angiography (MDCTA) of the intracranial circulation over a 9-year period, we developed a practical scoring system to predict the risk of an underlying vascular abnormality as the cause of the ICH (Table 1). A positive CT angiogram was defined as one in which a vascular lesion as the ICH etiology was identified. A high-probability NCCT was defined as one in which there were either (1) enlarged vessels or calcifications along the margins of the ICH, or (2) hyperintensity within a dural venous sinus along the presumed venous drainage path of the ICH. A low-probability NCCT was defined as one in which neither (1) nor (2) were present and the ICH was located in the deep grey matter or brainstem. An indeterminate NCCT was defined as one that did not meet criteria for a high or low-probability NCCT. We subsequently applied this scoring system to a prospective cohort of 140 ICH patients who presented to our emergency department over a 7-month period. Using receiver operating characteristic (ROC) analysis, we calculated the areas under the curve (AUC) for the scoring system in both the derivation and validation cohorts. Patients with subarachnoid hemorrhage in the basal cisterns were excluded.

Results: Overall, an underlying vascular lesion was found in 110 of 763 ICH patients evaluated with MDCTA (14.4%). These included 47 arteriovenous malformations (42.2%), 26 aneurysms with intraparenchymal rupture (23.6%), 19 venous sinus thromboses (17.3%), 11 arteriovenous fistulae (10%), 4 cases of vasculitis (3.7%), and 3 cases of Moy–Aoya (2.7%). Underlying vascular lesions were more frequent in patients with higher Secondary ICH scores (Table 2), with the highest yields of MDCTA observed in patients with scores of 3 (19%), 4 (39.4%), 5 (85.3%) and 6 (100%). There was no significant difference in the AUC between both patient cohorts after ROC analysis. Conclusion: This practical scoring system successfully predicted the risk of harboring a vascular etiology in patients with ICH. The Secondary ICH score shows promise in selecting ICH patients for emergency neurovascular imaging.

Table 1. Calculation of the Secondary ICH Score

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Points</th>
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<tbody>
<tr>
<td>High-Probability NCCT</td>
<td>2</td>
</tr>
<tr>
<td>Indeterminate NCCT</td>
<td>1</td>
</tr>
<tr>
<td>Low-Probability NCCT</td>
<td>0</td>
</tr>
<tr>
<td>Age &lt;46 years</td>
<td>2</td>
</tr>
<tr>
<td>Age 46-70 years</td>
<td>1</td>
</tr>
<tr>
<td>Age &gt;70 years</td>
<td>0</td>
</tr>
<tr>
<td>Female gender</td>
<td>1</td>
</tr>
<tr>
<td>Neither known HTN nor IC at presentation</td>
<td>1</td>
</tr>
</tbody>
</table>

The score is calculated by adding the total number of points for a given patient. NCCT: Non-contrast CT examination; HTN: hypertension; IC: impaired coagulation, defined as admission INR >3, PTT >80, platelet count <50,000, or daily anticoagulant therapy.

Table 2. Diagnostic Yield of the Secondary ICH Score

<table>
<thead>
<tr>
<th>Score</th>
<th>Retrospective Derivation Cohort (N=623)</th>
<th>Prospective Validation Cohort (N=140)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Positive CTAs</td>
<td>N:</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>37</td>
</tr>
<tr>
<td>1</td>
<td>1.4</td>
<td>144</td>
</tr>
<tr>
<td>2</td>
<td>5.2</td>
<td>210</td>
</tr>
<tr>
<td>3</td>
<td>18.1</td>
<td>138</td>
</tr>
<tr>
<td>4</td>
<td>39.3</td>
<td>61</td>
</tr>
<tr>
<td>5</td>
<td>85.7</td>
<td>28</td>
</tr>
<tr>
<td>6</td>
<td>100</td>
<td>5</td>
</tr>
</tbody>
</table>

AUC(95%CI): 0.86 (0.83-0.89) 0.85 (0.78-0.9)

N: number of patients; CT: CT angiogram; n/a: not applicable; AUC: area under the curve after receiver operating characteristic analysis; CI: confidence interval.
Blood Brain Barrier Permeability is Diffusely Elevated in Primary Intracerebral Hemorrhage.

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Background: The etiology of edema in intracerebral hemorrhage (ICH) is controversial. Although most studies are consistent with a vasogenic rather than cytotoxic process, it is unknown to what extent the blood brain barrier (BBB) is compromised in ICH. We assessed BBB permeability using CT perfusion (CTP) in ICH patients. We hypothesized that perihematomal edema would be associated with elevated permeability. Methods: Patients with ICH (n=19) were assessed with CTP within 24 hours of symptom onset. Maps of permeability surface area product (PS) were calculated. Mean (M) and median (MD) maps of extravasation fraction at peak leakage rate, were calculated from CTP source images. Mean PS was measured in regions of interest defining the hematoma, 1 cm radial peri-hematoma region, ipsilateral and contralateral hemispheres. The total perihemotoma edema volume was also measured objectively, based on Housesfield unit thresholds of ≥±19 HU for perihematomal edema, ≥±19 HU for the identical protocol within 24 h were used as a reference group. Results: ICH patients (median age 73, range 45-100) were imaged with a median time from onset of 17 (6.2-23.5) h. Mean hematoma and perihematoma volumes were 17.7 ± 21.6 ml and 7.2 ± 9.9 ml respectively. Diffuse increases in PS were evident in all patients. Relative to the contralateral unaffected hemisphere (0.85 ± 0.36 ml/100g/min), PS values were higher in the hematoma (0.94 ± 0.30 ml/100g/min, p = 0.027) and perihematoma regions (0.75 ± 0.37, p = 0.005). Ipsilateral hemispheric PS (0.77 ± 0.56 ml/100g/min) was not higher than that in the contralateral hemisphere (p = 0.24). However, contralateral hemispheric PS values were themselves elevated, relative to those in ischemic stroke patients (0.30 ± 0.09 ml/100g/min, p = 0.002). Visually apparent focal areas of elevated permeability were present in 14/19 ICH patients (74%). These focal increases in PS involved both the hematoma and perihematoma regions in all patients. Patients with focal permeability elevation had larger perihematoma edema volumes (22.5 ± 24.2 ml) than those without focal PS increase (9.3 ± 14.8 ml, p = 0.045). There was no relationship between these volumes in patients with focal permeability changes (21.2 ± 24.2 ml vs 7.8 ± 4.8 ml, p = 0.068). There were no differences in blood pressure (177 ± 14 vs 177 ± 15 mmHg, p = 0.94), NIHSS (10 ± 6 vs 8 ± 3, p = 0.40) or time from symptom onset to imaging (15.6 ± 5.7 vs 13.8 ± 6.2 h, p = 0.52), between patients with/w/o focal permeability elevation. Conclusions: ICH patients have a generalized increase in BBB permeability, which affects the entire brain diffusely. There are also focal areas of elevated permeability in the hematoma/perihematoma regions of the majority of patients. This appears to be associated with more extensive perihematoma edema. This novel finding may represent a potential treatment target and provides some rationale for interventions aimed at improving BBB integrity in acute ICH.

Inhibition of Substance P Reduces Edema and Blood-Brain Barrier Dysfunction Following Rat Collagenase Intracerebral Hemorrhage, but Does Not Improve Functional Outcome

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Introduction: Intracerebral hemorrhage (ICH) is a common, devastating illness without proven acute therapies. Substance P inhibition has proven beneficial in experimental traumatic brain injury and ischemic stroke with reputation, but has not been tested following ICH. Hypothesis: We hypothesize that intranasal substance P would be elevated following experimental ICH and that inhibition of the substance P neurokinin-1 receptor (NK-1) would ameliorate edema, blood-brain barrier (BBB) dysfunction, inflammation, brain lesion volume and functional deficits. Methods: 124 male Sprague-Dawley rats (weight 280-350) were studied. ICH was induced using collagenase (0.20). Levels of substance P were determined by semi-quantitative immunohistochemistry and ELISA. Edema and BBB dysfunction were assessed by the wet-weight dry weight method and quantification of Evans Blue, respectively. Inflammation was assessed by quantifying neutrophils and activated microglia at 24 hours. Final lesion volumes were assessed by quantifying histological volumes at 28 days. Functional deficits were assessed using a battery of tests, including the rotarod and the vibrisse-elicited stimulation test. Two structurally unrelated neurokinin-1 receptor antagonists were used, namely n-acetyl tryptophan (NAT) and L-733,060. Results: Substance P was elevated in the perihematomal zone following ICH, with peak at 6 and 48 hours. Treatment with NAT reduced edema at 24 hours (brain water 81.4% vs 92.9%, p = 0.001) and BBB dysfunction (9.8 mg/mcg Evans Blue vs 14.5 mg/mcg, p = 0.05). The effect of NK-1 antagonists was maintained at 28 days, with the L-733,060 group revealing no edema or BBB dysfunction. Conclusions: Substance P is involved in the pathophysiology of acute edema formation and BBB dysfunction in rat collagenase ICH, but that inhibition of substance P does not improve behavioral outcome or reduce eventual lesion volume.
The effect of NK-1 antagonism on edema
24 hours after collagenase ICH

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Education Moderates the Association of Leukoaraiosis With Cognitive Decline: The Northern Manhattan Study

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Background and Purpose: White matter hyperintensities (WMH) are frequently seen on MRI in elderly persons without stroke, and have been associated with microvascular disease, vascular cognitive impairment, and dementia. While some studies have found that the presence and severity of WMH are related to cognitive decline, few have measured WMH quantitatively. Moreover, few population-based studies have included black and Hispanic individuals, although both the rate of cognitive decline and WMH burden may be higher in blacks and Hispanics than in whites. We investigated the association between WMH as a proportion of total cranial; WMHv) and cognitive decline in an ethnically diverse population of older adults living in the same community.

Methods: Clinically stroke-free participants from the community-based Northern Manhattan Study (NOMAS) underwent brain MRI. Cognitive function was assessed at baseline and again at the time of MRI using the Mini-Mental State Examination (MMSE). Generalized linear models were fitted to examine log-transformed WMHV in relation to the difference in MMSE score between baseline and the time of MRI, adjusting for sociodemographic variables and vascular risk factors.

Results: Data on cognitive function (median MMSE=80 points) and WMHV (median 0.39; IQR 0.22-0.80) were available on 933 participants (median age 63, IQR 58-70; 60% women; 69% Hispanic, 17% black, 4% white). After adjustment for age, sex, race/ethnicity, education, socioeconomic status, baseline MMSE score and time between MMSES, greater WMHV was positively associated with more decline prior to MRI on the MMSE (β=0.86, 95% CI: 0.38-0.95, p<0.0001). Our findings remained significant, and were strengthened slightly, after adjusting for hypertension, history of coronary artery disease, diabetes, and depressive symptoms (β=0.75, 95% CI: 0.43-1.06, p<0.0001). We also found that education was an effect modifier of the relationship between WMHV and change in MMSE score; increasing education was associated with less decline (8-11 years: β~0.56, 95% CI: -0.12-0.09, p=0.022; 12+ years: β~0.91, 95% CI: -1.34-0.48, p=0.0001). Conclusion: Over a average follow-up of 7.3 years, decline on the MMSE was associated with a greater burden of WMHV, independent of socioeconomic and vascular risk factors, in those who participated in the NOMAS MRI sub-study. The interaction of education and WMHV suggests an effect of cognitive reserve.

This research has received full or partial funding support from the American Heart Association, National Center.

Neurological Signs Associated With Cerebral Age-Related White Matter Changes: The LADIS (Leukoaraiosis And DisAbility) Study

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Aims: Age related white matter changes (ARWMC) are associated with motor, cognitive, mood, and urinary disturbances, but little is known about the prevalence of neurological signs possibly associated with these brain lesions. Our aim was to investigate in a group of initially independently living elderly, the frequency of neurological signs, the occurrence of new neurological signs, and their relationship with baseline and progression of ARWMC.

Methods: The LADIS (Leukoaraiosis And DisAbility) Study involves 11 European centres and primarily aims at evaluating ARWMC as independent predictor of disability in the elderly. At baseline and during the 3-year follow-up, neurological signs assessed were: upper motor signs, gait and balance abnormalities, finger taps slowing, primitive reflexes, extrapyramidal, pseudobulbar, cortical, cerebellar, and sensory signs. Baseline and progression of ARWMC were scored on MRI by the Fazekas scale (range 0-3) and the modified Rotterdam Progression Scale (range 0 - 9), respectively. Results: Six-hundred-thirty-nine non-disabled subjects were enrolled (mean age 74.1±5.0, M/F:282/351; 44% mild, 31% moderate, and 25% severe ARWMC according to the Fazekas scale). Comparing the 3 ARWMC severity groups, the frequency of gait and balance abnormalities, finger taps slowing, and both reflexes abnormalities, finger taps slowing and upper motor and extrapyramidal signs increased with increasing severity of ARWMC. Adjusting for age, sex, and infa ras, severe ARWMC remained independently associated with gait and balance abnormalities, finger taps slowing, pseudobulbar and upper motor signs (all p<0.05). During follow-up, clinical information was available for 590 patients, while MRI and clinical data at both baseline and 3-year follow-up was available for 387 patients. The incidence of neurological signs was highest for primitive reflexes, gait abnormality and pseudobulbar signs (20-25%), followed by balance abnormality, upper motor, finger taps slowing and extrapyramidal signs (8-11%). Sensory, cortical and cerebellar signs had the lowest incidences (1-3%). Baseline ARWMC grade independently predicted the occurrence of new upper motor signs, gait and balance abnormalities, finger taps slowing, primitive reflexes, and cortical and sensory signs (all p<0.05). Subjects with incident upper motor signs, gait and balance abnormalities, extrapyramidal signs, and finger taps slowing showed increased ARWMC progression over time than subjects who did not develop neurological signs (all p<0.05). Discussion: In our cohort of non-disabled elders, severe ARWMC was associated with the presence of specific neurological signs, and both baseline and progression of ARWMC were related to the occurrence of neurological signs, thus confirming the fact that ARWMC has a clinical impact.

Acute Cortical Lesions “Disappear” on MRI but Are Associated With Cortical Atrophy in Stroke Patients: Implications for Brain Aging and Vascular Cognitive Impairment

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Introduction: High resolution diffusion weighted imaging (DWI) often reveals cortical lesions outside the volume of the perfusion deficit and in different vascular territories. Case studies have noted that over time some of these cortical lesions are difficult to visualize and may even become invisible on 3D T1-weighted (3DT1) and fluid-attenuated inversion-recovery (FLAIR) images. The purpose of this study is to examine the time course of these cortical lesions and their associations with cortical atrophy:

Methods: Thirty-six stroke patients with median age of 66 years, identified as regions of interest (ROIs) on acute DWI. Patients returned 1 to 3 years after stroke for 3DT1 and FLAIR imaging (median follow-up, 16 months). A reader blinded to acute DWI drew ROIs on follow-up images to indicate the presence and location of cortical lesions. The follow-up images and ROIs were registered to acute DWI images to determine whether the reader was able to detect the lesions. FSL-Voxel Based Morphometry v1.1 was used to evaluate cortical atrophy by comparing the volume fraction of grey matter (GM) in the region where the lesion occurred to that of the contralateral side on 3DT1 images. Relative to the contralateral side, less GM at the lesion site is considered as a marker of cortical atrophy. Results: Of cortical lesions, 22% and 47% were identified on follow-up 3DT1 and FLAIR, respectively. On both follow-up images, 47% of cortical lesions were undetected. Furthermore, 6% of lesions were identified on 3DT1 but not identified on FLAIR, and 31% were unidentified on 3DT1 but detected on FLAIR. The mean volume fraction of lesions identified (mI) of lesions that were identified on both follow-up images was significantly larger than the mean volume of lesions that were not identified, 13.0% (±2.0%), on the follow-up images were significantly larger than the mean volume of lesions that were not identified, 13.10% (±0.1), on the follow-up images were significantly larger than the mean volume of lesions that were not identified, 13.10, (p < 0.01). The average volume fraction of GM at the site of the lesion, 38.14, was significantly less than that of the contralateral side, 44.16, p < 0.01, suggesting cortical atrophy. The reduction in volume fraction of GM did not differ between lesions that were identified and lesions that were not identified on both follow-up images. Conclusion: Some cortical lesions can become undetectable on 3DT1 and FLAIR, yet still result in a decrease in GM. Unlike white matter lesions that remain hypointense on MRI, small cortical lesions are likely to go unnoticed because their conspicuity on MRI fades over time. These small cortical lesions may be another pathway to cortical atrophy and vascular cognitive impairment.

Increased Medial Temporal Lobe Atrophy in Memory-Dominant Cognitive Impairment After Stroke

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Backgrounds: Poststroke cognitive impairment - no dementia (PSCI-ND) has been conceptualized as a lesion rather than merely a concomitant of stroke, because lesion location of the frontal-subcortical circuit from ischemic damages involving subcortical white matter and deep gray matter. However, memory deficit, which has been considered as one of the early 2010 International Stroke Conference Oral Presentations e213
characteristics Alzheimer’s disease, is often found in stroke survivors with PSCI-ND. Hypoth-

esis: We hypothesized that the memory dysfunction in patients with PSCI-ND would be
originated from the subcortical neurodegenerative process, and medial temporal lobe atrophy (MTA) on MRI scan may be utilized to differentiate the underlying pathologic mechanisms.

Methods: Stroke survivors (n = 192) and non-stroke subjects who visited the outpatient memory clinic (n = 31), with cognitive impairment in only one domain, were enrolled to this study. All participants underwent MRI scans, Korean version of vascular cognitive impairment harmonization standards protocols, and clinical and neurological evaluation, after >90 days from stroke onset (interval after stroke, mean= ± SD: 452.6± 318.6 days). Subjects who scored less than 16 in MMSE were excluded. Learnt and recited delayed recall were deleted due to memory deficits. A standard five-point MTA visual rating scale was rated using coronal MRI scans by two independent raters blinded to the clinical and neuropsychological profiles (Spearman correlation coefficient = -0.71). Subjects were categorized into 1) case group (n = 77; stroke survivors with memory deficit), 2) amnestic mild cognitive impairment (aMCI) group (n = 31; no history of stroke, but memory deficit), and 3) disease control group (n = 115; stroke survivors without memory deficit).

Results: The distribution of age, education, cardiovascular risk factors and white matter hyperintensities (WMH) was not significantly different across the case, disease control and aMCI group. In cognition factor model, the estimated means of MTA scale from case group (mean ± SE, 0.94 ± 0.19; corrected p = 0.04) and aMCI group (1.13 ± 0.21; p = 0.01) were higher than that from disease control group (0.58 ± 0.15), after adjustment for gender, age, education, WMH, and MMSM score (ANOVA, F = 5.56 and p < 0.01). In cardiovascular risk factor model, the mean score from case group (2.2 ± 0.18; p < 0.01) and aMCI group (1.41 ± 0.23; p = 0.01) were also higher than that from disease control group (0.75 ± 0.18), after adjustment for gender, age, hypertension, diabetes, dyslipidemia and atrial fibrillation (ANOVA, F = 15.03 and p < 0.01).

Conclusions: Our data documented that MTA, an alleged marker of Alzheimer’s disease, was associated with memory deficits in PSCI-ND patients. In this context, MTA may be utilized to distinguish underlying pathology of patients with PSCI-ND.

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Cognitive Decline at 90 Days in Patients Presenting With Stroke: Relationships With Baseline Predictors and Functional Outcome

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Introduction: Stroke and impaired cognition are common, economically costly to society, devastating to patients and their family, and together catastrophic. 30% of people with stroke go on to develop dementia. Methods: The relationship between cognition (subset of Mini-Mental State Examination, ≥MMSE, at 90 days assessed by telephone) and baseline demographic and clinical factors was studied in 465 patients (UK/Stroke Research Network-452.5% patients) with acute stroke enrolled into the ongoing ‘Efficacy of Nitric Oxide in Stroke Trial’ (ENOS). A baseline relationship between ≥MMSE and other clinical outcomes at 90 days was also studied.

Results: The ≥MMSE ranged between 0-18/18 (mean 13.35, standard deviation 4.71). In univariate analysis, a low ≥MMSE at day 90 was associated with increasing age, female sex, previous stroke, atrial fibrillation, haemorrhagic stroke, TACS, low SSLS, and high systolic and diastolic BP (p < 0.001); the factors all remained significant in a multiple variable analysis (p < 0.001) except a history of previous stroke. There was no relationship with diabetes, temperature or glucose. Lower ≥MMSE was also associated, in univariate models, with increased dependency (modified Rankin scale, Pearson correlation coefficient, r = -0.368, p = 0.08), incontinence (Barrack index, r = 0.42, p < 0.001), quality of life (EuroQOL VAS, r = 0.314, p < 0.001) and depression (Zung, r = -0.135, p = 0.04) at 90 days. Conclusion: Poor cognitive function at 90 days post stroke is associated with multiple baseline factors, including high systolic and diastolic BP, and with a low functional outcome, quality of life and mood. Lowering BP in the acute phase of stroke is a potential target for reducing poor cognition.

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Differential Impact of Anterior and Posterior White Matter Lesion Progression on Vascular Cognitive Decline

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Background: White matter lesions (WMLs), generally thought to be due to “microvascular” disease, are commonly found on MRI scans in the elderly. Although a few large scale studies find an association between lesion progression and cognitive decline, the comparative impact of anterior vs. posterior WML progression on cognitive function has not been explored. Purpose: To determine the relationship between the pattern of regional WML progression and cognitive decline.

Methods: Subjects included 110 normal controls, ages 60 and older, from the Neurocognitive Outcomes of Depression in the Elderly study. All subjects had comprehensive cognitive evaluations and MRI scans at baseline and after 2 years. Cognitive composites were created for 5 domains: memory, immediate and delayed verbal memory, immediate and delayed visual memory, complex processing speed, working memory, visual-cognitive constructional skills, and language. Change in cognition was calculated utilizing standard regression-based models accounting for variables known to impact serial cognitive testing, such as practice effects and regression to the mean. A semi-automated segmentation method was utilized to measure WML extent in anterior and posterior brain regions. Multivariate analyses of covariance compared overall progression of WML load in subjects who did and did not have a cognitive decline. Hierarchical multiple linear regressions were then computed to evaluate cognitive predictors of regional (i.e., anterior vs. posterior) WML progression among normal elders. Cognitive outcomes associated with this regional variation can have clinical importance and need to be considered in studies evaluating the impact of WML on cognition.

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Distinctive RNA Expression Profiles of White Matter Hyperintensities in the Blood of Human Subjects Using Genome Wide Microarray Analyses

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Background: White Matter Hyperintensities (WMH) are areas of increased signal on T2-weighted and fluid attenuated inversion recovery MRI images. Clinically, they are associated with aging, cerebrovascular risk factors and cognitive impairment. The exact pathogenesis of WMH, however, remains unclear. Therefore, we examined RNA expression profiles from blood of individuals with WMH in a pilot study to explore whether there are unique molecular profiles associated with WMH independent of cognitive impairment.

Methods: We recruited non-demented subjects with minimal (n=11), below the 25th percentile of a normal population) or extensive (n=10, above the 75th percentile of a normal population) WMH and defined to have extensive WMH (n=10, above the 75th percentile of a normal population) or extensive WMH (n=10, above the 75th percentile of a normal population) as well as age matched dementia patients with minimal (n=9) or extensive WMH (n=6) for this study. All participants received a comprehensive assessment of cognitive status and a comprehensive assessment of cognitive status and a comprehensive microarray analysis.

Results: There were no significant differences in age, gender, race or history of vascular risk factors for the WMH subjects and controls. Total RNA was purified from peripheral whole blood. Affymetrix Human U133 plus 2.0 arrays were used to measure the expression of over 39,000 genes. Analysis of Covariance (ANCOVA) was performed on the microarray gene expression data in Partek Genomics Suite (Partek Inc., St. Louis, MI, USA). The ANCOVA was used to co-vari out confounding factors including batch effects in the microarray experiments, age, gender, heart disease and cognitive status. Results: We found a substantial number of genes differentially regulated in subjects with extensive WMH as compared to those with minimal WMH, regardless of coexisting cognitive status (50 genes at p < 0.005 and 1.5 fold change cutoff, and 241 genes at p < 0.005 and 1.2 fold change cutoff). Cluster analysis and principal component analysis showed that the expression profiles based upon these genes were able to distinguish subjects with extensive WMH from those with minimal WMH. Functional annotation of the genes significantly associated with extensive WMH suggested their potential roles in inflammation responses, hematological system and nervous system development and function and metabolism. Conclusion: The unique molecular expression profile associated with WMH suggests the potential role of systemic inflammatory processes in the etiology of WMH. Further work is necessary to understand how these findings relate to other WMH risk factors.

This research has received full or partial funding support from the American Heart Association, National Center.

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Does Aspirin Failure Increase the Chances of Recurrent Stroke and/or Death Among Patients With Ischemic Stroke: A Pooled Analysis of Two Prospective Trials

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Background: Patients who have an ischemic stroke while on aspirin are often designated as “aspirin failures” either in primary or secondary preventive role. This phenomenon is observed in up to 1 of every 3 patients admitted with ischemic stroke. It is a common belief that such patients are at high risk for recurrent ischemic events despite alternative antplatelet therapy. Objective: To determine the risk of recurrent stroke or death in patients already on aspirin at the time of ischemic stroke compared with those who were not being treated with aspirin at the time of ischemic event. Method: We analyzed the prospectively collected data from the National Institute of Neurological Disorders and Stroke (NINDS) intravenous recombinant tissue plasminogen activator (rtPA) trial and Trial of ORG 10172 in Acute Stroke Treatment (TOAST). We determined the 12 month risk of recurrent stroke and/or death by serial clinical follow-up contacts in patients (and patient subgroups) who were designated or not designated as “aspirin failure”. The risk factors of “aspirin failure” patients and patients not previously on aspirin including demographics, cardiovascular risk factors, severity, and stroke type subtypes were compared using a logistic regression analysis.

Results: We analyzed 1275 patients from TOAST 624 from NINDS IV rtPA trials; 40% and 35% were on aspirin at the time of ischemic stroke in these trials, respectively. In patients designated as “aspirin failure”, recurrent stroke was observed in 5% and 6% of the patients recruited in TOAST and NINDS IV rtPA trials, respectively. Patients designated as “aspirin failure” had higher prevalence of cardiovascular risk factors but no difference according to stroke subtypes. Analysis of the cumulative risk of stroke (odds ratio [OR] 1.1, 95% confidence interval [CI] 0.63-1.8) and of cumulative endpoint of stroke and death (OR 1.0, 95% CI 0.74-1.6). Among patients with large

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vessel atherosclerosis, “aspirin failure” patients had similar 1 year risk of stroke and of cumulative endpoint of stroke and death. **Conclusion:** In two studies which were performed prior to the widespread availability of alternative antiplatelet agents, there was no observed increase in the one year risk of recurrent stroke and/or death among “aspirin failure” patients with ischemic stroke or those with large vessel atherosclerosis.

This research has received full or partial funding support from the American Heart Association, National Center.

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**1.42; 95% CI 1.07-1.88 p = 0.01** were associated with good adherence over the 1st year and the entire cohort were receiving antithrombotic therapy after the stroke. The Table shows adherence and biomarker risk factor control after the hospitalization for an ischemic stroke.

In an emerging country, a hospital-based multidisciplinary program can significantly improve treatment and may represent opportunities to improve adherence.

**Conclusion:** From cohort data, it may be concluded that the multidisciplinary care that we provided might have contributed to our significantly better control of the cardiometabolic risk factors.

**Methods:** The Estudo de Mortalidade e Morbidade do Acidente Vascular Cerebral - EMMA Study is a surveillance study addressing mortality and morbidity from cerebrovascular diseases. We analyzed all 35,926 deaths classified as stroke from 1996 (first year of 10th Revision of the International Classification of Diseases) to 2007 (most recent year available) for people ages 35 to 74 years-old of both sexes. São Paulo is organized into 96 districts that were classified into four areas, from the wealthiest (#1) to the poorest (#4), according to the proportion of households with a family income less than or equal to five minimum wages identified on National Census data (1991 and 2000). The population estimate for each district was based on National Census data by extrapolation and estimation for the intercensuses years by the official demographic agency. Death rates were adjusted by the Segé’s standard population. “Jointpoint Regression Program 3.3.1” was applied to perform a survival to verify if the trends of stroke death rates in a log-linear model using Poisson regression; it created a Monte Carlo permutation test to identify points where the trend line changes significantly in magnitude or in direction; and it also allows calculation of the Annual Average Percent Change with 95% Confidence Interval. We also compared the ratio between the first interquintal (1996-98) to the most recent (2005-07).**Results:** For all areas, the pattern of stroke death was linear and continuous. For men, the Annual Average Percent Change for age-adjusted stroke death rates observed was area #1 (wealthiest): -5.2 (-6.6 to -3.7); area #2: -4.4 (-7.9 to -0.7); area #3: -4.2 (-5.3 to -3.1), and for area #4 (poorest): -4.2 (-5.3 to -3.1). For women, the Annual Average Percent Change was for area #1: -5.7 (-6.8 to -4.5); area #2: -4.7 (-5.8 a -3.8); area #3: -4.3 (-5.2 to -3.4), and for area #4: -4.3 (-5.3 to -3.3). The risk ratio of age-adjusted death rates from area #4 to area #1 increased slightly (with no statistical significance) from 1996-98 (men, 2.08; women, 2.21) to 2005-07 (men, 2.15; women, 2.38). **Conclusion:** An overall decline of stroke death rates was observed for all areas of the city according to socioeconomic classification for both sexes. However, the “double risk” of stroke death has been maintained in the poorest area compared to the wealthiest area.

**PROTEGE-ACV Program: Improving the Quality of Care of Stroke Patients in an Emerging Country**

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**Methods:** In an emerging country, a hospital-based multidisciplinary program can significantly improve treatment and may represent opportunities to improve adherence.

**Conclusion:** From cohort data, it may be concluded that the multidisciplinary care that we provided might have contributed to our significantly better control of the cardiometabolic risk factors.

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**Warfarin, Aspirin, and Their Combination in the Prevention of Stroke in Patients With Atrial Fibrillation: A Nested Case-control Study**

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**Background:** Vitamin K antagonists, such as warfarin, are under-prescribed in patients with atrial fibrillation (AF), a population at high risk of stroke who would normally benefit from this therapy. The objective of this study was to quantify the association between the use of warfarin and aspirin as monotherapy, as well as their use in combination, on the incidence of stroke in patients newly diagnosed with AF. **Methods:** We conducted a nested case-control study within a population-based cohort from the UK General Practice Research Database. The cohort included all patients at least 18 years of age with a first ever diagnosis of AF between January 1, 1993 and December 31, 2008. During follow-up, all subjects who experienced a stroke were identified as cases. Up to ten controls selected from the cohort were matched to each case on year of birth, gender, date of cohort entry, and duration of follow-up. Conditional logistic regression was used to estimate rate ratios (RR) of stroke associated with the use of warfarin monotherapy, aspirin monotherapy, and their combination, relative to the non-use of any of these agents. All RRs were adjusted for CHADS2 score and other relevant confounders, which included body mass index, alcohol abuse, and smoking status. **Results:** The cohort comprised 74,095 patients newly diagnosed with AF, of whom, 5,998 experienced a stroke during a mean follow-up of 3.8 years. The rate of stroke was 21.3 per 1000/year. Patients currently exposed to warfarin monotherapy were at a decreased risk of stroke compared with patients not using any other therapy (adjusted RR: 0.52, 95% CI: 0.47, 0.57). The rate of stroke was also reduced in patients currently exposed to aspirin monotherapy (adjusted RR: 0.88, 95% CI: 0.81, 0.95) and combination of warfarin and aspirin (adjusted RR: 0.57, 95% CI: 0.41, 0.78). **Conclusions:** The results of this large population-based study indicate that warfarin...
therapy, whether used in monotherapy or in combination with aspirin, reduces the risk of stroke in patients with AF. The use of aspirin in monotherapy also decreases the risk of stroke, but at a much lower degree than warfarin.

## Occult vs. Known Atrial Fibrillation After Acute Ischemic Stroke and Transient Ischemic Attack: Are There Any Differences?

### Background and Purpose
Occult atrial fibrillation (AF) can be detected after acute ischemic stroke (IS) and transient ischemic attack (TIA) by continuous electrocardiographic (ECG) monitoring. Given the low availability of continuous ECG monitoring facilities, the identification of patients with high risk for occult AF is mandatory. Age, female gender, and left atrial area (LAA) are recognized determinants of AF. The question of whether these traditional risk factors for AF are also related to occult AF remains unresolved. We sought to identify determinants of known and occult AF and to compare the characteristics of acute IS and TIA patients with known and occult AF.

### Methods
We assessed 196 patients with diagnosis of acute IS and TIA admitted between 01/01/2007 and 12/31/2008. We used continuous ECG monitoring during >3 days immediately after admission for the screening of occult AF. We defined occult AF if the arrhythmia was detected after the qualifying IS or TIA in patients with no history of AF. We used 2 and 1-t tests to compare baseline characteristics, risk factors, and outcome between the two groups. We developed multiple logistic regression models for identifying determinants of known and occult AF.

### Results
We assessed 38 patients with known AF and 24 with occult AF. The comparison between both groups is shown in the Table. The multiple logistic regression models, age (OR 1.04, 95% CI 1.00-1.08, P = 0.035), male gender (OR 0.23, 95% CI 0.10-0.54, P = 0.001), and LAA (OR 1.17, 95% CI 1.10-1.25, P < 0.0001) were associated with known AF; while diabetes mellitus (OR 2.78, 95% CI 1.01-7.68, P = 0.047) and infarct size (OR 3.93, 95% CI 1.44-10.72, P = 0.056) were associated with occult AF.

### Table 1. Baseline Characteristics and Outcome

| Baseline Characteristics | Known AF (n = 38) | Occult AF (n = 24) | P  Mentals 2.1, 3.0 | 0.787  Mean NIHSS ≤ SD | 7.8 ± 6.2 | 10.8 ± 7.0 | 0.083  Mean ABCD2 Score ≤ SD | 3.4 ± ±2.0 | 4.0 ± 1.8 | 0.237  Left hemispheric strokes, % | 27.8 | 72.2 | 0.002  Bilateral strokes, % | 5.6 | 11.1 | 0.763  Anterior circulation, % | 72.2 | 88.9 | 0.213  Infarct size >15 mm | 94.4 | 88.9 | 0.763  In-hospital mortality, % (95% CI) | 2.6 (0.4-13.5) | 12.5 (4.3-31.0) | 0.310  NIHSS: National Institutes of Health Stroke Scale

### Table 2. Risk Factors Profile

| Risk Factors Profile | Known AF (n = 38) | Occult AF (n = 24) | P  Mean age ≤ SD | 77.3 ± 10.4 | 66.8 ± 10.3 | 0.019  Male gender, % | 42.1 | 83.3 | 0.003  Systemic hypertension, % | 64.2 | 79.2 | 0.872  Diabetes mellitus, % | 15.8 | 41.7 | 0.049  Smoking, % | 44.7 | 37.5 | 0.768  Hyperlipidemia, % | 52.6 | 70.8 | 0.247  History of stroke, % | 21.1 | 12.5 | 0.602  Mean atrial area ≤ SD, cm2 | 28.6 ± 7.6 | 22.1 ± 4.5 | <0.0001  Atrial area > 20cm2 | 91.2 | 60.9 | 0.011

AF: atrial fibrillation; SD: standard deviation

### Conclusions
Patients with occult AF were younger, showed a higher proportion of males, had a smaller LAA, and had more severe strokes. Traditional determinants of AF were associated with known AF. Interestingly, we could not demonstrate this association for occult AF. Moreover, diabetes mellitus and infarct size were the only factors related to occult AF. Further studies are needed to confirm our findings. Meanwhile, we propose that diabetes mellitus and infarct size >15mm be considered as possible determinants of AF after IS or TIA of undetermined etiology and prompt to continuous ECG monitoring, even in younger patients with normal LAA.

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**Resistin, but Not Adiponectin or Leptin, is Associated With the Risk of Developing Ischemic Stroke Among Postmenopausal Women: The Women's Health Initiative Study**

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Adipose tissue is now considered an endocrine organ that secretes several substances called adipokines, including adiponectin, leptin and resistin, which are thought to mediate the effects of obesity on chronic diseases such as cardiovascular disease (CVD). As yet there are limited prospective data on the association between circulating levels of these adipokines and risk of developing ischemic stroke. Therefore, we conducted a case-control study (960 stroke cases and 1:1 age and race matched controls) nested within the Women's Health Initiative Observational Study, a prospective cohort study among postmenopausal women aged 55-79 years at enrollment. Overall, levels of these adipokines were positively associated (versus the case in the adiponectin) with established stroke risk factors, including age, presence of diabetes, systolic blood pressure, insulin resistance and circulating lipids. The odds ratios (OR) for the lowest vs. highest quartile of resistin were: 0.81 (95% confidence intervals [CI]: 0.61, 1.08; p for trend: 0.07) for adiponectin, 1.57 (95% CI: 1.18, 2.08; p for trend: 0.002) for resistin and 1.15 (95% CI: 0.83, 1.59; p for trend: 0.39) for leptin. The association for resistin remained significant even after accounting for other risk factors including smoking, physical activity, hypertension, diabetes, systolic blood pressure, hypertension medication use and history of coronary heart disease (OR: 1.39; 95% CI: 1.02, 1.88; p for trend: 0.035). We conclude that circulating levels of resistin, but not those of adiponectin or leptin, are associated with an increased risk of incident ischemic stroke, independent of obesity and other CVD risk factors. Future studies should confirm this finding and also evaluate the factors that modify circulating levels of resistin.

**Risk Factors for Childhood Arterial Ischemic Stroke: Results From the International Pediatric Stroke Study**

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Objectives: To describe the prevalence of idiopathic childhood arterial ischemic stroke (AES), to explore the spectrum of risk factors (RF) and their relationship with mode of presentation, age and infarct characteristics. Methods: Children aged 28 days-18 years with AES were prospectively enrolled in the International Pediatric Stroke Study. RF were divided into 10 (not mutually exclusive) categories. 9 tests were used to compare prevalence of RFs across geographical regions and age groups. Logistic regression models were used to determine whether specific RFs predicted presentation or infarct characteristics. Results: 676 children with AES were recruited between 2005-2007. 82% presented with focal and 63% with diffuse signs. Infarcts involved the anterior (67%), posterior (22%) or both circulations (11%). Complete RF data was available for 593 children. No recognisable AES RF was present in 54 (8%). RF categories in the remaining 539 included arteriopathies (59%), cardiac disorders (53%), chronic systemic conditions (CSC) (30%), infection (24%), acute head and neck disorders (AHD) (23%), acute systemic conditions (ASC) (22%), prothrombotic states (PTS) (13%), chronic head and neck disorders (CHND) (10%), RF for atherosclerosis (2%) and other RF (22%). 52% of children had multiple RF. Significant geographical variations were low rates of arteriopathy in Asia, high rates of PTS in Europe and high rates of ASC in Asia and South America (<0.05 in each). Rates of cardiac disease (0.01), AHD and infection were highest in children aged 1-5 years, arteriopathies were highest in children 5-9 years and CHND were highest in children aged >10 years (<0.05 in each). Focal signs predicted arteriopathies (<0.01) and diffuse signs were associated with ASC, AHD and CHND (<0.01). Cardiac disorders and ASC predicted focal infarction (<0.01) and cardiac disorders predicted haemorrhagic conversion (<0.05). Conclusions: Childhood AES is rarely idiopathic and multiple RF are common. Arteriopathies are the most common RF and are associated with focal presentations. Atherosclerosis related RFs are rare. Multiple lesion and haemorrhagic conversion are more likely with cardiac disorders. This study confirms childhood AES has a distinct RF profile and highlights the importance of vascular imaging to detect arteriopathy. Geographical variation in RF profiles may have substantial implications for diagnostic evaluations and prevention measures in different locales.

**Congenital Heart Disease Increases Childhood Stroke Risk Six-fold: Results of a Population-based Case-control Study**

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Background: Congenital heart disease (CHD) is considered an important risk factor for childhood stroke because of its prevalence in high hospital service areas, yet actual estimates of relative risk are lacking. Methods: We performed a nested case-control study within the cohort of all 2.3 million children up to 20 years of age enrolled in a Northern California managed care plan, 1/1993- 12/2004. Cases of symptomatic stroke were identified through electronic searches of inpatient and outpatient diagnoses and radiology reports, and confirmed through independent chart review. Three controls per case were randomly selected from the same cohort and pair-matched by birth year and primary care facility. Data were abstracted using standardized protocols and analyzed using conditional logistic regression to account for matching, or Fishers exact when appropriate. Results: We identified 370 cases of childhood stroke...
stroke (217 ischemic, 153 hemorragic). CHD was a risk factor for childhood stroke, regardless of whether it was cyanotic or acyanotic (Table). However, only children whose CHD had surgical repair were at increased risk. Of 11 cases with CHD repair, 5 had stroke within 14 days following their operation. One operation occurred pre-operatively, one occurred a month after repair, and the other four occurred 6-18 years after repair. Of six controls with CHD, three had surgical repair. Children with CHD had both ischemic (n=9) and hemorrhagic (n=3) strokes. None of the children with hemorrhagic stroke were on anti-platelet or anticoagulation therapy at the time of the stroke, or had prior ischemic stroke. Conclusions: CHD increases the odds of childhood stroke six-fold. While the postoperative period may be a time of particularly high stroke risk, children requiring cardiac surgery may remain at risk after the acute postoperative period.

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**Late Neurovascular Events in Pediatric Brain Tumor Patients**


Background: Brain tumors are the most common solid tumor in children. With increasing lengths of survival, late treatment effects including stroke and vasculopathy are becoming more evident. Radiation associated stroke is well documented in adults, but little has been written concerning this late effect in children. Objectives: To determine the incidence of neurovascular events as late complications in a cohort of pediatric brain tumor patients at one tertiary care center and to evaluate radiation as a risk factor for neurovascular events. Methods: Retrospective cohort study of patients in the pediatric brain tumor database of a large, pediatric tertiary care center. Patients were included if they had a diagnosis of a primary brain tumor, aged 21 years at diagnosis, initial treatment between 1/1/93-12/31/02 and at least two visits with Pediatric Neuro-Oncology. Patients with the following were excluded: diseases known to be associated with a higher risk of vascular abnormalities (e.g. neurofibromatosis type 1), extensive perioperative stroke and those patients not receiving treatment for their brain lesions. Radiation exposure was dichotomized as either involving the circle of Willis (COW) or not. The primary outcome was a neurovascular event, either stroke or transient ischemic attack (TIA). Results: A cohort of 380 subjects with a mean age of 8.5 years at diagnosis was followed for a median of 6.7 (interquartile range 2.9-9.3) years. Radiation was administered to 72%. Nineteen neurovascular events occurred in 14 subjects (8 stroke, 11 TIA) a median of 4.9 (1.7-7.5) years after diagnosis. The incidence rate of stroke or TIA was 5.9/1000 person-years, 72%. Nineteen neurovascular events occurred in 14 subjects (8 stroke, 11 TIA) a median of 4.9 (1.7-7.5) years after diagnosis. The incidence rate of stroke or TIA was 5.9/1000 person-years, 72%. Nineteen neurovascular events occurred in 14 subjects (8 stroke, 11 TIA) a median of 4.9 (1.7-7.5) years after diagnosis. The incidence rate of stroke or TIA was 5.9/1000 person-years, 72%. Nineteen neurovascular events occurred in 14 subjects (8 stroke, 11 TIA) a median of 4.9 (1.7-7.5) years after diagnosis. The incidence rate of stroke or TIA was 5.9/1000 person-years, 72%. Nineteen neurovascular events occurred in 14 subjects (8 stroke, 11 TIA) a median of 4.9 (1.7-7.5) years after diagnosis. The incidence rate of stroke or TIA was 5.9/1000 person-years, 72%. Nineteen neurovascular events occurred in 14 subjects (8 stroke, 11 TIA) a median of 4.9 (1.7-7.5) years after diagnosis. The incidence rate of stroke or TIA was 5.9/1000 person-years, 72%. Nineteen neurovascular events occurred in 14 subjects (8 stroke, 11 TIA) a median of 4.9 (1.7-7.5) years after diagnosis. The incidence rate of stroke or TIA was 5.9/1000 person-years, 72%. Nineteen neurovascular events occurred in 14 subjects (8 stroke, 11 TIA) a median of 4.9 (1.7-7.5) years after diagnosis. The incidence rate of stroke or TIA was 5.9/1000 person-years, 72%. Nineteen neurovascular events occurred in 14 subjects (8 stroke, 11 TIA) a median of 4.9 (1.7-7.5) years after diagnosis. The incidence rate of stroke or TIA was 5.9/1000 person-years, 72%.

**Risk of Recurrence in Children With Arterial Ischemic Stroke: A Prospective Consecutive Cohort Study**

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Objectives: To evaluate the incidence, timing and risk factors for recurrent arterial ischemic stroke (AS) among children in a prospective single-center cohort study. Methods: Prospective consecutive cohort study of children with AS managed by an established neurovascular service in a tertiary care pediatric hospital between January 2003 and June 2009. Inclusion criteria: 2 mo -18 year-old children with radiologically confirmed acute AS. Stroke risk factors were evaluated in all children according to an institutional stroke protocol, and included vascular imaging, echocardiogram and thrombophilia panel. Recurrence was defined as a second clinical event with onset ≥ 24 hrs after the index event, corresponding to a radiologically distinct infarct. Clinical data was abstracted from records of acute hospitalization and follow-up clinic visits. Incidence of recurrence was evaluated by survival analysis. Results: Ninety-three children met inclusion criteria, 70% male, median age at diagnosis 3.6 yrs (4 mo-17 yr). Primary stroke risk factors included: 26 cardioembolic, 37 cervical or intracranial arteriopathy, 7 tumor- or procedure related, 3 hemoglobinopathy, 4 thrombophilia, 2 other, 14 unknown. All 10 children with prior history of transient ischemic attack (TIA) were at increased risk of recurrence. Recurrence occurred at a median of 9.6 months (2 days-24 mo). Conclusions: Children with prior TIA are at an increased risk of recurrent stroke. The risk of recurrence was higher in children with TIA than in those without, regardless of other stroke risk factors. Counseling and close monitoring are warranted, and future studies should target primary stroke prevention in this population.
Elevated Body Mass Index: A Risk Factor for Childhood-onset Cerebral Sinus Venous Thrombosis

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Background: Cerebral Sinus Venous Thrombosis (CSVT) is a rare and serious disorder in children, with incidence estimated at 0.67/100,000 per year. Apart from thrombophilia and head trauma, few risk factors have been identified in children. Given that elevated Body Mass Index (BMI) is a risk factor for venous thromboembolism (VTE) in adults, we sought to determine whether this is also true for children. Methods: We collected data on height and weight in an institutional, prospective inceptional cohort study of pediatric VTE, comprising 23 children diagnosed with CSVT from March 2006-August 2009. Height and weight demographics were obtained within 3 months of radiologically-confirmed CSVT. A separate cohort of hospitalized controls was obtained. For each child with CSVT, we collected BMI data for three (3), for 25 child controls. Age- and gender-matched contemporaneous hospitalized controls without CSVT. BMI distributions were compared between cases and controls via Wilcoxon rank sum test, and the prevalence of overweight (defined as ≥85th percentile) for normative values, for age and gender using Centers for Disease Control and Prevention (CDC) data compared by chi-square test. Results: Median (range) BMI was 89.4% (3.5%-99.7%) in the CSVT group, as compared to 57.3% (0.2%-99.4%) for controls (P < 0.05). Furthermore, BMI was positively related to CSVT risk (OR 1.00-1.03; P < 0.01). Furthermore, BMI was positively related to CSVT risk (OR 1.00-1.03; P < 0.01). The prevalence of overweight patients was 57% (13/23) for CSVT cases versus 25% (17/69) among controls (P < 0.01). Furthermore, BMI was positively related to CSVT risk (OR 1.00-1.03; P < 0.01). The prevalence of overweight patients was 57% (13/23) for CSVT cases versus 25% (17/69) among controls (P < 0.01). Furthermore, BMI was positively related to CSVT risk (OR 1.00-1.03; P < 0.01). 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Stereotactic Radiosurgery for Intracranial Arteriovenous Malformations: A Meta-analysis of Current Therapeutic Applications

Justin F Fraser, Susan C Pannullo, Michelle J Smith, Baxter Allen, Philip E Stieg; Weill Cornell Med College, New York, NY

Stereotactic radiosurgery (SRS) is an important tool in neurosurgical management of intracranial arteriovenous malformations (AVMs). We performed quantitative meta-analysis of SRS applications in the treatment of AVMs, providing benchmarks for expected outcomes. Meta-analysis was conducted in accordance with established standards for observational data. Data were extracted from included studies to evaluate demographics and outcome. Outcome variables included radiographic obliteration rates, rebleeding, complications, and AVM-related mortality. 18 studies of 59 screened were included. The most common reason for exclusion was publication from a group with an already included study. 2423 patients were included with an overall age range of 2-79 years. The rate of AVM complexity grading (Spetzler-Martin Grades II-IV) varied between 20.0 and 76.4%. The majority of patients were not pre-treated with endovascular embolization. Overall radiographic obliteration rate was 67.6%. The actuarial annual rebleed rate could be calculated in 4 studies, and was 2.0% per annum. Overall complication rate was 7.3%. The rate of AVM complexity grading (Spetzler-Martin Grades II-IV) varied between 20.0 and 76.4%. The majority of patients were not pre-treated with endovascular embolization. Overall radiographic obliteration rate was 67.6%. The actuarial annual rebleed rate could be calculated in 4 studies, and was 2.0% per annum. Overall complication rate was 7.3%. The overall mortality rate attributable to AVM after treatment was 3.0%. SRS offers an important tool in the treatment of intracranial AVMs, providing a high rate of radiographic obliteration, with a relatively low complication rate. However, the risk of re-bleeding in patients with residual AVM remains a small but difficult problem.

Regional Deletion of Smad4 plus VEGF Stimulation Leads to Vascular Dysplasia in the Adult Mouse Brain

Espir Walker, Fanxia Shen, Ryan Halprin, Sarah Connolly, Stephen L. Nishimura, William L. Young, Hua Su; Univ of California, San Francisco, San Francisco, CA

Background and Purpose: Brain arteriovenous malformations (BAVMs) can cause life-threatening hemorrhage and stroke. The risk of developing BAVMs increases significantly in Hereditary Hemorrhagic Telangiectasia patients with haploinsufficiency of endoglin (ENG) or activin receptor-like kinase 1 (ALK1). The underlying mechanisms are unknown. Smad4 is a common downstream mediator of ENG and ALK1. We tested the hypotheses that: (1) regional gene deletion in the adult brain can be achieved by stereotactic injection of adenoviral vector expressing cre recombinase (AdCre); and (2) regional deletion of Smad4 plus vascular endothelial growth factor (VEGF) stimulation leads to vascular dysplasia. Methods: Rosa mice (n = 6) were injected stereotactically with 2X107 PFU AdCre into the basal ganglia; cell-specific LacZ gene expression was analyzed with immunohistochemistry. Smad4 floxed mice (loxP flanking Exon 8) were injected with AdCre and 2X109 genome copies of adeno-associated viral vector expressing VEGF (AAV-VEGF, n = 6), or AdCre and AAV-LacZ (n = 6) for controls. Capillary density (capillaries/10X field) and field size index (capillaries × 10 per 200 capillaries) were determined three weeks after vector injection on lectin stained sections. Results: Injection of AdCre into the basal ganglia of Rosa mice successfully activated LacZ gene expression locally, with minimal expression in the contralateral hemisphere. LacZ expression was mainly in neurons, endothelial cells, and astrocytes, but was absent in extracranial organs. Co-injection of AAV-VEGF and AdCre to Smad4 fixed mice increased vascular density as compared to AdCre/AAV-LacZ groups (mean ± SD: 212 ± 14 vs. 201 ± 13; P < 0.05), and also led to increased dysplastic vessel formation as compared to AdCre/AAV-LacZ co-injected brains (32 ± 2.4 vs. 1.0 ± 0.5; P < 0.05). Conclusions: Stereotactic injection of AdCre can mediate regional and conditional gene deletion. AdCre and AAV-VEGF injected into Smad4 fixed mice leads to a vascular dysplasia phenotype similar to the heterozygous ENG and ALK1 upstream mediators, but with homozgyous deletion of Smad4 focused in the adult mouse brain, greater vascular dysplasia was observed.

Notch Signaling in the Progression and Regression of Brain AVMs

Rong A Wang; UC San Francisco, San Francisco, CA

Brain arteriovenous malformations (BAVMs) can cause stroke and epilepsy and have no effective treatment. At their core, BAVMs are abnormal AV shunts that disrupt the normal AV hierarchy and shunt blood directly from feeding arteries to draining veins, bypassing intervening capillaries. Notch receptors compose a family of single-pass transmembrane receptors that promote arterial specification during embryonic development. We have reported that constitutively active Notch4 (Notch4*) induces BAVMs in mice (Murphy PA et al, PNAS Downloaded from http://stroke.ahajournals.org/ by guest on September 14, 2016 2010 International Stroke Conference Oral Presentations...
2008), and Notch signaling is upregulated in human BAVMs (Murphy PA et al, Lab Investigation 2009), raising the possibility that increased Notch signaling is a molecular mechanism of BAVM pathogenesis. BAVMs are not believed to regress spontaneously. However, in our mouse model, in which Notch4 is expressed in a temporally-regulatable manner, all mutants with hallmarks of BAVMs, including moribund mice with neurologic dysfunction such ataxia and seizure, regressed upon repression of Notch4. To study the mechanism of the disease reversal and stroke resolution following repression of Notch4, we built a custom-designed two-photon microscope to directly image BAVMs in the mutant mouse through a cranial window with cellular resolution. Our in vivo imaging data demonstrates the striking regression of all established BAVMs examined upon Notch4 repression. Without repression of the Notch4 transgene, most BAVMs continue to enlarge. Furthermore, during the repression of BAVMs, blood flow though BAVMs decreases, and blood flow through adjacent vessels increases, demonstrating a reversal of vascular “steal” effects. These data demonstrate that BAVM lesions can regress upon repression of Notch4 in our animal model of the disease. Our finding demonstrates that Notch4 is not only a sufficient molecular mechanism to cause BAVM pathogenesis, but is also required to sustain the disease. Our animal work leads to conceptual advances in BAVM pathogenesis, suggesting BAVM can regress if the causal molecular lesion is corrected. Notch signaling may be an important therapeutic target for the molecular treatment of the disease. Furthermore, our animal model of BAVM provides a platform to study the progression, regression, and treatment of the disease. We are currently studying the cellular mechanism of BAVM regression and will present our latest findings.

This research has received full or partial funding support from the American Heart Association, Western States Affiliate (California, Nevada & Utah).

Management of Pediatric Intracranial Arteriovenous Malformations: Experience With Multimodality Therapy

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Objective: Successful management of arteriovenous malformations (AVMs) in children often requires a balanced application of embolization, surgery, and radiosurgery. The authors describe their experience with multi-modality treatment for low and high-grade pediatric AVMs.

Methods: One hundred twenty cases of pediatric (<18 years) AVM treated with various combinations of radiosurgery, surgery, and endovascular techniques were analyzed. Results: From 1985 to 2009, 76 children with low Spetzler-Martin grade (I-III) and 44 with high-grade (IV-V) AVMs were treated. The risk of hemorrhage from presentation to initial treatment was 4.6% per year, and 3.0% per year after treatment initiation until obliteration. Treatment results were available in 101 patients. Initial single modality therapy led to AVM obliteration in 51/67 (76%) low-grade and 3/34 (9%) high-grade AVMs, improving to 58/67 (87%) and 9/34 (26%) respectively with further multimodality treatment. Permanent neurological complications occurred in 10/67 (15%) low-grade and 19/34 (56%) high-grade AVMs. The mean mRS score from pre-treatment baseline to final clinical follow-up (mean 9.2 years) improved for children with low-grade lesions by 0.24, whereas it deteriorated in children with high-grade AVMs by 1.15. On multivariate analysis, significant risk factors for poor final clinical outcome (mRS ≥ 2) included baseline mRS ≥ 2 (OR 9.51 [95% CI: 3.31, 27.37] p < 0.01), left-sided location (OR 3.03 [95% CI: 1.12, 0.90] p = 0.04), and high AVM grade (OR 4.35 [95% CI: 1.28, 14.28] p < 0.02). Conclusions: Treatment of low and high grades pediatric AVMs with combinations of embolization, surgery, and radiosurgery can improve obliteration rates and decrease the incidence of AVM hemorrhage. The poor natural history, as well as the risks of intervention must be carefully considered when deciding to treat high-grade AVMs.

Predicting In-hospital Stroke Mortality Using Data From the Get With The Guidelines-Stroke Registry

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Background: Few validated prediction models of stroke mortality exist, and most are limited to specific stroke types. We hypothesized that patient risk of in-hospital death, following admission for ischemic stroke (IS), intracerebral hemorrhage (ICH), or subarachnoid hemorrhage (SAH), could be discriminated well, using data from Get With The Guidelines-Stroke. Methods: Between 10/1/2001-12/30/2007 there were 1,046 hospitals that contributed complete data on 333,865 patients (82% IS, 11% ICH, 3% SAH, 4% unknown type). The sample was randomly divided for derivation (60%) and validation (40%). Logistic regression was used to determine the independent predictors of in-hospital patient death; the model beta coefficients were used to assign point scores for prediction. To determine the effect of the NIH stroke scale score (NIHSS) on model discrimination, we separately derived and validated a model in the 123,771 patients with NIHSS recorded. Results: Mortality varied by stroke type (IS: 5.5%, ICH: 27.2%, SAH: 25.1%, unknown type: 6.0%; p < 0.001). Points were assigned for the following: age (0-14 points), stroke type (0-60 points), method of arrival at the hospital (e.g. via ambulance vs. other, 0-46 pts), atrial fibrillation (16 pts), previous stroke (3 pts), previous MI (7 pts), carotid stenosis (6 pts), diabetes (3 pts), peripheral vascular disease (7 pts), hypertension (5 pts), dyslipidemia (12 pts), smoking (6 pts), and weekend or night admission (6 pts). The overall c-statistic, a measure of model discrimination, was 0.78. NIHSS was less frequently recorded in non-ischemic stroke (IS: 40%, ICH: 28%, SAH: 16%, unknown: 23%; p < 0.001). There was better discrimination in a model that included NIHSS (c-statistic 0.86). When each stroke type was considered separately, the models with NIHSS performed nearly as well in each stroke type as in the overall model including all types (c-statistics for IS alone: 0.85, ICH alone: 0.83, SAH alone: 0.83, unknown type alone: 0.86). The models validated well (Figure). Discussion: Individual risk of death following stroke can be predicted, with good discrimination, using a single prediction model for all stroke types. Incorporation of NIHSS information results in substantially better discrimination, with similar discrimination when each stroke type is considered separately.

Figure. Observed vs. Predicted Mortality in Development and Validation Samples

Overall Sample, not including NIHSS (n=333,865)

Subsample, including NIHSS as a Predictor (n=123,771)

This research has received full or partial funding support from the American Heart Association, National Center.

Predicting Mortality Among Hospitalized Patients With an Acute Ischemic Stroke: Derivation and Validation of a Clinical Risk Score

Gustavo Sapornisk, Moira K Kapral, Univ of Toronto, Toronto, Canada; Jack Tu, Univ of Toronto and ICES, Toronto, Canada; Ying Liu, Institute of Clinical Evaluative Sciences (ICES), Toronto, Canada; Ruth Hall, Peter Austin, Muhammad Mamdani, Univ of Toronto and ICES, Toronto, Canada; on behalf of the Investigators of the Registry of the Canadian Stroke Network (RCSN), for the Stroke Outcome Rsch Canada (SORCan) working group

Background: Stroke is a devastating medical condition with an adverse prognosis. A predictive score of mortality in ischemic stroke may aid clinicians decision making and help improve communication with and care of hospitalized patients. Objectives: To identify predictors of mortality and to develop and to validate a risk score model using information available at hospital presentation. Methods: Retrospective study of 12262 patients with an acute ischemic stroke in the Registry of the Canadian Stroke Network (RCSN) (6223 patients in the derivation cohort and 4039 patients in the validation cohort) from 2003-2007. Score for mortality was developed by using a regression coefficient scoring system based on the Framingham risk model for coronary disease. Integer scores were assigned by dividing risk-factor coefficients by...
Radiographic Surrogates of Ischemic Stroke Severity for Use in Risk Adjusting In-hospital Mortality

Jason J Sico, Michael S Phipps, Yale Univ Sch of Medicine, New Haven, CT; Dawn M Bravata; Indiana Univ Sch of Medicine, Indianapolis, IN

Background: Several organizations have proposed using post-stroke mortality as a measure of stroke care quality. However, given the strong association between stroke severity and post-stroke mortality, a method of adjusting for stroke severity is needed if post-stroke mortality is to be compared across hospitals. The NIH Stroke Scale (NIHSS) is a valid measure of stroke severity, stroke subtype, history of atrial fibrillation, myocardial infarction, cancer or renal failure, predissemination status and hyperglycemia on admission (all p < .001). Patients with very low-risk scores had a mortality rate of 1.15% at 30 days and 3.4% at 1 year. Patients with very high-risk scores had a mortality rate of 36.9% at 30 days and 58.6% at 1 year. For the derivation cohort, the area under the receiver operating characteristic curve for the NIHSS was 0.85 for 30-day mortality and 0.81 for 1-year mortality. Predicted mortality rates in the validation cohort closely matched observed rates across the entire spectrum of risk (Figure). Conclusions: Among patients with an acute ischemic stroke, factors identifiable within hours of hospital presentation predicted mortality risk at 30 days and 1 year. The externally validated predictive index may assist clinicians in estimating stroke mortality risk and in providing quantitative guidance for decision making in stroke care.

Figure: Mortality rates for the derivation and validation cohorts

<table>
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<th>Radiographic Surrogates</th>
<th>In-Hospital Mortality</th>
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<tr>
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<td>0.58</td>
</tr>
<tr>
<td>One</td>
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<td>Two</td>
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<td>Three</td>
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<tr>
<td>Four or more</td>
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</table>

Modified Oxfordshire

Lacunar

Posterior or partial anterior circulation

Brain stem

Total anterior circulation

Other

4.1

P-Value: 0.69

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Differences in Survival and Use of Life-Sustaining Interventions in Older Black versus White Patients With Acute Ischemic Stroke

Ying Xian, Robert G Holloway, Manish N Shah, Katia Noyes, Bruce Friedman; Univ of Rochester Med Ctr, Rochester, NY

Background: While most previous studies of acute ischemic stroke have shown excess mortality among blacks as compared with whites, several recent studies report better survival in blacks. We applied a novel propensity score-based approach to examine this question in a large statewide hospital database. Methods: Using 2005-2006 New York State Statewide Planning and Research Cooperative System (SPARCS) data, we identified 3,583 hospitalized non-Hispanic blacks age 65+ with a principal diagnosis of acute ischemic stroke (ICD-9-CM 433.x1, 434.x1, and 436). The Healthcare Cost and Utilization Project (HCUP) Clinical Classifications Software was used to identify 5 potential life-sustaining interventions (LSI): hemodialysis, gastrostomy, enteral/parenteral nutrition, tracheostomy, and respiratory intubation/mechanical ventilation. To include one-year all-cause mortality was calculated using Social Security Death Master File. Because of the substantial differences in baseline characteristics between blacks and whites, the propensity score “greedy matching” technique was applied to create 1:1 matched pairs. This approach created two comparable study groups and allowed a direct comparison of the racial differences in survival and use of LSI controlling for all observed confounding characteristics. Results: Nearly 80% of blacks were matched with whites (total N = 5,650). The distribution of age, gender, insurance, income, principal diagnosis, Charlson Comorbidity Score and conditions, hospital characteristics, and distance to the admitting hospital were similar among the matched pairs. Seven-, 14-, 30-, 60-, 90-, 180-, and 365-day all-cause mortality for blacks were lower than corresponding mortality estimates in whites (Chi-Square test all p < 0.05). The Kaplan-Meier survival curve showed a clear difference between the two matched groups, with the blacks having better survival (log rank test p = 0.013). In a Cox proportional hazard model, being black independently predicted lower mortality as compared with white after adjusting for baseline patient, clinical, and hospital characteristics (Hazard Ratio = 0.83; 95% CI 0.75-0.92). In separate multivariate logistic regression models predicting LSI during hospitalization, black race was associated with higher rate of hemodialysis (Odds Ratio = 2.01; 95% CI 1.31-3.07), gastrostomy (OR = 1.36; 95% CI 1.11-1.66), and enteral/parenteral nutrition (OR = 1.30; 95% CI 1.10-1.53) but not of tracheostomy and respiratory intubation/mechanical ventilation. Conclusion: In well-matched patients followed for one year after hospitalization, blacks had lower mortality as compared with matched whites. Their survival advantage may be due to greater use of LSI. Future studies should further examine differences in the use of LSI by race and adjust for stroke severity which was not recorded in hospital administrative data. This research has received full or partial funding support from the American Heart Association, Founders Affiliate (Connecticut, Maine, Massachusetts, New Hampshire, New Jersey, New York, Rhode Island, Vermont).
Does National Institutes of Health Stroke Scale Score Provide Additional Predictive Value in Good Grade Patients With Intracerebral Hemorrhage? Results From the Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) Study

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Background: Several studies have demonstrated the prognostic value of initial Glasgow Coma Scale (GCS) score in predicting outcome and mortality in patients with intracerebral hemorrhage (ICH). However, the three components of GCS score do not provide a detailed assessment of various neurological functions. The 14 component National Institutes of Health Stroke Scale (NIHSS) score may provide greater prognostic value in good grade patients.

Material and Methods: A post-hoc analysis of a multicenter prospective study recruiting patients with ICH and GCS score of 3–8 was performed. Both initial GCS and NIHSS scores were determined by certified study investigators. A comparative analysis was performed to determine the relative ability of initial GCS and NIHSS scores in predicting independent functional status as measured by modified Rankin scale (mRS) score of 3 or less at 3 months.

Results: A total of 60 patients were enrolled (aged 62.0 ± 15.1 years; 57% men). Ten subjects died within 3 months. The correlation between the GCS and NIHSS scores at baseline was -0.67. Thirty-one of 60 subjects (52%) had GCS score of 15. Seventy-five percent of subjects with NIHSS score of 15 had mRS 0-3 compared to 42% in subjects with GCS score<15. The odds ratio (OR) for good outcome (mRS 0-3) was 1.84 (95% confidence interval [CI]: 1.17; 2.30) for every unit increase in the GCS score. The mean (±SD) baseline NIHSS score was 11.78 (±7.66) with a median value of 10. NIHSS score also predicted good outcome with OR for good outcome of 1.15 (95% CI: 1.05, 1.26) for every 1 unit decrease in NIHSS score. When the two measures were simultaneously analyzed, for any given value of GCS score, NIHSS score remained unexplained.

Conclusions: We found a marginally higher predictive ability of NIHSS score which may not be enough justification for preferential use over GCS score for identifying good grade patients likely to have independent functional status at 3 months.

This research has received full or partial funding support from the American Heart Association, National Center.

The Quality of In-hospital Care for Veterans With Ischemic Stroke

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Background: Indicators of quality for acute stroke care have been developed by several organizations including the Joint Commission (JC). To date, the Department of Veterans Affairs (VA) has not systematically assessed quality of inpatient stroke care in VA facilities. Objectives: The objective of this project was to measure inpatient stroke care quality using both JC and VA-specific performance measures across the VA system. Methods: Veterans admitted to a VA hospital with a primary discharge diagnosis code of ischemic stroke in fiscal year 2007 were identified (N=5721) from the VA administrative data. A sample of 5000 medical records was identified using an approach that included all veterans at small volume centers (<55 annual ischemic stroke admissions) and 80% of veterans at high volume centers (>55 stroke admissions). Medical records were reviewed to assess the performance on 14 quality measures. Results: These data suggest that performance varies considerably across quality measures and across facilities. For example, relatively high rates of eligible patients are being treated with antithrombotic medications and receive smoking cessation counseling. The data suggest opportunities for improvement, with relatively few eligible patients receiving thrombolytic therapy, stroke education, or dysphagia screening prior to oral intake.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Estimate</th>
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<td>Var((\tau_{14}))</td>
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<td>0.0009</td>
<td>&lt;0.001</td>
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Table. Final multilevel linear regression model of composite care (%) showing fixed effect hospital-level, patient-level, and random effects variables
Conclusions: This project provides benchmark data about VA performance on inpatient stroke care; and is the first assessment of stroke care quality from a large integrated U.S. healthcare system. These data suggest that VA stroke care quality is comparable to or better than non-VA care for many processes, but opportunities for improvement exist for some processes of care. These data have been used by VA Patient Care Services and the Stroke Quality Enhancement Research Initiative program to identify targets for quality improvement projects. Several implementation projects are either underway or about to be instituted to improve care for veterans with stroke.

Temporal Trends in Age- and Sex-specific Cardiac Risk Score After Stroke in the United States

Amyta Towfighi, Univ of Southern California, Los Angeles, CA; Bruce Ovbiagele; Univ of California, Los Angeles, Los Angeles, CA

Background: Stroke survivors are at higher risk of dying from cardiac causes over the long term than from incident or recurrent stroke. Recent data suggest that among middle US individuals aged 45-74 for the last decade, myocardial infarction prevalence and risk of future cardiovascular events have decreased among men and increased among women. Little is known, however, about age-specific sex differences and temporal trends in risk of future cardiovascular events among stroke survivors. Objectives: To determine temporal trends in age- and sex-specific 10-year risk of hard cardiovascular events (using the Framingham Coronary Risk Score [FCRS]) and components of FCRS in stroke survivors without coronary artery disease who participated in the National Health and Nutrition Examination Surveys (NHANES) in 1988-1994 and 1999-2004. Methods: We determined sex-specific FCRS and components of FCRS among stroke survivors (n=1,103) in NHANES, a nationally representatively cross-sectional national sample of the US population, in 1988-1994 and 1999-2004. Age groups were: all adults, 35-64, and >65. FCRS was analyzed as FCRS 20% (high future cardiac risk) and mean FCRS. Variables were compared using the ANOVA/regression model while taking into account the complex survey design. Results: Mean age ranged from 63.8 to 67.8 years. More men than women had FCRS ≥ 20% in 88-94 (OR=7.20, 95% CI 3.92-14.72, p<0.0001) and 99-06 (OR=7.81, 95% CI 4.36-13.97, p<0.0001). Mean FCRS showed similar sex differences across epochs. Odds of FCRS ≥ 20% were higher in 88-94 vs. 99-06 in both men (OR=2.16, 95% CI 1.18-3.88, p=0.0129) and women (OR=3.25, 95% CI 1.18-8.48, p=0.0152). Men had lower mean FCRS in the latter period (p=0.0025) while women mean FCRS remained unchanged. Among FCRS components, in both epochs, women had higher total serum cholesterol levels than men (p<0.0001). Mean diastolic blood pressure and total serum cholesterol were lower in 99-06 vs. to 88-94 in both men and women (both p=0.01). Analysis of age-specific FCRS revealed that among individuals >65, odds of FCRS ≥ 20% was greater in men than women in both epochs (OR 35.6 in 88-94 and OR 18.8 in 99-06). A similar pattern was seen for mean FCRS. However, among stroke survivors aged 35-64, odds of FCRS ≥ 20% were comparable between sexes (OR 1.1 in both epochs) and the sex differential in mean FCRS was not pronounced as much in stroke survivors. Conclusion: Over the last two decades, temporal trends in risk of cardiac events among stroke survivors has declined, corresponding with improvements in blood pressure and cholesterol. Older male survivors are at significantly greater cardiac risk than their similarly aged female counterparts, but this sex disparity was not observed in younger age groups. Future studies should explore whether this latter finding is related to a boost in cardiac risk among older men or younger women with a history of stroke.

Dietary Fat Intake and Incidence of Ischemic Stroke in Postmenopausal US Women: The Women's Health Initiative

Sirin Yaemsiri, UNC Gillings Sch of Global Public Health, Chapel Hill, NC; Souvik Sen, UNC Sch of Medicine, Chapel Hill, NC; Lesley Tinker, Fred Hutchinson Cancer Rech Ctr, Seattle, WA; Wayne Rosamond, UNC Gillings Sch of Global Public Health, Chapel Hill, NC; Sylvia Wasserman-Smoller, Albert Einstein College of Medicine, Bronx, NY; Ka He; UNC Gillings Sch of Global Public Health, Chapel Hill, NC

Background: Inconsistent findings on the associations between types of dietary fat intake and ischemic stroke could be due to the different effects of fats on various subtypes of ischemic stroke. This analysis is the first time that the associations between types of fat intake and ischemic stroke or its subtypes. Table. Multivariable hazard ratios (95% confidence interval) of ischemic stroke and its subtypes comparing the highest quartile of total, saturated, monounsaturated, polyunsaturated, and trans fat intake with the lowest quartile.

Periodontal Disease Associated With Recurrent Vascular Events in Stroke/TIA Patients

Souvik Sen, Roxanne Poole, Omid Akhavan, Jennifer Simmons, Kevin Moss, James Beck, Steven Offenbacher; Univ of North Carolina, Chapel Hill, NC

Background: Periodontal disease is associated with cardiovascular disease; however, it is not known if periodontal disease is independently associated with recurrent vascular events in stroke and TIA patients. Methods: Periodontal disease was measured by assessing mean attachment level (MAL) in 88 consecutive stroke/TIA patients. Periodontal disease was defined as MAL=2.25 mm. On admission for their index stroke or TIA, patients were assessed for stroke risk factors and laboratory parameters known to be associated with stroke risk (fasting lipid profile, complete blood count, high sensitivity C-reactive protein and homocysteine levels). They were followed for 24 months from the index stroke or TIA for vascular events including stroke, TIA, myocardial infarction and vascular death. Time to event was analyzed using univariate log rank test, multivariate Cox proportional hazard regression model and hazard rate ratio (HRR) analysis. Results: Eighty-eight patients (71% stroke, 29% TIA, mean age 58 years, 50% male, 59% white, 36% black, 5% other) were enrolled and followed for up to 2 years. Of these, 21 (23%) had recurrent composite vascular events and 15 (17%) showed moderate periodontal disease. At enrollment, patients with moderate periodontal disease tended to be males but did not differ significantly by age, race, or traditional risk factors including smoking, hypertension and cholesterol levels. Kaplan-Meier curves (Figure 1) showed that a significantly greater proportion of patients with periodontal disease experienced composite events in stroke/TIA/myocardial infarction/death (47% compared to those who did not exhibit periodontal disease 19%; p=0.02). Moderate periodontal disease was significantly associated with composite vascular events before hazard ratio 3.2, 95% CI, 1.3-8.1) and after adjustment for age, gender and race (adjusted hazard ratio 3.1, 95% CI, 1.0-9.8). Conclusion: Periodontal disease is associated with recurrent vascular events in stroke/TIA patients. Further studies are needed to confirm this finding and to test if treatment of periodontal disease can reduce the rate of recurrent vascular events in stroke/TIA patients.

Figure 1: Kaplan-Meier survival functions for stroke/TIA patients with and without moderate periodontal disease and composite event-free survival

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Judith H Lichtman, Sara B Jones, Yun Wang, Emi Watabane, Yale Sch of Medicine, New Haven, CT; Larry B Goldstein, Duke Univ and Durham VAMC, Durham, NC

Background: Although some studies find variations in the provision of preventive therapies by sex, it is not known whether there have been sex-related differences in national stroke hospitalization rates in the United States, or whether patterns have changed over time.

Purpose: To examine trends in ischemic stroke hospitalizations by sex for elderly Medicare fee-for-service (FFS) beneficiaries from 1998 through 2006.

Methods: The annual numbers of ischemic stroke hospitalizations (ICD-9 codes 433, 434, and 436) by sex were determined for FFS Medicare beneficiaries aged ≥65 years or old and discharged with ischemic stroke from January 1, 1998 through December 31, 2006. Annual hospitalization rate was calculated as the total number of hospitalizations per year divided by the total number of person-years accounting for death and crossover in coverage. Logistic regression was used to determine the odds of changes in hospitalization rates over time relative to the baseline year of 1998, adjusting for age. Results: Stroke hospitalization rates steadily declined from 1998 to 2006 for both men and women (rates declined for men from 151 per 10,000 person-years in 1998 to 112 in 2006, OR 0.72, 95%CI 0.71-0.73; and for women from 132 to 100 hospitalizations per 10,000 person-years, OR 0.73, 95% CI 0.73-0.74). Although adjusted rates were lower for women than men (OR 0.81, 95% CI 0.81-0.81), more hospitalizations occurred among women each year (209,209 for women vs. 163,794 for men in 1998 and 163,794 for women vs. 134,930 for men in 2006, OR 0.81-0.81), more hospitalizations occurred among women each year (209,209 for women vs. 163,794 for men in 1998 and 163,794 for women vs. 134,930 for men in 2006, unadjusted for age). Conclusions: Hospitalization rates for ischemic stroke have decreased similarly over time for both women and men, possibly reflecting the success of primordial and primary prevention efforts. Men had higher annual stroke hospitalization rates, whereas women had a higher burden of disease as reflected by a greater number of hospitalizations. This observation likely reflects the longer life expectancy of women. These data on national hospitalization rates will be important for anticipating the future healthcare needs of our aging population.

Figure 1: Trends in Ischemic Stroke Hospitalization Rates by Sex, 1998-2006

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<th>Year</th>
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<th>Women</th>
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<td>1999</td>
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<td>2001</td>
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Hospitalizations for Infections/Trigger Acute Ischemic Stroke: The Cardiovascular Health Study

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Objective: To determine whether hospitalization for infection triggers acute ischemic stroke. Background: Triggers of acute ischemic stroke are largely unknown. We hypothesized that hospitalization for infection would increase the risk of acute ischemic stroke during the following 90 days in the prospective Cardiovascular Health Study, a biracial cohort of 5888 elderly participants from four US sites. Methods: Using a case-crossover design in which participants served as their own controls, we analyzed data from 665 participants without history of stroke at baseline but who had incident ischemic stroke during a median 12.2 years of follow-up. Exposure was defined as hospitalization for infection within 90, 30, or 14 days prior to stroke (case period) or during equivalent time periods exactly 1 or 2 years prior to stroke (control periods). Hospitalizations that occurred ≤4 days before stroke were not treated as exposures, to avoid including hospitalizations for the stroke itself. We used conditional logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs). To confirm our case-crossover findings, we also fit a Cox proportional-hazards model with hospitalization for infection as a time-varying exposure and adjusted for baseline age, race, and sex. Results: Approximately 48% of cases had an eligible hospitalization anywhere before their stroke. The OR (95% CI) of stroke following hospitalization for infection within the previous 90 days was 3.4 (1.8-6.5); 30 days, 7.3 (2.9-26.3); and 14 days, 8.0 (1.7-37.7). Because the number of participants with stroke who had been hospitalized with infection during the 30 days 14 and 30 day windows was small (8 and 11, respectively), exact conditional logistic regression methods were also used, with similar results. In the survival analysis, hospitalization for an infection was associated with an increased risk of ischemic stroke in the following 30 days, adjusted hazard ratio=2.9, 95% CI 1.4-4.6, p=0.002. Conclusions: Hospitalization for infection is associated with a short-term increase in risk of acute ischemic stroke, with higher risks observed for shorter intervals preceding stroke. Case-crossover findings may be subject to bias from time-varying factors, including age and medication use, although these confounders are unlikely to fully explain the findings, and preliminary results from survival analyses are consistent with case-crossover results. Additional studies are warranted to confirm these findings and to demonstrate whether more aggressive stroke preventive measures are warranted in patients with recent hospitalization for infection.

Stroke in the Young is Increasing Over Time: Temporal Trends in the Age of Stroke Incidence in a Large, Bi-racial Population

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Introduction: Previously, we reported that stroke incidence was significantly higher for blacks than whites in our population-based study, with the greatest disparity in young and middle age (<65 years old). Here we describe temporal trends in the age of stroke. Methods: The Greater Cincinnati/Northern Kentucky region includes 2 southern Ohio counties and 3 contiguous Northern Kentucky counties, an estimated population of 1.3 million. Our study ascertained first ever hospitalized strokes that occurred in the population between 7/1/93-6/30/94 and in the calendar years of 1999 and 2005. The denominator for the calculation of incidence rates (in those aged ≥20 years) was extracted from the U.S. Census Bureau website (www.census.gov). Age-, race-, and gender-specific incidence rates were calculated with 95% confidence intervals (CI) that were calculated assuming a Poisson distribution. We tested for differences in age trends using students t-test, x2, and Poisson regression as appropriate. Results: The mean age (SD) of stroke was significantly decreased in 2005 at 68.4 ± 14.4 years vs. 71.3 ± 13.6 in 1993-94 (p < 0.0001). The proportion of all strokes under age 45 has increased from 4.5% to 5.5% and 7.3% in 1993-94, 1999, and 2005 respectively; the overall age distribution has significantly changed over time (x2 p < 0.0001), and Poisson regression showed an overall shift to younger strokes in 2005 vs. 1999 & 1993-94 (p < 0.0001). Age-specific stroke incidence rates stratified by race and study period are presented in the Table. This shows a statistically significant decrease in incidence rates in 2005 for blacks over age 65 and whites over age 45. Incidence rates of stroke in young (those aged ≥ 20-45) has increased in blacks and whites, although statistically significant only for whites. Discussion: Stroke incidence is increasing at younger ages and decreasing at older ages, especially for whites. This is of great public health significance as younger strokes carry the potential for greater lifetime burden of disability. Further study is needed to determine the reasons for these trends.

Age-Specific Incidence Rates for First-Ever Stroke

<table>
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<tr>
<td>20-44</td>
<td>45 (95% CI)</td>
<td>46 (95% CI)</td>
<td>51 (95% CI)</td>
<td>12 (95% CI)</td>
<td>17 (95% CI)</td>
<td>23 (95% CI)</td>
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<tr>
<td>45-54</td>
<td>232 (95% CI)</td>
<td>235 (95% CI)</td>
<td>302 (95% CI)</td>
<td>74 (95% CI)</td>
<td>82 (95% CI)</td>
<td>96 (95% CI)</td>
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<tr>
<td>55-64</td>
<td>400 (95% CI)</td>
<td>403 (95% CI)</td>
<td>521 (95% CI)</td>
<td>235 (95% CI)</td>
<td>218 (95% CI)</td>
<td>207 (95% CI)</td>
</tr>
<tr>
<td>65-74</td>
<td>929 (95% CI)</td>
<td>777 (95% CI)</td>
<td>846 (95% CI)</td>
<td>539 (95% CI)</td>
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<tr>
<td>75-84</td>
<td>1309 (95% CI)</td>
<td>1051 (95% CI)</td>
<td>945 (95% CI)</td>
<td>1029 (95% CI)</td>
<td>1003 (95% CI)</td>
<td>773 (95% CI)</td>
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onset of extravasation, possibly impairing reperfusion. This study illustrates the feasibility of two-photon microscopy to image and analyze in vivo, over time, individual vascular dynamics and demonstrates its potential impact for future studies.

The Immunomodulatory Sphingosine-1-phosphate Analogue FTY720 (fingolimod) Reduces Lesion Size and Improves Functional Outcome in a Mouse Model of Cerebral Ischemia

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Introduction: Early invasion and activation of immune cells and a breakdown of the blood-brain barrier are two major pathophysiological events in stroke. FTY720 (fingolimod), which has been analyzed in a clinical phase III study for the treatment of multiple sclerosis is metabolized to FTY720 phosphate which acts on Sphingosine-1-phosphate (S1P) receptors. Especially the S1P receptor 1 is highly expressed on endothelial cells and lymphocytes. FTY720 leads to lymphopenia by preventing the egress of lymphocytes from the lymph nodes and apoptosis at the S1P receptor 1 was shown to reduce pulmonary edema in a sepsis model. Methods: MCAO was performed in C57Bl/6 mice for 90 min. FTY720 (1 mg/kg) was administered i.p. at the onset of ischemia and the lesion size was determined after 24 h by cresyl violet staining. Infiltrating blood leukocytes and macrophages/activated microglia in the ischemic lesion were analyzed by immunohistochemistry. Blood-brain barrier disruption was assessed by Evans blue staining. We used flow cytometry to evidence lymphocyte depletion after the administration of FTY720. Results: FTY720 led to a 24 % reduction in lesion size after cerebral ischemia (44.8 mm3 in treated animals/n=11 vs. 53.5 mm3 in controls/n=10, p=0.033) predominantly reducing the cortical share of the lesion and greatly reduced the number of severely impaired animals (1/11 in the FTY group vs. 6/10 in control mice). Immunohistochemical staining showed a drastic reduction of neutrophil infiltration in the FTY group after cerebral ischemia. One hour after the induction of ischemia, there was no significant difference of Evans blue extravasation into the ischemic lesion between treated animals and controls. Conclusions: FTY720 reduces lesion size and considerably ameliorates functional outcome 24 h after MCAO. It reduces immune cell infiltration into the lesion without influencing early blood-brain barrier disruption. These findings suggest that the protective effects occur via the inhibition of immune cell infiltration rather than via reperfusion and the blood-brain barrier is an early stage of lesion development. Our results demonstrate that the immunomodulatory drug FTY720 for which a phase III trial in relapsing-remitting MS has been completed, might also be a promising drug for the treatment of cerebral ischemia.

Increased Plasma but Not Brain Matrix Metalloproteinase Levels Are Associated With Early Blood-Brain Barrier Disruption Following Experimental Stroke

Ayush Batra, Lawrence L Latour, Christl A Rueßtler, John M Hallenbeck, Maria Spatz, Steven Warach, Erica C Henning; NINDS, Bethesda, MD

Background: Matrix metalloproteinases (MMPs) play a prominent role in blood-brain barrier (BBB) disruption following ischemic injury. In this study, we compared blood levels of MMP-2 and MMP-9 with brain tissue levels at various time points following transient middle cerebral artery occlusion (MCAO) and associated these levels with BBB disruption. Methods: Spontaneously-hypertensive rats underwent 45 minutes of transient right MCAO and were divided into three experimental groups (n=18/group): 1 hr, 48-hr post-reperfusion; control group (n=6) underwent sham surgery with no occlusion. BBB integrity was assessed through pre/post-gadolinium contrast fluid-attenuated inversion recovery (FLAIR) imaging. Tissue and blood samples were acquired following imaging and MMP levels were assessed through gelatin zymography. Results: CSF enhancement was visualized only at 1 hour post-reperfusion (6 of 6, arrow, Figure 1). Increased plasma levels of MMP-9 were associated with CSF enhancement at 1 hour post-reperfusion (P<0.05), but not at 24 or 48 hours. Parenchymal enhancement of the entire infract was visualized only at 48 hours (P<0.01), but not at 1 hour or 24 hours. Conclusions: The pattern of change of MMPs in the blood differs significantly from that in the tissue, and specific imaging markers of BBB disruption such as CSF- and parenchymal enhancement on post-contrast FLAIR may give a better understanding of the related changes within the blood and brain, reconciling the differences between the support of the use of imaging markers of BBB status in conjunction with measured MMP levels in order to monitor efficacy of MMP inhibitor therapy for translation to the clinical setting.

AA/W Hazard Ratio (and 95% CI) as a function of Age

In vivo Blood Flow Dynamics After Focal Ischemia in Mice

Maria Grazia De Simoni, Stefano Fumagalli, Fabrizio Ortolano, Francesca Pischitella, Mario Negri Institute, Milan, Italy; Pasquale Matthia, Hilary Carswell, Paul Garside, Paul Garside; Univ of Strathclyde, Glasgow, United Kingdom

Background. Cerebral ischemia/reperfusion triggers vascular modifications whose onset and temporal evolution are largely unknown. We analyzed cerebral vascular dynamics (blood flow speed and extravasation) in vivo over time, in a mouse model of ischemia/reperfusion using two-photon microscopy. Methods and Results. The middle cerebral artery (MCA) cortical territory was exposed through a cranial window. Craniotomized mice received a fluorescent-drug for the treatment of cerebral ischemia. Which a phase III trial in relapsing-remitting MS has been completed, might also be a promising drug for the treatment of cerebral ischemia.

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Bone Marrow-derived Cells Contribute to Vascular Endothelial Growth Factor-induced Angiogenesis in the Adult Mouse Brain by Supplying Matrix Metalloproteinase-9
Qi Hao, Fanxia Shen, Hua Su, William L. Young; Univ of California, San Francisco, San Francisco, CA

Background and Purpose: We have previously shown that the angiogenic response to vascular endothelial growth factor (VEGF) overexpression is greatly reduced in the brain of mice with homozygous deletion of matrix metalloproteinase -9 (MMP-9 -/-). We hypothesized that bone marrow-derived cells (BMDCs) contribute to VEGF-induced angiogenesis by supplying MMP-9. Methods: BM cells from MMP-9 -/- (KO) or wild-type (WT) donor mice were transplanted into lethally-irradiated KO or WT recipients (n = 6). Adeno-associated viral vector (AAV) expressing VEGF (AAV-VEGF) or LacZ (AAV-LacZ) (2X10⁹ genome copies) were injected into the striatum four weeks after BM transplantation. Four weeks after vector injection, vascular density (capillaries/10X objective field) was determined on lectin-stained sections; MMP-9 activity was detected in AAV-VEGF injected brain of KO mice transplanted into WT BM. (AAV-LacZ-injected KO mice vs KO mice with WT BM, P = 0.05). Overexpression of VEGF did not increase the vessel density in the brain of KO mice transplanted with KO BM (229 ± 36 vs 212 ± 40; VEGF vs LacZ, P = 0.4). Transplantation of BM from WT to KO mice partially rescued brain angiogenic response to VEGF stimulation (206 ± 26 vs 229 ± 36, KO mice with WT BM vs KO mice with KO BM, P < 0.01). However, transplantation of KO BM to WT mice showed a trend towards reduced angiogenic response to VEGF stimulation (270 ± 33 vs 320 ± 51, WT mice with KO BM vs WT mice with WT BM, P = 0.11). MMP-9 activity was detected in AAV-VEGF injected brain of KO mice transplanted with WT BM, indicating that BMDCs provide MMP-9 to VEGF-induced angiogenic foci. MMP-9 activity in WT mice with KO BM was midway between that observed for KO mice with WT BM and WT mice with WT BM. Conclusions: BMDCs migrating to the angiogenic foci provide MMP-9 to facilitate VEGF-induced angiogenesis. Transplantation of WT BM cells can rescue the angiogenic response to VEGF stimulation of MMP-9 KO mice.

Hyperglycemia Increases IPA-induced Hemorrhage and Worsens Stroke by a Mechanism Involving NADPH Oxidase
Xian N Tang, Seok Joon Won, Sang Won Suh, Miodor A Yenari, Raymond A Swanson; UCSC, San Francisco, CA

The thrombolytic agent, tissue plasminogen activator (tPA), can reduce stroke infarct volume if given within a few hours after symptom onset. However, the clinical use of IPA is limited by the risk of IPA-induced brain hemorrhage. The likelihood of IPA-induced hemorrhage is increased 2-5 fold by hyperglycemia, but the reason for this increase is unknown. We recently reported that hyperglycemia exacerbates ischemia-reperfusion brain injury by fueling the production of NADPH oxidase, the substrate required by the superoxide producing enzyme, NADPH oxidase (NOX). Here, we developed a rat model of IPA-induced brain hemorrhage to determine whether NOX may contribute to the increased rate of hemorrhage in hyperglycemic stroke patients treated with IPA. Adult male rats were subjected to transient focal ischemia by occluding both common carotid arteries and the distal middle cerebral artery for 90 minutes. At the time of reperfusion, the rats were treated in five ways: with normoglycemia (n = 6); hyperglycemia (n = 6); normoglycemia with IPA (n = 6); hyperglycemia with IPA (n = 14); and hyperglycemia with IPA and the NOX inhibitor, apocynin (n = 6). Normoglycemic rats had blood glucose levels of 5 - 6 mM, and hyperglycemic rats had blood glucose levels of 15 - 20 mM at the time of reperfusion. Apocynin (2.5 mg/kg) was administered i.v. immediately before reperfusion. Rats were evaluated 3 days later for infarct volume and severity of cerebral hemorrhage. Among the given IPA, the hemorrhage score was increased in hyperglycemic rats compared to normoglycemic rats (7.5 ± 0.6 vs 6.6 ± 0.5, P < 0.05). This hemorrhage score was reduced to 4.2 ± 0.7 by apocynin (P < 0.05). As expected, hyperglycemia + IPA rats also had larger infarct volumes than normoglycemia + IPA rats (358 ± 28 vs 184 ± 73, P < 0.01), and this difference was also attenuated by apocynin (358 ± 29 vs 220 ± 64, P < 0.05). These results suggest that the rat model replicates the effect of hyperglycemia on the risk of brain hemorrhage observed with clinical use of IPA. In addition, the results obtained with apocynin provide preliminary evidence that NADPH oxidase may be involved in this effect of hyperglycemia.

Reactive Astrocytes and Stroke Recovery: A Potential Role of IL-1beta and ERK Signaling in the Release of HMGB1
Kazuhide Hayakawa, Ken Arai, Eng H. Lo; MGH - Harvard Med Sch, Charlestown, MA

Background and Objective: Traditionally, reactive astrocytes are thought to impede brain plasticity after stroke. However, emerging data now suggest that reactive astrocytes may also contribute to stroke recovery, in part via the release of high-mobility group box 1 (HMGB1) protein. Here, we show that the inflammatory cytokine IL-1beta mediates the release of HMGB1 via ERK MAP kinase signaling. Methods: Primary astrocyte cultures were prepared from 2-day-old Sprague-Dawley rats. Astrocytes were exposed to recombinant IL-1beta for 24 hrs and HMGB1 protein levels in both media and cell lysates were measured by western-blot analysis. Three major MAP kinases ERK, p38 and JNK were assessed, and chemically inhibited with U0126, SB203580 and SP600125 respectively. HMGB1 is a nuclear protein. So we hypothesized that the nuclear protein exporter, CRM-1, may be a candidate mechanism for linking MAP kinase signaling to HMGB1 release. Results: IL-1beta significantly enhanced the expression of HMGB1 in astrocytes (P < 0.001). Concomitantly, HMGB1 was released into extracellular media (P = 0.0169) without affecting proliferation or cell death. The IL-1beta-stimulated elevation of HMGB1 in astrocytes was attenuated after inhibition of ERK signaling with U0126 (1, 10 microM, P = 0.0001), but not by inhibitors of p38 (SB203580, 0.1-10 microM or JNK (SP600125, 0.1-10 microM). IL-1beta also increased expression of CRM-1 in concert with a translocation of HMGB1 from nucleus into cytoplasm. Blockade of IL-1beta-stimulated HMGB1 release with the ERK inhibitor U0126 (10 microM) was accompanied by a downregulated expression of CRM-1 (P = 0.0086). Conclusions: IL-1beta may mediate the secretion of HMGB1 from astrocytes by activating ERK MAP kinase signaling. This process is mediated by increased translocation of HMGB1 from nucleus into cytoplasm by CRM-1. These data suggest a novel pathway by which inflammatory cytokines may enhance the ability of reactive astrocytes to contribute to stroke recovery. Further studies are needed to evaluate how astrocytic HMGB1 may interact with other cell types during neurovascular remodeling after stroke.

Repetitive Peri-infarct Depolarizations Lead to Infarct Growth in Human Ischemic Stroke by Secondary Infarction of Peri-infarct Tissue
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Objective: Peri-infarct Depolarizations (PD) have been shown to cause infarct expansion in numerous animal experiments. Recently, PD have been found to occur with high incidence in patients with large “malignant” middle cerebral artery (MCA) infarction. Since decades it has been speculated that PDs lead to infarct growth in human ischemic stroke. In the present study we measured PD by Electrocoagrogram (ECoG) and infarct growth by MRI in patients with malignant middle cerebral artery infarction. Methods: This study is part of the Co-operative Study on Brain Injury Depolarisations (COISID). A subdural strip electrode with 6 linear contacts were placed over the peri-infarct region of 2 patients with subtotal infarction of the MCA territory who underwent decompressive hemicraniectomy. From the 6 electrodes, 4 channels of ECoG were acquired. Bedside monitoring for PID was performed for 5 days. The MRI (3 T, Philips Interia Master) was performed on day 2 after stroke within 24 h after surgery and start of monitoring. The second MRI was performed on day 7 after stroke and at the end of monitoring to assess infarct growth. Results: ECoG monitoring was started 29 h and 38 h after stroke, respectively. A total of 172 PDs were performed (n = 92, patients 1, 92, patients 2, 82 PDs). The ECoG was defined as gradually developing depression of ECoG activity accompanied by a slow potential change spreading between channels and subsequent recovery of ECoG activity. At start of monitoring, PDs were detected in channels acquired from the electrodes located more proximal to the infarct rim. At later time points, PDs progressively expanded spatially along the electrode strip involving the channels from electrodes positioned further from the infarct. Additionally, we observed an increasingly prolonged duration of ECoG depression and recovery.
Mechanical Embolectomy in Octogenarians: Is It Wise?

Kashif Hameed, Harish Jhaeveri, Naveed Akhtar, Coleman Martin, Marilyn M Rymer; Saint Lukes Brain and Stroke Institute, Kansas City, MO

Background: People over the age of 80 are reported to have a poorer clinical outcomes than younger people after treatment with intravenous (IV) tissue plaminogen activator (tPA), not specifically related to an increase in symptomatic intracerebral hemorrhage (SICH). Stroke clinical trials generally exclude octogenarians. We sought to assess technical success and compare clinical outcomes and mortality rates in patients over and under the age of 80 treated with mechanical embolectomy using the Merci Retriever. Methods: Since 2008, Saint Lukes Brain and Stroke Institute (SLBS) has enrolled 62 patients in the Merci Registry. We analyzed those cases dichotomized according to age over or under age 80 in regard to the modified Rankin Score (mRS) at 90 days and mortality at 90 days adjusting for baseline stroke severity, and time from symptom onset to time of completion of the procedure using multivariable modified poisson regression models. Age was analyzed as both a continuous and categorical variable (under 80 versus 80 or older). Technical success of the procedure was evaluated using the Thrombolysis in Cerebral Infarction (TICI) score in the patients over age 80. We also looked at the principal site of occlusion and whether intra-arterial (IA) tPA was used adjunctively. Results: Technical success in the patients over age 80 as measured by TICI scores of 2 or 3 was achieved in 70% (14/20) of cases. Table I summarizes the rest of the results. Good outcomes (mRS 0–2) were achieved in 69% of patients under age 80 and 5% in patients over age 80 despite the high degree of technical success in the group over 80 and longer time between symptom onset and end of procedure in the group under 80. The 90-day mortality rate in the patients over the age of 80 was 80% as compared to 9.5% in patients under age 80. Age was a significant predictor of high mortality in the unadjusted model and remained a significant predictor of mortality after adjusting for baseline NIHSS score and time from symptom onset to end of procedure.

Table I Results of Mechanical Embolectomy in Patients Over or Under 80 Years of Age

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Mean Age</th>
<th>Baseline NIHSS</th>
<th>90-Day Mortality</th>
<th>P-value</th>
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<tr>
<td>&gt; 80 years</td>
<td>86.3 ± 3.9</td>
<td>61.3 ± 12.7</td>
<td>16 (80.0%)</td>
<td>0.209</td>
</tr>
<tr>
<td>&lt; 80 years</td>
<td>63.1 ± 8.7</td>
<td>62.9 ± 13.7</td>
<td>4 (9.5%)</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

Conclusions: Reperfusion can be achieved in a high percentage of internal carotid and middle cerebral artery occlusions in people over the age of 80 using the Merci Retriever. However, in this small cohort, people over the age of 80 had a very high mortality rate compared to younger people even after correcting for stroke severity and the time from symptom onset to the end of the procedure. It is important to consider these outcomes when recommending mechanical embolectomy to the elderly. Next steps would be to evaluate larger cohorts in this age group and investigate co-morbidities that may define an octogenarian population that could do well.

Neither Time to Treatment Nor the Use of Adjunctive Intra-arterial Thrombolytics Increase the Risk for Symptomatic Intracranial Hemorrhage After Endovascular Treatment of CT Perfusion or MRI-selected Stroke Patients Treated at Late Time Windows: Analysis of the Pre-DAWN Dataset

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Background: Current selection criteria for reperfusion therapies in stroke utilize rigid time windows. However, many studies support a physiological rather than chronological selection approach. The risk of symptomatic intracranial hemorrhage (SICH) at later time windows remains a major concern. Recent data suggest that the risk of SICH after reperfusion therapies is not time dependent but rather a function of the amount of ischemic core at the time of treatment. We sought to establish whether time from last seen well to treatment (TSLWT) or the use of intra-arterial (IA) thrombolysis increase the risk for SICH in anterior circulation occlusion (ACO) patients undergoing imaging-based endovascular treatment at late time windows. Methods: Databases from 10 U.S. stroke centers were interrogated to identify all consecutive CTP or MRI-selected stroke patients in whom the first angiography confirming ACO was performed ≥8 hours from last seen well. Uni- and multivariate analyses of baseline variables (age, gender, baseline NIHSS, TSLWT, recanalization status, use of lytics, Glycoprotein IIb/IIIa inhibitors [Gp IIb/IIIa], and mechanical devices as well as major co-morbidities) was performed to identify predictors in this cohort. Results: Data from 2 prospective clinical trials (MERCI, n=863) involving thrombectomy with the Merci device for the treatment of AIS due to proximal intracranial arterial occlusion were combined in a dataset totaling 968 patients. The entry criteria for the current analysis included: age ≥80 years; alteplase use, or major co-morbidities, including hypertension, coronary artery disease, atrial fibrillation, congestive heart failure, and diabetes. At 90 days, the rates of good outcomes were significantly higher (24.5% vs. 0%, p<0.001) and mortality was significantly lower (47.5% vs. 75%, p<0.05) in successfully revascularized as compared to non-revascularized...
patients. **CONCLUSION:** Despite an overall guarded prognosis, successful recanalization is strongly associated with improved outcomes in elderly AIS patients treated with thrombectomy. The risk of sICH after thrombectomy does not appear to be significantly increased in this population. Our data suggest that the decision to provide endovascular therapy should not be solely based on patients age.

95 Intracranial Stenting is Associated With Higher Rates of Vessel Recanalization During Endovascular Therapy for Acute Ischemic Stroke

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**Background and Purpose:** Repertusion therapy for acute ischemic stroke has evolved over the years, with the development of multiple endovascular modalities which can be used alone or in combination. We sought to determine which pharmacologic or mechanical modality may be associated with higher recanalization rates. **Methods:** A cohort of 841 patients at 12 stroke centers underwent endovascular therapy (IAT) for acute stroke between 2006 and 2009. Patients with anterior circulation strokes treated within eight hours from symptom onset were included in the study. Demographic information, stroke risk factors, admission NIHSS, time from symptom onset to treatment, mechanical and pharmacologic treatments used, recanalization grade, hemorrhage and 90 day Modified Rankin Scores (mRS) results were reviewed. Symptomatic hemorrhage (sICH) was defined as Parenchymal Hematoma type 1 or 2 by the ECASS classification. Asymptomatic hemorrhage was defined as persistence of hyperintensity of follow up head CT. Successful recanalization was classified as a grade 2 or 3 by the Thrombolysis in Myocardial Infarction (TIMI) scale. Univariate modeling was performed and variables with a p-value < 0.10 were placed in a binary logistic regression model to determine independent predictors of successful recanalization. **Results:** The mean age was 67 ± 16 years and median NIHSS was 16 [IQ Range 12-20]. Successful recanalization was achieved in 66% of patients. The rate of asymptomatic intracranial hemorrhations was 21.5% and symptomatic hemorrhage (sICH) occurred in 8% of patients placed under GA prior to IAT. The following summarizes the pharmacologic or mechanical approach utilized in the cohort (more than one intervention may have occurred in a patient): intra-arterial t-PA 449(53%), patients, Merci retriever 503(60%) patients, Penumbra aspiration catheter 99(12%) patients, glycoprotein IIb/IIIa antagonists 173(21%) patients, angioplasty 210(25%) patients, and placement of an intracranial stent 135(16%) patients. The following variables were independent predictors of successful recanalization: use of intra-arterial thrombolitics [OR 1.56(95% CI 1.11-2.17), p<0.01] and placement of an intracranial stent [OR 1.96(95% CI 1.16-3.33), p<0.001]. Successful recanalization was achieved in 79% of patients placed under GA versus 66% of patients placed under GA prior to IAT. An increase in hemorrhagic complications. **Conclusions:** Intracranial stenting and intra-arterial thrombolysis are associated with higher rates of successful recanalization without increases in hemorrhage rates. Further study is required to determine the medical co-morbidities and physiologic changes that may account for these differences.

96 General Anesthesia During Endovascular Therapy for Acute Stroke Intervention is Associated With Increased Mortality and Worse Clinical Outcomes

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**Background and Purpose:** Patients undergoing endovascular therapy (IAT) for acute ischemic stroke receive either general anesthesia (GA) or conscious sedation (CS). GA may delay time to treatment whereas CS may result in patient movement and compromise the safety of the procedure. We sought to determine if there were differences in safety and outcomes in patients intubated prior to initiation of IAT. **Methods:** A cohort of 841 patients at 12 stroke centers underwent IAT for acute stroke between 2006 and 2009. Patients with anterior circulation strokes treated within eight hours from symptom onset were included in the study. Demographic information, stroke risk factors, initial NIHSS, procedural time, pharmacologic and mechanical approaches utilized, recanalization grade, hemorrhage and 90 day Modified Rankin Scores (mRS) results were reviewed. Symptomatic hemorrhage (sICH) was defined as Parenchymal Hematoma type 1 or 2 by the ECASS classification. Good outcomes were defined as a mRS of ≤ 2 and poor outcome a mRS > 2. A univariate analysis was performed and variables with a p-value < 0.10 were included in a binary logistic regression model to determine independent predictors of good outcome and death. **Results:** The mean age was 67 ± 16 years and median NIHSS was 16 [IQ Range 12-20]. GA was utilized in 40% of patients with a mean time to puncture of 295±150 minutes from symptom onset and successful recanalization was achieved in 66% of patients. The overall mortality rate was 25% and 37% of patients who died did a good outcome and were admitted under GA prior to IAT. Independent predictors of a poor outcome included: GA during the procedure [OR 3.0 (95% CI 2.0-4.5), p<0.0001], older age [OR 1.04 (95% CI 1.02-1.06), p<0.0001], higher NIHSS (OR 1.05 (95% CI 1.00-1.09), p<0.001), and age < 75 years (OR 1.6 (95% CI 1.34-1.4), p=0.004) and sICH [OR 5.6 (95% CI 2.5-12.4), p<0.001]. Patient placed under GA for IAT had a significantly higher mortality rate compared to CS [OR 1.89 (95% CI 1.25-2.86), p<0.003]. **Conclusions:** Patients who are given CS prior to IAT for acute ischemic stroke are not at a higher risk for intracranial hemorrhage. Moreover, patients placed under GA prior to IAT are at a higher risk for mortality and poor outcomes. Future study is required to determine the medical co-morbidities and physiologic changes that may account for these differences.

97 The Albumin in Acute Stroke (ALIAS) Trial: Part 1 Safety Analysis

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**Excessive experimental studies have shown that moderate- to high-dose human albumin (ALB) therapy has the potential to blunt neurologic injury and improve neurologic outcome.** A phase II randomized, double-blind, placebo-controlled trial to ascertain whether ALB therapy (2 g/kg given within 5 hours of ischemic-stroke onset) would increase favorable outcome at 3 months. In Dec. 2007, after 434 subjects had been enrolled at 62 North American clinical sites, the trials Data and Safety Management Board (DSMB) suspended subject recruitment in order to review a safety concern. In response, we conducted semi-unblinded safety analyses and instituted corrective protocol revisions that were accepted by the FDA, DSMB, and NNDS, and have allowed the trial to go forward as a separate ALIAS-Part 2 trial. Here we present safety data from the Part-1 trial in the 424 subjects (age 69.5, baseline NIHSS 13.3) who received at least 20% of study drug. 80% of these subjects received tPA. The proportions of neurological deterioration within 48h, neurological death within 7d, and recurrent stroke within 30d were comparable in the ALB and saline groups. Pulmonary edema occurred in 12.3% of ALB subjects – similar to the 13% rate in the ALIAS Pilot Trial. The essence of the DSBs safety concern was an increased 90-day death rate in ALB- (21.5%) compared to saline-treated subjects (13.4%) – corresponding to 14 excess deaths (a of a total of 91) in the ALB group. An Excess IV fluid administration (defined as >=4200 ml total IV fluids received in the first 48h) accounted strongly for excess deaths in ALB-treated subjects: In subjects without excess IV fluids, 90-d death rates did not differ by treatment assignment, while in subjects with fluid excess, death rates were two-fold greater in ALB than saline subjects (p<0.05). A multivariate model of death and death-censoring identified a significant effect of treatment (p<0.03), baseline NIHSS (p<0.0001) and age (p<0.0005). These results, taken together, suggested that ALB-related mortality might be minimized, going forward, by excluding the very elderly from the trial and by instituting strict fluid management guidelines. More specifically, we excluded elderly patients whose age was 83 or less and who did not experience fluid overload, 90-day death rates were similar in ALB (14.8%) and saline (12.9%) subjects (p=NS). Accordingly, in the ongoing ALIAS Part-2 Trial, subjects older than 83 years are excluded, as are subjects with elevated baseline plasma troponin levels, and strict fluid management guidelines and mandatory diuretic therapy have been instituted.
18 patients were in the OSH group. The mean age for patients was 63 in INH and 52 in OSH (p<0.05). Median admission NIHSS was 18 in both groups. The LSN2IA was significantly delayed in the OSH patients (339 min) compared with 272 min in INH (p<0.05). There were 11 cases of siCH, 1 of them in the OSH group. LOS was similar between the two groups. The incidence of mRS≥2, mRS = 2, early good outcome, recanalization, and death were not different. All patients from OSH underwent brain imaging once they arrived at our center. Conclusions: In this limited cohort of patients, the drip-and-ship strategy for delivering IV t-PA at a local hospital followed by IAT at a comprehensive center may be safe. This approach could increase the number of patients treated with IA therapy at larger institutions after patients receive IV-tPA at local facilities. Effort to reduce the time from LSN2IA in patients treated with IV-tPA at outside hospitals may improve outcome.

### Table: Odds Ratio of Stroke Subtype

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Univariate Odds Ratio</th>
<th>Adjusted Odds Ratio</th>
<th>95% CI Lower Limit</th>
<th>95% CI Upper Limit</th>
<th>P Value</th>
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<tr>
<td>Ischemic Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lacunar</td>
<td>0.14</td>
<td>0.09</td>
<td>0.29</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0.15</td>
<td>0.17</td>
<td>0.27</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Large artery</td>
<td>0.38</td>
<td>0.34</td>
<td>0.23</td>
<td>0.52</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lacunar</td>
<td>0.27</td>
<td>0.23</td>
<td>0.17</td>
<td>0.30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>0.14</td>
<td>0.16</td>
<td>0.09</td>
<td>0.29</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, Charlson comorbidity index and stroke severity (using the Canadian Neurological Scale).

**Validation of the HAT-Score Scale as a Predictor of Hemorrhagic Transformation in a Large Cohort of Acute Stroke Patients Treated With Intravenous IVA**

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**Background:** The “HAT” score scale (0-5), which is based on medical history of diabetes or high baseline glycemia levels (0-1), baseline stroke severity (NIHSS) (0-2) and early signs of ischemia on CT at baseline (0-2), has been recently developed to predict the individual risk of hemorrhagic transformation (HT) after intravenous thrombolytic treatment in acute stroke patients. Our aim is to validate the accuracy of this scale for the prediction of the risk of HT as well as the prognosis in a large cohort of patients treated with intravenous IVA. **Methods:** A retrospective analysis of a prospective registry of patients treated with IVA in two different stroke centers during the last 6 years was performed. A total of 507 patients with a middle cerebral artery territory infarction treated with IVA within the first 3 hours from symptom onset were included. The HAT score was calculated for each patient. The presence of HT was evaluated in a CT scan performed at 24-36h. Symptomatic intracranial hemorrhage (siCH) was considered when associated with neurological deterioration (increase >4 points in the NIHSS). Good outcome was considered as a modified Rankin score ≤2 at three months. **Results:** HT was observed in 133 (26.2%) patients. The higher the HAT score, the greater the probability of HT. Overall, 6.8% of patients developed siCH and the risk increased accordingly with the HAT score: siCH 4.6% (HAT 0), 4.1% (HAT 1), 6.3% (HAT 2), 11.9% (HAT 3), 18% (HAT 4-5) (p<0.001). Moreover, the HAT score was also strongly associated with a lower probability of good outcome, as the percentage of patients with good outcome decreased with higher HAT scores: 71.2% (HAT 0), 61.3% (HAT 1), 26.1% (HAT 2), 6.8% (HAT 3), 4% (HAT ≥3). Overall, the HAT score was independently associated with a higher risk of HT, siCH and poor outcome in the regression models adjusted by age: OR of HT 1.6 (1.5-2.1; p<0.001), OR of siCH 1.5 (IC 95% 1.1-2.0; p=0.005) and OR of poor outcome 3.0 (IC 95% 2.4-3.7; p<0.001). **Conclusions:** The validation of the HAT score in our large cohort demonstrates that it is a simple, quick and useful tool for predicting hemorrhagic transformation and poor outcome in acute stroke patients treated with intravenous IVA.
Concordance Between Patient Bedside Dysphagia Assessment Results Obtained From Neurological Nurses and Speech Pathologists

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Background
HAMORRHAGIC and ischemic stroke patients are at high risk for aspiration, pneumonia and poor outcomes. Guidelines from the American Heart Association recommend assessing ability to swallow before any intake by mouth. Purpose This study examines the concordance levels between patient bedside swallow screens performed by neurological nurses and more extensive bedside dysphagia evaluations by speech language pathologists for hemorraghic and ischemic stroke. Methods This retrospective, nonrandomized study compared nursing (NNRN) bedside swallow screens to speech language pathologists (SLP) dysphagia evaluation. Data were collected from charts of hospitalized stroke patients admitted to the neurological units. Audits were done to collect: a) NNRN swallow screen results, b) SLP dysphagia evaluation results, and c) patient demographics and clinical characteristics. Staff nurses on the study units were educated independently using written tools, explanation, and policy review with verbal re-demonstration, prior to the study implementation. Results Our study included 57 stroke patients with a mean age of 65.2 years. On SLP evaluation, there were 30 patients with oral, 25 patients with pharyngeal and 24 patients with oropharyngeal dysphagia. McNemars Tests of marginal homogeneity and Kappa statistic were used to analyze the concordance and agreement between swallow screens and dysphagia evaluations. Analysis revealed a poor concordance (p < 0.050) and poor agreement (63.2% agreement, δ = −0.29, 95%CI: −1.22, 2.55), P = 0.042) between the NNRN swallow screen and SLP dysphagia evaluation in detecting oral dysphagia. The concordance (p = 0.21) and the agreement (71.9% agreement, δ = −0.41, 95%CI: −1.22, 0.22, P = 0.001) were a little better, but still suboptimal in detecting pharyngeal dysphagia. There was marginal improvement in the concordance (p = 0.30) and agreement (73.7% agreement, δ = −0.44, 95%CI: −1.34, 1.31, P = 0.006) in recognizing oropharyngeal dysphagia. These disparities were significantly associated with presence of mild dysphagia by SLP evaluation (p < 0.001), speech disturbance (p < 0.032) and facial asymmetry (p < 0.001). A gender, stroke type, and patient admitted or stroke severity were not significant. Conclusion Our study suggests that there are considerable differences between NNRN swallow screens done at the bedside and speech language pathologists bedside evaluations. The differences are more significant in patients with oral dysphagia. Nurse re-education focusing on the sources of discrepancies may improve efficiency of NNRN swallow screens.

DVT Prophylaxis With Low Molecular Weight Heparin or Unfractionated Heparin Does Not Increase Hematoma Volume in Patients With Intracerebral Hemorrhage


Objective: Intracerebral Hemorrhage (ICH) patients frequently receive prophylaxis to prevent deep vein thrombosis (DVT). This study aimed to examine the association between treatment with low molecular weight heparin (LMWH) or unfractionated heparin (UFH) and hematoma growth. Methods: This was an observational study of 301 patients with ICH admitted to 3 stroke units in a single academic hospital in Atlanta, Georgia. Patients receiving either LMWH or UFH were included. The primary outcome was hematoma volume change from admission to follow-up imaging. Statistical calculations were performed using a published method of hand drawn regions of interest (ROI) multiplied by the slice thickness. Subgroup analysis was performed on patients that received either LMWH or UFH within 4 days of admission, and also by diagnosis (ICH only, ICH + IVH). Results: In total, 272 patients were included in the analysis, of which 164 received LMWH and 108 UFH. The median age was 72 years (IQR 60-83). The median hematoma volume was 20.8ml and the median volume on subsequent CT after starting DVT prophylaxis was 23.4ml. Conclusion: The study found no statistically significant association between the use of LMWH or UFH and hematoma growth.

Systemic Inflammation but No Evidence of Immunodepression Following Stroke

Angela Kalil, Pat Tanzi, Kevin Cain, Dannielle Zierath, Kelly Carter, Jessica Hadwin, Anna Savos, Kyra J Becker; Univ of Washington Sch of Med, Seattle, WA

Background: There is a relatively robust inflammatory response following acute stroke, but animal data suggest that brain injury is associated with a temporary paralysis of the immune response, predisposing to systemic infection. Clinical data regarding the ability to mount an effective immune response following stroke are lacking. Methods: The study included 175 patients admitted to the local IRB. Patients were enrolled within 72 hours of ischemic stroke onset and followed prospectively for 1 year. Markers of non-specific inflammation were assessed at multiple time points after stroke onset. At these same time points, the cellular immune response to phytohemagglutinin (PHA) and tetanus toxoid (TT) were assessed by ELISPOT assay. Stroke severity was assessed using the NIH Stroke Scale score (NIHSS). Results: A total of 109 patients were enrolled; 64% were male, the median age was 57 (18-80) and the median NIHSS 11 (0-32). There was a strong correlation between stroke severity and markers of systemic inflammation at each time point following stroke. At 24 hours post stroke the Spearman rank correlations between NIHSS and the number of WBCL, number of PMNS and hscCRP were 0.62, 0.62, and 0.64, respectively. At 72 hours the respective correlations were 0.61, 0.60, and 0.67; at 1 week the correlations were 0.50, 0.61 and 0.69. All correlations are p < 0.001 (by 1 month, these correlations were no longer significant.) There was a strong inverse correlation between stroke severity and lymphocyte number at 24 and 72 hours (-0.59, -0.29; p<0.01 for both) and 1 week following stroke (-0.19; p<0.085). Despite the decrease in lymphocyte numbers in patients with more severe strokes, there was no decrease in the ability of these lymphocytes to respond to PHA or TT at these same time points. Further, there was no difference in the response to PHA or TT among control subjects (n=40) and patients at any time point after stroke. Plasma cortisol concentrations were also strongly correlated with stroke severity; Spearman rank correlations with NIHSS were 0.724, 0.519, 0.504 and 0.339 at 24 hours, 72 hours, and 1 week and 1 month respectively (p<0.001 for all). The decrease in lymphocyte numbers correlated with systemic cortisol levels at 72 hours (-0.40, p<0.001), but there was no correlation between lymphocyte responses and cortisol concentrations at any time point. Conclusions: There is a systemic inflammatory response following ischemic stroke; the more severe the stroke, the more robust the inflammation. While severe strokes are associated with a relative lymphopenia, these lymphocytes appear capable of responding to mitogenic and antigenic stimuli, arguing against a general immune defect and “systemic immunodepression” following stroke.

Stroke Severity is the Primary Predictor of Early Infection

Pat Tanzi, Angela Kalil, Kevin Cain, Dannielle Zierath, Anna Savos, Kelly Carter, Jessica Hadwin, Kyra Becker; Univ of Washington Sch of Med, Seattle, WA

Background: Infection following stroke is common and associated with worse outcome, yet prophylactic antibiotics have not been shown to improve outcome in large cohorts of patients with stroke. If one could identify patients at the highest risk for developing infection, it might allow for more selective prophylaxis. The goal of this study was to test whether clinical and immunological variables from the first 72 hours post-stroke were predictive of subsequent infection. Methods: The study was approved by the local IRB. Patients with ischemic stroke were enrolled within 72 hours of stroke onset and followed prospectively. Infection was diagnosed by the constellation of clinical symptoms, imaging findings and culture results. A number of clinical and immunological variables were assessed at 72 hours and their association with the occurrence of infection by day 14 determined. To ensure that the 72 hour biomarkers were not affected by concurrent infection, patients diagnosed with infection in the first 5 days after stroke onset were excluded from analysis. Results: A total of 111 patients were enrolled in the study; two patients died within the first 15 days and 11 developed infection before day 5. Of the remaining 98 patients, 64% were male with a median age of 57 (18-80) and a median NIHSS of 10 (0-32). Among these 98 patients, 17 (17%) developed infection within 15 days of stroke onset. Of the 17 patients with infection, 6 developed pneumonia (PNA), 12 developed urinary tract infection (2 of whom also had PNA) and 2 developed other non-severe infections. Increased risk of infection on days 6-15 was associated with higher NIHSS (OR = 1.18, 1.09-1.28, p=0.005), intubation (OR = 1.18, 1.01-1.30, p=0.001), total leukocyte count (OR = 1.41, 1.14-1.75, p=0.001), plasma cortisol (OR = 1.10, 1.02-1.19, p=0.016), IL-6 (OR = 1.09, 1.03-1.15, p=0.007) and plasma TNF-α (OR = 1.56, 1.18-2.07, p=0.001) at 72 hours. After controlling for
ischemic stroke, and confirms others previously reported (higher prevalence of AF and CE in whites was not statistically significant).

To MCAO.

in-vivo or in vitro models of cerebral ischemia. Studies are underway to determine the effect of disruption of the MyD88 or TRIF arms of the TLR signaling pathway does not confer protection in either the WT or MyD88 -/- mice and infarct volume was assessed 3 days later. MCA occlusion resulted in larger infarcts in LPR6 +/- (mice: 60 ± 7 vs. 35 ± 8 mm3 in controls; p<0.05). Wt), signaling is neuroprotective through inhibition of GSK3β activity (Exp Neurol 188:378, 2004). Therefore, in LPR6 +/- /mice reduced Wt signaling could exacerbate the injury by promoting GSK3β activation. Consistent with this prediction, in LPR6 +/- /mice post-ischemic GSK3β phosphorylation at serine 9 was reduced (<6±18%; p<0.05; n=3/group), while GSK3β phosphorylation at tyrosine 216 was increased (4±24%; suggesting GSK3β activation (PNAS 97:11071, 2004). Conclusions: These observations indicate that LPR6 is a critical component of an endogenous neuroprotective pathway that safeguards the brain from cerebral ischemia through Wt signaling. We conclude that loss of function of LPR6 increases the susceptibility to cerebral ischemia, and may provide the mechanistic bases for further increased stroke risk in patients with LPR6 mutations. Supported by NS34179 and NS35806.

Differences in Index Ischemic Stroke Characteristics in a Multiracial Medically Underserved Population

Amyt Towfighi, Mary Ann Gallup, Amy Tai, Univ of Southern California, Rancho Los Amigos National Rehabilitation Ctr, Los Angeles, CA; Erika Guarnara, Bruce Dubois; UCLA-Ohve View Med Cntr, Sylmar, CA

Background Ethnic and socioeconomic stroke care disparities are a major public health concern; estimates suggest they will result in greater future economic burden. A better understanding of socio-demographic stroke profile may assist care providers and policy makers in bridging disparities. However, most available race-ethnic or socioeconomic stroke population data lack detailed information on index strokes. In addition, Asians are often excluded. Los Angeles County, the most populous in the US, is ethnically diverse, and its local government hospitals may provide insights into race-ethnic stroke differences. Objectives To assess stroke characteristics in an ethnically diverse, underserved patient population. Methods From 9/05 to 6/09, demographic characteristics, ischemic stroke subtype (per TOAST classification), medical and medication history, time from symptom onset to presentation, initial NIH stroke scale, biomarkers, diagnostic exam findings, and discharge modified Rankin score were collected for 542 consecutive ischemic stroke patients admitted to two Los Angeles County hospitals serving similar patient populations. Results Of 542 stroke patients, 53.3% were Hispanic, 19.4% were non-Hispanic white, 16.1% were Asian, and 1.5% were in black. Overall, patients were relatively young (mean age 59.7 yrs), overweight (mean BMI 27.9 kg/m2), had elevated HbA1c (mean 7.5%), and dyslipidemia (mean LDL cholesterol 123.0 mg/dL, mean HDL cholesterol 36.8 mg/dL, and mean triglycerides 161.1 mg/dL). Half were on antiplatelet agents prior to admission, while few were on lipid lowering (22.4%) or antihypertensive agents (39.4%). Comparisons across race-ethnicities revealed no differences in age, initial NIH stroke scale, or number of days since onset. Small vessel disease (SVD) was the predominant stroke mechanism for all racial-ethnic groups. Compared to other race-ethnicities, Asians were most likely to have SVD (p=0.02), blacks to have "other" stroke (p=0.0057), and whites to have cardioembolic (CE) stroke (p=0.0045). Hispanics were most likely to be diabetic (p=0.0158), whites most likely to have atrial fibrillation (AFp) (p=0.0527), and blacks were most likely to smoke (p<0.0001). Blacks had higher BMI (p=0.0002) and Asians were most likely to have left ventricular hypertrophy, cerebral microbleeds, and dyslipidemia. Conclusions This exploratory analysis of an ethnically diverse population with poor access to care reveals some previously unreported differences in characteristics (risk factors, biomarkers, end-organ damage) of an index ischemic stroke, and confirms others previously reported (higher prevalence of AF and CE in whites was not statistically significant).

The Role of the Toll-like Receptor Signaling Pathway in Cerebral Ischemia

Bolane M Fatumik, Yongshang Mou, Joel Y Bemby, John M Hallenbeck; National Institutes, Bethesda, MD

Background and purpose: Stroke remains a leading cause of disability in the US. Deletion or mutation of some toll-like receptors (TLRs) confers protection towards cerebral ischemia. Molecular mechanisms underlying the neurogenesis are not fully understood. MicroRNAs (miRNAs) are small non-coding molecules that play a crucial role in gene regulation. The present study comprehensively examined alterations in miRNA expression in ischemic neural progenitor cells with an aim to build signaling pathway networks using predicted targets for the miRNAs. METHODS: Genome-wide profiles of miRNAs were measured in cultured non-ischemic and ischemic SVZ neural progenitor cells using custom designed microRNA microarray. The data were validated using real-time PCR based TaqMan miRNA assays on an independent set of the neural progenitor cells acquired by laser capture microdissection in brain tissues. Transcriptome data for miRNA target genes were analyzed by means of Bioinformatics. RESULTS: The miRNA array analysis identified significant (p<0.05) increases and decreases in 15 and 10 miRNAs, respectively, after stroke. Among them, miR-124, a brain specific miRNA, was the most down-regulated in the cultured ischemic neural progenitor cells and confirmed by RT-PCR in vivo samples (0.58±0.21, n=3, versus 1.0±0.18, n=3 in ischemia). To gain unbiased global perspective on miRNA expression levels, we used the R/qtl software for analysis. Conclusions: Targeted predicted inhibitors of miR-124 were analyzed using in vivo experiments. In mouse brain ischemia after stroke, inflammation and oxidative stress are prominent pathological hallmarks, and microRNA expression profiles of whole brain were generated using Agilent DNA microarrays. The R/qtl software was used to identify expression quantitative trait loci (eQTL) for the mouse homologs of the GWAS genes listed above. Results: An Oligo eQTL were identified for known and candidate genes with LOD scores of 2.5 and 10.8, respectively (See figure). Expression levels across genotypes support an additive mode of gene action (See figure) with both genes being more highly expressed in the resistant than the susceptible strain. Abstracts and presentations are embargoed for release at date and time of presentation or time of AHA/ASA news event. Information may not be released before then.

107 Mutations of the Lipoprotein Receptor-Related Protein-6 Modulate Ischemic Brain Injury

Takato Abe, Ping Zhou, Munehisa Shimamura, M. E Ross, Costantino Iadecola; Weill Cornell Med College , New York, NY

Background: Low density lipoprotein receptor-related protein 6 (LRP6), a member of the lipoprotein receptor family, is a co-receptor of the Fz7d protein and plays a key role in Wnt signaling. A missense mutation in the LRP6 gene causes ischemic heart disease in young individuals (Science 315: 1278, 2007), suggesting a link between LRP6, Wnt signaling and cardiovascular diseases including stroke. To investigate the role of LPR6 in ischemic brain injury, we used mice with a LPR6 loss of function (LPR6 +/- /mice) (nature 407: 535, 2000), or mice with a gain of function LPR6 mutation (C4+), in which Wnt signaling is hyperactive (PNAS 102: 12843, 2005). Methods and Results: The middle cerebral artery (MCA) was transiently occluded in male C4+ or LPR6 +/- /mice and post-ischemic phosphorylation at serine 9 was reduced (4±18%; p<0.05; n=3/group), while GSK3β phosphorylation at tyrosine 216 was increased (4±24%; suggesting GSK3β activation (PNAS 97:11071, 2004). Conclusions: These observations indicate that LPR6 is a critical component of an endogenous neuroprotective pathway that safeguards the brain from cerebral ischemia through Wt signaling. We conclude that loss of function of LPR6 increases the susceptibility to cerebral ischemia, and may provide the mechanistic bases for further increased stroke risk in patients with LPR6 mutations. Supported by NS34179 and NS35806.

106 Genomic Profiling of microRNAs in the Subventricular Zone After Cerebral Ischemia: miR-124 is Associated With Neurogenesis Induced by Stroke

Xian Shuang Liu, Michael Chopp, Rui Lan Zhang, Long Fei Jia, Hua Teng, Charles Chen, Zheng Gang Zhang; Dept of Neurology, Henry Ford Health System, Detroit, MI

BACKGROUND: Ischemic stroke induces neurogenesis in the subventricular zone (SVZ). Molecular mechanisms underlying the neurogenesis are not fully understood. MicroRNAs (miRNAs) are small non-coding molecules that play a crucial role in gene regulation. The present study comprehensively examined alterations in miRNA expression in ischemic neural progenitor cells with an aim to build signaling pathway networks using predicted targets for the miRNAs. METHODS: Genome-wide profiles of miRNAs were measured in cultured non-ischemic and ischemic SVZ neural progenitor cells using custom designed microRNA microarray. The data were validated using real-time PCR based TaqMan miRNA assays on an independent set of the neural progenitor cells acquired by laser capture microdissection in brain tissues. Transcriptome data for miRNA target genes were analyzed by means of Bioinformatics. RESULTS: The miRNA array analysis identified significant (p<0.05) increases and decreases in 15 and 10 miRNAs, respectively, after stroke. Among them, miR-124, a brain specific miRNA, was the most down-regulated in the cultured ischemic neural progenitor cells and confirmed by RT-PCR in vivo samples (0.58±0.21, n=3, versus 1.0±0.18, n=3 in ischemia). To gain unbiased global perspective on miRNA expression levels, we used the R/qtl software for analysis. Conclusions: Targeted predicted inhibitors of miR-124 were analyzed using in vivo experiments. In mouse brain ischemia after stroke, inflammation and oxidative stress are prominent pathological hallmarks, and microRNA expression profiles of whole brain were generated using Agilent DNA microarrays. The R/qtl software was used to identify expression quantitative trait loci (eQTL) for the mouse homologs of the GWAS genes listed above. Results: An Oligo eQTL were identified for known and candidate genes with LOD scores of 2.5 and 10.8, respectively (See figure). Expression levels across genotypes support an additive mode of gene action (See figure) with both genes being more highly expressed in the resistant than the susceptible strain. Abstracts and presentations are embargoed for release at date and time of presentation or time of AHA/ASA news event. Information may not be released before then. Failure to honor embargo policies will result in the abstract being withdrawn and banned from presentation.
Oligodendrocyte Injury and Leukoaraiosis in an Animal Model of Hypoxic-Ischemic Encephalopathy

Ahmed Shereen, Niza Nemkul, Dianer Yang, Cincinnati Childrens Hosp, Cincinnati, OH; Ning Gang, Pennsylvania State university, Univ Park, PA; Diana Lindquist, Chia-yi Kuan; Cincinnati Childrens Hosp, Cincinnati, OH

Introduction: Leukoaraiosis refers to white-matter abnormalities characterized by demyelination and hyperintensities on T2-weighted MRI. Leukoaraiosis is associated with cognitive impairment, and likely caused by chronic hypoxic hypoperfusion in small subcortical vessels. However, there are no animal models of leukoaraiosis to study its pathological mechanism and prophylactic treatment. We previously reported that a combined hypoxic-ischemic insult to adult rodent brains produces rapid, pervasive thrombosis in both cortical and subcortical regions (AJP 169: 566, 2006). Hypothesis: We hypothesize that a modified Levine/Vannuci procedure poses insults to oligodendrocytes, leading to widespread self-destruction of axons in the forebrain. Methods: Eight-to-ten week-old C57 mice were subjected to unilateral occlusion of the common carotid artery followed by inhalation of hypoxic gas (7.5% O2) for 50 minutes. After the hypoxic challenge, mice were returned to the ambient environment and were examined at 6, 15, or 24 hours of recovery for various analyses. One set of mice underwent T2 and ADC imaging, followed by histological assays (Nissl, myelin, silver degeneration, and astrocyte stain). A second set of mice underwent ex vivo diffusion tensor imaging (DTI), followed by electron microscopy exam. A third set was directly sacrificed at the same time points for biochemical and immunohistochemical analyses. Results: The combination of hypoxia and ischemia produces a high level of superoxide along cerebral vessels within 1 hr, correlated with widespread thrombosis, and hypoperfusion of cortical and subcortical vessels. At 6 hrs, lipid peroxidation was detected in the carotid-occluded side of brain, but not tissue damage. By 15 hrs of recovery, increased T2 and decreased ADC signals showed up on the MRI scan. So unilateral fractional anisotropy reduction and demyelination in all major forebrain axon tracts, including anterior commissure, internal capsule, corpus callosum, and the hippocampal fimbria. EM examination showed swelling and disintegration of myelin sheaths, as well as, separation of the axon-myelin interface from as early as 6 hrs of recovery. Accumulation of Fe(II) and apoptosis of oligodendrocytes within these axonal tracts were noted at 15-24 hrs. Moreover, demyelination in the fimbria appeared to occur earlier than the apoptosis of hippocampal neurons. Conclusions: The modified Levine/Vannucci procedure produces white-matter injury with features resembling leukoaraiosis in the forebrain in a spatial- and temporal-specific manner. In this paradigm, hypoxia-ischemia causes direct insults to oligodendrocytes leading to demyelination and self-destruction of the axons. A high iron content and the resultant reactive oxygen stress may be a critical factor of hypoxia/ischemia-induced oligodendrocyte injury.

Bone Marrow Stromal Cells and Bone Marrow-derived Mononuclear Cells: Which Are Suitable as Cell Source of Transplantation for Mice Infarct Brain?

Hideo Shichihone, Satoshi Kuroda, Katsukio Maruichi, Toshiya Osanai, Taku Sugiyama, Yasuhiro Chiba, Ayumi Yamaguchi, Yoshinobu Iwasaki; Dept of Neurosurgery, Hokkaido Univ, Sapporo, Japan

There are few studies that denote whether the bone marrow stromal cells (BMSC) and bone marrow-derived mononuclear cells (MNC) show the same therapeutic effects, when directly transplanted into the infarct brain. This study, therefore, was aimed to compare their biological properties and behaviors in the infarct brain. Mouse BMSC were harvested and cultured. Mouse MNC were obtained through centrifugation technique. Their cell markers were analyzed with FACS analysis. The MNC (10 6 cells; n=10) or BMSC (2x10 5 cells; n=10) were stereotactically transplanted into the ipsilateral striatum of the mice subjected to permanent middle cerebral artery occlusion at 7 days after the insult. Their survival, migration, and differentiation in the infarct brain were precisely analyzed using immunohistochemistry 4 weeks after transplantation. The MNC were positive for CD34, CD45, CD100, but were negative for Sca-1. The BMSC were positive for CD90 and Sca-1. The transplanted BMSC, but not MNC, extensively migrated into the peri-infarct area (Figure A). About 20% of the transplanted BMSC expressed a neuronal marker, NeuN in the infarct brain, although only 1.4% of the transplanted MNC expressed NeuN (Figure B). These findings strongly suggest that there are large, biological differences between the MNC and BMSC as cell source for regenerative medicine for ischemic stroke.

Conclusion: Our data show genetically determined differences in expression of two candidate genes identified in human stroke GWAS. The results for Ninj2 support the hypothetical mechanism proposed in the original paper. These experiments both support further investigation of the biology and genetic regulation of these candidates and serve as a proof of concept for this approach more generally. Exploiting multiple strains with differential susceptibility to cerebral ischemia is a promising avenue of research. Comparison of responses to a middle cerebral artery occlusion model, analysis of candidate gene expression before and after ischemic injury, and parsing the role of these genes and the pathways by which they act may allow for the identification of novel therapeutic targets for cerebrovascular disease.

Treatment of Global Cerebral Ischemia by Virally-Mediated shRNA Suppression of TRPM7 Channels

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Introduction: Survivors of cardiac arrest who experience transient hypoperfusion of the brain incur a delayed death of hippocampal CA1 neurons and cognitive impairment. These disorders were prevented in adult rats by inhibiting the expression of transient receptor potential-melastatin 7 (TRPM7), a cation channel protein that is essential for embryonic development, whose global deletion in mice is lethal, and which was deemed in-vitro as necessary for cell survival. Failure to honor embargo policies will result in the abstract being withdrawn and barred from presentation.

Conclusions: The modified Levine/Vannuci procedure poses insults to oligodendrocytes, leading to widespread self-destruction of axons in the forebrain. Leukoaraiosis is associated with cognitive impairment, and likely caused by chronic hypoxic hypoperfusion in small subcortical vessels. However, there are no animal models of leukoaraiosis to study its pathological mechanism and prophylactic treatment. We previously reported that a combined hypoxic-ischemic insult to adult rodent brains produces rapid, pervasive thrombosis in both cortical and subcortical regions (AJP 169: 566, 2006). Hypothesis: We hypothesize that a modified Levine/Vannuci procedure poses insults to oligodendrocytes, leading to widespread self-destruction of axons in the forebrain. Methods: Eight-to-ten week-old C57 mice were subjected to unilateral occlusion of the common carotid artery followed by inhalation of hypoxic gas (7.5% O2) for 50 minutes. After the hypoxic challenge, mice were returned to the ambient environment and were examined at 6, 15, or 24 hours of recovery for various analyses. One set of mice underwent T2 and ADC imaging, followed by histological assays (Nissl, myelin, silver degeneration, and astrocyte stain). A second set of mice underwent ex vivo diffusion tensor imaging (DTI), followed by electron microscopy exam. A third set was directly sacrificed at the same time points for biochemical and immunohistochemical analyses. Results: The combination of hypoxia and ischemia produces a high level of superoxide along cerebral vessels within 1 hr, correlated with widespread thrombosis, and hypoperfusion of cortical and subcortical vessels. At 6 hrs, lipid peroxidation was detected in the carotid-occluded side of brain, but not tissue damage. By 15 hrs of recovery, increased T2 and decreased ADC signals showed up on the MRI scan. So unilateral fractional anisotropy reduction and demyelination in all major forebrain axon tracts, including anterior commissure, internal capsule, corpus callosum, and the hippocampal fimbria. EM examination showed swelling and disintegration of myelin sheaths, as well as, separation of the axon-myelin interface from as early as 6 hrs of recovery. Accumulation of Fe(II) and apoptosis of oligodendrocytes within these axonal tracts were noted at 15-24 hrs. Moreover, demyelination in the fimbria appeared to occur earlier than the apoptosis of hippocampal neurons. Conclusions: The modified Levine/Vannuci procedure produces white-matter injury with features resembling leukoaraiosis in the forebrain in a spatial- and temporal-specific manner. In this paradigm, hypoxia-ischemia causes direct insults to oligodendrocytes leading to demyelination and self-destruction of the axons. A high iron content and the resultant reactive oxygen stress may be a critical factor of hypoxia/ischemia-induced oligodendrocyte injury.

Bone Marrow Stromal Cells and Bone Marrow-derived Mononuclear Cells: Which Are Suitable as Cell Source of Transplantation for Mice Infarct Brain?

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There are few studies that denote whether the bone marrow stromal cells (BMSC) and bone marrow-derived mononuclear cells (MNC) show the same therapeutic effects, when directly transplanted into the infarct brain. This study, therefore, was aimed to compare their biological properties and behaviors in the infarct brain. Mouse BMSC were harvested and cultured. Mouse MNC were obtained through centrifugation technique. Their cell markers were analyzed with FACS analysis. The MNC (10 6 cells; n=10) or BMSC (2x10 5 cells; n=10) were stereotactically transplanted into the ipsilateral striatum of the mice subjected to permanent middle cerebral artery occlusion at 7 days after the insult. Their survival, migration, and differentiation in the infarct brain were precisely analyzed using immunohistochemistry 4 weeks after transplantation. The MNC were positive for CD34, CD45, CD100, but were negative for Sca-1. The BMSC were positive for CD90 and Sca-1. The transplanted BMSC, but not MNC, extensively migrated into the peri-infarct area (Figure A). About 20% of the transplanted BMSC expressed a neuronal marker, NeuN in the infarct brain, although only 1.4% of the transplanted MNC expressed NeuN (Figure B). These findings strongly suggest that there are large, biological differences between the MNC and BMSC as cell source for regenerative medicine for ischemic stroke.
Intracranial Angioplasty and/or Stent Placement in Octogenarians is Associated With A Threefold Greater Risk of Peri-procedural Stroke or Death
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Background and purpose: Recently, higher rates of poor outcomes have been reported with endovascular treatment of ischemic acute stroke and carotid stent placement among patients aged >80 years (octogenarians). With the increasing octogenarian population and greater utilization, efforts were made to identify clinical outcomes based on age with intracranial angioplasty/stent placement prior to broad applicability. Materials and methods. We analyzed pooled data for all patients who underwent endovascular angioplasty and/or stenting for intracranial atherosclerotic disease at 5 specialized centers. Baseline, peri-procedural (1-month), and follow-up clinical and angiographic information was collected. Rates of clinical and angiographic end-points were compared between patients aged >80 years and those <80 years. Results: A total of 244 patients underwent intracranial angioplasty and/or stent placement. Patients >80 years (n=15) were more likely to be hypertensive (87% versus 69%, p<0.05) and have underlying coronary artery disease (23% versus 36%, p<0.05) compared to younger patients. Rate of peri-procedural stroke and/or death was three folds higher among patients aged >80 years compared with those <80 years (23% versus 7%, p<0.11). No recurrent stroke and/or death (excluding peri-procedural events) was documented during follow-up angiography. In the octogenarian group, patients who had follow-up angiography, similar rate of recurrent stenosis of 50% or greater was observed among patients >80 years and those aged <80 years (25% versus 29%, p>0.1). Conclusion: The three fold higher peri-procedural higher periprocedural death and stroke rate mandate cautious use of intracranial angioplasty and/or stent placement in octogenarians. This research has received full or partial funding support from the American Heart Association, National Center.

Collaterals Avert Neurovascular Complications and Recurrent Stroke in Stenting of Intracranial Atherosclerosis
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Background: Collateral flow may sustain perfusion beyond an intracranial stenosis, reducing the chance of critical ischemia and possibly improving washout of distal emboli. The role of collaterals in early and late complications of stenting for intracranial atherosclerosis remains unexplored. We analyzed the impact of collaterals noted at angiography on periprocedural neurovascular complications and stroke outcomes after stenting. Methods: Retrospective review of clinical, imaging, and angiographic data in a consecutive series of stenting procedures for intracranial atherosclerosis at a single center. Angiographic collaterals were graded with the ASITN/SIR scale based on pre- and post-stenting views of the target vascular territory. Degree of luminal stenosis was also measured. Pen-procedural (30 days) stroke and recurrent clinical stroke up to 2 years after the procedure were analyzed. Restenosis within the stent was noted when documented by serial angiography. Results: Among 36 cases, mean age was 63.9±14.3 years, 28% were female, and time from last symptomatic event to stenting was median 15.5 (IQR 27) days. Target stenosis sites were intracranial ICA in 5, VA in 10, and BA in 10. Overall, the baseline degree of luminal stenosis ranged from 6% to 99% (median 85%) and collateral grade varied across cases (0-4). More robust collateral flow at baseline was associated with a reduced rate of peri-procedural stroke (p=0.04). Most (8/12 or 67%) cases with grade 3 or 4 collateral flow and marked involution of collaterals on post-procedural angiography once stenting had restored antegrade perfusion. Poor collateral flow at baseline did not change in the peri-procedural period. Interestingly, poor collateral flow was associated with in-stent restenosis on follow-up angiography (p=0.03). Subsequent stroke in the treated vascular territory was also reduced with more vigorous collateral flow noted at baseline (p<0.04). Most strokes observed in followup were documented as small, scattered lesions on diffusion-weighted imaging. Serial angiography, before, immediately after, and at later timepoints showed early remodeling of collaterals and then subsequent stability. Conclusions: Collateral flow may reduce the occurrence of neurovascular complications and subsequent stroke following stenting for intracranial atherosclerosis. In-stent restenosis may be associated with relatively poor collateral flow. Validation of these novel findings regarding collateral flow and treatment of intracranial atherosclerosis is warranted.

Intermediate-term Angiographic and Clinical Outcomes With the Wingspan Intracranial Stent System (WIS) for Treatment of Symptomatic Intracranial Arterial Disease (sICAD): A Single-center Experience in 133 Consecutive Lesions Treated
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Background: The natural history of sICAD confers a high rate of recurrent stroke despite best medical management, prompting treatment with angioplasty +/- stenting. Coronary stent technology was utilized for sICAD with variable outcomes limited by periprocedural clinical and technical complications. This became the impetus to develop a self-expanding stent designed for sICAD applications. Preliminary experience with WIS has been encouraging, although there is limited technical, clinical, and angiographic cumulative outcome data. This led us to critically review our single center “real life” experience with WIS in a consecutive series. Methods: A prospective database of all patients undergoing endovascular treatment of sICAD with WIS between 12/2005 and 7/2009 was the basis for this study. The indication, lesion location, stenosis severity, periprocedural complications, and clinical/angiographic follow up were recorded. Standard outcome endpoints were statistically analyzed and compared to historical controls. Results: There was an intention to treat 133 lesions in 106 patients, with 1 technical failure of stent deployment (technical success rate >99%). Mean patient age was 60 ±14; 69% male. Lesion location was as follows: MCA 32%, distal ICA 7%, proximal ICA 22%, vertebral 6%, and BA 21% (n=133). Mean lesion stenosis was 77% (IQR 40-100). Penetrance mean residual stenosis was 18%-60). 88 follow up DSA were performed with mean days to follow up: 141(1-825). The binary restenosis rate was 20% at 3-6 mos angiogram. 11 patients demonstrated luminal improvement at follow up. Standard primary endpoint rate at 30 days (major stroke, ICH, and death) was 6% (1 death). The ~300-700ms patolase stroke and death rate and/or death (excluding peri-procedural events) was 0% over 2 years. Conclusion: Our centers “real life” experience with WIS supports a high level of technical efficacy and safety for treatment of sICAD. Further, lower morbidity, mortality, and restenosis rates compared to previous reports suggest better overall outcomes are achievable, which may be linked, 1990-2008, mean age 42; 81% women. Associated triggers were identified in 60% including vascoconstrictive drugs (51%) and childbirth (9%). Onset headache occurred in 75% [thunderclap in 85%]; seizures in 17%; 40% had prior migraine; focal deficits developed in 45%. CSF results were entirely normal in 85%. Brain pathology, available in 17%, showed no acute changes. Initial NIHSS was normal in 45%. Serial brain imaging showed findings in 39% [typically ‘watershed], small cortical surface SAH (34%), lobar ICH (20%), and/or reversible edema. RCVS diagnosis was based on abnormal DSA (performed in 70%), MRA (61%) or CTA (53%); only 1 patient had TCD alone. Follow-up angiography showed complete or partial reversal in 98%. Therapy was non-standardized and included EIT (53%), CCB (21%), or simple observation. At discharge, 11% had poor outcome (mRS 4-6) including death in 2%. In the combined cohort, CCB had no effect on outcome, however patients receiving EIT tended to have poor outcome (Fisher exact p=0.099). This unexpected result was essentially driven by the impact of CCB (mainly inpatients) where the RCVS effect was significant. Patients receiving EIT and 50% CCB; EIT was the only predictor of poor outcome (p=0.002), focal deficits (p=0.02), and increased length of stay (p=0.008) in regression models adjusting for baseline factors such as age, gender, triggers, seizures, and initial CT/MR results. Conclusion: RCVS has characteristic clinical, laboratory, and imaging features that can be used in combination to distinguish from mimics such as PACSs. CCB has no effect on clinical outcome. EIT have little effect in stopping disease progression or may paradoxically worsen outcome. Further studies are warranted to confirm this result and understand effects of the timing and duration of EIT.
harboring high stroke recurrence has been studied at ≥50% (WASID) and under investigation for ≥70% (GAMPRIS) stenoses. We aimed to determine TCD/DSA correlation at laboratories that share the same standardized and previously validated TCD scanning protocol.

**Subjects and Methods:** Consecutive patients with symptoms of cerebral ischemia evaluated by TCD and DSA at 3 tertiary care centers were prospectively studied. Baseline stroke severity (NIHSS) was documented. TCD measurements of peak systolic (PSV), end-diastolic (EDV) and mean flow (MVF) velocities were performed. The following MVF cut-offs were used for identification of ≥50% stenosis using published SONIA criteria: MFV MCA >100 cm/s, TICA >80 cm/s, MCA >70 cm/s. Current velocity data were applied to predict cut-offs for the ≥70% stenosis (measured by the WASID trial method). We also evaluated whether the addition of stenotic to pre-stenotic ratio (SPR) would increase the accuracy of velocity prediction of ≥70% IAD. Results: Among a total of 172 patients with DSA/TCD data, 33 had confirmed 50% IAD (ρ = 0.54, 95% CI: 0.46-0.63), 70% IAD, 10% (n = 17) had a total occlusion, 15% (n = 26) Carotid, 15% African-American, 32% Asian; median NIHSS 3, interquartile range 6 providing 375 TCD/DSA measurement pairs for comparison. On DSA, ≥50% stenoses were located in 56 vessels: M1MCA (48%), M2 (4%), TICA (16%), ACA (7%), VA (14%), BA (8%), PCA (2%). IAD ≥70% on DSA was found in 21 arteries (anterior circulation 19, posterior circulation 3). The accuracy parameters of TCD (SONIA MFV cut-offs) against DSA for ≥50% were as follows: sensitivity (89%), specificity (99%), PPV (93%), NPV (88%), overall accuracy (97%) [54 true positive, 310 true negative, 4 false positive and 7 false negative]. The predictive ability of PSV and MFV for detection of IAD on DSA did not differ (p > 0.05) both in anterior and posterior circulation. The optimal PSV cut-off for detection of ≥70% IAD was >196 cm/s (sensitivity 78%, specificity 95%) and >166 cm/s (sensitivity 100% and specificity 97%) in anterior and posterior circulation respectively. The optimal MFV cut-off for detection of ≥70% IAD was >128 cm/s (sensitivity 78%, specificity 86%) and >119 cm/s (sensitivity 100% and specificity 99%) in anterior and posterior circulation respectively. The addition of a MFV SPR >3 in the MFV criteria (>128 cm/s in anterior and >119 cm/s in posterior circulation) increased the TCD accuracy for detecting ≥70% IAD (sensitivity 90%, specificity 95%).Conclusions: At laboratories with a standardized scanning protocol, SONIA MFV cut-offs reliably predict ≥50% stenosis. The new velocity/ratio criteria for detection of ≥70% intracranial stenosis show good agreement with invasive angiography.

**Assessment of Cerebral Vasodilatory Reserve in Patients With Severe Steno-occlusive Disease and Intracranial Internal Carotid and Middle Cerebral Artery Stenosis**

**Aim:** To report endovascular treatment of intracranial stenosis with Moyamoya pattern of collaterals. **Methods:** Data collected after retrospective chart review of 6 patients treated between 2005 and 2009 included age, sex, comorbidities, presentation, lesion and treatment characteristics, clinical and angiographic follow-up. Results: All 6 patients were women, symptomatic, had previous strokes and were young (mean age 38, 28-51). Lesion location included 5 unilateral M1 occlusions and one patient having bilateral disease with one side ICA and one AcomA stenosis. The supratentorial internal carotid stenosis at M1 was 74.5 ± 14.3% (95-100%). 5 patients had balloon angioplasty for their M1 stenosis. In one patient balloon angioplasty (Gateway) failed and a wispanded stent was deployed successfully. At the end of this primary treatment the mean post-treatment stenosis at M1 was 39.3 ± 30.4% (0-54%). One patient who had a 100% occlusion had a vessel rupture during angioplasty that was controlled by sacrifice of the MCA with glue. This resulted in a large MCA infarct that led to severe disability (mRS-5). Of the remaining 5, there were 2 patients who are asymptomatic for 4 years (angiography 1 year after treatment showed no restenosis) and 6 months after their primary treatment. Three of the remaining patients became symptomatic 1, 2 and 5 months after their primary treatment. These patients had 54%, 33% and 35% stenosis after their primary treatment respectively. The first patient had the same 54% stenosis, had a repeat balloon angioplasty with a Gateway balloon that left her with a residual stenosis of 5% after treatment. She has been asymptomatic for 6 months and angiography after 2 months showed no restenosis. The second patient had an endovascular encephaloduroarteriosynangiosis after a failed Gateway balloon angioplasty and has been asymptomatic for 10 months. The third patient was asymptomatic, had increased stenosis (81%) on follow-up angiogram after 5 months, had wispanded stent placement that made it 42%. After 3 months, she had an asymptomatic IS 58% that was balloon angioplastied to 30%. She has been asymptomatic for 4 months since then and angiography after 1 month after last retreatment showed a 28% stenosis. Conclusion: Endovascular treatment of intracranial stenosis with moyamoya collaterals is feasible. There is a high rate of symptomatic restenosis and target lesion revascularization after endovascular therapy. Careful patient, tool, and technique selection are necessary to decrease complications.

**Multiparametric Magnetic Resonance Imaging Characteristics of Stroke Recovery**

Panayiotis Mtisas, Quan Jiang, Angelos Katramados, Qingming Zhao, Brian Silver, Li Jin, Lonni Schultz, Michael Chopp, Henry Ford Hosp, Detroit, MI

**Introduction:** Experimental preclinical stroke MRI studies demonstrate that elevated cerebral blood volume and flow (CBV and CBF) and fractional anisotropy (FA) in the ischemic lesion are markers of increased axon reorganization and angiogenesis, which, in turn, correlate with improved functional outcomes. **Objectives:** To define the values of FA, CBF and CBF in the ischemic lesion at various time points after stroke onset and correlate these values with the clinical neurological scores in patients with ischemic stroke. **Main Hypotheses:** Elevated CBV, CBF and FA values in the ischemic lesion at 1 month after stroke correlate with a lower NIHSS score at 3 months. **Methods:** We prospectively studied ischemic stroke patients with clinical scores and MRI at 3 baseline scans (1-3 days, 1 month and 3 months). The clinical neurological deficit was graded with NIHSS at each time point. The baseline scan was used for definition of lesion size. Subsequent scans were done in a 3 T GE scanner. Multiparametric MRI protocol included: diffusion tensor imaging, perfusion imaging, T1WI, T2WI and DWI, which were acquired at each time point. The ischemic lesion at 1 and 3 months was divided into the infarct core and recovery regions. CBV, CBF, and FA values were defined in the infarct core and recovery regions as well as the corresponding normal appearing regions of the contralateral hemisphere. The values were expressed as the ratio between the ischemic region and contralateral normal regions. Spearman correlation coefficients were computed to assess the association between MRI measurements at 1 and 3 months and the clinical scores at 3 months. The study was approved by the Institutional IRB. **Results:** We studied 18 patients. The baseline NIHSS score was 10 (9-17). There was a significant negative correlation between the two follow up NIHSS values in the infarct core region and the 3 month NIHSS (r = -0.30, p = 0.039), but no significant correlation between 1-month core CBF or recovery FA values and 3-month NIHSS (r = -0.476, p = 0.073, and r = 0.340, p = 0.167, respectively). There was however a significant correlation between the 3-month recovery region core FA and FN3 and NIHSS (r = 0.607, p = 0.048). **Conclusions:** Elevated CBV values in the ischemic lesion at one month after stroke onset correlate with improved clinical neurological outcome. It is likely that the changes in the FA values occur later in the course of stroke recovery. A larger study is needed to further clarify these findings and establish MRI markers of stroke recovery.

**Altered Neural Control of Postural Sway Following Right-hemisphere Cerebral Infarction**

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**Background:** Balance impairment is common following cerebral infarction. Yet, the effects of lesion hemisphere on postural control in individuals with right and left hemisphere middle cerebral artery (MCA) infarcts. **Objectives:** To define the values of FA, CBF and CBF in the ischemic lesion at various time points after stroke onset and correlate these values with the clinical neurological scores in patients with ischemic stroke. **Main Hypotheses:** Elevated CBV, CBF and FA values in the ischemic lesion at 1 month after stroke correlate with a lower NIHSS score at 3 months. **Methods:** We prospectively studied ischemic stroke patients with clinical scores and MRI at 3 baseline scans (1-3 days, 1 month and 3 months). The clinical neurological deficit was graded with NIHSS at each time point. The baseline scan was used for definition of lesion size. Subsequent scans were done in a 3 T GE scanner. Multiparametric MRI protocol included: diffusion tensor imaging, perfusion imaging, T1WI, T2WI and DWI, which were acquired at each time point. The ischemic lesion at 1 and 3 months was divided into the infarct core and recovery regions. CBV, CBF, and FA values were defined in the infarct core and recovery regions as well as the corresponding normal appearing regions of the contralateral hemisphere. The values were expressed as the ratio between the ischemic region and contralateral normal regions. Spearmans correlation coefficients were computed to assess the association between MRI measurements at 1 and 3 months and the clinical scores at 3 months. The study was approved by the Institutional IRB. **Results:** We studied 18 patients. The baseline NIHSS score was 10 (9-17). There was a significant negative correlation between the two follow up NIHSS values in the infarct core region and the 3 month NIHSS (r = -0.30, p = 0.039), but no significant correlation between 1-month core CBF or recovery FA values and 3-month NIHSS (r = -0.476, p = 0.073, and r = 0.340, p = 0.167, respectively). There was however a significant correlation between the 3-month recovery region core FA and FN3 and NIHSS (r = 0.607, p = 0.048). **Conclusions:** Elevated CBV values in the ischemic lesion at one month after stroke onset correlate with improved clinical neurological outcome. It is likely that the changes in the FA values occur later in the course of stroke recovery. A larger study is needed to further clarify these findings and establish MRI markers of stroke recovery.
with eyes-closed compared to eyes-open. In this group, smaller occipital lobe volumes associated with greater eyes-open sway velocity (R = -.64, p = .012) and ML range (R = -.82, p < .001) (see Figure 1 for illustration and comparison to individuals with left hemisphere infarct and controls). Smaller cerebellar volumes associated with greater eyes-closed sway velocity (R = -.60, p = .015), ML range (R = -.70, p = .007) and ML variability (R = -.85, p < .001). These associations were not observed in left hemisphere infarct subjects or controls. AP sway was unaffected by infarct hemisphere or visual condition and did not correlate with regional brain volumes. Conclusion: Right hemisphere MCA infarcts associated with increased dependence on vision and non-infarcted brain regions (i.e., occipital lobes, cerebellum) to control postural sway. Strategies emphasizing postural tasks under reduced visual conditions may enhance functional recovery in these individuals.

Integrity of Transcallosal Motor Fibers Predicts Recovery Potential in Chronic Stroke

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Objectives: Down-regulation of contra-lesional motor cortex with non-invasive brain polarization methods has been shown to improve motor function in chronic stroke patients. It is assumed that this effect is due to the modulation of inter-hemispheric interactions. Using diffusion tensor imaging (DTI), we investigated the structural integrity of motor fibers connecting contra-lesional primary motor (M1) and dorsal premotor cortices (PMd) with intact motor areas of the lesional hemisphere and their relationship to improvements seen in an experimental neurorehabilitation trial. Methods: Fifteen chronic stroke patients participated in a 5-day-intervention of non-invasive brain stimulation (30 min) and simultaneous occupational therapy (60 min). Using bhemispheric transcranial direct current stimulation (tDCS), the ipsilesional motor region was up-regulated and the contra-lesional motor region down-regulated at the same time. Before and after the intervention, patients underwent motor assessment (e.g., Wolf Motor Function Test) and DTI (25 non-collinear directions with b-value of 1000/s/mm2 and one image with b-value of 0/s/mm2). To trace transcallosal motor fibers, seed regions in M1 and PMd were combined with a region of interest in the corpus callosum. In a regression analysis, tract-specific diffusivity parameters were compared with changes in impairment scores. Here, fractional anisotropy (FA) serves as a measure of the diffusion directions coherence. Axial and radial diffusivity reflect diffusion in the primary and perpendicular direction, respectively; higher axial diffusivity values suggest axonal integrity and restricted radial diffusivity suggests denser alignment of myelinated fibers in the primary diffusion direction. Results: FA values, radial diffusivity and the ratio of axial over radial diffusivity of transcallosal motor fibers at baseline were significantly correlated with proportional changes in motor impairment scores. Higher FA values, lower radial diffusivity and a higher axial/radial diffusivity ratio were associated with greater gains through the experimental intervention. Conclusions: As indicators of structural integrity, diffusivity measures of transcallosal motor fibers connecting intact motor regions of lesional and contralesional hemisphere predicted motor improvement in an experimental neurorehabilitation trial. Thus, DTI-derived measures might help to optimize therapeutic strategies (i.e., assessing potential benefits of brain stimulation applied to contralesional motor regions) for individual patients and to understand treatment effects.

Lesion Load of the Arcuate Fasciculus Predicts Fluency in Patients With Brocas Aphasia After Stroke

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Objectives: Previous studies have shown that patients potential for post-stroke language recovery is related to lesion size. However, lesion size alone does not account for all of the variability in recovery; lesion location is of additional importance particularly when there is damage to fiber tracts critical to the sensorimotor mapping of sounds for articulation such as the arcuate fasciculus (AF). In the current study we quantitatively tested the hypothesis that the amount of AF fiber volume affected by a lesion is inversely related to the level of fluency in aphasic patients after stroke. Methods: Fifteen chronic stroke patients with residual dysfluent Brocas aphasia and relatively unimpaired comprehension underwent high-resolution anatomical MRI imaging (0.83x0.83x1.5mm) and evaluations of speech impairment. All patients were at least 12 months post-onset of their first ischemic stroke and presented with non-fluent aphasia in the subacute phase. Fluency was measured by the number of correct information units (CIUs) per minute produced during spontaneous speech. Individual lesion maps were manually outlined on spatially normalized MRI images. To quantitatively analyze the relationship between fluency scores and the AF, we first identified the AF in the 3D image space for each patient using a probabilistic map of the AF derived from the Diffusion Tensor Images (2.6mm3 voxel size; 30 non-collinear directions with b-value of 1000/s/mm2 and 6 image sets with b-value of 0/s/mm2) of 12 age-matched healthy subjects. We refer to this new variable as the AF-lesion load. Results: The regression analysis that showed AF-lesion load to significantly predict CIUs per minute remained significant even after effect of lesion size was taken into account. Lesion size, despite correlating significantly with CIUs per minute, did not significantly predict fluency. Conclusions: Our results confirm that the level of fluency in stroke patients with chronic aphasia on presentation on lesion size as well as the lesion size per se. This new combined variable, AF-lesion load, complements established voxel-based lesion mapping techniques and may potentially estimate recovery potential after stroke, and perhaps refine inclusion criteria for experimental rehabilitation programs.

Post-stroke Falling and Injury Due to Fall Among Elderly Population: Health and Retirement Study Survey 2002-2006

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Background and Purpose: Disability after stroke constitutes a major burden to stroke recovery. Loss of balance, sensory deficits, weakness, and neglect secondary to stroke may predispose patients to falling accidents that can lead to further complications, thus augmenting disability. Methods: We used the Health and Retirement Study (HRS) to analyze the incidence and frequency of falling among stroke survivors. We used 2002 and 2004 interview-waves in HRS to study incidence and frequency of falling. Falling accidents were identified by number of falls, injury due to fall, and hip fracture due to fall among subjects with history of stroke and controls with matched age/sex. We extracted demographic data (age, gender, and race), self-evaluated general health, co-morbid conditions (neurological and sensory conditions, diabetes, cancer, lung disease, psychiatric, memory loss, urinary incontinence, impaired mobility, and pain), and the incidence of fall and fall-related injuries in the following interview-waves (2004 and 2006). We analyzed the risks of falling accidents (as repeated measurements) within in stroke survivors aged 65 years and older and compared them to controls in multivariate models. Results: We analyzed 739 subjects (mean age = ±75 ± 8 years, 53% female) with history of stroke that were matched for age and sex to 739 controls. We observed 46% and 34% falling accidents (p < 0.0001), 16% and 12% injury due to fall (p = 0.01), and 2% and 1% hip fracture (p = 0.16) among stroke and non-stroke subjects, respectively. The average falling accidents were significantly higher among stroke vs. non-stroke subjects (8 vs. 4.7 times, p = 0.0005, respectively). For subjects diagnosed with stroke, the odds were higher for the overall risk (falling and fall-related injury; OR: 2.2, 95%CI: 1.4-3.5; CI: 1.1-1.8), and hip fracture due to fall (OR: 1.7, 95%CI: 1.1-2.8) vs. non-stroke subjects. The overall risk and frequency of falling remained significantly higher between stroke vs. non-stroke subjects after adjusting for general health, psychiatric problems, urinary incontinence, and pain. The same result persisted after further adjusting for concurrent falling accidents. Conclusions: We observed a significantly higher occurrence of falls and injury due to falls among stroke survivors compared to non-stroke subjects. Rehabilitation assessment and treatment should be particularly tailored to address this problem to enhance the recovery process and independence for the stroke survivors.

Factors Associated With Treatment Response Combined to Psychosocial and Antidepressant Treatment of Post-Stroke Depression (PSD)

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Objective: The Living Well with Stroke Study (LWSS) has demonstrated effectiveness of a brief psychosocial treatment in reducing depressive symptoms. Key variables associated with prevalence of PSD and possibly response to treatment are age, gender, stroke severity, depression severity, level of social support, depression history, antidepressant adherence, stroke hemisphere location, and serotonin transporter gene polymorphisms. Methods: Secondary analysis of a clinical trial wherein 101 clinically depressed patients with ischemic stroke were randomly assigned to receive a 9 session brief psychosocial/behavioral intervention plus antidepressant or usual care, including antidepressants. Hamilton Depression Rating Scale (HRS) score at 9 weeks measured response to treatment, with a score of ≤ 9 indicating remission from depressive symptoms. Measures included initial NIH Stroke Scale, Diagnostic Interview and Structured Hamilton, medication log, ENRICH Social Support Inventory, stroke hemisphere location from the hospital record, polymorphisms of the serotonin transporter (5HTT) gene by DNA obtained from blood or saliva. Statistical analyses used ANOVA models, post-treatment HDRS as outcome, treatment group and one of the factors described above as factors. Interaction between treatment group and the other factor tested whether that factor identified subgroups with differential treatment effect. Findings: Interven...
differing prevalence of depression post-stroke. The greater response in those carrying one or two alleles at the 5-HTTLPR polymorphism is interpreted consistently with treatment (p = 0.04). The treatment effect was strongest among those carrying 2-alleles. Conclusion: The LWSM intervention appears equally effective across a number of factors previously associated with depression and is consistent with the concept that depression in stroke patients and may influence recovery from acute stroke. Our hypothesis was that SLL may slow the cognitive recovery after the stroke by interfering with interaction between the frontal cortex and the posterior areas. Methods: We hereby present preliminary results of mild ischemic stroke and transient ischemic attack (TIA) patients from the TABASCO prospective consecutive cohort of 220 first-ever patients. All patients did not have cognitive decline before the event, had an MRI on admission along with cognitive assessment using the Montreal Cognitive Assessment (MoCA) test (a multilevel cognitive assessment battery ranging from 0 to 30 which is normal). The same battery was repeated 90 days after the index event. SLL was estimated semi-quantitavely using a simple 0 to 3 score for the white matter and basal ganglia. The total score ranged from 0 (no lesions) to 6 (confluent lesions in both white matter and basal ganglia). Results: 47 patients were available for assessment. On admission, the mean age was 65, median NIHSS was 2 and median MoCA was 24. The median of difference in MoCA between day 90 and baseline was 1 (range -4 to 7), while 29.8% of the patients had lower MoCA scores at day 90 vs. baseline. The median SLL was 1 (range 0 to 6). Patients with SLL were less educated (median 12 years of education vs. 16 for patients who had no SLL, p = 0.048). Spearman’s correlation showed an inverse correlation between the SLL and the magnitude of cognitive improvement in 90 days (r = 0.41, p = 0.004). When we controlled for age, gender, baseline modified Rankin scale, NIHSS and education the correlation remained significant (r = 0.42, p = 0.017). Conclusion: Our results suggest that patients with higher SLL may have poorer cognitive recovery after ischemic stroke. It is possible that SLL disrupts the white matter pathways necessary for cognitive recovery. Alternatively, patients with higher SLL may have lower cognitive “reserve” and are less capable of dealing with additional insults.

Outcomes From Cerebral Vasospasm Following Subarachnoid Hemorrhage at a Tertiary Care Center

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Background: Cerebral vasospasm following aneurysmal subarachnoid hemorrhage (SAH) has been associated with significant morbidity and mortality. The impact of vasospasm on clinical outcome in the advent of modern neurointerventional treatments has yet to be quantified. The goal of our study is to determine the effect of vasospasm on clinical outcomes in a tertiary care referral center with aggressive interventional therapy. Methods: A retrospective review of patient-concorded aneurysmal SAH presenting within 72 hours of symptom onset to the University of California, San Francisco was conducted from July 2003 to December 2007. Patients were also consented for clinical follow-up at 6 months. Patients received standard medical management in the neurointensive care unit for symptomatic vasospasm including nimodipine, volume resuscitation, and induced hyperventilation. Clinical vasospasm was determined by a treating neurointensivist based on clinical deficits and/or elevated velocities on transcranial Doppler. Patients underwent inpatient treatment with transluminal angioplasty and/or intraarterial verapamil in medically refractory cases. Clinical outcomes were measured using the modified Rankin scale score (mRS) at discharge and at 6-month follow-up. Univariate standard and multivariate logistic regression models were used to determine the effect of vasospasm on poor clinical outcomes defined as mRS ≥ 3. Results: During the study period, 546 patients were admitted to UCSF with SAH within 72 hours of symptom onset. Of these, 231 (42%) patients experienced symptomatic vasospasm. Patients with vasospasm were younger (51 ± 11 vs. 55 ± 14, p = 0.02), higher Hunt-Hess grade (2.7 vs. 3.0, p = 0.003), had higher SAPS II (13 ± 9 vs. 3 ± 3, p = 0.003), and higher stroke volume (90 ± 21 vs. 76 ± 17, p < 0.001). Other significant differences included increased vasospasm at the site of the aneurysm, increased vasospasm at the circle of Willis, and increased vasospasm in patients with vasospasm on poor clinical outcomes defined as mRS ≥ 3 (OR 3.2, 95% CI 1.9-5.7, p = 0.002). Conclusion: Cilostazol was shown to improve outcomes after SAH, but without any significant prevention of symptomatic vasospasm or infarction.

Cilostazol Improves Outcome After Subarachnoid Hemorrhage

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Background: Cilostazol, a selective inhibitor of phosphodiesterase 3, protects vessel endothelium and has shown efficacy in the prevention of ischemia-reperfusion injury. We evaluated the safety and efficacy of cilostazol use in patients with subarachnoid hemorrhage (SAH). Methods: We enrolled 100 SAH patients who meet the following criteria: neck clipping within 72 hours after onset, or better Hunt and Kosnik (HK) grade, and no serious cardiovascular complications. Patients were divided into 2 groups: cilostazol was externally administered for 2 weeks after surgery in the cilostazol group (n = 49). We primarily focused on the effect of cilostazol on the incidences of symptomatic vasospasm and cerebral infarction, and the modified Rankin scale (mRS) score on discharge. Results: Patients age, male/female ratio, mRS prior to icus, HK grade, Fisher group on CT scan, site of aneurysm were not different between the groups. Cilostazol use tended to decrease the incidence of symptomatic vasospasm (27.3% in control vs. 22.4% in cilostazol group, p = 0.183) and cerebral infarction (27.5% vs. 10.2%, p = 0.091), but without statistical significance. However, mRS was significantly improved on discharge (2.6 vs. 1.5, p = 0.041) in the cilostazol group. Age 65 and under (OR 8.0, [95% CI 2.6-24.7], p = 0.0003), Fisher grade 3 and under (OR 4.7, [95% CI 1.1-19.7], p = 0.037), HK grade 1 or 2 (OR 3.2, 95% CI 1.1-19.7, p = 0.038), and cilostazol use (OR 5.9, [95% CI 1.8-18.7], p = 0.0027) were independent predictors of good outcome (mRS ≤ 2) and better conclusion. Cilostazol was shown to improve outcomes after SAH, but without any significant prevention of symptomatic vasospasm or infarction.

Should Provision of Angioplasty for Cerebral Vasospasm Be a Mandatory Component for Hospitals Treating Patients With Subarachnoid Hemorrhage?

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Background/Objective: Primary angioplasty has been introduced for the treatment of symptomatic cerebral vasospasm in patients with subarachnoid hemorrhage. The data regarding the impact of angioplasty on patients outcomes is limited and hence its availability at hospitals treating patients with subarachnoid hemorrhage remains controversial. Methods: We analyzed the data from Nationwide Inpatient Sample (NIS) which is representative of all admissions in the United States from 2002-2006. We compared various outcomes between hospitals performing angioplasty with those not performing angioplasty for subarachnoid hemorrhage-related vasospasm. Results: vasospasm was not associated with poor outcome at hospital discharge, but was associated with poor outcome at 6-months, particularly in the setting of infarct on CT. 128

Impact of Systemic Inflammatory Response Syndrome on Vasospasm, Cerebral Infarction and Outcome After Subarachnoid Hemorrhage

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Introduction: Immune system activation after subarachnoid hemorrhage (SAH) can cause systemic inflammatory response syndrome (SIRS), leading to poor outcome. We investigated factors associated with development of SIRS after SAH and whether SIRS was associated with cerebral infarction, vasospasm and poor clinical outcome. Methods: Data from the CONSCIOUS-1 trial involving 413 patients who underwent clinical assessments, baseline and follow up angiography and computed tomography were used. SIRS was diagnosed by presence of at least two of four variables (hypothermia/fever, tachycardia, tachypnea and leukocytosis/leukopenia) within 4 days of admission. The relationship between variables of interest and developing SIRS, vasospasm (angiographic and clinical), cerebral infarction, vasospasm-related infarction and poor outcome were modeled with univariate and multivariate analysis. Results: Over 60% of patients developed SIRS. Many factors were correlated with SIRS in univariate analysis but only SIRS burden and duration of intensive care stay were independently associated with SIRS. SIRS burden was independently associated with poor clinical outcome, but not with vasospasm, cerebral infarction or vasospasm-related infarction. Whether the aneurysm was treated by clipping or coiling was not associated with SIRS. Conclusion: Increased inflammation, as measured by SIRS was associated with poor outcome after SAH, but the mechanism remains unclear. Previously reported associations of SIRS with clinical vasospasm could not be confirmed. Additionally, this study contradicts the notion surgical clipping is associated with SIRS, contributing to poor outcome.

Cilostazol Improves Outcome After Subarachnoid Hemorrhage

Methods: We hereby present preliminary results of Cilostazol use in patients with subarachnoid hemorrhage (SAH). In patients age, endovascular aneurysm obliteration, and disease severity. Vasospasm could not be confirmed. Additionally, this study contradicts the notion surgical clipping is associated with SIRS, contributing to poor outcome.

Conclusion: Cilostazol was shown to improve outcomes after SAH, but without any significant prevention of symptomatic vasospasm or infarction.
125,590 estimated patients with subarachnoid hemorrhage, 42% (n = 52816) were admitted to hospitals that perform angioplasty for cerebral vasospasm. A higher proportion of large volume, urban teaching hospitals were performing angioplasty (p < 0.0001). Hospitals performing angioplasty also had a significantly higher use of endovascular aneurysm obliteration (29% vs 20%, p < 0.001). This is consistent with recent guidelines of the American Heart Association and the American Stroke Association. The proportion of patients discharged home (58% versus 37%, p < 0.001) and lower in-hospital mortality (21% versus 27%, p < 0.001) in multivariate analysis, patients admitted to hospitals performing angioplasty had lower in-hospital mortality (odds ratio [OR] 0.85, 95% confidence interval [CI] 0.78-0.93) and higher rates of discharge to home (OR 1.6, 95%CI: 1.4-1.8).

Conclusion: Hospitals that perform vascular interventions had lower mortality and higher discharge rates to home. The analysis indirectly supports the mandatory availability of angioplasty as a therapeutic modality in hospitals treating patients with subarachnoid hemorrhage.

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Radiation Exposure From Computed Tomography in Patients With Subarachnoid Hemorrhage
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Introduction: Subjects admitted to the hospital with an acute subarachnoid hemorrhage (SAH) undergo frequent CT-scans for neurological deterioration and also for “follow-up”. With the availability of portable CT scanners, the use of CT scanning is likely to increase. We conducted this study to quantify the degree of radiation exposure from CT scans in patients with SAH.

Objectives and Methods: We conducted a retrospective study of all subjects with an acute aneurysmal SAH (ASA) or angiographically negative SAH (NSAH) admitted to the University of Illinois Medical Center over a 12-month period. All CT scans performed during hospitalization were tabulated. We obtained the dose length product (DLP) from the scanner generated dose report and calculated the effective dose (ED). When added to the ED from diagnostic and therapeutic angiographic procedures that these patients underwent, the total radiation exposure might be quite substantial.

Results: We studied 107 subjects (mean age 58 ± 13.6 yrs., 73 female, 92 aneurysmal SAH). Patients with NSAH underwent a significantly higher number of CT scans compared to patients with NSAH (14.7 ± 7.3 vs 6.7 ± 0.003). There was also a significant correlation between the number of CT scans and ICU length of stay (Pearson correlation 0.860, p < 0.001). The total ED/subject ranged from 2-210 mSv (median 31 mSv) and on multivariate regression significantly correlated only with ICU length of stay (R2 0.570, p < 0.001) but not with the cause of SAH.

Conclusion: The median radiation exposure from CT scans in subjects admitted with SAH is quite high and approximately 10 times the annual ED from natural background radiation of about 0.3 mSv. The duration of stay in the ICU is a significant predictor of a higher number of CT scans and a higher ED. When added to the ED from diagnostic and therapeutic angiographic procedures that these subjects undergo, the total radiation exposure might be quite substantial.

Non-invasive Cerebrovascular Monitoring
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Background: Monitoring intracranial pressure (ICP) and cerebral vasculature yields essential information for diagnosis/management of traumatic brain injury (TBI) and stroke. Knowing ICP and cerebrovascular autoregulatory capacity enables assessment/tracking of patient state for conditions such as subarachnoid hemorrhage and intracranial hypertension. However, current methodologies for ICP measurement are invasive, therefore only applied to severe cases. Without knowledge of ICP, assessments of cerebral perfusion pressure (CPP) are also inaccurate, thus compromising assessment of autoregulation. Objective: We propose and validate an approach - using algorithms based on mathematical models of applicable physiology - for real-time continuous (beat-by-beat) estimates of ICP, cerebrovascular resistance R and compliance C, from minimally- or non-invasive measurements of arterial blood pressure (ABP) and cerebral blood flow (CBF) velocity waveform. Methods: We use a reduced-order model of cerebrovascular dynamics, with ICP, R and C as the only parameters to be estimated from clinical measurements. The algorithm processes waveforms of ABP and CBF velocity (via transcranial Doppler) to derive estimates of these three parameters for each cardiac cycle. Dynamic variations in estimates of R and C, with a simultaneous generation of corresponding CPP estimates (- ABP - estimated ICP), allow characterization of autoregulation. Results: We compared our ICP estimates with invasive measurements of ICP, obtained in 10 patients with TBI at Addenbrookes Hospital, Cambridge, UK. Our ICP estimates tracked true ICP closely over a range of variations, including sharp transients associated with on- and off-patient brain waves. Root-mean-square normalized error (RMSNE) over all beats was <10% in 5 subjects, and <15% in 8 subjects. Appropriately variations of R and C estimates in response to abrupt changes in CPP estimate served to mark autoregulation. Conclusion: Our model-based continuous non-invasive estimates track invasive ICP measurements closely, and allow assessment of autoregulation. The simple enough to run in real-time and display to bed-side monitors. Further testing is underway to validate and refine the approach.

Defining the Extent of Irreversible Brain Ischemia Using Perfusion Computed Tomography
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Background: Computed tomography perfusion (CTP) imaging in acute stroke may allow assessment of irreversibly damaged and potentially salvageable brain tissue. However, the perfusion thresholds for intact core and penumbra require further validation before CTP can be used routinely in patient selection for thrombolysis. We hypothesized that perfusion thresholds using CTP could accurately identify the infarct core as defined by the acute diffusion-MRI lesion. In particular, we were interested in comparing the accuracy of relative perfusion thresholds derived from normal hemisphere values to the commonly used absolute cerebral blood volume (CBV) threshold.

Method: Imaging data from 57 ischemic stroke patients with concurrent CTP and MRI between 3-8 hours after symptom onset (<1 hour between scans) were assessed. Furthermore, 23 patients were treated with rt-PA and showed successful reperfusion on follow-up MRI 2 days post symptom onset and were included as a sub-group. Acute diffusion weighted imaging (DWI) maps were co-registered with the following acute CTP maps: CBV, cerebral blood flow (CBF), mean transit time (MTT), and time to peak of the residual function (Tmax). A pixel-based Receiver Operator Characteristic (ROC) curve analysis was undertaken to calculate sensitivity and specificity for a broad range of thresholds for each CTP map, and an area under the curve (AUC) for predicting infarct core was calculated for each threshold. For CBV we used absolute as well as relative thresholds. For MTT and CBV we used relative thresholds alone, and for Tmax we used delay thresholds (in seconds compared to normal hemisphere). Pixels with CBV > 6 ml/100g (corresponding to vessels) were
eliminated from the analysis. Analyses were repeated following noise elimination using ‘clustering’ (Perfusion lesions of <5 or <10 mm were excluded from analysis), or using separate perfusion thresholds for gray and white matter. **Results:** Setting a minimum pixel cluster volume improved accuracy for all parameters. Applying different relative thresholds for grey and white matter did not improve lesion detection. **Conclusion:** All relative CTP thresholds were more accurate than the commonly used absolute CBV threshold for identifying infarct core, with a CBF of 40% being the most accurate across all techniques. Application of this finding should increase the diagnostic accuracy of CTP scans in acute stroke and potentially enable treatment decisions based on tissue viability rather than time.

A summary of the strongest predictors of infarct by measure

<table>
<thead>
<tr>
<th>Best</th>
<th>Absolute</th>
<th>Mean Normal</th>
<th>AUC: No Noise</th>
<th>AUC: Grey/White Separation</th>
<th>AUC: Pixel Cluster 5mm</th>
<th>AUC: Pixel Cluster 10mm</th>
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<tbody>
<tr>
<td>method</td>
<td>Value</td>
<td>Hemisphere</td>
<td>Value</td>
<td>Elimination</td>
<td>Separation</td>
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<tr>
<td>Relative CBV</td>
<td>12.6 ± 4.32</td>
<td>31.5 ± 10.8</td>
<td>0.736</td>
<td>0.700</td>
<td>0.752</td>
<td>0.774</td>
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<td>40%</td>
<td>ml/100g/min</td>
<td>ml/100g/min</td>
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<td>Relative MTT</td>
<td>7.74 ± 0.74</td>
<td>5.16 ± 0.74</td>
<td>0.686</td>
<td>0.676</td>
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<td>100%</td>
<td>Seconds</td>
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<td>Tmax delay</td>
<td>&lt; 0.2</td>
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<td></td>
<td>2.2 ± 0.17</td>
<td>0.17</td>
<td>0.695</td>
<td>0.687</td>
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<tr>
<td>Relative CBV</td>
<td>1.35 ± 0.43</td>
<td>2.7 ± 0.97</td>
<td>0.651</td>
<td>0.614</td>
<td>0.664</td>
<td>0.706</td>
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<tr>
<td>50%</td>
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<tr>
<td>Relative CBV</td>
<td>2 ml/100g</td>
<td>2.7 ± 0.97</td>
<td>0.651</td>
<td>0.610</td>
<td>0.688</td>
<td>0.708</td>
</tr>
</tbody>
</table>

**CTA Source Images in the Era of Fast, Volume CT Scanning: Are They Still “DWI” Weighted?**

Ranliang Hu, Albert Yoo, Reza Hakimelahi, Michael Lev, Raul Nogueira, Joshua Hirsch, Ramon O Gonzalez, Pamela Schaefer; Massachusetts General Hosp, Boston, MA

**Purpose:** Studies performed on 4 to 16 slice scanners suggest that CTA source image (CTA-SI) hypodensity delineates infarct core. The advent of faster, multi-detector(CTD) CT raises the question as to whether CTA-SI lesion volumes, acquired under non-steady state conditions still correspond to infarct core. We sought to compare 64-slice CTA-SI to DWI lesion volumes, to assess the role of CTA-SI in evaluating infarct size and outcome. **Methods:** We reviewed consecutive cases of acute anterior circulation stroke that had CTA on a 64-slice scanner and MRI within 9 hours of onset, with CTA to MRI interval <2 hours. Lesions on CTA-SI and DWI were segmented with semi-automated software (Analyze 9, Mayo Clinic) by a research assistant and corrected by two neuroradiologists. Modified Rankin Scale(mRS) at 3-6 months was obtained from a stroke database. **Results:** Forty-nine patients with mean age of 71(26-94) were included. Mean time from stroke onset to CTA was 238 min(45-420) and from CTA to MRI was 36 min(7-119). CTA-SI significantly correlated with DWI lesion volumes(2= 0.763, p<0.001). However, there was considerable variability among smaller lesions(<50 cm3); in 17/32, CTA-SI underestimated DWI lesion volume by >50%. Thirty of 31 proximal occlusions(CA, M1) exhibited large CTA-SI to DWI volume difference(>20 cm3), while only 2/16 more distal occlusions had a large difference(p <0.001). Relative perfusion deficits, likely to be associated with ischemic neuronal dysfunction, were defined as mean transit time >10 seconds. Multiple regression was used to clarify the relationship between ischemic volume, laterality, and NIHSS scores. **Results:** Among 111 patients, mean age was 66.1 years old, 44.1% were female, and mean total presenting NIHSS was 10.5. Laterality was balanced with 58 left- and 53 right-sided infarcts. Mean time interval between last know well and DWI was 480 minutes in left and 486 minutes in right brain infarcts. Mean ischemic volume was 75.90 cm3 in left and 88.49 cm3 in right hemispheric ischemic stroke. However, mean total NIHSS was larger with left brain strokes, 12.0 vs. 8.9. For individual subcomponents of the NIHSS, volume of ischemic lesion correlated most closely with visual, gaze, and dysphasia deficits and most weakly with ataxia, aphasia, and neglect. Left hemisphere ischemic stroke predicted higher scores of total NIHSS and components of questions, commands, right arm and leg weakness, and language. Right hemisphere ischemic stroke predicted higher scores of left arm and leg weakness and neglect. **Conclusion:** Larger perfusion defects contribute to higher scores on total and most components of the NIHSS. However, lesion laterality independently contributes substantially to half the subcomponent scores, with greater influence of left than right brain side. These findings indicate that imaging-deficit correlations will be improved by atlasing of lesions, taking into account side in addition to size.

**Table: Relationship between lesion laterality and NIHSS**

<table>
<thead>
<tr>
<th>Mean scores of NIHSS(left, right)</th>
<th>Standardized coefficients (between ischemic volume and NIHSS)*</th>
<th>Standardized coefficients (between lesion laterality and NIHSS)***</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Level of consciousness</td>
<td>0.26 (.02)</td>
<td>0.25 (.06)</td>
</tr>
<tr>
<td>2. LC Questions</td>
<td>0.17 (.03)</td>
<td>0.19 (.05)</td>
</tr>
<tr>
<td>3. LC Commands</td>
<td>0.17 (.03)</td>
<td>0.19 (.05)</td>
</tr>
<tr>
<td>4. Gaze</td>
<td>0.43 (.047)</td>
<td>0.45 (.067)</td>
</tr>
<tr>
<td>5. Visual</td>
<td>0.69 (0.79)</td>
<td>0.70 (0.8)</td>
</tr>
<tr>
<td>6. Facial palsy</td>
<td>1.26 (1.3)</td>
<td>1.3 (1.5)</td>
</tr>
<tr>
<td>7. Motor arm, left</td>
<td>0.95 (0.9)</td>
<td>1.00 (1.0)</td>
</tr>
<tr>
<td>8. Motor arm, right</td>
<td>1.19 (1.2)</td>
<td>1.20 (1.2)</td>
</tr>
<tr>
<td>9. Motor leg, left</td>
<td>1.19 (1.2)</td>
<td>1.20 (1.2)</td>
</tr>
<tr>
<td>10. Motor leg, right</td>
<td>1.19 (1.2)</td>
<td>1.20 (1.2)</td>
</tr>
<tr>
<td>11. Limb asymmetry</td>
<td>0.07 (0.09)</td>
<td>0.08 (0.10)</td>
</tr>
<tr>
<td>12. Sensory</td>
<td>0.23 (0.27)</td>
<td>0.24 (0.28)</td>
</tr>
<tr>
<td>13. Language</td>
<td>1.00 (1.0)</td>
<td>1.00 (1.0)</td>
</tr>
<tr>
<td>14. Dysphasia</td>
<td>0.94 (0.79)</td>
<td>0.96 (0.81)</td>
</tr>
<tr>
<td>15. Neglect</td>
<td>0.21 (0.29)</td>
<td>0.22 (0.30)</td>
</tr>
<tr>
<td>Total</td>
<td>12.85 (1.9)</td>
<td>13.04 (2.0)</td>
</tr>
</tbody>
</table>

*LOC level of consciousness; **negative value denote left hemisphere dominant and positive value denote right hemisphere dominant. ***p<0.05

**Predicting Clinical Outcome in Comatose Cardiac Arrest Patients Using Early CT**

Ona Wu, Leonardo M Batista, Fabricio O Lima, Karen L Furie, David M Greer; Massachusetts General Hosp, Boston, MA

**Background:** The early assessment of the likelihood of recovery in comatose cardiac arrest survivors remains difficult. We assessed the hypothesis that early changes in non-contrast CT (N CCT) are predictive of poor outcome in patients who are comatose after resuscitation post-cardiac arrest. **Methods:** We retrospectively analyzed patient datasets acquired as part of a single-center prospective observational study of 500 patients with non-traumatic coma. Within this cohort, 200 patients were comatose due to cardiac arrest. Of these, 162 were included in our analysis. Patients were included if they had no evidence of hemorrhage or previous stroke, or if there was poor imaging quality, leaving a total of 149 patients. Some patients received repeat imaging resulting in a total of 179 imaging studies performed within 3 days of cardiac arrest. Using ICBM probabilistic atlases, CT were semi-automatically segmented into the following regions: white matter, caudate nucleus, putamen, thalamus, cerebellum, frontal lobe, insula, occipital lobe, parietal lobe and temporal lobe. Median Hausdorff units (HU) were measured in each region as well as the whole brain, limited between 15 and 100 to exclude CSF and artifacts. Differences in patients with poor outcomes based on 6-month modified Rankin Scale (mRS) score >3 were compared (two-tailed Wilcoxon-test) with patients with good outcome (mRS <3). **Results:** All values are reported as mean±SD.
Evolution of Lacunar Stroke: Leukoariosis or Lacune? 

Steven M McClendon, Rita Bhatia, Sebastian Koch; Univ Miami, Miami, FL

Background: Lacunes are defined pathologically as CSF filled cavities less than 15mm in diameter. In patients with lacunar stroke DWI may overestimate eventual infarct size and the evolution of acute MRI lesions on follow up imaging has only recently been described. In addition some lacunar strokes may not progress to lacunes i.e. will not develop a cavity and remain indistinguishable from white matter lesions. Our objective is to examine eventual infarct size and incidence of cavity formation in patients presenting with acute lacunar strokes. Methods: Patients with lacunar strokes, defined as a subcortical DWI lesion < 25mm in diameter on the distribution of a penetrating artery, with follow up MR or CT at least one month from stroke onset, were identified from a prospective registry. Initial DWI and T2 or FLAIR lesion size as well as follow up T2 or FLAIR and CT lesion size were measured. Follow up images were assessed for the formation of a cavity, defined as the appearance of a CSF equivalent lesion on MR or CT, within the original area of acute DWI abnormality. Results: MR images were analyzed in 64 subjects. Follow up MR and CT were obtained in 34 and 59 patients respectively. Mean age was 63±14 years, 31 were men, 59 (92%) had hypertension and 30(47%) had diabetes. Initial DWI lesion size was 14±6mm and 13±5mm on T2 FLAIR (p=0.01). Follow up FLAIR/T2 lesion size was 8±3mm (p=0.01, compared to initial DWI size), obtained on average 20±17 months after symptom onset. Average reduction in lesion size was 36%. Lesion size on follow up CT was 6±4mm, obtained 19±17months after initial scanning. A cavity was noted on 23/34 (69%) MR and 46/59 (78%) CT images, with the remainder of the lesions appearing identical to non-specific white matter changes. In a multi variable model we found no predictors of cavity formation by MR or CT. Conclusion: Acute DWI significantly overestimates final infarct size and initial lesions larger than 15mm should not exclude a diagnosis of lacunar stroke. A third of lacunar strokes do not develop a cavity and remain indistinguishable from non-specific white matter changes. These findings contribute to the understanding of the etiology of white matter lesions. Imaging studies assessing infarct load based on cystic lesions only may underestimate total disease load.

Echocardiographical Classification of Mobile PLAques of Carotid Artery, Corresponding to Histology 

Kazuyuki Nagatsuma; National Cardiovascular Cntr, Osaka, Japan

Background: Recently we found some carotid artery plaques showing localized movements unlike floating thrombus in ultrasound moving images. We reported that this finding is dangerous especially when it is symptomatic. The aim of this study is to classify the mobile plaques, including floating plaques, and to figure out their pathogenesis by comparing them with histopathological findings and following the course of moving parts. Methods and Subjects: The plaque movements on ultrasound B-mode images were carefully observed and recorded as video files. We classified the mobile parts into 4 types. First are localized movements at the surface of plaque (jellyfish sign). Second are localized movements of fluctuation in the plaques (liquefaction sign). Lastly are localized movements in the ulcers (moving thrombus in ulcer). Last are plaques showing movements at protruding parts, called floating thrombus. Forty-three patients with 45 mobile plaques were analyzed. Results and Conclusion: Mobile plaques showed 23 jellyfish signs, 17 liquefaction signs, 15 moving thrombus in ulcers and 4 floating thrombus. Twelve plaques had double signs and 2 plaques had triple signs simultaneously. The interventional therapies (16 CEA and 7 stenting) were performed on 24 lesions including 8 asymptomatic lesions. Three symptomatic lesions and 18 asymptomatic lesions were treated by medical therapy. Out of 16 plaques that received CEA, we compared the moving types and histopathological findings. Seven of 8 removed plaques with jellyfish sign revealed previous fibrous cap disruption. Five plaques with 9 liquefaction sign had intraplaque hemorrhage. Four of 6 moving thrombus in ulcer showed at mixed large thrombus and atheromatosus gruel with ulceration in the ulcer. None of floating thrombus was seen histologically, because free thrombus was easily gone in preparation for slides. We followed 18 plaques with the medical treatments. Nine plaques showed disappearance of the localized movements, 3 plaques with jellyfish sign became ulcer formation and 4 plaques were unchanged. Two plaques received interventions: one with large ulcer and another with atheromatosus gruel. The ulceration in the ulcer and the plaque rupture. Moving thrombus in ulcer may indicate a large amount of fragile and unorganized thrombus and may act as an embolic source.

Brain Tissue Ischemic Transitions During Permanent Middle Cerebral Artery Occlusion in Rats 

Edwin M Memoto, Univ of New Mexico, Albuquerque, NM; Lesley M Foley, T. K Hitchens, Brent Barbe, Chien Ho; Carnegie Mellon Univ, Pittsburgh, PA

Background: A basic premise for neuroprotection in acute stroke is the presence of salvageable tissue i.e. ischemic penumbra, at therapeutic intervention. Clinical trials assessing the penumbra by qualitative perfusion/diffusion mismatch are contested by: 1) studies showing that ADC does not only identify tissue destined for infarction; and 2) penumbral distribution heterogeneity precludes visual estimation of mismatch volumes. We examined the utility of dual parameter voxel analysis using quantitative ADC by DTI and cerebral blood flow (CBF) by continuous arterial spin labeling (ASL) in tracking brain tissue ischemic transitions during permanent suture left middle cerebral artery occlusion (pMCAO) in rats. Methods: Eleven rats were studied in a 4.7-Tesla, 40 cm bore Bruker AVANCE MR system. Continuous ASL was used to quantify CBF and DTI for quantitative ADC. Nine rats were scanned prestroke and for 4 hrs after pMCAO. Two were recovered and rescanend at 7, 14 and 21 days. CBFIADC voxel analyses were done on both left (ipsilateral) and right (contralateral) hemispheres ([Fig.). ADC and CBF thresholds were based on the hemispheric mean ± 2SD used to define the compartments (COM). The voxels in each COM were transferred to the T1 MR image (Fig.): 1 = Normal; 2 = Ischemic Penumbra; 3 = Ischemic core; 4 = Hyperemic core; and 5 = Hyperperfused Infarction (tissue dissolution); 6 = Hyperemic Infarction. Results: A progressive migration of voxels into the penumbra (COM 2) and the ischemic core (COM 3) was observed. By 4 hrs most of the penumbra had migrated into the core and hyperemic core (COM 5) may not progress to lacunes i.e. will not develop a cavity and remain indistinguishable from white matter lesions. Our objective is to examine eventual infarct size and incidence of cavity formation in patients presenting with acute lacunar strokes. Methods: Patients with lacunar strokes, defined as a subcortical DWI lesion < 25mm in diameter on the distribution of a penetrating artery, with follow up MR or CT at least one month from stroke onset, were identified from a prospective registry. Initial DWI and T2 or FLAIR lesion size as well as follow up T2 or FLAIR and CT lesion size were measured. Follow up images were assessed for the formation of a cavity, defined as the appearance of a CSF equivalent lesion on MR or CT, within the original area of acute DWI abnormality. Results: MR images were analyzed in 64 subjects. Follow up MR and CT were obtained in 34 and 59 patients respectively. Mean age was 63±14 years, 31 were men, 59 (92%) had hypertension and 30(47%) had diabetes. Initial DWI lesion size was 14±6mm and 13±5mm on T2 FLAIR (p=0.01). Follow up FLAIR/T2 lesion size was 8±3mm (p=0.01, compared to initial DWI size), obtained on average 20±17 months after symptom onset. Average reduction in lesion size was 36%. Lesion size on follow up CT was 6±4mm, obtained 19±17months after initial scanning. A cavity was noted on 23/34 (69%) MR and 46/59 (78%) CT images, with the remainder of the lesions appearing identical to non-specific white matter changes. In a multi variable model we found no predictors of cavity formation by MR or CT. Conclusion: Acute DWI significantly overestimates final infarct size and initial lesions larger than 15mm should not exclude a diagnosis of lacunar stroke. A third of lacunar strokes do not develop a cavity and remain indistinguishable from non-specific white matter changes. These findings contribute to the understanding of the etiology of white matter lesions. Imaging studies assessing infarct load based on cystic lesions only may underestimate total disease load.
3 and 4. Color coded maps show pronounced heterogeneity. Rats studied at 7, 14 and 21 days after pMCAO showed migration of voxels into COM 5 consistent with tissue dissolution. Summation of voxels in each COM allows estimates of tissue volume transitions in time. **Conclusions:** Dual parameter voxel analysis with quantitatively defined thresholds for CBF and ADC may be used to define ischemic tissue transitions in acute stroke to provide accurate estimates of quantitative parenchymal and core tissue volumes. Fig. CBF vs ADC voxel analysis of left MCAO in a rat before and hourly for up to four hrs. COM are numbered and color coded.

**Background:** Multiple genome-wide association studies, including our own, have discovered that multiple common variants previously shown to associate with AF, significantly associate to cardioembolic stroke with per allele OR ranging from 1.22 to 1.52 (rs2200733: OR 1.58, P = 5.8 × 10-12; rs7193343: OR 1.27, P = 6.1 × 10-4; tHcy: OR 1.22, P = 0.0021). Combining the risks from 3 markers using a multiplicative risk model is supported by the data, the upper ten-percentile of risk for cardiogenic stroke ranged from 0.35 to 3.5 fold. Interestingly, rs2200733 also showed significant association to ischemic stroke after subtracting patients with known cardiogenic stroke. It also showed that extra monitoring in patients with higher genetic risk substantially improves the association to cryptogenic stroke and large vessel stroke, although with lower magnitude of risk, to define patients who may benefit from extra cardiac monitoring for intermittent AF. Clinical utility studies are needed to show that extra monitoring in patients with higher genetic risk substantially improves the diagnostic sensitivity of cardiogenic stroke.

**Methods:** Three SNPs were used to genotype 5 large case-control studies of ischemic stroke patients, totalling 6235 cases and 39,888 controls. They included two SNPs which represent 2 independent association signals on 4q25, rs2200733 and rs1003346, and rs7193343 on 16q22.

**Results:** rs2200733 and rs7193343 showed highly significant association to ischemic stroke with per allele OR of 1.26 ± 0.01, and 1.13 ± 0.01, respectively. All three SNPs showed significantly greater association to cardioembolic stroke with per allele OR ranging from 1.22 to 1.52 (rs2200733: OR = 1.52, P = 5.8 × 10-12; rs1003346: OR = 1.27, P = 6.1 × 10-4; rs7193343: OR = 1.22, P = 0.0021). Combining the risks from 3 markers using a multiplicative risk model is supported by the data, the upper ten-percentile of risk for cardiogenic stroke ranged from 0.35 to 3.5 fold. Interestingly, rs2200733 also showed significant association to ischemic stroke after subtracting patients with known cardiogenic stroke. It also showed association to cryptogenic stroke and large vessel stroke, although with lower magnitude of risk, to define patients who may benefit from extra cardiac monitoring for intermittent AF. Clinical utility studies are needed to show that extra monitoring in patients with higher genetic risk substantially improves the diagnostic sensitivity of cardiogenic stroke.

**Multiple Biomarkers and Risk of Clinical and Subclinical Vascular Brain Injury:** The Framingham Offspring Study

**Background:** White matter hyperintensities (WMH) on MRI are highly prevalent and part of the spectrum of small vessel disease (SVD). The pathophysiology of WMH may be similar to the mechanism of SVD in other organs, particularly the kidney. Renal dysfunction has been linked to an increase in prevalence and severity of WMH, but its association has not been explored in patients with lacunar stroke. **Methods:** Participants: In the ongoing multicenter Secondary Prevention of Small Subcortical Stroke (SP3S) study were included in this cross-sectional analysis. SP3S includes participants with MRI-defined lacunar stroke. The first 600 participants as well as the 369 participants enrolled in the Proteiniuria and Albuminuria in Small Subcortical Strokes substudy were included. Estimated GFR (eGFR) and spot urine albumin/creatinine ratio (ACR) were collected, and WMH were scored blinded to renal function using the Age-Related White Matter Changes (ARWMC) and Fazekas scales. Patients with eGFR < 40 ml/min/1.73m ² are ineligible for SP3S. Continuous and categorical variables were compared across groups using ANOVA and Chi-square tests respectively. **Results:** Older age, females, and hypertension (HTN) were associated with decreased eGFR, while diabetes (DM), HTN, and CAD were associated with increased ACR. Decreased eGFR, but not increased ACR, was associated with increased WMH, and the relationship remained after adjusting for age, smoking, DM, HTN, and hyperlipidemia in multivariate analysis.

**Conclusions:** In this well-characterized cohort with lacunar stroke, WMH are associated with renal dysfunction. These findings support the concept that cerebral SVD shares a similar pathological mechanism to renal SVD. Patients with renal dysfunction may benefit from targeted interventions for stroke prevention and cognitive decline. This association warrants further investigation in prospective studies.

**Objectives:** To explore the association of multiple biomarkers with incident stroke and TIA, and with subclinical measures of brain injury in a large community-based sample. **Background:** Several biomarkers have been individually associated to vascular brain injury. However, no prior study has explored the association between a panel of biomarkers representing distinct biological pathways and incidence of stroke/TIA or prevalence of subclinical brain disease. **Methods:** Two approaches were used. For 3127 Framingham Offspring (59 = 10 yrs, 54%F) free of stroke, we assessed the association between a panel of 8 biomarkers measured at the sixth examination (1995–96) and incident stroke/TIA occurring prior to December 2007, using Cox regression. In a subset of 1901 participants (58 = 10 yrs, 54%F), with brain MRI, we used linear and logistic regression to examine the association between the same biomarker panel and cross-sectional MRI measures of total cerebral brain volume (TCBV, which is expressed as a percent of intracranial volume), covert brain infarcts (CBI), and large white matter hyperintensity volume (z-LWMHV, defined as age-group specific z-score). The biomarkers evaluated represented the following biological pathways previously associated with cardiovascular risk: inflammation (C-reactive protein [CRP]), homostasis (D-dimer and plasminogen activator inhibitor-1), neuroendocrine activity (aldosterone-to renin ratio, B-type [BNP] and N-terminal pro-atrial natriuretic peptides) and endothelial function [fomocytobase (tHcy) and urinary albumin/creatinine ratio (UACR)]. **Result:** During a median follow-up of 9.2 years, 130 participants experienced incident stroke/TIA. In multivariable analyses adjusted for traditional stroke risk factors, the biomarker panel was associated with incident stroke/TIA and cross-sectional TCBV (p < 0.05 for both), but not with cross-sectional CBI or z-LWMHV (p > 0.05). We used backwards elimination to identify a parsimonious set of biomarkers associated to outcomes of interest: higher BNP (harzard ratio [HR] 1.39/SD, p = 0.002), and UACR (HR 1.31/SD, p = 0.042) were associated with increased risk of incident stroke/TIA; elevated CRP (β = 0.20/SD, p = 0.008), D-dimer (β = 0.18/SD, p = 0.041), tHcy (β = 0.21/SD, p = 0.005), and UACR (β = 0.15/SD, p = 0.042) were associated with lower TCBV. **Conclusion:** Our investigation of a large, middle-aged, community-based sample free of stroke at baseline identified distinct biomarkers that were associated with risk of incident stroke/TIA (UACR and BNP) and with concurrently determined brain atrophy (UACR, CRP, tHcy and D-dimer). Such biomarker approaches can help elucidate the pathophysiology of clinical and subclinical brain injury. Their role in risk stratification for preventing brain injury warrants further investigation.
The Relationship of Oral Glucose Tolerance Test With All-cause and Stroke Mortality in a General Urban Japanese Cohort: The Suita Study

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Introduction: Recent studies have shown that diabetes mellitus (DM) is a risk factor for cardiovascular disease (CVD) and strokes. However, few prospective studies have examined the relationship between impaired glucose tolerance (IGT) and ischemic stroke with CVD in general populations. We assessed the hypothesis that there would be a significant relationship of IGT and insulin resistance with all-cause, CVD, and stroke mortality in a general urban Japanese cohort. Methods: We studied 6,467 Japanese individuals (mean age 55.8 years) who had no stroke or cardiovascular disease at baseline (45% men and 55% women) and followed up for an average of 13 years. The glucose categories were defined as follows: DM (fasting plasma glucose levels [FPG] > 126 mg/dL), 2-hour post-load glucose levels [2h-PG] > 200 mg/dL, or receiving medication for DM; IGT (FPG < 126 mg/dL and 2h-PG 140 to 189 mg/dL; impaired fasting glucose [IFG] FPG 100 to 125 mg/dL, and 2h-PG < 140 mg/dL; and normal glucose tolerance (NGT) FPG < 100 mg/dL and 2h-PG < 140 mg/dL). The multivariable HRs for all-cause mortality in women with IGT were 1.57 (1.11-2.21) and 2.21 (1.13-4.31). The multivariable HRs for stroke mortality in men and women, with NGT as a risk factor for all-cause and cardiovascular mortality in women. Postprandial hyperglycemia and hyperinsulinemia, and smoking and drinking status at baseline. Results: In 59,979 person-years of follow-up, we documented 676 deaths, including 153 due to CVD (50 strokes, 67 ischemic heart diseases) and 260 due to cancers. Compared with NGT, men and women with DM had a risk of all-cause mortality (HR1.74 [95% CI 1.35 to 2.23), CVD (HR = 2.10 and 95% CI 1.25 to 3.54), stroke (HR = 3.46 and 95% CI 1.41 to 8.01), cerebral infarction (HR = 1.67 and 95% CI 2.27 to 17.08), and cancer (HR = 1.94 and 2.62) mortality. Compared with NGT, the multivariable HR (95% CI) of all-cause and cardiovascular mortality in men with IGT were 1.57 (1.11-2.21) and 2.21 (1.13-4.31). The multivariable HR (95% CI) of CVD and stroke mortality in all participants with pre-diabetes (IFG or IGT) were 1.93 (1.16-3.23) and 3.04 (1.33-6.96), respectively, compared with NGT. Postprandial hyperglycemia (FPG > 140 mg/dL) in women had higher risks of all-cause mortality (HR = 1.79 [95% CI 1.02 to 3.14]) and CVD (HR = 1.40 [95% CI 1.01-1.94]) with NGT. Compared with HOMA-IR < 1.5, women with insulin resistance (HOMA-IR > 2.0) and more) had higher risks of all-cause mortality, CVD, stroke, ischemic heart disease, and cancer mortality. Conclusions: DM is a risk factor for all-cause, CVD, and stroke mortality in men and women, while IGT is a risk factor for all-cause and cardiovascular mortality in women. Postprandial hyperglycemia and insulin resistance may be predictors for all-cause and CVD mortality in women.

Association of Five Variants in the LRP, NOS3, SCNNA1 and MMP12 Genes With Ischemic Stroke

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Background: Environmental and genetic factors contribute to the development of complex diseases such as ischemic stroke (IS). In order to identify stroke susceptibility variants, we aimed to study single nucleotide polymorphisms (SNPs), which had been associated with several complex diseases involving IS such as inflammation, coagulation, hypertension, coronary heart disease, angiogenesis, lipid metabolism or diabetes. Methods: A two phases case-control study was designed which consisted in genotyping 210 SNPs (by SNPlex technology at the Spanish National Center for Genotyping): 1) in 267 IS patients with occlusion in the middle cerebral or basilar artery and 263 controls, free of neurosis, coagulation, hypotension, coronary heart disease, angiogenesis, lipid metabolism or diabetes. Comparison between the RRE-90 and ABCD 2 scores was performed using receiver operating characteristic (ROC) curves. We defined subsequent stroke as a clinical deterioration associated with new infarction spatially distinct from the index lesion. Results: There were 255 patients with "TIA with infarction" diagnosed by DWI within 24 hours of symptom onset. Subsequent stroke developed in 15 patients (5.9%) within 7 days. The area under the ROC curve (AUC) was 0.83 (95%CI, 0.76-0.91) for the RRE-90 score. The sensitivity and specificity of RRE-90 score >2 for predicting 7-day stroke risk were 87% and 63% respectively. The AUC for the ABCD2 score was 0.56 (95%CI,0.44-0.68). The p value for comparison between the RRE-90 and ABCD2 scores was >0.01. Conclusion: The RRE-90 score performs well at predicting 7-day risk of subsequent stroke in TIA patients with infarction on DWI. This suggests that RRE-90 score can be adapted to the general population. An easy tool to assess stroke risk in TIA with infarction could allow to identify those with imminent risk of developing recurrent stroke. Accurate identification of high-risk patients may facilitate early intervention with targeted stroke prevention strategies.

Diabetes Continues to Be a Risk Factor for Stroke in the Young in a Large Bi-Racial Population

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Background We previously reported an increased incidence of stroke in the population with diabetes, especially for those younger than 55 in both blacks and whites. With the rising epidemic of diabetes in the last decade, we are revisiting the impact of diabetes on stroke incidence in the same region of 1.3 million people, 10 years later. Methods Ischemic strokes among residents of the 5-county Greater Cincinnati/Northern Kentucky region were ascertained and verified by a study physician at all 16 area hospitals using ICD-9 codes 430 to 436 for initial identification. First ischemic strokes in patients aged 20 years and older were included in this analysis. Population age-group specific rates of diabetes were extracted from the 2005-2006 NHANES database, and local population numbers for calculation of incidence rate denominators were extracted from the US Census Bureau website. Rates were adjusted by gender and gender and age, as appropriate, to the 2000 US population. Estimation of the 95% confidence intervals for the rates was made assuming a Poisson distribution, and the delta method was used for the risk ratio. Results Of the 2179 ischemic strokes in black or white patients, 1673 were first strokes, and 544 (13.1%) had a history of diabetes. The rates of stroke and associated 95% confidence intervals, by age group and overall, for the black and white population by diabetes status, adjusted to the 2000 US population, are shown in the Table. It can be seen that within the white and black population, diabetes exerts overall a 3- to 4-fold greater risk of stroke, compared with those without diabetes; however, the risk varies by age. Stroke patients with diabetes were more likely to be black (27% vs. 18%), and also had a greater burden of other co-morbidities such as hypertension (89% vs. 70%) and high cholesterol (52% vs. 31%). Although stroke patients with diabetes were less likely to be smokers (20% vs. 28%), they still had increased stroke risk. Conclusions: Those with diabetes are at increased risk for stroke at all ages, regardless of race. The excess burden continues to be enhanced in the younger (< age 55) population. However, there is an increased rate of stroke for all ages for those with diabetes except for blacks more than 75 years of age. These trends are similar to those observed in the previous study periods during the 1990s, but the significance of these findings continues to increase given the epidemic of increasing diabetes and metabolic syndrome throughout the US and the world.
Endovascular Repair of the Ruptured Anterior Communication Artery Complex and Wide Neck Aneurysms: A Single Center Experience

Yahia M Lodi, John Cullen, Jonathan Naysan, Veena Yashaswi, Ravi Patel, Adham Kamel, Amar Swankar, Eric Deshaies, Tara Ramachandran, Julius-Gene Latorre; Updated Med Univ, Syracuse, NY

Background: Due to the presence a complex anatomic and a hemodynamic profile at the anterior communication artery (AComA), especially when both A2 segments originate from a single A1 segment of the anterior cerebral artery (ACA), a successful surgical or endovascular repair of AComA aneurysm may not always guarantee good outcome. Surgical clipping not only pose difficulties but also may induce spasm to the ACA leading to stroke despite a successful procedure. Therefore, more aneurysms in AComA are being treated with endovascular technique including complex and wide neck aneurysms. Objectives: To report our experiences of endovascular repair of ruptured AComA aneurysms including wide neck and complex aneurysms. Methods: From a prospectively maintained aneurysm database consecutive patients with the diagnosis of ruptured AComA aneurysms who underwent endovascular coiling from July 2006 to July 2008 were enrolled. Patients demographics including Hunt and Hess (H&H) grade, Fisher scale, procedural related complication and outcome were collected. 30 days outcome was measured using Glasgow Outcome Scale (GOS). Results: 52 patients with mean age of 52 ± 14 years old were diagnosed with AComA ruptured aneurysms among which 51/52 (96%) were symptomatic and 1 (2%) were asymptomatic. Aneurysm repair of their aneurysm. Only one patient required surgical clipping who achieved GOS 3 in 30 days. H&H V was present in 4%, IV in 21.5%, III in 31.3%, II in 29.4% and I in 9.8%. Procedure related morbidity was observed in 3/52 without mortality or permanent disability. Intraoperative rupture of aneurysm without any clinical manifestations (dilated pupils, hypertension or bradycardia) was observed in two wide neck cases which resolved with subsequent coils placement. First case was a 74 years old woman with H&H II and Fisher 4 who achieved GOS 3 in 5 days. The second case was a 46 years old woman with H&H 2 and Fisher 4 who achieved GOS 4 in 30 days. Right middle cerebral artery occlusion was observed in a 56 years old woman with H&H III and Fisher 4 who presented with H&H II and Fisher 4. The MCA was completely revascularized using 2 mg TPA and MERCI retrieval device. Post procedure examination was non-focal and achieved GOS 5 in 30 days. Complete (100%) and near complete (>/=95%) obliteration of aneurysms was observed in 49/51 (96%) and subtotal (<95%) in 2 cases. 30 days neurological outcome was observed in 70.9% of cases (GOS 5 in 49%, GOS 4 in 21.4%), disability in 15.6% (GOS 3 in 15.6%) and poor outcome in 13.7% (GOS 1 dead in 13.7%). Poor outcome and disabilities was associated with high H&H grade. Conclusions: Endovascular coiling to repair ruptured AComA could be offered in most of the cases including those with wide neck and complex in nature. The most common but rare challenges are intraoperative rupture of aneurysm and thromboembolic event, which could be successfully treated with good outcome.

Distribution and Risk Factors of Site and Size of Unruptured Intracranial Aneurysms

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Introduction: The distribution and risk factors of unruptured intracranial aneurysm (UIA) provides information on the etiology and magnitude of prognostic risk for hemorrhage. Hypothesis: The hypothesis was that the location and size of development of a UIA varies by patient risk factors. Methods: Patients with a UIA were prospectively entered at 61 centers for the NIH-sponsored International Study of Unruptured Intracranial Aneurysms. 4060 patients were entered into the prospective cohort between 1991-1998. 5852 aneurysms were found using central radiological review of the cerebral angiograms. Measures of location, diameter in three dimensions, and morphologic characteristics were obtained. Results: The largest aneurysms (>12 mm) were most commonly located on the cavernous, internal carotid and middle cerebral, and basilar arteries. Small aneurysms, particularly 3mm or less, were observed on anterior cerebral distribution. Using univariate comparisons and logistic regression models of UIA status, the age were the most consistent risk factors for aneurysm distribution. Family history and hypertension were not related to location. Within locations there was considerable variation of risk factors for aneurysm size. Family history and age were significant predictors of internal carotid location, smoking for anterior cerebral, hypertension, family history and gender for anterior communicating, and family history and gender and hypertension for middle cerebral. No factors predicted basilar termination or basilar trunk. Conclusions: These prospectively collected data demonstrate the differential role of patient characteristics, behavioral and medical factors for the location and size of formation of intracranial aneurysms. There factors need to be considered in modeling aneurysm site, size and growth.

Safety and Feasibility of Elective Endovascular Coiling of Very Small (2-7 mm) Unruptured Cerebral Aneurysms (EOSA Study): A Multicenter Experience Analysis

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Background: International Study of Unruptured Intracranial Aneurysms (ISUA) reported the rupture rate of smaller aneurysms less than 7 mm to be dependent on the location, with 2.5% rupture rate over 5 years for patients with unruptured aneurysm. The ISUA results are controversial with many reports showing the vast number of ruptured aneurysm sizes that are encountered in clinical practice is less than 7 mm. Treatment of smaller aneurysms is debatable. However, advances in endovascular coiling made it feasible and safe to coil smaller aneurysm. The goal of this study is to evaluate the safety of coiling aneurysms ≤ 7 mm in maximum diameter. Methods: Data was collected retrospectively and prospectively by seven medical centers with active neurointerventional service in United States. Inclusion criteria included un-ruptured cerebral aneurysm ≤ 7 mm treated electively using endovascular coiling. Data including basic demographics, location, and all procedural complication with all procedural and clinical/radiological follow-up was collected and analyzed. The main study outcome presented is the symptomatic procedural ischemic and hemorrhagic cerebral complication defined as neurological deficit lasting more than 24 hours. Results: A total 485 unruptured aneurysms were treated in 445 patients with mean age of 54 ± 11 years. Seventy-six percent of the patients were females and 72% of the study population was white. Hypertension was present in 54.6%, diabetes in 10.3%, and smoking in 37.7% of patients. The study aneurysms mean maximum diameter was 4.8 ± 1.4 mm (range of 1.5 to 7.7 mm). There were 378 (77.3%) asymptomatic aneurysm while 77 (17.2%) were symptomatic. The overall rate of thrombo-embolic complications was 3.14% (14/445) while asymptomatic hemorrhage in 0.67% (3/445). The overall rate of thrombo-embolic complications was 3.14% (14/445) while asymptomatic hemorrhage in 0.67% (3/445) and symptomatic hemorrhage in 0.88% (4/445) was asymptomatic hemorrhage in 0.67% (3/445). There were 20 patients with no procedure related mortality. Conclusion: Advancement in the endovascular intervention has made possible for safe coiling of small aneurysm (≤ 7 mm) with symptomatic hemorrhagic and ischemic complications of 1% and no procedure related mortality in this series. Further studies are required to evaluate the natural history of rupture for small unruptured aneurysms compared with endovascular coiling.

Hemodynamic Factors Contributing to Intracranial Aneurysm Initiation in a Rabbit Model

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Objective: To characterize in detail the critical hemodynamic conditions associated with aneurysm initiation, we applied a novel hemodynamics-histology co-mapping technique on a rabbit aneurysm model. Methods: Eight rabbits received bilateral common carotid artery ligation to induce compensatory flow increase in basilar artery (BA) and subsequent basilar terminal (BT) aneurysm, while the rabbits underwent sham operations. Real-time topographic images of the basilar bifurcation and blood flow velocity measured at the BA provided the input for computational fluid dynamics (CFD) analysis. Basilar bifurcation tissues were harvested 5 days post-surgery for histological sectioning. A plane presenting IEL loss (marker for aneurysmal change) was mapped onto the corresponding plane in the 3D computational geometry, and the events of internal elastic lamina (IEL) loss was co-registered with the local wall shear stress (WSS) and wall shear stress gradient (WSSG). Results: IEL damaged segments were found to segregate from intact segments and confined in the perilapical regions of accelerating flow with high WSS and positive WSSG. Thresholds of WSS and WSSG for the onset of IEL loss were found. Furthermore, the severity of aneurysmal change was characterized against the degree of hemodynamic insult. An aneurysm development score incorporating IEL loss, media thinning and bulging was found to increase with the hemodynamic score, which accounts for both the laminar length exposed to above-threshold WSS and WSSG and the integrated magnitudes of the above-threshold stresses. Conclusion: The combination of high WSS and positive WSSG above certain thresholds can be identified as aneurysmogenic hemodynamics.
Relationship Between Gene Variants and Smoking in the Familial Intracranial Aneurysm (FIA) Study

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Background: Smoking is the most important environmental risk factor for IA and may modify the influence of genetic polymorphisms that have been associated with increased risk of IA.

Methods: Caucasian subjects with intracranial aneurysms were identified from families with multiple affected individuals with IA (one subject per family) as well as from prior population-based studies of ruptured intracranial aneurysm from Greater Cincinnati and Australia. Unrelated Caucasian controls were selected from population-based studies in the Greater Cincinnati region and Australia. Detailed quality assessment of SNPs and samples were performed. Genotyping was performed using the Affymetrix 6.0 array as well as the TaqMan (fluorogenic 5 nuclease) assay for the few SNPs not included in the Affy 6.0 array. Multiple logistic regression modeling was performed to examine the independent effects of smoking and the five most significant and replicated SNPs reported by Gunel and colleagues (Nature Genetics - 2008) from chromosomal regions 9p21.3, 8q11.2-12.1 and 2q33.1. Results: The final sample consisted of IA cases (710) and controls (594). We replicated allelic association with IA for rs1333040 on chromosome 9 (risk allele frequency (RAF) cases 0.63/controls 0.58, p = 0.0001, OR = 1.23) and for rs 10958409 on chromosome 8 (RAF cases 0.20/controls 0.12, p = 0.0001, OR = 1.87) but not for the SNP rs9298506 on chromosome 8 (p > 0.05) or either SNP on chromosome 2 (p > 0.05). In the model focusing on rs1333040 (chr. 9), pack-years of smoking (p < 0.0001) and rs1333040 (p ≤ 0.008) were significantly associated with IA. In the model focusing on rs10958409 (chr. 8), pack-years (<0.0001) and the rs10958409 (p < 0.0001) were significantly associated with IA. The relationship between smoking and the respective SNPs is demonstrated in Table 1.

Table 1: Relationship Between Smoking (Smokers/Non-smokers) and rs1333040, rs10958409 and Risk of IA

<table>
<thead>
<tr>
<th>SNP</th>
<th>Genotype</th>
<th>Smoking Group</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs1333040</td>
<td>TT</td>
<td>smokers</td>
<td>5.25</td>
<td>3.01–9.16</td>
</tr>
<tr>
<td></td>
<td>TT</td>
<td>nonsmokers</td>
<td>1.69</td>
<td>0.94–3.05</td>
</tr>
<tr>
<td>Chr. 8p21.3</td>
<td>T</td>
<td>smokers</td>
<td>3.45</td>
<td>2.01–5.93</td>
</tr>
<tr>
<td></td>
<td>T</td>
<td>nonsmokers</td>
<td>1.13</td>
<td>0.64–2.02</td>
</tr>
<tr>
<td>rs10958409</td>
<td>C</td>
<td>smokers</td>
<td>3.98</td>
<td>2.16–7.32</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>nonsmokers</td>
<td>1.00</td>
<td>Referent Group</td>
</tr>
<tr>
<td>Chr. 8q11.12–12.1</td>
<td>A</td>
<td>smokers</td>
<td>10.82</td>
<td>3.13–37.36</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>nonsmokers</td>
<td>0.46</td>
<td>0.05–4.27</td>
</tr>
<tr>
<td>rs10958409</td>
<td>A</td>
<td>smokers</td>
<td>4.87</td>
<td>3.39–6.99</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>nonsmokers</td>
<td>1.54</td>
<td>1.00–2.38</td>
</tr>
<tr>
<td>rs1333040</td>
<td>G</td>
<td>smokers</td>
<td>2.82</td>
<td>2.11–3.75</td>
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<tr>
<td></td>
<td>G</td>
<td>nonsmokers</td>
<td>1.00</td>
<td>Referent Group</td>
</tr>
</tbody>
</table>

Conclusions: We replicated the relationship of SNPs on chromosome 8 and 9 with an increased risk of IA but failed to replicate findings on chromosome 2. The risk of IA is multiplied in smokers who had the risk allele rs10958409 on chromosome 8 although smoking was the dominant risk factor in both models. These findings emphasize the importance of smoking cessation, particularly in individuals who are genetically susceptible to IA.

Stent-assisted Repair of the Ruptured Intracranial Wide Neck Aneurysm: A Single Center Experience


Background: Stent-assisted coiling of wide neck intracranial aneurysm requires therapeutic dose of antplatelets to prevent stent thrombosis. Stent-assisted coiling of the ruptured intracranial aneurysms also requires a loading of both aspirin and plavix to prevent stent thrombosis. Object: To report any potential complication associated with the loading dose of both aspirin and plavix prior to the stent-assisted coiling of ruptured wide neck intracranial aneurysm.

Methods: Consecutive patients who underwent stent-assisted coiling for ruptured wide neck intracranial aneurysm were enrolled from 2005 to 2009. Patients demographics (e.g. Hunt & Hess grade, Fished scale, use of ventriculostomy catheter, location and size of aneurysm were collected. Any complication such as rupture of aneurysm or hemorrhage related to ventriculostomy or systemic hemodynamic event. There were two episodes of stent thrombosis; one was an asymptomatic partial stent thrombosis which developed during stent-assisted coiling procedure and resolved spontaneously, the other was symptomatic which required intra-arterial administration of thrombolytic. There was no mortality and good outcome (GSS 5 & 4) was observed in 85% of patient. Conclusion: stent-assisted coiling of ruptured intracranial wide neck aneurysm. Therefore, antplatelets should not be withheld prior to a stent-assisted coiling of ruptured wide neck aneurysm. Further study requires.

Preinterventional Clopidogrel Response Variability for Coil Embolization of Intracranial Aneurysms: Clinical Implication

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Background & Purpose. Thrombembolism is one of the most serious complications in coil embolization for intracranial aneurysms, and antplatelet premedication may reduce this complication. However, individual variation exists in the efficacy of clopidogrel. This study sought to elucidate the clinical implication of preinterventional clopidogrel response variability in patients who undergo coil embolization for intracranial aneurysms. Material & Methods. Clopidogrel premedication was given to 186 consecutive patients with 208 aneurysms who underwent elective coil embolization, and the response to the premedication was measured by a point-of-care antplatelet function test (VerifyNow assay). Patients were stratified into four quartiles according the test results, and their correlation with occurrence of perioperative complications was analyzed. The contribution of a variety of variables to the high residual platelet reactivity was also tested. Results. In this cohort, rates of thromboembolic events and all adverse events were 7.5% and 9.1%, respectively. The quartiles of the P2Y12 reaction unit (PRU) showed significant tendency of thromboembolic events (p = 0.013) and all procedure-related adverse events (p = 0.009) while those of isothrombin receptor activating peptide channel (BASE) and percentage inhibition did not. Thromboembolic events occurred in 17.0% and procedure-related adverse events in 21.3% of the fourth quartile patients. The female gender was the only significant factor related to the fourth quartile of PRU in the multiple logistic regression analysis (p = 0.014). Conclusion. Procedure-related thromboembolic events occurred more frequently in the upper-quartile PRU patients, especially in the fourth quartile. More aggressive antplatelet therapy may be required in these patients.

The Neurovascular Dysfunction Induced by Angiotensin II Requires Activation of EP1 Receptors by Cyclooxygenase 1-Derived Prostaglandin E2

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Hypertension (HTN) disrupts vital homeostatic mechanisms regulating the cerebral circulation and is a leading cause of stroke and dementia. Angiotensin II (AngII) is a major factor in the pathogenesis of HTN and associated cerebrovascular dysfunction (Cell Metab 7:476, 2008). Prostaglandin E2 (PGE2) derived from cyclooxygenase enzymes (COX), contributes to AngII-induced HTN by acting on EP1 receptors (EP1R) (JCI 117:249E, 2007), but it is unclear whether EP1R play a role in the deleterious cerebrovascular effects of AngII. Therefore, we investigated whether EP1R are also involved in the cerebrovascular dysregulation induced by AngII. Cerebral blood flow (CBF) was monitored by a laser-Doppler probe in anesthetized (urethane-chloralose) C57BL/6 mice AngII (0.25, equipped with a cranial window, AngII (250 mg/kg/min; i.v.) elevated mean arterial pressure (MAP) from 70 to 94 mmHg (p < 0.05) and attenuated (p < 0.05) the CBF increase in somatosensory cortex induced by whisker stimulation (WS; -36 ± 7%), or topical application of the endothelium-dependent vasodilator acetylcholine (ACh; -48 ± 8%). Although not adenosinergic (p > 0.05), the EP1R inhibitor ZK939849 (100 nM; neocorticall superfusion) did not alter baseline CBF responses (p > 0.05) or the MAP increase (p > 0.05), but prevented the effects of AngII on the CBF response to WS and ACh (p < 0.05 from vehicle), AngII
unveil a previously unrecognized role of EP1R in the cerebrovascular dysfunction induced by AngII. Neocortical superfusion with PE2 (1μM) reinstated the AngII-induced cerebrovascular dysfunction after COX1 inhibition (p = 0.05 from before SC560). The increase in reactive oxygen species (ROS) induced by Angl (n = 150; ±23%), assessed with hydroethidine, was not observed after COX1 or EP1R inhibition and in EP1R-null mice (p = 0.05). However, after COX1 inhibition, exogenous PE2G, which had no effect on ROS by itself, reinstated the increase in ROS induced by Angl (p = 0.05 from before SC560). COX1 immunoreactivity was observed exclusively in microglia, and EP1R immunoreactivity in endothelial cells and neurons. The vascular dysregulation induced by Angl requires COX1-derived PE2G acting on EP1R. PE2G and EP1R exert this effect by modulating the ROS production induced by Angl. The localization of COX1 in microglia and of EP1R in cerebral arteries suggests that PE2G originates from microglia and acts on vascular EP1R to enable Angll-induced vascular oxidative stress. These observations unveil a previously unrecognized role of EP1R in the cerebrovascular dysfunction induced by Ang and suggest that microglia are capable of modulating cerebrovascular responses through COX1-derived PE2G. Supported by HL81974 and HL86571.

Table 1. Causes of Death

<table>
<thead>
<tr>
<th>Known IA</th>
<th>Known IA</th>
<th>No History</th>
<th>No History</th>
<th>All subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 55 Yrs (n=549)</td>
<td>&gt; 55 Yrs (n=524)</td>
<td>Yrs (n=1120)</td>
<td>Yrs (n=601)</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>3</td>
<td>7</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Other Causes</td>
<td>4</td>
<td>5</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>5</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Respiratory</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Other neurological</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Cardiac</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Ruptured IA</td>
<td>3</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ICH</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Ruptured AAA</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Totals</td>
<td>13</td>
<td>31</td>
<td>8</td>
<td>36</td>
</tr>
</tbody>
</table>

Mortality and Causes of Death in the Familial Intracranial Aneurysm (FIA) Study

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Background: Studies have described higher mortality for patients with intracranial aneurysm (IA) in a high-risk cohort of families with a history of IA, we sought to determine if mortality among IA subjects ("affected") is related to aneurismal rupture or to other causes, compared with family members without an IA at study entry ("unaffected"). Methods: Subjects in this study were enrolled in the IA protocol. The study was approved by the IRBs/EOs at each of the study sites. Participants, or their proxies, were contacted on the yearly anniversary of their study entry (± 30 days) and the subjects current status was obtained (alive or deceased). If the subject was reported to be deceased, the date and cause of death was recorded. Available medical records and/or death certificates were used to verify the cause of death. Results: Of the 2,794 subjects enrolled, 1,073 had a diagnosis of IA at the time of study entry, and 1,721 subjects had a diagnosis of IA at the time of study entry. There were 8,495 person-years of follow-up, with the overall mean follow-up time of 3.04 ± 1.73 years. There was no significant difference (p = 0.12) in the length of follow-up between the affected IA (3.11 ± 1.68 years) and unaffected (3.00 ± 1.76) groups. Age at study entry for affected (54.8 ± 11.7 years) was significantly (p < 0.0001) older than for unaffected (48.6 ± 25.9). A Cox proportional hazards model was utilized taking into account age, race, gender, affected status, rupture status, smoking history, and hypertension. After adjusting for age, the overall mortality rate for affecteds was not significantly different than unaffecteds. However, in affected subjects under the age of 55, the risk of death was 4.3 times that of unaffected subjects in the same age group (95% CI 1.58-11.7, p = 0.004). The annual mortality rate was 13.2 per 1000 for affecteds and 8.5 per 1000 for unaffecteds. The reported causes of deaths for each group are listed in Table 1. Conclusion: All but one of the deaths attributed to ruptured IA occurred shortly after study entry due to the initial rupture, the overall causes of death in this high-risk cohort during follow-up were more commonly unrelated to their aneurysms. None of the 1721 family members without known IA at study onset died from a subsequent ruptured IA.

Statin Cessation After Ischemic Stroke

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Background: A few retrospective studies mostly in coronary artery disease patients and one small randomized trial in ischemic stroke patients have suggested that statin discontinuation after ischemic stroke may promote cardiovascular events and death. We aimed to validate this association in a large, prospective cohort of ischemic stroke patients. Methods: Patients with ischemic stroke discharged from Kaiser Permanente Northern California (KPN) hospitals from 1/2004 through 12/2006 were followed for a 1 year period for recurrent ischemic strokes. All patients had participated in a randomized trial of standardized discharge order sets in acute stroke. KPN pharmacies monitored statin and other medication use at different time points. Statis were considered discontinued if prescriptions were filled at initial discharge but not at 6 months. Patients not taking statins at discharge and those who died or left the KPN insurance plan before 6 months were excluded from analysis. Logistic regression models were used to evaluate demographic and clinical variables as potential predictors of statin cessation, while Cox proportional hazard models were used to assess for independent predictors of recurrent ischemic stroke and the composite outcome of ischemic stroke, MI, or death. Factors significantly associated (p < 0.10) with the outcome in univariate analysis were inserted into the final multivariate model. Results: Among 3147 patients with ischemic stroke initially discharged on a statin (mean age 71, 49% women), 814 (26%) had discontinued statins within 6 months. Multivariate predictors of statin cessation were male sex (OR 1.29, 95% CI 1.09-1.54, p = 0.004) and lack of prior ischemic stroke (OR 1.34, 95% CI 1.06-1.70, p = 0.01). Statin discontinuation independently predicted the composite outcome recurrent ischemic stroke, MI, or death (HR 1.45, 95% CI 1.13-1.87, p = 0.004), but not recurrent ischemic stroke in isolation (p = 0.42). However, events may not have been attributable to statin discontinuation because patients who stopped statins were also less likely to take antihypertensive medication at 6 months (OR 0.21, 95% CI 0.16-0.26, p = 0.001), to be on warfarin (if indicated) at 6 months (OR 0.50, 95% CI 0.38-0.67, p < 0.001), to have controlled outpatient blood pressures (OR 0.57, 95% CI 0.48-0.69, p < 0.001), and to have outpatient follow-up (OR 0.77, 95% CI 0.68-0.88, p < 0.001). Conclusions: In our cohort, statin cessation was associated with an increased risk of major cardiovascular events. However, this association may not be causal given that statin cessation was linked with adherence to other secondary prevention measures and may also reflect inherently less favorable prognoses.

Stroke Incidence as the Major Contributor to Racial and Regional Disparities in Stroke Mortality: The RESons for Geographic and Racial Differences in Stroke (REGARDS) Study

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Background: The racial and regional disparities in stroke mortality are well documented. The black (B) to white (W) stroke mortality ratio at age 50 is over 3, with a decreasing magnitude with increasing age. Stroke mortality is 20% higher in the stroke belt and 40% higher in the stroke buckle. It is unknown if these disparities are attributable to differences in stroke incidence or case fatality. Methods: REGARDS is a national, population-based, longitudinal study of B and W participants aged ≥ 45 years old, with over sampling from stroke belt states. Between January 2003 and October 2007, 30,239 participants were enrolled. Participants are contacted by telephone every 6 months for self- or proxy-reported hospitalizations for potential stroke; medical records were retrieved and adjudicated. For this analysis, 2,979 participants with a physician-diagnosed stroke/TA at baseline were excluded, reducing the cohort to 26,580. Stroke incidence rates (with 95% confidence limits) were calculated as the number of stroke events divided by the person-years at risk. B/W stroke incidence rate ratios and stroke incidence rate ratios contrasting the stroke belt and buckle to the rest of the nation were computed, and these incidence ratios were compared to similar stroke mortality ratios calculated from the comprised mortality files from CDC. Results: There were 299 incident strokes and 779 deaths over 86,535 person-years of follow-up. Overall stroke incidence rates of 337.7/100,000 (95% CI: 301.5 - 378.3), with higher incidence in blacks, the stroke belt/buckle, men and older participants. The magnitude and pattern of racial and regional disparities in incidence rates were generally similar to the patterns of disparities in mortality (see figures). Discussion: These are the first national data describing racial and regional differences in stroke incidence and confirm and expand prior excess stroke mortality among blacks and in the stroke belt region of the US. The similarity of the disparities in stroke incidence and stroke mortality suggest that incidence (rather than case fatality) is the prime contributor to these immense disparities in stroke mortality.
Declining Stroke Recurrence Rates in Secondary Prevention Trials Over the Past 50 Years and Consequences for Current Trial Design

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Background: It is widely supposed, but not well demonstrated, that the advances in post-stroke management have reduced the rate of recurrent stroke and cardiovascular events. Consequently, it would be more arduous to demonstrate the effectiveness of newer stroke prevention therapies. Methods: Systematic literature review identified all randomized controlled trials (RCTs) of medical therapy for secondary stroke prevention published from 1950 to 2009. RCTs in atrial fibrillation (AF) were excluded. From the control arm of each trial, we extracted data for baseline characteristics and annual rates for recurrent stroke, fatal stroke, and composite of stroke, myocardial infarction, and vascular death and analyzed trends with descriptive and multivariate statistics. Results: 55 RCTs were identified, enrolling 65,617 patients in the control arms. Since 1990s, individual risk factors showing marked declines included: average SBP/DBP at enrollment (from 156/91 mm Hg to 144/63 mm Hg), and frequency of smoking (from 44% to 26%) and AF (from 3.4% to 1.4%). Use of antithrombotics rose from 34% to 93%. Data for BP and lipid lowering agents were too scarce to allow adequate analyses. Annual event rates declined substantially for all endpoints, including recurrent stroke (correlation coefficient \( r = 0.29 \), \( p = 0.002 \)), fatal stroke (\( r = -0.52, p = 0.003 \)), and major vascular events (\( r = -0.42, p = 0.003 \)). For recurrent stroke, annual rates fell from 8.71% in trials launched in the 1960s, through 6.37% in 1970s, 5.43% in 1980s, 4.04% in 1990s, to 4.98% in 2000s. Multivariate analysis identified increase in antithrombotics use and decline in enrollment of patients with AF as the strongest contributors to the decline in vascular events. The sample size needed for a secondary prevention trial with 2 years of follow-up to have 80% power and 5% alpha error to detect a 20% relative risk reduction of a new medical intervention increased from 3930 in 1960s through 6130 in 1980s to 6843 in 2000s.

Conclusion: In RCTs over the last 5 decades, control of stroke risk factors has improved, use of effective concomitant therapies increased, and rate of recurrent vascular events has declined substantially. Considerably larger sample sizes are now needed to demonstrate incremental improvements in medical secondary prevention.
Very Low Cerebral Blood Volume Predicts Hemorrhagic Transformation Better Than Diffusion Lesion Volume in Acute Ischemic Stroke

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Background and Purpose: Preliminary analysis of EPITHET trial data suggested that very low cerebral blood volume (VLCBV) strongly predicts hemorrhagic transformation (HT). We tested this hypothesis using pooled imaging data from the EPITHET and DEFUSE studies. Methods: VLCBV was defined as <2.5th percentile of CVB distribution in the non-stroke hemisphere. The volume of VLCBV was calculated within the acute DWI ischemic lesion and was also visually rated as present or absent blinded to calculated volume and HT outcome. Vascular occlusion was assessed on MRA as none, partial or complete and recanalization defined as ≥1 grade improvement. HT was graded using ECASS criteria. Results: The pooled EPITHET and DEFUSE data had 146 patients with baseline DWI and /WI imaging of whom 41 had hemorrhagic infarctions (HI) and 22 had parenchymal hematoma (PH). Mean VLCBV volume was higher in patients with PH compared to those with HI (p=0.006) and no PH (p=0.001) and strongly predicted PH in ROC analysis (AUC 0.82). VLCBV remained a predictor of PH in multivariate logistic regression after accounting for established clinical predictors (age, baseline stroke severity, diabetes, baseline glucose, atrial fibrillation, baseline blood pressure, p<0.001). DWI lesion volume also predicted PH independent of clinical factors (p<0.001) but when combined with VLCBV in multivariate analysis, VLCBV remained significant (0.04) but DWI did not (p=0.22). In EPITHET (50% treated with tPA), a cut-point of VLCBV>2ml had 100% sensitivity for PH and, in patients treated with tPA, was associated with a 43% increase in PH (95% CI 22-66% increase in likelihood ratio LR=16, p<0.003). Using DEFUSE (100% treated with tPA) as an independent cohort, a cut-point of VLCBV>2ml had 89% sensitivity, 71% specificity for PH, LR 11.6, p<0.001. In the pooled dataset, VLCBV>2ml had 95% sensitivity, 65% specificity. Visual inspection had 88% agreement with VLCBV>2ml (kappa 0.76) and comparable sensitivity (95%) and specificity (60%) for PH. Specificity of VLCBV>2ml and visual VLCBV increased to 69% in tPA treated patients. Recanalization (assessed in 84 patients) occurred in 10 of 11 PH cases and was an independent predictor of PH in multivariate logistic regression with VLCBV (p<0.01). Conclusions: VLCBV predicts PH better than DWI lesion volume and recanalization is a key co-factor in the pathogenesis of HT. VLCBV>2ml has been validated as having high sensitivity and specificity in an independent dataset. Visual inspection of VLCBV has comparable accuracy. Assessment of VLCBV can contribute to clinical risk-benefit decisions regarding thrombolysis.
The Upper Time Limit of DWI Positive - FLAIR Negative MRI in Witnessed-onset Acute Ischemic Strokes is Less Than 6 hours: Implications for the Design of Wake-up Stroke Treatment Trials

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Purpose: Because Fluid-Attenuated Inversion Recovery (FLAIR) signal intensity changes over time, this parameter has been proposed as a “tissue clock” when the precise time of symptom onset is unknown. We investigated patients with witnessed stroke onset to define the upper time limit of DWI positive- FLAIR negative (DPFN) MRI for acute ischemic strokes. Defining this time window may help identify more patients who are eligible for thrombolytic therapy. Methods: 85 patients were included based on 1) acute ischemic stroke, 2) last seen normal (LSN) time — time first seen with symptoms, 3) pre-treatment MRI within 24 hours of LSN, and 4) left anterior circulation stroke. Right hemisphere strokes were excluded because the risk of anastomosis leads to incorrect tissue onset times. Lacunar strokes and lesions with hemorrhagic transformation were also excluded. Readers blinded to time of MRI from LSN, scored FLAIR hyperintensity corresponding to DWI-bright lesions as none, subtle or bright hyperintensity, based on the region of brightest signal intensity on FLAIR. Results: Ninety-five percent of DPFN MRIs were within 0 to 6 hours from witnessed symptom onset (p < 0.001). Negative FLAIR was not seen beyond 6.8 hours. Scans with early, bright FLAIR hyperintensity had confounding factors where acute within subacute or chronic lesions were seen. As readers were blinded to time, the ADC scan was not used to determine if the FLAIR hyperintensity within a DWI lesion was indeed acute. When non-acute lesions were excluded, bright FLAIR hyperintensity was seen at 9.3 hours. Subtle hyperintensity was seen as early as 1.3 hours and many FLAIR scans still appeared subtle at 24 hours. Conclusion: The sensitivity of FLAIR hyperintensity as a marker for ischemic stroke onset is not precise. Findings of FLAIR hyperintensity seen as early as 1.3 hours challenges the notion that patients with 3 hours from symptom onset have negative FLAIR. Subtle FLAIR hyperintensity may have been categorized as negative in prior studies. However, DPFN is a highly sensitive test to recognize patients who are < 6 hours on the tissue clock. Using DPFN as a conservative marker for time range can help enroll eligible patients in wake-up stroke treatment trials.
Risk of Early Carotid Endarterectomy for Symptomatic Carotid Stenosis

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Objectives: Pooled analyses of the randomized clinical trials of carotid endarterectomy for symptomatic disease have unequivocally showed that the benefits of revascularization are maximized if surgery is done within 2 weeks of the TIA or stroke. However, surgeons have traditionally been reluctant to operate within this time window because of a perceived increased risk of perioperative complications. For this reason, there is paucity of data outside the randomized clinical trials regarding the safety of “early” CEA. Methods: We conducted a retrospective analysis of all CEA performed in the Department of Neurosurgery between January 2004 and May 2009. Patients were divided into three groups: 1) asymptomatic patients; 2) symptomatic patients operated after 2 weeks of their TIA or stroke; and 3) symptomatic patients operated within 2 weeks of their TIA or stroke. Similarly to the randomized CEA trials, our primary end points were any stroke and death occurring within 30 days after the surgery. Secondary end points were myocardial infarction (MI) and TIA occurring within the first month after surgery. Results: A total of 534 CEA’s were performed during the study period. Thirty-seven patients were discharged home from the hospital and did not have further follow-up visits. Of the remaining 497 surgeries, 262 (53%) were performed in asymptomatic patients. Of the 235 CEAs performed in symptomatic patients, 137 (58%) were performed within 2 weeks of TIA or stroke. Stroke and death within 30 days occurred in 4/262 (1.5%) in asymptomatic patients, 0/102 (0.0%) in symptomatic patients operated after 2 weeks and in 4/437 (2.9%) operated within 2 weeks. The rate of perioperative TIAs was 0.4%, 3.1% and 1.5%, respectively in the three groups. There were 3 symptomatic MIs in this series, 2 occurred in asymptomatic patients and one occurred in a patient operated early. Overall, combined perioperative and secondary end points occurred in 2.7% of asymptomatic patients, 3.1% of patients operated on after 2 weeks of the presenting event, and 5.8% of patients operated on within two weeks. Conclusions: Although the periprocedural risk of TIA’s, stroke, death and MI is slightly higher in symptomatic patients operated early, CEA can be done with an acceptable risk in properly selected symptomatic patients within 2 weeks of their TIA or stroke.

Outcomes of Carotid Stenting and Predictors of Stroke in a Large, Multi-center Post-Market Clinical Trial

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Background: Carotid artery stenting (CAS) is an option for revascularization in subjects at high risk for endarterectomy. Previous studies have reported improved results over time with CAS. Previous analyses have also identified certain predictors of perioperative stroke such as symptomatic status and increased age. Objective: To provide updated information on the largest, multi-center, neurologically-audited, and independently adjudicated post-market clinical trial in the United States. Results: 5,297 evaluable patients have been enrolled at 186 US and Canada study sites in the CAPTURE 2 post-market clinical trial between March 2006 and January 2009. 1,166 patients (22%) were age 80 or above at study entry. The mean age in the octogenarian group was 83.9, compared to 69.0 years in the younger group. Octogenarian patients were more likely to have cardiac arrhythmia (28.3% vs. 19.0%) and less likely to have diabetes (29.4% vs. 38.5%) or current smoking status (7.3% vs. 27.5%) compared to non-octogenarians. Other risk factors are summarized as follows:

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Non-octogenarians</th>
<th>Octogenarians</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>88.9%</td>
<td>90.2%</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>18.0%</td>
<td>19.3%</td>
</tr>
<tr>
<td>Prior MI</td>
<td>26.8%</td>
<td>23.5%</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>73.1%</td>
<td>73.2%</td>
</tr>
<tr>
<td>COPD</td>
<td>24.2%</td>
<td>15.6%</td>
</tr>
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</table>

Symptomatic status was present in 15.0% and 14.0% of patients above and below age 80, respectively. Thirty day outcomes for the endpoint stroke/death in important subgroups are as follows:

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Non-octogenarians</th>
<th>Octogenarians</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>2.7% (95%CI: 2.1–3.3%)</td>
<td>3.2% (95%CI: 2.1–4.5%)</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>4.2% (95%CI: 2.7–6.2%)</td>
<td>10.7% (95%CI: 6.5–16.4%)</td>
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Conclusions: In this largest CAS registry reported to date, symptomatic status and increased age continue to be associated with an increased perioperative stroke/death rate. Symptomatic patients above age 80 represent only 3% of patients enrolled in this study. For the remaining 97% of patients, CAS results are at or very close to the thresholds recommended by previous guidelines, established for subjects under 80 years old. Additional multivariable predictor analyses of procedural variables associated with stroke will be presented.

The Importance of Early Carotid Endarterectomy After Transient Ischemic Attack

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Background: Early stroke risk after TIA is high, but optimal timing of carotid endarterectomy (CEA) after TIA is unclear. Many surgeons delay CEA for more than 4 weeks after TIA because of concerns about perioperative stroke risk. We sought to determine the benefits and risks of...
Introduction: Prior population-based studies have estimated that 15% of ischemic strokes are caused by atherosclerotic, large vessel cerebrovascular disease. However, these studies have generally not distinguished between vessel stenosis and occlusion, anterior and posterior circulations, or extracranial and intracranial locations. Such factors are relevant to the prevention and treatment of cerebrovascular disease. We determined the types of large vessel occlusion were 12.6 (0.6, 14.5) and 5.7 (4.4, 7.0) per 100,000 persons, respectively. We included 328 patients among these cases 78% had vascular imaging (carotid ultrasound 1099 (53%), MRA 900 (4%)). There were 329 patients with extracranial internal carotid artery injection (A), external carotid artery injection (B), early-arterial-phase, 12-month post-transient). The figure demonstrates angiograms from a representative patients pre-operative internal carotid artery (ICA) 165 (8.0%), cases of all strokes* Cases of all strokes* 177 Occlusion n=62 Occlusion n=11 Extracranial large vessel n=270 Intracranial large vessel n=73 Stenosis n=177 Stenosis n=62 MCA 22 1.1% NA** NA** Basilar Artery 9 0.4% NA** PCA 19 0.9% Cases of all strokes* 7 0.3% NA** *Percent of all ischemic strokes (n=2065) of any mechanism. **Isolated occlusions of the MCA, ACA, and basilar artery were not classified as large vessel etiology due to the inability to distinguish embolic occlusion from in situ thrombosis.

Conclusions: Indirect revascularization by EDAS and bur holes for Moyamoya disease results in resolution of ischemic and hemorrhagic manifestations in over 95% of patients. The middle meningeal artery appears to contribute significantly to the revascularization observed on follow-up angiograms with increase in size and neo-vascularity comparable to that of the STA. Angiographically, pial arterial bur holes do not contribute as significantly as frontorial bur holes.
Cerebral Metabolism Measured by 18-FDG-PET Improves Over Time in Patients Following Carotid Endarterectomy

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Introduction: Carotid endarterectomy (CEA) improves brain perfusion as shown by nuclear medicine techniques, but it is not known if CEA has any impact on cerebral metabolism. Hypothesis The aim of the study was to evaluate brain metabolism with 18-FDG-PET in patients with severe unilateral carotid stenosis before and after CEA. Methods: We included asymptomatic patients with severe unilateral carotid stenosis, which present with no acute lesions on DWI/PWI MRI or which had a minor stroke more than six months before first PET imaging and CEA. We excluded patients with recent stroke or postoperative complications. We performed a 18-FDG-PET before and three months after CEA. A voxel-by-voxel analysis was performed using SPM5. A comparison of the brain PET images between basal and postintervention images was performed using a paired t-test analysis. The SPM maps were obtained using a cluster and voxel level threshold of p < 0.05 corrected for multiple comparisons by False Discovery Rate (FDR). Results: We included 23 patients undergoing CEA (left=13; right=10), 15 men and 8 women, mean age 67. Mean time from PET imaging to CEA was 9 days (1–40) and between first and second PET imaging, 111 days (92–143). 12 patients were asymptomatic. 4 patients had suffered an amaurosis fugax, 3 patients had suffered a TIA without lesion on MRI and 4 patients had suffered a minor stroke or TIA more than 6 months before PET and CEA. A statistically significant improvement in 18FDP uptake was found on voxel-by-voxel and ROI analysis in the temporal, frontal, parietal and occipital regions, as well as in the basal ganglia, thalamus, and midbrain. Differences were maintained after excluding patients with recent TIA. No statistically significant differences were seen on patients scheduled for right CEA. Discussion: Mild differences can be seen on brain metabolism measured by 18-FDG-PET in asymptomatic/minor stroke patients scheduled for CEA. It seems possible that CEA not only affects the autoregulation of brain perfusion but also brain metabolism and glucose consumption. Conclusions: This is the first reported evidence that in selected group of patients CEA may improve longterm brain metabolism.

Efficacy of Combined Tissue Plasminogen Activator and Annexin 2 in Embolic Stroke Rats: An MRI Study

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BACKGROUND Tissue plasminogen activator (tPA) is an effective treatment of acute ischemic stroke but it has high risk of fatal hemorrhage and a narrow treatment time window. The search for a more effective and safer to tPA that can retain the hemorrhagic (H) and ischemic (I) balance, is activated following stroke. Emerging data demonstrated that activation of AMPK is a key neuroprotective pathway in stroke. Inhibition of Calcium/Calmodulin Dependent Protein Kinase Kinase (CaMKK, α and β isoforms) is a kinase traditionally known for its role in calcium signaling. Interestingly, CaMKK has recently been reported to be one of the upstream kinases that activate AMPK. Therefore, we assessed the hypothesis that inhibiting CaMKK is neuroprotective in experimental stroke as the inhibition may subsequently reduce AMPK activity. Methods: Focal stroke was induced by reversible middle cerebral artery occlusion (MCAO-50 minutes) in male C57Bl/6 mice and wild-type (WT) mice. In the pharmacological approach, a CaMKK inhibitor, STO-609, or vehicle (DMSO) was administered via intracerebroventricular injection (i.C.V.) 30 min prior to MCAO. Stroke outcome was determined with TTC staining at 24 hrs. Data are presented as mean ± SEM. Results: CaMKK α KO mice had significantly larger infarct volumes (percentage of contralateral structure) than their WT controls (cortex: KO 56.7 ± 3.8% vs WT 40.8 ± 2.5% p < 0.05, striatum: KO 69.3 ± 4.8% vs WT 46.5 ± 3.8% p < 0.05, total: KO 56 ± 5.7% versus WT 40.6 ± 3.8% p < 0.05, n =4/8/group). Consistently, treatment with STO-609 in WT mice exacerbated stroke outcome when compared to vehicle treatment (cortex: drug 61.9 ± 5.9% versus vehicle 40.8 ± 4.2% p < 0.05, striatum: drug 75.9 ± 4.2% versus vehicle 51.2 ± 4.2% p < 0.05, total: drug 59.8 ± 4.2% versus vehicle 42.8 ± 3.6% p < 0.05, n =4/8/group). When STO-609 was injected to CaMKK β KO mice, no significant effect was observed in stroke outcome (data not shown), confirming the mechanistic action of STO-609. There were no differences in mean arterial pressure, pO2, pCO2, or pH between the STO-609-treated and vehicle-treated groups. In addition, local cerebral blood flow as assessed by Laser Doppler flowmetry was equivalent in both groups. Conclusion: Inhibition of Calcium/Calmodulin Dependent Protein Kinase Kinase is Detrimental in Experimental Stroke

Phosphoinositide 3-kinase Gamma and Delta Isoform, a Promising Novel Target for the Treatment of Ischemia-reperfusion Brain Injury

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Background: Inflammation plays an important role in the pathogenesis of ischemic stroke. Phosphatidylinositol 3-kinase gamma (PI3Kγ) and delta (PI3Kδ) are the two major PI3K isoforms in brain and participate in several pathological processes such as atherosclerosis, myocardial ischemia-reperfusion injury, asthma, and rheumatoid arthritis. Recently we have demonstrated that genetic deletion of PI3Kδ attenuates cerebral inflammation and infarct size after focal ischemia/reperfusion injury. In this study, we further investigate whether a specific functional inhibition of PI3Kγ (and PI3Kδ) by isoform-specific PI3K inhibitor AS605240 (a selective PI3K γ inhibitor), IG7114 (a selective PI3K δ inhibitor), and TG100-115 (a selective PI3K γ/δ inhibitor, IC50 = 83 and 235 nM, respectively), were intravenously administered to mice immediately after the onset of ischemia. The optimal dose for each inhibitor used in this study was identified by performing dose-effect experiments (as determined by measurement of infarct volumes at 24h after MCAO/reperfusion) in our preliminary study. We demonstrated that AS605240 (1.0 mg/kg) and TG100-115 (1.0 mg/kg) significantly reduced infarct volume by Approx. 45% and 57% respectively, and most importantly, both compounds were effective when administered up to 3h after reperfusion. Importantly, both compounds were equally effective when administered up to 3h after reperfusion, the same time period when patients with acute ischemic stroke are most accessible for therapeutic intervention. However, treatment with IG7114 (1.0-2.0 mg/kg) only slightly reduced infarct volume (by approx.17% reduction, P > 0.05, vs untreated group, n = 10/group). These observations suggest that PI3Kγ is the predominant isoform (but to a lesser extent PI3Kδ) involved in the ischemic brain injury in mice. Furthermore, we demonstrated that TG100-115 and AS605240 administered after the onset of ischemia significantly reduced MMP-9 activity in the ischemic brain and blood-brain barrier (BBB) dysfunction, as assessed by zymography and Evans blue extravasation method, respectively. Intravital videomicroscopy during the reperfusion period showed that leukocyte recruitment was greatly blunted in the TG100-115 and AS605240-treated mice compared with untreated control mice. Conclusions: These results suggest that PI3Kγ isoform (to a lesser extent, PI3Kδ) is crucially involved in cerebral ischemia-reperfusion injury and might be a promising target for treatment of ischemic stroke. This research has received full or partial funding support from the American Heart Association, National Center.

Inhibition of Calcium/Calmodulin Dependent Protein Kinase Kinase is a Promising Novel Target for the Treatment of Ischemia-reperfusion Brain Injury

Jun Li, Sharan Dimauro, Matthew Janczyk, Louise McCullough; Univ of Connecticut Health Cnt, Farmington, CT

Introduction and objectives: AMP-activated protein kinase (AMPK), a master sensor of energy balance, is activated following stroke. Emerging data demonstrated that activation of AMPK is detremental in experimental stroke. Calcium/Calmodulin Dependent Protein Kinase Kinase (CaMKK, α and β isoforms) is a kinase traditionally known for its role in calcium signaling. Interestingly, CaMKK has recently been reported to be one of the upstream kinases that activate AMPK. Therefore, we assessed the hypothesis that inhibiting CaMKK is neuroprotective in experimental stroke as the inhibition may substantially reduce AMPK activity. Methods: Focal stroke was induced by reversible middle cerebral artery occlusion (MCAO-50 minutes) in male C57Bl/6 mice and wild-type (WT) mice. In the pharmacological approach, a CaMKK inhibitor, STO-609, or vehicle (DMSO) was administered via intracerebroventricular injection (i.C.V.) 30 min prior to MCAO. Stroke outcome was determined with TTC staining at 24 hrs. Data are presented as mean ± SEM. Results: CaMKK α KO mice had significantly larger infarct volumes (percentage of contralateral structure) than their WT controls (cortex: KO 56.7 ± 3.8% versus WT 40.8 ± 2.5% p < 0.05, striatum: KO 69.3 ± 4.8% versus WT 46.5 ± 3.8% p < 0.05, total: KO 56 ± 5.7% versus WT 40.6 ± 3.8% p < 0.05, n =4/8/group). Consistently, treatment with STO-609 in WT mice exacerbated stroke outcome when compared to vehicle treatment (cortex: drug 61.9 ± 5.9% versus vehicle 40.8 ± 4.2% p < 0.05, striatum: drug 75.9 ± 4.2% versus vehicle 51.2 ± 4.2% p < 0.05, total: drug 59.8 ± 4.2% versus vehicle 42.8 ± 3.6% p < 0.05, n =4/8/group). When STO-609 was injected to CaMKK β KO mice, no significant effect was observed in stroke outcome (data not shown), confirming the mechanistic action of STO-609. There were no differences in mean arterial pressure, pO2, pCO2, or pH between the STO-609-treated and vehicle-treated groups. In addition, local cerebral blood flow as assessed by Laser Doppler flowmetry was equivalent in both groups. Conclusion: Inhibition of CaMKK, either genetically or pharmacologically, is detrimental in stroke. Our results suggest that the role of CaMKK as an upstream kinase for AMPK may be less important in the setting of cerebral ischemia, and imply that CaMKK plays a neuroprotective role in stroke by its positive involvement in an as-yet unidentified pro-survival pathway. This research has received full or partial funding support from the American Heart Association, National Center.
Mash1 Lineage Cells Contribute to Ischemia Induced Neurogenesis and Oligodendrogenesis
Ruiian Zhang, Michael Chopp, Longfei Jiang, Cindi Roberts, Mei Wei, Zheng Gang Zhang; Henry Ford Hosp, Detroit, MI

Background: Mash1 is a basic helix-loop-helix transcription factor and directs neurogenesis and oligodendrogenesis in the adult brain. However, lineages of Mash1 expressing cells after stroke have not been examined. Utilizing Cre recombinase in an in vivo genetic fate-mapping strain, we investigated Mash1 expressing cells in the ischemic brain. Methods: Adult male Mash1-CreERT2/R26R-stop-yellow fluorescent protein (YFP) mice were subjected to the permanent middle cerebral artery occlusion (MCAo). Tamoxifen was injected (i.p) for 5 consecutive days starting 72h after MCAo. Upon tamoxifen treatment of Mash1-CreERT2/R26R-stop-YFP mice, CreERT2 is transiently activated, resulting in permanent expression of YFP from the R26R locus in Mash1-expressing cells and all their progeny, which permits in vivo tracing neuronal and oligodendrocyte fate of Mash1 expressing lineage cells. Animals were sacrificed (14–n=6) and 30 (n=7) days after MCAo and immunostaining was performed for detecting phenotypes of oligodendrocytes and neurons. Unbiased stereology method was used for quantifying the number of Mash1 expressing cells. Results: Stereological analysis revealed that 14 day stroke significantly (p<0.001) increased the number of Mash1-YFP+ cells in the ipsilateral subventricular zone (SVZ, 4423±267 vs 2264±125 in the contralateral), striatum (9113±304 vs 1412±18) and corpus callosum (6114±219 vs 1491±109). Double immunostaining showed that Mash1-YFP+ cells in the SVZ were doublecortin+ (DCX, neuroblasts) or SOX2+ (neural progenitors), while 20% of Mash1-YFP+ cells in the ischemic striatum and corpus callosum were NG2+ (oligodendrogligitor progenitors,OPC). None of Mash1-YFP+ cells were NeuN+ (mature neurons). However, 30 days after MCAo, 33% of Mash1-YFP+ cells in the ischemic striatum were NeuN+ and some Mash1-YFP+ cells were calcineurin+ (inter neurons), although the number of Mash1-YFP+ cells was significantly reduced (6520±222) compared with the number at 14 days (9113±304). Mash1-YFP+ cells in the ipsilateral striatum and corpus callosum also exhibited mature oligodendrogligocyte morphology, forming myelin sheaths. Conclusion: The present data for the first time demonstrate that Mash1 is involved in neurogenesis and oligodendrogenesis in the adult ischemic brain.

RBC Coupled tPA Prevents Impairment of Hypercapnic and Hypotensive Cerebrovasodilation After Piglet Photothermalism Through Inhibition of JNK and Potentiation of p38 MAPK
William Arntstead, Univ of Pennsylvania, Philadelphia, PA; Kurunm Ganguly, Los Alamos National Laboratory, Los Alamos, NM; John Riley, Willis Kesselring, Douglas Dines, Abd Higazi, Vladimir Muzykant; Univ of Pennsylvania, Philadelphia, PA

Introduction: Ischemic stroke is a poorly understood, yet clinically important, problem in the neonatal population. The sole FDA approved treatment for acute stroke is tissue type plasminogen activator (tPA). However, exogenous tPA potentiates cerebral hypoxia/ischemia (H/I)-induced impairment of pial artery dilation (PAD) to hypercapnia and hypotension in newborn pigs which is prevented by blockade of tPA vasoreactivity. Mitogen activated protein kinase (MAPK), a family of at least 3 kinases, ERK, p38 and JNK, is upregulated after cerebral ischemia. We observed that coupling of tPA to red blood cells (RBC) prevented H/I induced impairment of cerebrovascular dilation through inhibition of ERK MAPK. This study examined the effect of RBC-tPA on cerebrovascular dilation in a more translationally relevant model, photothermalism, and the role of MAPK in this effect. Methods: Photothermal injury (PTI) was produced by directing a laser (532 nm) onto piglet pial arteries after injection of erythrosine B. RBC-tPA (0.1 mg/kg iv) or tPA (2 mg/kg iv) were administered 30 min before PTI. CPF phosphorylated and total ERK, p38, and JNK MAPK were determined by ELISA and CBF phosphorylation (activated) JNK and p38 MAPK but not ERK MAPK were elevated by PTI, an effect potentiated by RBC-tPA. Results: CPF phosphorylated (activated) JNK and p38 MAPK but not ERK MAPK were elevated by PTI, an effect potentiated by RBC-tPA. Conclusion: Photothermalism activates infiltrated T lymphocytes, resulting in the production of IL-17, which enhances brain damages. Our study also indicates that the IL23/IL17 axis could be a therapeutic target for the later infarcting events.

MyD88-dependent IL-23 Production From Infiltrated Macrophages and IL-17 From γδT Cells Exacerbate Brain Infarction
Takashi Shichita, Dept of Microbiology and Immunology, Sch of Medicine, Keio Univ, Tokyo, Japan; Hiroaki Oboshi, Dept of Internal Medicine, Fukuoka Dental College Med and Dental Hosp, Fukuoka, Japan; Takashi Kobayashi, Yuki Sugiyama, Dept of Microbiology and Immunology, Sch of Medicine, Keio Univ, Tokyo, Japan; Hiroshi Sugimori, Mitsuo Iida, Dept of Medicine and Clinical Science, Graduate Sch of Med Sciences, Kyushu Univ, Fukuoka, Japan; Akitoku Yoshimura; Dept of Microbiology and Immunology, Sch of Medicine, Keio Univ, Tokyo, Japan

Objective: Recently, inflammatory cytokines and lymphocyte recruitment/activation have been implicated in the progression of cerebral ischemia-reperfusion (I/R) injury. However, the roles of specific lymphocyte subpopulations and their cytokines in stroke remain to be clarified. Because both IL-23 and IL-17 are critical cytokines for many inflammatory responses in central nervous system, we examined the role of IL-23 and IL-17-producing T lymphocytes in the evolution of brain infarction. Method: Transient focal ischemia using a suture occlusion model was used. IL-23 and IL-17 expression and their infiltrating inflammatory cells in the ischemic brain were collected by Percoll gradient centrifugation and were analyzed by quantitative real time PCR or intracellular FACS analysis. Result: In the ischemic brain, IL-23 expression increased 1 day after I/R. Bone marrow chimera studies revealed that the major source of brain IL-23 was infiltrated macrophage, which was completely dependent on MyD88-related pathway. IL-17-producing cells were observed in the brain after day 3, which was dependent on IL-23. Infarct volume of IL-23p19Δ/Δ mice was significantly smaller than wild-type at 1–7 days after ischemia, while that of IL-17−/− mice was smaller at 4 and 7 days but not at 1 day after ischemia. The expression of IL-17, MIP-3α, and CCL2 in the ischemic brain was significantly reduced in the ischemic brain by IL-17 and IL-23 deficiency at day 4. Intracellular cytokine staining indicated that γδT lymphocytes, but not CD4-positive helper T cells, were a major source of IL-17. Depletion of γδT lymphocytes by gene disruption or by anti-TCRγδ antibody pre-treatment significantly ameliorated the brain I/R injury. Moreover, FTY720, an immunomodulatory product which inhibits T cell infiltration into inflammatory tissues, reduced ischemic brain injury. Conclusion: Our findings indicate that brain infarction results in immediate activation of infiltrated macrophages, which promotes IL-23 secretion through the MyD88 pathway. Then IL-23 activates infiltrated γδT lymphocytes, resulting in the production of IL-17, which enhances brain damages. Our study also indicates that the IL23/IL17 axis could be a therapeutic target for the later infarcting events.

Hypothermia Modulates Apoptosis-Inducing Factor (AIF) Activation in the Ischemic Neonatal Rat Brain
Rand Askalan, Carol Xiaoxi Wang, Hui Shi, Hosp for Sick Children, Toronto, Canada; Edward Armstrong, Jerome Yager; Stollery Childrens Hosp, Edmonton, Canada

Background and Objective: Hypothermia is the only proven neuroprotective therapy thus far against cerebral hypoxic–ischemic injury but with limited efficacy. Several reports have shown that hypothermic neuroprotection may be mediated by inhibiting caspase-dependent cell death. However, the effect of hypothermia on other forms of neuronal death is not well understood yet. We sought to investigate whether AIF-mediated, caspase-independent neuronal death was modulated by hypothermia in the neonatal ischemic rat brain. Methods: Seven-day old rat pups were randomly assigned to control group or cerebral hypoxia-ischemia (HI) group. In the HI group, the right common carotid artery was ligated and cut while the animal was anaesthetized with halothane. Ischemia was produced in the hemisphere ipsilateral to the occlusion by subjecting the animal to hypoxia (85% oxygen) for 80 min. Control animals consisted of sham-operated rat pups subjected to a normoxic environment. Immediately after the hypoxic episode, the HI group was divided into two subgroups. The first subgroup was placed in water baths maintained at 28°C for 24 h. The second subgroup remained in their normothermic environment. The animals were sacrificed at 48 h after the hypoxic–ischemic insult. Results: Rats were processed for nuclear (activated) AIF immunofluorescent staining. Number of nuclear AIF positive cells were counted by a blinded investigator and compared between the HI groups and the control group. Results: Positive nuclear AIF cells were present in the hypothermic and normothermic HI groups but not in the control group. The number of nuclear AIF positive cells was significantly higher in the core compared to the ischemic penumbra in the hypothermic HI group (p=0.03). This pattern was reversed in the normothermic HI group (p=0.02). Comparing the two HI groups, hypothermia significantly lowered the number of nuclear AIF positive cells in the ischemic penumbra (p=0.03) but not in the core (p=0.03). Conclusion: Hypothermia modulates ischemia-induced AIF activation in the developing brain. These novel findings on the effects of hypothermia on caspase-independent neuronal death may explain the incomplete hypothermic neuroprotection and provide new insights into the development of therapies that may augment hypothermic neuroprotection.

National Stroke Awareness Campaign Increases Early Stroke Presentation and Numbers Thrombolysed
Dulika Manawadu, Laszlo Sztrha, Jeff Keep, Maria Fitzpatrick, Jozef Jarosz, Lalit Kalra; Kings College Hosp, London, United Kingdom

Introduction: Failure of early patient presentation with stroke limits numbers thrombolysed. Several papers suggest that increasing public awareness of stroke symptoms and early presentation to hospital can significantly improve thrombolysis rates. This has yet to be proven.
demonstrated in clinical practice. Hypothesis: We tested the hypothesis that a national stroke awareness campaign will increase the number of patients presenting in a therapeutic time window and thrombolysis rates at a stroke centre. Methods: A campaign to promote public stroke awareness using FAST - Face, Arm, Speech, Time to call the emergency medical services - was launched by the Department of Health in the UK in February 2009. Campaign material, on television, radio, online and in print, showed stroke spreading like fire in the brain and that immediate emergency action could significantly increase survival and reduce disability. We compared a 6 month period following the campaign with the same period for the previous year, for patients presenting to a centre with an established thrombolysis protocol that includes an extended treatment time window using perfusion scanning. We recorded total stroke admissions, presentation times, thrombolysis rates and treatment times. Results: 30-day risk adjusted stroke mortality for stroke unit admission by stroke subtype

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Jan-Jun 08</th>
<th>Jan-Jun 09</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>All strokes</td>
<td>154</td>
<td>273</td>
<td>+119 (77%)</td>
</tr>
<tr>
<td>Thrombolysed</td>
<td>38 (25%)</td>
<td>80 (29%)</td>
<td>+42 (111%)</td>
</tr>
<tr>
<td>Presenting 0-3 hrs of stroke onset</td>
<td>32/154 (21%)</td>
<td>87/273 (32%)</td>
<td>+55 (172%)</td>
</tr>
<tr>
<td>Thrombolysed 0-3 hours</td>
<td>19/32 (59%)</td>
<td>49/87 (56%)</td>
<td>+30 (158%)</td>
</tr>
<tr>
<td>Median onset to treat (0-3 hrs)</td>
<td>118 min</td>
<td>108 min</td>
<td>-10 min</td>
</tr>
<tr>
<td>Presenting 3-6 hrs of stroke onset</td>
<td>43/154 (28%)</td>
<td>87/273 (32%)</td>
<td>+44 (102%)</td>
</tr>
<tr>
<td>Thrombolysed 3-6 hours</td>
<td>19/43 (44%)</td>
<td>31/87 (36%)</td>
<td>+12 (63%)</td>
</tr>
<tr>
<td>Median onset to treat (3-6 hrs)</td>
<td>240 min</td>
<td>240 min</td>
<td>0 min</td>
</tr>
</tbody>
</table>

Conclusions: An increase in stroke activity, early presentation and thrombolysis was seen in the time period following the national stroke awareness campaign. We observed a particular increase in presentation of strokes within the 3 hour time window with a reduction in time to thrombolysis. All other factors remaining equal, we conclude, that such a campaign works.

Do All Ischemic Stroke Subtypes Benefit From Stroke Unit Admission?

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Background: It is well established that organized stroke care results in better outcomes following ischemic stroke. However, limited evidence is available on the benefit of stroke units in the "real world" after adjusting for important confounders. In particular, it is not known whether all ischemic stroke subtypes benefit equally from stroke unit admission. Objective: To determine whether the benefit of stroke unit admission is similar among all ischemic stroke subtypes. Methods: We used the data from the Registry of the Canadian Stroke Network (RCSN) including patients admitted with an acute ischemic stroke between July 2003 and September 2007. Ischemic stroke subtype information was determined according to the modified TOAST criteria and categorized as small vessel disease, large artery atherosclerotic disease, cardioembolic, or other (including both other determined and undetermined causes). Logistic regression and survival analyses were used to determine the association between stroke unit admission and 30-day mortality. Results: Among 6,223 ischemic stroke patients admitted to Regional stroke centers in Ontario, mean age was 71.9 ± 18.5 years and 52.4% were male. Overall 30-day mortality was 12.2%. The 30-day risk-adjusted stroke fatality for lacunar, LAO, CE and other stroke subtypes was, determined. respectively (Figure). In multivariable analysis, controlling for age, sex, number of medical comorbidities and stroke severity, there was a significant reduction in stroke mortality associated with stroke unit admission in all stroke subtypes p < 0.001. (Figure). The results remained similar after excluding 670 patients on palliative care. Conclusion: This study provides evidence in a "real world" setting that all ischemic stroke subtypes do benefit from a stroke unit admission regardless of the etiology. Stroke subtype should not influence the decision whether to admit to a stroke unit Figure: 30-day risk adjusted stroke mortality for stroke unit admission by stroke subtype

Medical Complications Among Ischemic Stroke Hospitalizations in the United States: 1999-2006

Xin Tong, Elena V Kuklina, Mary G George; CDC, Atlanta, GA

Background: Medical complications such as pneumonia (PN), deep vein thrombosis (DVT) and urinary tract infection (UTI) after acute ischemic stroke are recognized as indicators of quality of stroke care since they may adversely impact the outcome and extend the length of hospital stay (LOS). Limited research exists on population-based estimates of such complications. Methods: The study population consisted of total of 919,245 adult hospitalizations with ischemic stroke as a primary diagnosis identified with ICD-9-CM codes from the in the 1999-2006 Nationwide Inpatient Sample of the Healthcare Cost and Utilization Project. Hospitalizations with PN, DVT and UTI were identified through secondary ICD-9-CM codes. Multiple logistic regression analyses were used to examine changes between 1999-2000 and 2005-2006 in the prevalence of PN, DVT and UTI as well as in-hospital mortality controlling for age, gender, payment type and hospital location. Results: In 2005-2006 the prevalence of hospitalizations with a secondary diagnosis for PN, DVT and UTI was 3.0%, 0.7% and 10.1% respectively. The prevalence of at least one of these three secondary diagnoses was 12.9%. The mean LOS during the same study period was significantly longer for hospitalizations with PN, DVT, and UTI compared to hospitalizations without these conditions (p < 0.001): for PN 13.4 vs. 4.6 days; for DVT 12.7 vs. 4.8 days, and UTI 8.3 vs. 4.5 days. The adjusted odds ratios for hospitalizations with DVT and UTI were 1.51 (95% CI, 1.37-1.66) and 1.19 (95% CI, 1.15-1.23) in 2005-2006, respectively, as compared to 1999-2000. Pneumonia did not change significantly between 2005-2006 and 1999-2000. Overall in-hospital mortality was significantly lower in 2005-2006 as compared to 1999-2000 (Adjusted odds ratio: 0.82; 95% CI: 0.79-0.86). Overall LOS also decreased significantly for those with and without these conditions in 2005-2006 as compared to 1999-2000 (p < 0.001). Conclusion: The prevalence of ischemic stroke hospitalizations with secondary diagnosis for DVT and UTI increased significantly from 1999-2000 to 2005-2006. These hospitalizations as well as hospitalizations with PN had more than twice the LOS compared to hospitalizations without these conditions. Our nationwide surveillance data underlined the need to further investigate socio-demographic, clinical and health care factors associated with these complications and the recent increase in their prevalence.

A Comprehensive Profile of Outcomes in a Population of Acute Ischemic Stroke Patients

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Background: We describe the frequency and time course of various post-stroke outcomes using a population-based database of acute ischemic stroke patients. Over a 5-year post-stroke period, we assess mortality and rehospitalizations rates for complications including pneumonia, pulmonary embolism, hip fractures, recurrent stroke, and coronary heart disease. Methods: The Project for Improvement of Stroke Care Management in Minnesota (PRISMM) identified all acute ischemic stroke patients hospitalized from July 1 – December 31, 2000 in 19 Minneapolis-St. Paul metropolitan area hospitals and abstracted detailed information on their care. The PRISMM database was linked to 5 years of Medicare hospitalization data. 683 patients were included in the long-term outcomes study; they were: i) a Minnesota resident at the time of the index stroke; ii) age 65 years or older at the time of the index stroke; iii) enrolled in Medicare Part A and B; iv) had a Medicare hospitalization record for stroke that matched the PRISMM information. Time to outcome event was defined in days from date of discharge to event. Only the first occurrence of each outcome (i.e. incident event) after discharge was counted. Transfers to other hospitals from the index hospitalization were not counted as re-hospitalizations. Patient-time at risk was censored on patient death or when they dropped out of complete Medicare enrollment. Time to the first occurrence of each outcome event was plotted using Kaplan-Meier survival curves and the cumulative incidence percentage of each outcome and 95% confidence intervals (CI) were derived from these curves. Results: Discharge destinations of these 683 patients following the index stroke hospitalization were: home
The Prevalence of Anticoagulation With Warfarin and Its Effects on Risk of Stroke and Medical Costs in Medicare Beneficiaries With Atrial Fibrillation

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BACKGROUND: Well-controlled warfarin therapy reduces the risk of stroke in patients with atrial fibrillation (AF). Clinical trials show that compared to antplatelet therapy, adjusted-dose warfarin reduces risk of ischemic stroke by 52% in patients with AF. This study analyzes the prevalence of warfarin use and its effects on risk of stroke and medical costs in Medicare patients with AF. METHODS: We used medical claims from Centers for Medicare and Medicaid Services 5% Sample Standard Analytic File to analyze patients between 2004-2005 who had at least 2 outpatient diagnosis claims or 1 inpatient claim for AF and no evidence of valvular heart disease or transient causes (e.g., cardiac surgery) of AF. Because these data do not include pharmacy claims, we used a validated surrogate marker for warfarin use: patients were considered on warfarin if they had at least 3

METHODS: We used medical claims from Centers for Medicare and Medicaid Services 5% Sample Standard Analytic File to analyze patients between 2004-2005 who had at least 2 outpatient diagnosis claims or 1 inpatient claim for AF and no evidence of valvular heart disease or transient causes (e.g., cardiac surgery) of AF. Because these data do not include pharmacy claims, we used a validated surrogate marker for warfarin use: patients were considered on warfarin if they had at least 3

Table: Long-term Outcome Events After Ischemic Stroke

<table>
<thead>
<tr>
<th>Event</th>
<th>7-days</th>
<th>30-days</th>
<th>1-year</th>
<th>5-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All deaths</td>
<td>57</td>
<td>8.2 (6.2-10.3)</td>
<td>89</td>
<td>10.0 (7.7-12.2)</td>
</tr>
<tr>
<td>Rehospitalization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent ischemic stroke</td>
<td>2</td>
<td>0.3 (0.0-0.8)</td>
<td>12</td>
<td>1.9 (0.8-3.3)</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unrelated hemorrhage</td>
<td>0</td>
<td></td>
<td>1</td>
<td>2.1 (0.5-8.5)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>2</td>
<td>0.3 (0.0-0.8)</td>
<td>3</td>
<td>5.3 (2.0-11.0)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0</td>
<td></td>
<td>1</td>
<td>2.1 (0.8-5.8)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1</td>
<td>0.2 (0.0-0.8)</td>
<td>4</td>
<td>6.8 (2.1-21.3)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0.0 (0.0-0.8)</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>1</td>
<td>0.2 (0.0-0.8)</td>
<td>3</td>
<td>5.3 (2.0-11.0)</td>
</tr>
<tr>
<td>Any rehospitalization</td>
<td>33</td>
<td>6.8 (4.6-9.7)</td>
<td>92</td>
<td>21.6 (18.4-24.8)</td>
</tr>
</tbody>
</table>

CONCLUSIONS: Recurrent strokes, pneumonia and heart failure are the most common causes of rehospitalization after stroke. The high incidence of recurrent stroke appears to be maintained over a 5-year period. The long-term outcomes presented here have implications for late secondary and tertiary prevention (i.e. prevention of complications) programs.

Rehabilitation

Recurrent strokes, pneumonia and heart failure are the most common causes of rehospitalization after stroke. The high incidence of recurrent stroke appears to be maintained over a 5-year period. The long-term outcomes presented here have implications for late secondary and tertiary prevention (i.e. prevention of complications) programs.

Reliability of GWTG Stroke Data Abstractions

Alice Liskey, Siobhan Martin, Nancy Konrad, MetroHealth Med Ctr, Cleveland, OH; Irene Katanz; Cleveland Clinic Feuda, Cleveland, OH

Background: Objectives: (1) To determine the inter-rater reliability of abstraction of 8 NQF-endorsed stroke performance measures that are likely to be mandated by CMS in the future (2) To determine which elements collected in the GWTG - Stroke Patient Management tool have lowest inter-rater reliability. METHODS: Re-abstraction of 5% of GWTG - Stroke data collection forms in 14 Ohio Cordello hospitals over 6-months was performed in 2009 and 2010. The ISPA was below 90% for 2 of the 8 NQF-endorsed stroke performance measures: “DVT prophylaxis initiated by end day 2” (0.90 [95%CI 0.85-0.96]), and “discharge on anticoagulation for patients with afib/flutter” (0.89 [95%CI 0.81-0.96]). In addition, the ISPA was below 90% for the stroke performance measure “discharge to SNF” (0.89 [95%CI 0.85-0.93]). Of the 8 NQF-endorsed elements, items having the lowest ISPA included: Hispanic ethnicity 0.74 [95%CI 0.68-0.80], diabetic ethnicity 0.67 [95%CI 0.61-0.74], or antithrombotics (0.73 [95%CI 0.67, 0.79]) medications prior to admission, documentation of DVT or PE (0.77 [95%CI 0.71, 0.83]), and treatment of UDI during admission (0.80 [95%CI 0.75, 0.86]). Conclusion: In this audit of GWTG stroke data collected in 14 Ohio Cordello hospitals, there was 10% disagreement in 2 of the 8 NQF-endorsed stroke performance measures between hospital abstractors and a central group. This raises issues of accuracy should these measures be adopted for public reporting. The GWTG-Stroke data elements with the lowest agreement between raters related to Hispanic race, medications prior to admission and medical complications DVT/PE and UDI. These items should receive special attention when hospitals are beginning GWTG-Data collection.

Participation of Women and Minorities in NINDS Stroke Trials

James F Burke, Devin L Brown, Lynda D Lisabeth, Brisa N Sanchez, Lewis B Morgenstern; Univ of Michigan, Ann Arbor, MI

Introduction Women and minorities are underrepresented in clinical trials. There are little data measuring participation of women and minorities in stroke trials. Established guidelines for reporting race, ethnicity and gender in clinical trials exist, however, their effect on subject recruitment and participation is uncertain. Methods All stroke-related phase III trials with published results funded by NINDS were identified using clinicaltrials.gov. Reporting of race, ethnicity, and gender was abstracted from the primary publication. Percent of trials reporting data on enrollment of African Americans, Hispanics and women was tabulated. Percent of African Americans, Hispanics and women enrolled in the trials was also tabulated for those trials reporting these data. Analyses were repeated excluding trials that exclusively enrolled women or minorities. Z-tests were used to compare data from before (<1995) and after (≥1995) NIH enacted their mandatory race/ethnicity reporting policy. Results Of the 22 trials identified, all (100%) reported the number of women enrolled. Of the 25,474 total subjects enrolled, 10,330 (40.6%) were women. There was an increase in the percent of women enrolled across time periods (37.6% before 1995 vs. 45.7% after 1995, p < 0.001). African American race was reported in 12 (54.5%) of trials. The 4,249 African Americans enrolled constituted 21.1% of the trial population, which declined to 13.3% when the one race specific trial was excluded. African American enrollment increased by time period (12.1% before 1995, 16.0% after, p < 0.001). Hispanic ethnicity was reported in 22.7% (n=5) of trials. The 450 Hispanics enrolled constituted 6.5% of subjects in trials reporting ethnicity. Hispanic enrollment decreased over time (6.6% before 1995, 2.0% after 1995, p < 0.001). Conclusions Stroke is more common in African Americans and Hispanics than non-Hispanic whites. However, reporting of race and ethnicity in stroke clinical trials has been poor and continues to be so, particularly for Hispanics. As Hispanics made up 12.5% of the US population in 2000, this subgroup is significantly under-represented in stroke trials. Women are also under-represented in stroke trials, although this has improved over time.
Abstracts From the 2010 International Stroke Conference: Oral Presentations

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