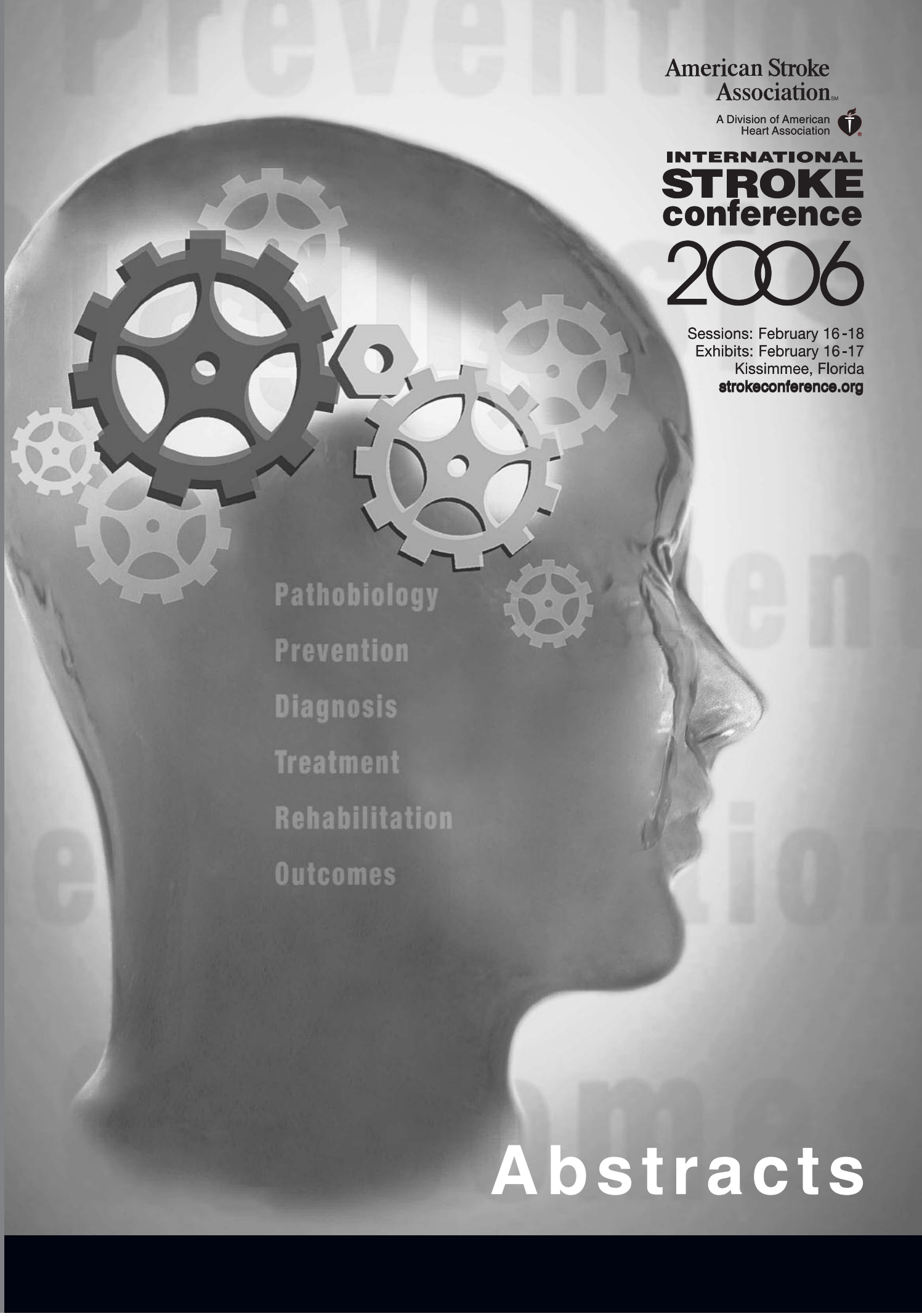


International Stroke Conference Oral Presentations

Prevention

1

1-Year Restenosis After Carotid Stenting in the Lead-in Phase of the Carotid Revascularization Endarterectomy vs Stenting Trial (CREST)

Helmi L Lutsep, Oregon Stroke Ctr, OHSU, Portland, OR; George Howard, Virginia J Howard, Jenifer Voeks, Univ of Alabama at Birmingham, Birmingham, AL; Wayne M Clark, Oregon Stroke Ctr, OHSU, Portland, OR; Alice Sheffet, UMDNJ-New Jersey Med Sch, Newark, NJ; Thomas G Brott, Mayo Clinic Jacksonville, Jacksonville, FL; Robert W Hobson, II, UMDNJ-New Jersey Med Sch, Newark, NJ; for the CREST Investigators

BACKGROUND AND PURPOSE: The rate of restenosis following carotid artery stenting (CAS) has not yet been well elucidated in multi-center trials. This study evaluated restenosis rates and potentially associated clinical risks in the lead-in phase of the NIH/NINDS-supported Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST). METHODS: The lead-in phase of CREST, a credentialing phase of approximately 20 cases per interventionalist prior to initiating randomization, included both symptomatic patients with $>=$50% carotid stenosis and asymptomatic patients with $>=$70% stenosis. Carotid ultrasound examinations done at local labs were performed at prespecified time periods that included a follow-up one year after CAS. The percentage of patients with restenosis of 50–69% (moderate), 70–99% (severe), or occlusion by ultrasound by one year was determined. Characteristics were compared for those with restenosis of at least 50% versus those without, including gender, race (white or not), age, symptomatic status at baseline, diabetes, dyslipidemia, hypertension, previous and current smoking history, coronary artery bypass grafting history, baseline angiographic features (presence of an eccentric lesion and ulceration, lesion length and degree of stenosis) and stroke occurrence in the year post procedure. RESULTS: One-year ultrasound results were available for 442 patients, 32% symptomatic and 68% asymptomatic. Moderate restenosis was seen in 89 patients (20%), severe in 8 (2%) and occlusion in 1 (0.2%). Moderate or greater restenosis (n=98; 22%) tended to be more frequent in patients with a history of diabetes (36% vs 26%; p=0.07); however, there was not an apparent association between moderate or greater restenosis at one year and other demographic, risk factor and vessel characteristics (p>0.12). CONCLUSIONS: In the lead-in phase of CREST, restenosis of 50% or more by ultrasound developed in 22% of patients. This is comparable to the 20% restenosis rate seen at one year in the CAS arm of the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial. The durability of CAS relative to endarterectomy awaits results from the randomized phase of CREST and other ongoing trials.

2

Low Complication Rates for Carotid Artery Stenting in the Credentialing Phase of the Carotid Revascularization Endarterectomy Versus Stenting Trial

Gary Roubin, Lenox Hill, New York, NY; Wayne Clark, Oregon Stroke Ctr, Portland, OR; Elie Chakhtoura, St Michael's Med Ctr, Newark, NJ; William Brooks, Central Baptist Hosp, Lexington, KY; Robert J Hye, Kaiser Permanente, San Diego, CA; Virginia Howard, Univ of Alabama, Birmingham, AL; Susan Hughes, MeeLee Tom, UMDNJ/New Jersey Med Sch, Newark, NJ; Jamie Roberts, Mayo Clinic, Jacksonville, FL; Larry B Goldstein, Duke Univ, Durham, NC; Thomas Brott, Mayo Clinic, Jacksonville, FL; Robert W Hobson, II; UMDNJ/New Jersey Med Sch, Newark, NJ

BACKGROUND AND PURPOSE: The benefit of carotid endarterectomy (CEA) or stenting (CAS) is dependent upon periprocedural risk. In the US, statewide 30-day complication rates for asymptomatic patients have ranged from 1.4–6.0%, and the overall rate of stroke and death rate for symptomatic patients is 7.7%. As examples from randomized controlled trials (RCTs), the 30-day stroke and death rate was 5.8% in the North American Symptomatic Carotid Endarterectomy Trial (NASCET) in the 70–99% stenosis cohort and 2.8% in the Asymptomatic Cartoid Surgery Trial (ACST). Safety results for CAS have varied and so we examined them in CREST. METHODS: Interventionalists were CREST approved based on low morbidity and mortality of audited cases by the Interventional Management Committee. Device training was provided. Prior to randomization approval, interventionalists performed up to 20 CAS for symptomatic ($>=$50% stenosis) and asymptomatic ($>=$70% stenosis) patients at conventional or higher risk using the ACCULINK™ Carotid Stent and ACCUNET™ Embolic Protection Systems. Patients were pretreated with aspirin and clopidogrel and continued on for at least 30-days post. Neurological examinations and NIH Stroke Scales were performed by CREST neurologists pre-procedure, 24-hours and 30-days post CAS. Stroke, myocardial infarction (MI), death and other adverse events within 30-days of CAS were ascertained clinically and reviewed by an independent clinical events committee. RESULTS: As of June 2005, data on 1246 lead-in participants makes this the largest cohort of CAS patients with protocol-driven neurological exams. By 30-days, 46 patients (3.7%) had a stroke (8 hemorrhagic), 10 (<1%) had an MI and 7 (< 1%) died; the combined stroke or death rate was 3.9% (95% CI: 2.9%–5.2%) with 5.6% (95% CI: 3.3%–8.7%) being for symptomatic patients and 3.4% (95% CI: 2.3%–4.9%) for asymptomatic patients. CONCLUSIONS: The 30-day stroke and death rate for symptomatic patients was similar to rates reported for CEA in symptomatic RCTs. For asymptomatic patients, despite inclusion of higher risk subsets (>80y/o) and more rigorous stroke detection methodology, the 30-day stroke and death rate for CAS was only slightly higher than that reported for CEA in asymptomatic RCTs.

3

Intracranial Stenosis, "Failure" of Antithrombotic Therapy, and Risk of Stroke

Lucian Maidan, Emory Univ, Atlanta, GA; Michael Lynn, Rollins Sch of Public Health, Atlanta, GA; George Cotsonis, Emory Univ, Rollins Sch of Public Health, Atlanta, GA; Timothy Upchurch, Emory Univ, Atlanta, GA; Steven Levine, Mount Sinai Sch of Med, New York, NY; Jose Romano, Univ of Miami, Miami, FL; Marc Chimowitz, Emory Univ, Atlanta, GA; for the WASID investigators

BACKGROUND: Based on previous studies we hypothesize that 1. Intracranial stenosis (IS) patients who present on antithrombotic therapy are at higher risk of stroke compared with patients presenting off antithrombotic therapy; 2. Warfarin is not an effective rescue therapy for IS patients presenting on antiplatelet therapy. METHODS. Data on 568 patients enrolled in the Warfarin Aspirin Symptomatic Intracranial Disease (WASID) trial were used for this analysis. WASID was a clinical trial in which patients with TIA or stroke due to 50–99% IS were randomized to warfarin (W) or aspirin (A). We compared features in 299 patients on v. 269 patients off antithrombotic therapy at presentation. The rates of stroke (S) or vascular death (VD) and stroke in the territory (SIT) of the stenotic artery were compared between these 2 groups. We also compared the effectiveness of A v. W in patients i. on antiplatelet therapy only and ii. off antithrombotic therapy at presentation. RESULTS. Features that were significantly more common (p<0.01) in patients on v. off antithrombotic therapy at presentation were: TIA (rather than stroke) at presentation, white race, hypertension, hyperlipidemia, smoking, CAD, prior stroke, statin use, and older age. The 2-year rates of S or VD (21% on vs. 22% off) and SIT (14% on vs. 15% off) were not significantly different in patients on v. off antithrombotic therapy at presentation. In patients on antiplatelet therapy at presentation, the hazard ratios (HRs) (A / W) were 1.32 (95% CI 0.77 - 2.28, p=0.31) for S or VD and 1.92 (95% CI 0.95 - 3.91, p=0.07) for SIT. In patients off antithrombotic therapy at presentation, the HRs were 0.75 (95% CI 0.45 - 1.25, p=0.27) for S or VD and 0.85 (95% CI 0.45 - 1.61, p=0.62) for SIT. The difference in the relative efficacy of A v. W for patients on antiplatelet or off antithrombotic therapy at presentation was not significant for S or VD (p = 0.13) or SIT (p = 0.10). CONCLUSIONS: 1. The risk of stroke is similar in IS patients who present on v. off antithrombotic therapy; 2. Although we did not find differences in the relative efficacy of A v. W in patients on or off antithrombotic therapy at presentation, the sample size limited the power to detect a difference.

4

Patient Subgroups in the Randomized SAPPHIRE Study of Carotid Stenting with Distal Protection vs Endarterectomy

Pierre B Fayad, Univ of Nebraska Med Ctr, Omaha, NE; Kenneth Ouriel, Cleveland Clinic Foundation, Cleveland, OH; Marc Wholey, Allegheny Univ Hosp, Cleveland, OH; Barry Katzen, Miami Cardiac and Vascular Inst, Miami, FL; Sidney Cohen, Cordis, Warren, NJ; Jay Yadav; Cleveland Clinic Foundation, Cleveland, OH

Background and study objective: Main results of the randomized portion of SAPPHIRE demonstrated non-inferiority (with a trend for superiority) of carotid artery stenting with emboli-protection device (CAS-EP) versus endarterectomy (CEA) for the ***primary outcome*** (cumulative 1-year rates of major adverse events (MAE), including all-cause mortality, any stroke, and MI to 30 days post-procedure plus death (all-cause) and ipsilateral stroke between days 31 and 360 post-procedure) in the treatment of patients at high-risk for CEA. We examine the applicability of the main results to patients with different risk characteristics. **Methods:** The SAPPHIRE trial evenly randomized 334 patients (mean age=72.4±8.7 years) to CAS versus CEA, of whom 96 (28.8%) were symptomatic, 86 (26.4%) were diabetic, 219 (67.0%) were men, and 65 (19.9%) were >80 years of age. We report the ***primary outcome*** in the two groups according to intention-to-treat analysis. **Results:**

MAE at 360 days, % (n of events/n of patients in group)

	CAS	CEA	Δ (95% CI)	*P*
Asymptomatic	10.3% (12/117)	19.2% (23/120)	-8.9%[-17.8%, 0.0%]	0.07
Symptomatic	16.0% (8/50)	19.6% (9/46)	-3.6%[-18.9%, 11.8%]	0.79
Men	12.6% (14/111)	22.2% (24/108)	-9.6%[-19.6%, 0.4%]	0.07
Women	10.9% (6/55)	15.1% (8/53)	-4.2%[-16.9%, 8.5%]	0.58
Diabetic	16.7% (7/42)	31.8% (14/44)	-15.2%[-32.9%, 2.6%]	0.13
Non-diabetic	10.5% (13/124)	15.5 (18/116)	-5.0%[-13.5%, 3.5%]	0.26
Age >80 years	18.8% (6/32)	21.2% (7/33)	-2.5% [-21.9%, 17.0%]	1.00
Age ≤80 years	10.5% (14/134)	19.5% (25/128)	-9.1% [-17.7%, -0.5%]	0.06

There are no statistically significant differences or interaction among the major subgroups but a consistent trend for superiority for CAS over CEA. **Conclusions:** Although the trial was not powered to detect significant differences among subgroups of patients, the results shows consistency across patients with diverse characteristics and supports the applicability of the main results to major categories of patients randomized to the study.

5

Paradoxical Rebound Platelet Activation After NSAIDS or COX-2 Inhibitor Withdrawal: Which Patients Are at Higher Risk for Vascular Events?

Victor Serebruany, Alex Malinin, HeartDrug Rsch, Towson, MD; Deepak Bhatt; Cleveland Clinic, Cleveland, OH

Background: Several reports strongly indicate that use of non-steroidal antiinflammatory drugs, and cyclooxyginase-2 inhibitors (NSAID/COXI) is associated with the increased risk of

myocardial infarction, ischemic stroke, and vascular death. Therefore, the lowest dose for the shortest duration necessary is now recommended.Considering the key role of platelets, and the fact that aspirin, and recently clopidogrel have been implicated in the reduced vascular mortality, we thought to determine the effect of NSAID/COXI therapy and withdrawal on platelet activity. Methods: Platelet characteristics from 34 aspirin-naive volunteers who were receiving NSAID/COXI inhibitors were compared with 138 drug-free controls. Platelets were assessed twice at baseline (at least one month of NSAID/COXI), and then after 14 days washout. We employed ADP-induced conventional aggregometry, point-of-care Ultegra® analyzer, and whole blood flow cytometry. Results: The demographics, clinical characteristics, and platelet activity during NSAID/COXI were similar and unremarkable between groups. However, there was a highly significant ($p=0.00001$) increase of aggregability, platelet activation units by Ultegra analyzer ($p=0.004$), and expression of GPIIb/IIIa ($p=0.002$), P-selectin ($p=0.00001$), and PECAM-1 ($p=0.003$) receptors after withdrawal from NSAID/COXI. Conclusion: These data suggest that discontinuation, rather than continuous therapy with NSAID/COXI may represent the highest risk to develop vascular events. This hypothesis requires intensive testing in the crossover randomized studies, and may justify more aggressive antiplatelet regimens in patients after NSAID/COXI withdrawal.

6

Local TV News Reporting of Stroke: A National Perspective

James M Pribble, Jennifer J Majersik, William G Barsan, Lewis B Morgenstern; Univ of Michigan, Ann Arbor, MI

Introduction: Local television news is the number one source of information for Americans. Health information is a prominent part of local television broadcasts yet little is known about what or how health is reported. This study aimed to describe and characterize local TV news stroke reporting across the United States. Methods: Content of health stories reported on 122 local television stations from the country's top 50 media markets during the entire month of October 2002 was systematically analyzed. Full length broadcasts were clipped and coded to identify all health stories reported as well as those stories specifically about stroke. Two health professionals independently coded each stroke story for main focus, whether they discussed signs and symptoms of stroke, gave recommendations, discussed risk factor modification or reported information about the time-sensitive nature of stroke treatment. Results: Of the 1799 health stories identified from 2795 broadcasts, only 9 unique stroke stories aired a total of 13 times during our study period (0.7% of all health stories). Most (9/13) stories were from medical research and the median story length was 24 seconds (IQR: 21–48). Only 1 story listed all the common symptoms of acute stroke recommended by the NINDS. Only 2 stories indirectly discussed risk factors and only 2 stories recommended patients present to the hospital within 3 hours. Of the four stories that discussed treatment, only one discussed t-PA. The others discussed antioxidants and Citicoline as effective treatments for stroke and stated that they were useful if taken within 7 hours and 14 hours respectively of symptom onset. Discussion: Stroke stories were nearly non-existent in our sample and those that were reported failed to discuss important messages that are needed to improve stroke prevention and treatment. Moreover, 75 percent of the treatment stories implied that receiving treatment between 7 and 14 hours was effective for stroke treatment. To directly impact the public health, stroke researchers need to seek media attention, however, they need to ensure that useful messages are incorporated into the media reporting to take advantage of the powerful reach of local television news.

7

Sarpogrerale-Aspirin Comparative Clinical Study for Efficacy and Safety in Secondary Prevention of Cerebral Infarction (S-ACCESS): A Randomized, Double-Blind, Aspirin-Controlled Trial

Yukito Shinohara, Ctr for Stroke and Neurological Diseases, Tokai Univ, Tokyo Hosp, Tokyo, Japan; Hideo Tohgi, Iwate Med Univ, Morioka, Japan; Yasuo Fukuuchi, Ashikaga Red Cross Hosp, Ashikaga, Japan; Shinichiro Uchiyama, Tokyo Women's Med Univ, Tokyo, Japan; Takenori Yamaguchi, National Cardiovascular Ctr, Osaka, Japan; Shotai Kobayashi, Shimane Univ Faculty of Med, Izumo, Japan; Eiichi Otomo, Yokufukai Geriatric Hosp, Tokyo, Japan; Fumio Gotoh, Keio Univ, Tokyo, Japan; Shunsaku Hirai, Kunihiko Hayashi, Gunma Univ, Maebashi, Japan; Tohru Sawada, Aino Hosp, Osaka, Japan; Akiro Terashi, Nippon Med Sch, Tokyo, Japan; Shunnosuke Handa, Tokai Univ, Tokyo, Japan; Kazuoki Kondo, Mitsubishi Pharma Corp, Tokyo, Japan; Katsuya Nishimaru; Fukuoka Univ, Fukuoka, Japan

Background: Aspirin is the most commonly used agent for secondary prevention of ischemic stroke throughout the world. Sarpogrelate is an antiplatelet agent that decreases 5-hydroxytryptamine (5-HT) levels in platelets via blockade of 5-HT2 receptors. We aimed to evaluate and compare sarpogrelate and aspirin for secondary prevention of cerebral infarction. **Methods:** Using a double-blind design, we randomly assigned patients with recent cerebral infarction to receive either sarpogrelate (100 mg three times daily) or aspirin (81 mg once daily). The primary endpoints were recurrence of cerebral infarction and safety-related events. In the planning stage, the annual event rate for recurrent cerebral infarction was expected to be 5.5 % with sarpogrelate and 6 % with aspirin. Statistical power was sufficient to establish noninferiority of sarpogrelate vs aspirin within a margin of 1.33 per year difference in recurrence rates. **Findings:** 1510 patients (male 1082, female 428, mean age 65.6 $\pm$ 9.8 years) with a history of recent cerebral infarction (atherothrombotic stroke 31.2 %, lacunar stroke 63.8 %, others 5.0 %) had a mean follow-up of 1.59 years. Recurrence of cerebral infarction was seen in 72 of 747 patients in the sarpogrelate group and 58 of 742 in the aspirin group (6.1 % per year with sarpogrelate and 4.9 % per year with aspirin; hazard ratio 1.25 [95 % CI 0.89 to 1.77]). The incidence of bleeding events such as nasal hemorrhage, internal bleeding, intracranial hemorrhage, gingival bleeding, and so on, was lower with sarpogrelate than aspirin (11.9 % vs 17.3 %, $P=0.004$). **Interpretation:** This is the first randomized, double-blind, aspirin-controlled trial of sarpogrelate in Japan. Although sarpogrelate did not meet the predefined criterion of noninferiority to aspirin for efficacy against recurrence of cerebral infarction, it was better tolerated than aspirin, with significantly fewer bleeding events.

Thrombolysis

8

Efficacy of Microbubble-Enhanced Sonothrombolysis Among Stroke Subtypes

Marta Rubiera, Marc Ribo, Raquel Delgado-Mederos, Esteban Santamarina, Rafael Huertas, Pilar Delgado, Joan Montaner, José Alvarez-Sabín, Carlos A Molina; Hosp vall d'Hebron, Barcelona, Spain

Aim: Experimental and clinical studies suggest that administration of microbubbles (MB) may further accelerate ultrasound-enhanced systemic thrombolysis. We aimed to evaluate the impact of MB administration during sonothrombolysis on the success of recanalization among different stroke subtypes. **Methods:** We studied 155 consecutive stroke patients due to MCA occlusion treated with iv tPA. Patients were allocated to receive tPA plus continuous 2-h TCD monitoring ($n=37$; US group), or tPA plus placebo monitoring ($n=36$; tPA group), or tPA/US plus 3 doses of MB given at 2 min, 20 min and 40 min after tPA bolus ($n=67$; MB group). Recanalization on TCD at 2h of tPA bolus was recorded. Stroke subtypes were assessed by means of TOAST criteria. Modified Rankin Scale (mRS) score was used to assess outcome at 3 months. **Results:** Median admission NIHSS was 16. On TCD, 118 (76%) patients had a proximal and 37 (24%) a distal MCA occlusion. Stroke was categorized as cardioembolic (CE) in 76 (49%) atherothrombotic (AT) in 37 (24%), undetermined (UD) in 35 (23%) patients, and others 4%. Baseline NIHSS, clot location, and time to treatment were similar among stroke subtypes. Two-hour complete recanalization rate was significantly ($p=0.039$) higher in MB group (52%) as compared to tPA/US (40.2%) and tPA (24%) groups. MB administration significantly ($p=0.021$) increased de rate of 2-h recanalization in patients with AT stroke. Among patients with AT stroke (96% tandem ICA/MCA occlusions), MB increased in 1.5- and 2-fold, the rate of 2-h recanalization compared to tPA+US (39% vs 26%) and tPA (39% vs 21%). Treatment allocation did not affect recanalization rates in CE and UD stroke patients. At 3 months, AT stroke was significantly associated with a poor outcome in US ($p=0.043$) and tPA ($p=0.021$) groups, but not in the MB group. In the MB group, 36% of AT, 48% of CE, and 47% of UD strokes became independent ($mRS\leq2$). **Conclusion:** Efficacy of MB-enhanced sonothrombolysis varies among stroke subtypes. MB administration during continuous 2-MHz monitoring and systemic thrombolysis increases recanalization rates and improves outcome in patients with tandem ICA/MCA occlusion.

9

"Mild Stroke" Should Not Exclude Patients from Thrombolytic Therapy

Nicole R Gonzales, Karen C Albright, Elizabeth A Noser, Aslam M Khaja, Hashem M Shaltoni, Adam Romman, Neal Zimbaldi, Mary S Baraniuk, Lemuel A Moye, James C Grotta; Univ of Texas Med Sch, Houston, TX

Background and Purpose Many patients with acute ischemic stroke (AIS) eligible for IV rt-PA are excluded from thrombolytics because of mild symptoms and the assumption that this group of patients will do well without thrombolytic therapy. We sought to determine the outcome of patients with mild AIS who received IV rt-PA compared to those who did not. **Methods** Consecutive patients with NIHSS ≤7 were identified. Baseline NIHSS, use of thrombolytics, and reason for thrombolytic exclusion were recorded. Patients were further divided into two groups, *minimal symptoms* (NIHSS 1–3) and *mild symptoms* (NIHSS 4–7). Excellent outcome was defined as a discharge modified Rankin Scale (mRS) of 0–1. **Results** We screened 885 patients with AIS. Of these, 238 patients had NIHSS ≤7 (103 *minimal symptoms*, 135 *mild symptoms*). Forty-one patients (17%) were treated with rt-PA. Of those presenting within 3 hours and not treated, the most common reason for exclusion was minor symptoms (59%). Median admission NIHSSs were 4 (untreated) and 5 (rt-PA). Only 10% of patients with *minimal symptoms* received rt-PA compared to 23% with *mild symptoms* ($p<.01$, Fisher's exact). Patients treated with rt-PA were more likely to have an excellent outcome, OR 2.48 (95% CI 0.17–0.52, $p=0.01$). As a whole, 59% of the rt-PA group had an excellent outcome compared to 44% of the untreated group. When treated with rt-PA, 90% of patients with *minimal symptoms* had an excellent outcome compared to only 58% of the untreated group. This effect was also seen in the 'mild symptom' group: those treated with rt-PA had a 48% chance of an excellent outcome compared to only 32% in the untreated group. No patients in the rt-PA treated group died compared to 1% in the untreated group. **Conclusions** Patients presenting within 3 hours are frequently excluded from thrombolytics for minor symptoms (59% in our sample). Less than half of these patients have an excellent outcome without treatment. Even in patients with *mild symptoms*, the chance of excellent outcome was higher with treatment. Risk of death was low in both groups, however, this risk was higher in the untreated group. Our data argue strongly not to exclude patients from rt-PA treatment based on mild stroke.

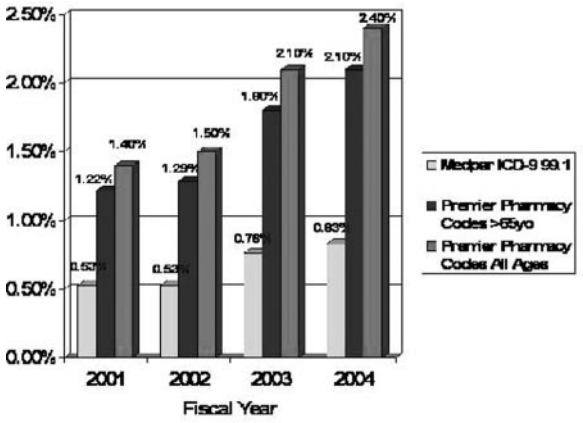
10

National US Estimates of rtPA Use: ICD-9 Codes Substantially Underestimate

Dawn Kleindorfer, Christopher Lindsell, Univ of Cincinnati, Cincinnati, OH; Greg White, Tonja Curtis, Johnson and Johnson Inc, New Brunswick, NJ; Lawrence Brass, Yale Univ, New Haven, CT; Walter Koroshetz, Massachusetts General Hosp, Boston, MA; Joseph P Broderick; Univ of Cincinnati, Cincinnati, OH

Introduction: Current US national estimates of rt-PA use have been based either on extrapolation of regional studies, or on the Medpar database from the Center for Medicare and Medicaid Services. However, limitations of regional extrapolations, or coding, may bias these estimates. We compared the use of rt-PA in acute ischemic stroke in Medpar to the national Premier database. **Methods:** Premier contains approx. 1 out of every 6 inpatient discharges in the US, has no age exclusion, and includes pharmacy billing records. Medpar contains Medicare inpatient admissions (age >65 only). Both databases were queried for stroke-related admissions using Diagnosis Related Group codes 14/15, and for the rt-PA use ICD-9 code 99.1,

for the fiscal years of 2001–04. Premier was queried for rt-PA use in pharmacy records as well. Change over time and difference between databases were tested using Poisson regression. **Results:** The number of stroke discharges in Medpar was 293,214 in 2001 and 474,366 in 2004, and 59,634 to 94,578 in Premier. In both databases, the use of rt-PA significantly increased over time by an average of 20%/yr, p<0.001(Figure). When pharmacy records were used, the estimate of rt-PA use in 2004 was more than double the ICD-9-based estimate (0.83% vs 2.4%). **Discussion:** In the US, rt-PA use for ischemic stroke increased over time by approximately 20% per year. The ICD-9 code 99.1 underestimates rt-PA use when compared to pharmacy records. Using an annual estimate of 600,000 ischemic strokes in the US, we estimate that at least 14,400 ischemic stroke patients were treated with rt-PA in the US during 2004. Figure: A Comparison of Rt-PA Use: % of DRG 14 and 15 Cases Receiving Rt-PA.



11

Robust Confirmation of Treatment Effect by Baseline Severity-Adjusted End Point Reanalysis of the NINDS-tPA Stroke Trials

Jeffrey L Saver, Banafsheh Yafeh; UCLA Stroke Ctr, Los Angeles, CA

Background: Baseline severity-adjusted endpoint analysis is an emerging approach to the evaluation of primary endpoints in acute stroke trials. Prognosis-adjusted endpoints assess enrolled patients on achievable goals given their presenting stroke severity, rather than a fixed target outcome inappropriate for very mildly or severely affected individuals. Severity-adjusted analysis also is a novel means of adjusting trial analysis for baseline imbalances in presenting stroke severity among treatment groups, a factor that has complicated interpretation and reception of the results of the pivotal NINDS-TPA Trials. **Methods:** The sliding scale dichotomy endpoint applied in recent acute ischemic stroke clinical trials (AbESTT, GAIN) was employed to analyze the NINDS-TPA Stroke Trials 1 and 2. Good outcomes were: 3 month Rankin Scale = 0 if pretreatment NIHSS scores was 0–7; 3 month Rankin Scale = 0–1 if pretreatment NIHSS scores was 8–14; 3 month Rankin Scale = 0–2 if pretreatment NIHSS scores was >14. **Results:** Both of the NINDS TPA Stroke Trials showed a statistically significant beneficial treatment effect of TPA. In Trial 1, good outcomes in TPA vs placebo patients were 39.6% vs 28.6%, OR 1.64, p=.049; in Trial 2, 35.7% vs 24.2%, OR 1.74, p=.024. Among all 624 patients in Trials 1 and 2 combined, good outcomes occurred in 37.5% vs 26.3% patients, OR 1.68, p=.0034. As an imbalance of a greater number of mild presenting severity patients among early (≤90 minute) treated patients was known to have occurred in the trial, the 0–90 and 91–180 minute groups were also analyzed separately. In the 0–90 minute group, good outcomes in TPA vs placebo patients were noted in 38.9% vs 29.0%, OR 1.56, p=.089; in the 91–180 minute cohort, 36.1% vs 24.0%, OR 1.80, p=.021. Odds ratios favoring TPA further increased after adjustment for 15 additional covariates known to predict acute stroke outcome. **Conclusion:** Baseline-adjusted severity endpoint reanalysis of the NINDS Stroke TPA trials confirms a robust beneficial treatment effect of intravenous TPA. This entirely novel approach to adjustment for imbalances in entry stroke severity demonstrates that the treatment benefit from intravenous tissue plasminogen activator extends through the full 3 hour time window.

12

Vessel Size Explains Gender Differences in Response to Intravenous Thrombolysis for Acute Stroke

David S Liebeskind, Amelia L Laughton, Doojin Kim, Sidney Starkman, Noriko Salamon, J P Villablanca, Jeffrey L Saver; UCLA, Los Angeles, CA

Background: Prior studies have demonstrated that achievement of arterial recanalization and final good clinical outcome following intravenous thrombolysis with tissue plasminogen activator (tPA) occurs more frequently in women than men with acute ischemic stroke. We hypothesized that vessel size may contribute to this differential gender response to intravenous fibrinolytic therapy. **Methods**: The cross-sectional lumen areas of the proximal middle cerebral, supraclinoid internal carotid, and distal basilar arteries were directly measured on 3-dimensional CT angiograms acquired in 200 adults. Individual height and weight data from the same patients were used to calculate tPA dose. With these inputs, clot volume and ratio of exposed surface area to total clot volume were modeled. The model included baseline values and progressive changes related to alterations in clot morphology with recanalization. **Results**: Vessels were measured in 200 patients (100 men, 100 women; mean age 57 years, range 15–96). The intracranial arteries all showed smaller lumen areas in women than men: proximal MCA, .049 vs .052 cm^2; distal ICA, .085 vs .099; distal basilar, .059 vs .073, all p<0.05. Clot volumes were all smaller in women than men, proximal MCA, .078 vs .089 cm^3; distal ICA, .079 vs .109; distal basilar, .066 vs .096, all p=0.001. The ratios of exposed surface area to target clot volume were greater in women for all lesion types, proximal MCA, .697 vs .659 cm^{-1}; distal ICA, 1.156 vs 1.023; distal basilar, 1.039 vs .855, all p=0.001. Women also showed more frequent and greater excursions of actual body weight above ideal body weight. In dynamic modeling, after initiation of recanalization, increases in the radius or length of the patent channel further accentuate the differences in surface area/clot volume ratios in women vs men. **Conclusions**: Women have smaller intracranial arteries than men and form thrombi of lesser clot volume. Women are also likely to receive relatively higher doses of tPA due to discordance of body weight and vessel size. These factors likely contribute to the greater responsiveness of women than men to intravenous fibrinolytics. Adjusting dosing of tPA to bodyframe size is a potential strategy to optimize recanalization rates in both men and women.

13

Microcatheter Contrast Injections During Intra-arterial Thrombolysis Increase Intracranial Hemorrhage Risk

Pooja Khatri, Joseph P Broderick, Jane C Khoury, Janice Carrozzella, Thomas Tomsick, Univ of Cincinnati, Cincinnati, OH; IMS-1 and 2 Investigators

Background: As intra-arterial (IA) therapy becomes more widespread, studying the impact of procedural factors becomes critical. We hypothesized that microcatheter contrast injections (MCIs) may lead to contrast extravasation (CE) and subsequent intracranial hemorrhage (ICH) in the Interventional Management of Stroke (IMS) I and II trials of combined IV/IA rt-PA. **Methods**: All arteriograms with M1, M2, and ICA occlusions were reanalyzed (n=98). Based on available imaging, the number of MCIs at/distal to the target occlusion was assigned for every case. Post-procedure CTs were reviewed for CE (i.e., a hyperdensity suggestive of contrast, present/persisting at 24 hours with/without ICH, distinct from contrast *enhancement* which clears at <24 hours) and ICH. **Results**: The median number of MCIs was 2 (range 0–12). Median MCIs were 2 in the ICH group (n=56) and 1 in the non-ICH group (n=42; p=0.03). Increasing MCIs were associated with increased ICH risk (p=0.03). After excluding proximal ICA occlusions (n=7), MCIs still trended towards an association with ICH (p=0.07). In addition, MCIs remained associated with ICH after adjustment for significant ICH risk factors (Table). Tested nonsignificant covariates included age, gender, race, systolic blood pressure, myocardial infarction, diabetes, NIHSS, proximal ICA occlusion, and rt-PA dose. **PREDICTORS Median MCIs were 3.5 in the CE group (n=18) and 1.0 in the non-CE group (n=80; p=0.03). MCIs trended towards association with CE after adjusting for significant covariates of rt-PA dose, NIHSS, and proximal ICA occlusion (OR 1.60; 95% CI 0.98–2.60; p=0.06). All CE cases (18/18) developed ICH (vs. 48% non-CE; p<0.0001) and 5/18 developed PH2s (n=12; 28% CE vs. 9% non-CE, p=0.04). Conclusions**: MCIs are significantly associated with ICH risk. This may be due to increased contrast extravasation, or possibly pressure transmission. Our data suggest that MCIs should be minimized during IA revascularization procedures.OF ICH

Variable	Odds Ratio (95% CI)	p-value
# of MCIs (categorized as 0, 1–2, 3–4, 5+)	1.70(1.06–2.62)	0.03
Atrial Fibrillation	6.49(1.65–25.45)	0.01
Edema/Mass Effect on HCT	3.84(1.35–10.97)	0.01
Serum Glucose (linear)	1.01(1.00–1.02)	0.07
TIMI Score (0, 1, 2, 3)	0.50(0.29–0.89)	0.02

14

Acute Stroke Management in the Elderly

Neer Zeevi, Univ of Connecticut, Hartford, CT; Nora Lee, Isaac Silverman, Hartford Hosp, Hartford, CT; Louise McCullough; Univ of Connecticut, Hartford, CT

Introduction. Though the proportion of elderly stroke patients is increasing, patients over age 80 are often excluded from clinical stroke trials. We reviewed the management of older patients presenting with acute ischemic stroke (AIS) and assessed the safety and efficacy of recombinant tissue plasminogen activator (rt-PA) administration in a community-based setting. **Methods**. A retrospective review of patients over age 80 (n=275) admitted to a community stroke center with AIS were compared to their younger counterparts (n=540) using the stroke center database from March 2003 to April 2005. Parameters that were measured included admission and discharge NIH stroke scale (NIHSS), rate of thrombolytic treatment, the frequency and etiology of thrombolytic exclusion criteria and complications from rt-PA. Data was collected for length of stay, Barthel Index (BI) at 30 days and discharge destination (home vs. institution). **Results**. The lower rates of rt-PA administration seen in older patients were not due to delays in reaching the hospital within 3 hours of stroke onset (135/540;25% in <80 vs.67/275; 24% in >80 cohort). Older patients were less likely to be treated with rt-PA because of reasons not listed as exclusion criteria (40% in >80 vs. 26% in <80). Despite equivalent NIHSS on admission (13 in <80 vs. 13.5 in >80), the older group did not have an excess risk of intracranial hemorrhage following rt-PA infusion or an increased mortality. Both groups showed improvement in NIHSS following thrombolytic treatment with a drop of 6.9 points in the younger age group and 4.0 points in the older group. Elderly patients treated with rt-PA had an improved BI at 3 months compared to the untreated elderly. Additionally only 78% of elderly were discharged on antiplatelet medications vs. 97% of the younger cohort. **Conclusion**. Early treatment with rt-PA in patients over the age of 80 is both safe and efficacious. Treated patients showed improvements both acutely (a decrease in NIHSS) and chronically, as shown by a sustained improvement in the BI. The elderly were more likely to be inadequately treated for secondary stroke prevention. Older patients with AIS can be treated safely with thrombolytic therapy in a community setting. This therapy should not be withheld on the basis of age.

Hemorrhage

15

The Increasing Burden of Anticoagulant-Associated Intracerebral Hemorrhage

Matthew L Flaherty, Mary Haverbusch, Padmini Sekar, Brett M Kissela, Dawn Kleindorfer, Charles J Moomaw, Laura Sauerbeck, Joseph P Broderick, Daniel Woo; Univ of Cincinnati, Cincinnati, OH

Background: Anticoagulant associated intracerebral hemorrhage (AAICH) is a feared complication of anticoagulant treatment, but its epidemiology has not been well studied in a population-based setting. We sought to determine the incidence and outcome of AAICH in two large, population-based ICH cohorts. **Methods:** All patients age $\geq$ 18 hospitalized with nontraumatic ICH in the Greater Cincinnati area were identified during 1988 (cohort 1) and from 5/98–7/01 and 8/02–4/03 (cohort 2). AAICH was defined as ICH in patients receiving warfarin or heparin. Incidence rates were calculated and adjusted to the 2000 US population. A Cox regression model was created to assess the impact of anticoagulation on outcome. **Results:** AAICH occurred in 9 of 183 (5%) cases in cohort 1 and 190 of 1041 (18%) cases in cohort 2 ($p< 0.001$). Warfarin accounted for 180 of 190 AAICHs in cohort 2. The age-, sex-, and race-adjusted annual incidence rates of AAICH per 100,000 persons $\geq$ 18 were 1.0 (95% CI 0.4–1.7) for cohort 1 and 5.3 (95% CI 4.6–6.1) for cohort 2. We estimate that approximately 11,000 AAICHs now occur annually in the United States. For cohort 2, the incidence of AAICH was similar in blacks and whites (5.5 vs. 5.2 cases per 100,000), but AAICH was responsible for a higher percentage of ICH cases in whites than blacks (20% vs 11% of cases, $p=0.002$). Compared to the total number of ICHs at each brain location, the highest percentage of AAICH occurred in the cerebellum (31% of all cerebellar ICH), compared to deep cerebral (17%), lobar (16%) and brainstem (19%) locations ($p=0.004$). A Cox regression model of outcome after AAICH will be presented. **Conclusions:** The incidence of AAICH quintupled during the 1990s. AAICH now constitutes an important subgroup of all ICH, with an estimated 11,000 cases in the United States annually. Cerebellar ICH is most likely to be anticoagulant related. Despite its association with amyloid angiopathy, lobar ICH is not more likely to be anticoagulant associated than deep cerebral ICH. The incidence of AAICH is similar in whites and blacks, but AAICH accounts for a larger percentage of total ICH among whites, likely reflecting community patterns of atrial fibrillation.

16

Early Hematoma Evacuation After Fibrinolysis in a Porcine Intracerebral Hemorrhage Model Markedly Decreases Proinflammatory Cytokine Gene Expression in Perihematomal White Matter

Kenneth R Wagner, Shauna Beiler, Christian Beiler, Michael J Linke, Gabrielle M de Courten-Myers; Univ of Cincinnati College of Med, Cincinnati, OH

Introduction: Our previous studies have demonstrated that expression of the pro-inflammatory cytokine genes, interleukin-1-beta (IL-1 beta) and tumor necrosis factor-alpha (TNF-alpha), is rapidly up-regulated in perihematomal white matter in a porcine intracerebral hemorrhage (ICH) model. Also, in this model, early (3 hours) hematoma removal after lysis with tissue plasminogen activator (tPA), markedly reduces perihematomal edema development and protects the blood-brain-barrier (BBB) at 24 hours. Presently, we tested the hypothesis that early clot removal can reduce the increased expression of these pro-inflammatory cytokine genes. **Methods:** We infused arterial blood (3 ml) into frontal hemispheric white matter of pentobarbital anesthetized (35 mg/kg) male pigs (~20 kg, N=6) and monitored and controlled physiologic variables. At 3 hours, in the treated group (N = 3), we infused 0.3 mg of tPA in 0.3 ml of saline into the hematoma and aspirated the liquefied blood. In the non-treated group, we infused saline (0.3 ml) into the clot, but did not aspirate. We then froze the brains of pigs in both groups *in situ* at 6 hours. We sampled perihematomal and similarly located contralateral white matter, extracted RNA and prepared first-strand cDNA. We performed real-time-PCR using Invitrogen's LUX primers for IL-1 beta and TNF-alpha. Cytokine gene expression levels were determined by threshold cycle analyses and normalized to expression of the housekeeping gene, glyceraldehydes-3-phosphate dehydrogenase (GAPDH). **Results:** In the non-treated group, IL-1 beta and TNF-alpha gene expression were significantly ($p<0.05$) upregulated by 3.8- and 1.8- fold, respectively at 6 hrs post-ICH in edematous perihematomal white matter versus contralateral control values. Hematoma aspiration after clot lysis with tPA at 3 hours post-ICH reduced these elevated gene expression levels to control values. **Conclusions:** Early clot removal after ICH decreases pro-inflammatory cytokine gene expression hypothetically by removing 'toxic' blood products. Down-regulation of IL-1 beta and TNF-alpha expression by early surgery may improve outcome after ICH by reducing these cytokines that can contribute to BBB opening, vasogenic edema development and white matter damage.

17

Safety Profile of Recombinant Factor VIIa in Patients with Intracerebral Hemorrhage

Michael N Diringer, Washington Univ Sch of Med, St Louis, MO; Daniel Selchen, Trillum Health Ctr, Mississauga, Canada; Stephen Davis, Royal Melbourne Hosp, Parkville, Australia; Stephan A Mayer, Columbia Univ College of Physicians and Surgeons, New York, NY; Nikolai C Brun, Novo Nordisk A/S, Copenhagen, Denmark; Joseph Broderick, Univ of Cincinnati Med Ctr, Cincinnati, OH; Brett E Skolnick, Novo Nordisk Inc, Princeton, NJ; Thorsten Steiner, Univ of Heidelberg, Heidelberg, Germany; Recombinant Activated Factor VII Intracerebral Hemorrhage Trial Investigators

Introduction: Pooled data to assess the safety of recombinant Factor VIIa (rFVIIa) in treatment of patients with spontaneous intracerebral haemorrhage (ICH) was used to better define the risk of thromboembolic complications. **Methods:** Data from 3 randomised, placebo-controlled studies of rFVIIa in ICH patients (mean age 65) diagnosed within 3 hours of onset received a single dose of rFVIIa (5–160 mcg/kg; n=371) or placebo (n=115) were pooled. Safety parameters included adverse events (AEs) until discharge/day 15, serious AEs (SAEs) and mortality to day 90. Thromboembolic event monitoring (including clinical and laboratory evaluations, lower extremity Doppler, oedema/haematoma ratio on 72 hour CT scan) was performed on all patients. **Results:** AEs were comparable across groups; 50% were mild in severity. Mortality was significantly lower in rFVIIa patients (combined) versus placebo. Regression analysis indicated no significant treatment effect on overall risk of thromboembolic SAEs. However, an increased risk for arterial thromboembolic SAEs was observed for the 160 mcg/kg dose (OR=7.17; $P=0.0004$ versus placebo). Arterial events occurring within 3 days of drug administration included myocardial ischemia (n=11, 1 with sequela), and ischemic stroke (n=13, 2 with new deficits and 1 fatal). **Conclusion:** No significant differences in AEs were found between rFVIIa dosed patients compared to placebo. Thromboembolic SAEs did not differ between treatment and placebo groups, with no increases in the risk for DVT and/or PE despite concerns. However, in the 160 μg/kg group the frequency of arterial events was significantly greater than placebo, suggesting that in elderly patients with atherosclerosis risk factors, higher doses, although reducing overall mortality, may also increase the frequency of arterial thromboembolic events. This should be further explored.

OVERVIEW OF AES

	Placebo	5–40 mcg/kg	80 mcg/kg	120–160 mcg/kg	Combined rFVIIa
No. of subjects	115	150	106	115	371
Subjects with AEs, n (%)	109 (95)	137 (91)	98 (92)	108 (94)	343 (92)
Subjects with SAEs, n (%)	43 (37)	43 (29)	29 (27)	45 (39)	117 (32)
Subjects with TE events, n (%)	6 (5.2)	11 (7.3)	6 (5.7)	13 (11.3)	30 (8.1)
Serious TE	4 (3.5)	9 (6.0)	5 (4.7)	10 (8.7)	24 (6.5)
Arterial TE	2 (1.7)	6 (4.0)	3 (2.8)	11 (9.6)	20 (5.4)
Venous TE	4 (3.5)	5 (3.3)	3 (2.8)	4 (3.5)	12 (3.2)
DVT	1 (0.8)	2 (1.3)	3 (2.8)	2 (1.7)	7 (1.9)
PE	2 (1.7)	3 (2)	1 (0.85)	2 (1.7)	6 (1.6)
Other venous TE	1 (0.8)	0	1 (0.85)	1 (0.85)	3 (0.8)
90-day mortality, %	27	18	16	20	18 ($P=0.0264$ vs placebo)

18

Myocardial Injury in Patients with Intracerebral Hemorrhage Treated with Recombinant Factor VIIa

Rebecca M Sugg, Nicole R Gonzales, Dawn E Matherne, Marc Ribo, Hashem M Shaltoni, Elizabeth A Noser, John Y Choi, Andrei V Alexandrov, James C Grotta; The Univ of Texas–Houston Med Sch, Houston, TX

Background:Recombinant factor VIIa (rFVIIa) reduces hematoma growth after intracerebral hemorrhage (ICH). However, rFVIIa also contributes to thrombogenesis. We report findings of myocardial injury in rFVIIa treated and non-treated (NT) patients with acute ICH. Methods:We identified consecutive patients with primary ICH from June 2004 to March 2005. After obtaining informed consent, patients presenting within 4 hrs of onset were treated with 80mcg/kg rFVIIa. Exclusion criteria were ICH $\geq$5cm with mass effect and GSC $\leq$8, or ICH score $\geq$4. After the 3rd patient, those with history of acute or chronic thrombotic events were excluded. All patients received standard medical management, electrocardiogram (ecg), and cardiac enzyme panel. All rFVIIa, and most NT patients received serial ecg and enzymes q 8 hrs X 24 hrs. Elevation of troponin was defined as >0.1 ng/mL. Myocardial infarction (MI) was defined as serial elevation of troponin, S-T elevation or T-wave inversion, and clinical symptoms. Results:137 patients with ICH were screened; 7 were excluded due to the presence of subarachnoid hemorrhage. 20 patients were treated with rFVIIa (45% male, age 58$\pm$15), and 110 were NT (55%, 62$\pm$14). Median NIHSS in the rFVIIa group was 15 (7–20) vs 16 (3–35) NT. Hematoma volume in the rFVIIa group was 22 $\pm$ 17cc vs 35$\pm$ 38cc NT ($p=0.012$). Baseline troponin was 0.011$\pm$ 0.02 in the rFVIIa group vs 0.016$\pm$ 0.02 NT ($p=0.52$). Average number of troponin measurements per patient within 30 hours of admission was 2.45$\pm$0.99 in the rFVIIa group vs 2.04$\pm$0.89 NT ($p=0.07$). 10% of troponins were elevated in the rFVIIa group compared to 2.7% NT ($p=0.004$). Elevated troponin occurred in 4 patients (20%) in the rFVIIa group vs 4 (3%) NT group ($p=0.02$). MI occurred in 2 (10%) of rFVIIa patients (one had history of coronary artery disease, both had initial normal ecg, symptoms occurred within 1 hour of treatment, and one died) vs 1(1%) NT ($p=0.01$). Mortality with rFVIIa was 20% vs 31% NT($p=0.56$). Conclusion:Troponin elevation is uncommon after ICH. However, we found a significant increase in myocardial injury in patients treated with rFVIIa compared to NT patients. Although rFVIIa is a promising new treatment for ICH, further study should explore how to exclude patients at risk for thrombotic cardiac complications.

19

Neuroprotection by Intravenous Human Neural Stem Cell Transplantation in Intracerebral Hemorrhage with Anti-inflammatory and Anti-apoptotic Effects

Kon Chu, Manho Kim, Keun-Hwa Jung, Soon-Tae Lee, Dong-In Sinn, Jeong-Min Kim, Song-Yi Ko, Stroke and Neural Stem Cell Lab, Seoul National Univ Hosp, Seoul, Republic of Korea; Seung U Kim, Brain Disease Res Ctr, Ajou Univ, Suwon, Republic of Korea; Jae-Kyu Roh; Stroke and Neural Stem Cell Lab, Seoul National Univ Hosp, Seoul, Republic of Korea

Backgrounds: The transplantation of neural stem cells (NSCs) has been tried to achieve the regeneration of damaged brain in many neurological disorders. However, it has been recently reported that NSCs may rescue the degenerating neurons from imminent injury rather than mere replacement. We previously showed that intravenously injected NSCs promoted neurological recovery in intracerebral hemorrhage (ICH). Here we investigate whether the injection of NSCs in the acute period of ICH can induce neuroprotection. **Methods and Results:** ICH was induced by collagenase infusion into basal ganglia of adult rats. Human NSCs (H1 clone, 5 million cells [iv] or 1 million cells [ic]; prelabeled with PKH26) were injected intravenously (iv) or intracortically (ic) in 2 hours or 24 hours after ICH induction. At 72 hours after ICH, $PKH26^+$ human NSCs migrated intensely around the hematoma area. While

hematoma volumes were not different between groups, the water content decreased to 80.10 ± 0.25 % in the 2hr-NSCs-iv group, compared with all other groups ($p<0.01$). The inflammatory infiltrates (myeloperoxidase+ neutrophils, and OX-42+ microglia/macrophages) were reduced in 2 hr-NSCs-iv group significantly ($p<0.01$, respectively), not in 24hr-NSCs-iv group. TUNEL$^+$ cells were detected within the hemorrhage itself, and also in the periphery of the hemorrhage. The 2hr-NSCs-iv group evidenced a reduced number of TUNEL$^+$ cells ($p<0.01$) as compared to the ICH-only group or 24 hr-NSCs-iv group. In 2hr-NSCs-iv group, protein expression of eNOS (~13.3 folds) and bcl-2 (~10.2 folds) was increased and NF-κB (-25%) was decreased. Also, mRNA expressions of Fas, Fas ligand and TNF-α decreased and those of PAI-1 (~12.2 folds) were significantly upregulated in 2 hr-NSCs-iv group. In modified limb placing test, 2hr-NSCs-iv group showed the earlier (from day 1) and the better recovery than 24hr-NSCs-iv group (from week 4) and ICH-only group ($p<0.05$). **Conclusions:** These results suggest that intravenous injections of adult human NSCs have relevant therapeutic potential in ICH because they display anti-inflammatory and anti-apoptotic functions that promote acute neuroprotection.

20

A Tool for Predicting Outcome After Spontaneous Supratentorial Intracerebral Hemorrhage

Barbara A Gregson, A David Mendelow, Univ of Newcastle upon Tyne, Newcastle upon Tyne, United Kingdom; STICH Investigators

Introduction The international surgical trial in intracerebral haemorrhage (STICH) was undertaken to determine whether there was a benefit from early surgery compared to initial conservative treatment. Over one thousand patients from 27 countries were randomised to the study and randomisation CT scans were obtained for 960 patients. This study provides a rich source of data to examine the relationship between the characteristics of the patient and the haematoma and outcome at six months. From this we have developed a tool for predicting likely outcome at six months which can be used as an aid to treatment decisions or in prognosis based outcome assessment for future studies. **Methods** STICH was a multicentre randomised parallel group trial comparing early surgery with initial conservative treatment. For this analysis complete data were available for 837 patients. These data included demographic data, neurological status at admission, time from ictus and detailed independent analysis of site and size of haematoma from CT scans, together with presence of intraventricular haemorrhage and hydrocephalus. Outcome was measured using the extended Glasgow Outcome Scale which was recorded using structured postal questionnaires. Logistic regression was undertaken to examine the relationships between the characteristics of the patient and haematoma and outcome and to develop a prediction algorithm. **Results** The most important predictors of an unfavourable outcome were presence of a neurological deficit on admission ($p<0.0001$), lower Glasgow Coma Score (GCS) ($p<0.0001$), increasing age ($p<0.0001$), presence of an intraventricular haemorrhage (IVH) ($p=0.0001$), larger midline shift ($p=0.0001$), shorter time between ictus and admission ($p<0.0001$), site of haemorrhage ($p<0.0001$), larger volume of haemorrhage ($p<0.0001$), presence of hydrocephalus ($p<0.0001$). Independent predictors identified by this study were neurological deficit, GCS, age, IVH and midline shift. **Conclusions** This prognostic information can be used with a PDA or laptop to provide reliable and instant prognostic information to assist with clinical decisions at the bedside or in the clinic.

21

New York Islands AVM Study: 5-Year AVM Detection Rates and Age-Dependent Incidence of AVM Hemorrhage

C Stapf, C Hofmeister, J H Choi, H Mast, J P Mohr, Stroke Ctr, Columbia Univ, New York, NY; for the New York Islands AVM Study Collaborators

Background: Only little data exist on the effect of age on incident rupture of brain arteriovenous malformations (AVMs). **Methods**: The New York Islands AVM Study is an ongoing prospective population-based survey since March 15, 2000. The catchment area (Manhattan Island, Staten Island, and Long Island) comprises 9,429,541 residents (census 2000). All major NY islands hospitals prospectively report demographic data on consecutive patients with a diagnosis of brain AVM and whether or not the patient had suffered AVM hemorrhage. Referral patients living outside the ZIP code-defined study area were excluded from the study population. **Results**: As of March 14, 2005, 638 prospective AVM patients (mean age 41 years, ±18SD, 53% women) were encountered leading to a calculated AVM detection rate of 1.35/100,000 person-years (95% CI: 1.25 to 1.46) with an estimated incidence of first-ever AVM hemorrhage (n=246, mean age 38 years ±19SD, 52% women) of 0.52/100,000 person-years (95% CI: 0.46 to 0.59). The prevalence of AVM hemorrhage among detected cases (n=301) was 0.64/100,000 (95% CI: 0.57 to 0.71). The relative frequency of hemorrhagic presentation decreased with age ($p<0.0001$) and was significantly higher in patients aged <20 (58%) when compared to those ≥20 years (45%; p=0,02). **Conclusions**: The 5-year data suggest stable rates for AVM detection and incident AVM hemorrhage in this geographically defined population. Overall, approximately half of AVM patients may suffer intracranial hemorrhage. The relative proportion of incident AVM rupture among detected cases is inversely associated with age at presentation.

In-hospital Treatment

22

Stent-Assisted Angioplasty in Ostium of Vertebral Artery

Bin Du, Ning Ma, Wei-Jian Jiang; Beijing Tiantan Hosp, Beijing, China

Purpose: This prospective, non-randomized, single center study evaluated the safety and feasibility of stent-assisted angioplasty in atherosclerotic stenoses of vertebral artery (VA) ostium. ***Materials and methods***: Patients with posterior circulation stroke and/or transient ischemic attack attributed to a stenosis at VA ostium ≥50% in digital subtraction angiography were approached for consent to participate in the study. Each eligible patient had ≥1 atherosclerotic risk factor and evidence of perfusion deficit referable to the posterior circulation. High-grade stenosis was defined as ≥70%. Technical success was residual stenosis ≤20%. ***Results:*** Eighty-eight patients (100 ostial stenoses) were recruited from June 2001 to March 2005. Seventy-nine patients were men. Mean age was 61 years (range 36–80). Sixty-nine lesions were high grade stenoses. Technical success was achieved in 98 lesions (98%), including in 8 procedures where the lesions were approached via ipsilateral brachial artery. Distal emboli protection device was applied in 9 procedures. Complications occurred in 3 patents (3.4%), consisting of 1 stent migration, 1 acute in-stent thrombosis and 1 thrombo-embolic stroke. No deaths, intracranial hemorrhage, vascular rupture or dissection was observed. Follow-up angiography (after 6 months) in 29 patients (34 stented lesions) showed re-stenosis (≥50%) in 9 patients (26.5% of lesions), although 7 patients remained asymptomatic. ***Conclusion:*** Stent-assisted angioplasty for atherosclerotic stenosis of VA ostium appears safe and feasible.

23

Get With The Guidelines–Stroke Produces Sustainable Improvements in Hospital-Based Acute Stroke Care

Lee H Schwamm, Massachusetts General Hosp, Boston, MA; Kenneth A LaBresh, MassPRO, Waltham, MA; Wenqin Pan, Duke Clinical Res Inst, Durham, NC; Michael Frankel, Emory Univ Sch of Med, Atlanta, GA; on behalf of the GWTG Steering Committee and Investigators

Background: Background: QI interventions are difficult to maintain over time. We assessed sustainability of improvement over 8 consecutive quarters at 65 hospitals who have participated in the Get With The Guidelines (GWTG)-Stroke hospital-based stroke QI program since its inception. **Methods**: We used collaborative meetings, best practice sharing and an Internet tool for data collection, reporting and decision support in 37,753 clinically identified patients at 65 participating hospitals. Data included baseline (≥30 records prior to 4/03) and 8 consecutive quarters of patient records up to 4/05. Measures included use of IV tPA or documentation of ineligibility (why no tPA) in patients who arrived <2 hr or <3 hr after symptom onset (ED<2 hr + tPA; ED<3 hr + tPA), symptomatic ICH (IV-tPA Comp), antithrombotics (Rx AT<48hr) or DVT prophylaxis (DVT-Risk) ≤48 hours, and discharge antithrombotics (Rx-AT-DC), anticoagulation for atrial fibrillation (WAR-AF-Rx-DC), treatment for LDL >100 (LDL-100-Rx-DC), diabetes mellitus (DM-Rx-DC), and counseling for smoking cessation (SMOKE-Rx-DC) and BMI>25 (BMI-Rx-DC). Compliance (%) for eligible patients per quarter (Q) and baseline (B) was recorded. Q8 was compared to baseline and trends over time assessed. All tests were performed using Mantel-Haenszel (MH) chi-square test controlling for hospital site. **Results**: There was improvement in Q8 vs. B and over time. Q5–8 performance was sustained at the Q4 level in all measures except weight management (-0.7%, p<.0001). Intervention for lipids (+5.5%), diabetes (+6.2%) and smoking (+19.9%) all showed further improvement (p<.0001). There was no increase in the rate of bleeding after IV tPA.

Measure (n)	B (%)	Q1 (%)	Q2 (%)	Q3 (%)	Q4 (%)	Q5 (%)	Q6 (%)	Q7 (%)	Q8 (%)	(Q8 - B) (%Δ)	p value	MH
ED<2 hr + tPA (n=1919)	27.6	35.2	41.1	57.7	51.2	53.8	56.7	55.3	50.5	22.9	<.0001	<.0001
ED<3 hr + t-PA (n=2440)	23.2	27.1	34.4	45.2	38.4	41.5	48.0	43.2	40.1	16.9	<.0001	<.0001
Why no tPA (n=5551)	70.1	82.3	87.4	88.8	92.0	90.3	90.0	91.6	88.3	18.2	<.0001	<.0001
IV tPA comp (n=1148)	3.9	2.0	5.8	2.7	4.3	5.7	3.6	6.7	5.1	1.2	NS	NS
Rx-AT<48hr (n=28547)	87.5	92.8	94.7	95.2	95.6	96.2	96.1	96.1	95.9	8.4	<.0001	<.0001
DVT-Risk (n=15917)	88.9	81.8	78.3	77.1	82.6	81.9	81.9	79.6	82.7	-6.2	<.0001	0.002
Rx-AT-DC (n=32141)	92.5	93.9	96.3	96.9	97.4	97.5	97.2	97.4	97.9	5.4	<.0001	<.0001
WAR-AF-Rx-DC (n=2489)	78.9	85.0	92.2	97.5	96.1	95.1	96.0	98.7	97.1	18.2	<.0001	<.0001
LDL-100-Rx-DC (n=15670)	56.0	67.5	68.1	72.3	75.5	80.0	79.5	79.9	81.0	25.0	<.0001	<.0001
DM-Rx-DC (n=9255)	45.3	73.9	73.4	74.0	79.9	85.4	83.1	85.2	86.1	40.8	<.0001	<.0001
SMOKE-Rx-DC (n=4991)	39.1	43.6	41.8	57.0	56.9	61.1	66.0	74.2	76.8	37.7	<.0001	<.0001
BMI-Rx-DC (n=11343)	25.9	26.1	32.5	41.1	39.1	34.3	34.6	42.5	38.4	12.5	<.0001	<.0001

Conclusion: GWTG-Stroke was associated with sustained and significant improvements in a wide variety of acute stroke care and secondary prevention performance measures over 2 consecutive years. These data suggest that QI efforts in acute stroke do not need to be limited to only a few domains.

24

Safety and Feasibility of Intra-arterial Autologous Bone Marrow Mononuclear Cell Transplantation in Acute Ischemic Stroke

Gabriel R de Freitas, Univ Federal do Rio de Janeiro, Rio de Janeiro, Brazil; Maria Lúcia F Mendonça, Daniel C Bezerra, Suzana A Silva, Carlos Henrique Falcão, Constantino S Gonzales, Rodrigo C Moreira, Andrea F Haddad, Fabio A Tuche, Pró-Cardíaco Hosp, Rio de Janeiro, Brazil; Daniel P Santos, Charles Andre, Univ Federal do Rio de Janeiro, Rio de Janeiro, Brazil; Claudio T Mesquita, Amarino A Oliveira, Pró-Cardíaco Hosp, Rio de Janeiro, Brazil; Vinicio Elia, Hosp Municipal Miguel Couto, Rio de Janeiro, Brazil; Hans J Dohmann, Pró-Cardíaco Hosp, Rio de Janeiro, Brazil; Radovan Borojevic, Rosália Mendez-Otero, Univ Federal do Rio de Janeiro, Rio de Janeiro, Brazil; Hans Dohmann; Pró-Cardíaco Hosp, Rio de Janeiro, Brazil

Introduction: In animal models, stem cells enhanced functional recovery after stroke. Moreover, recent publications have demonstrated the safety of autologous bone marrow mononuclear cells (BMMC) in humans when injected intracoronary. **Hypothesis:** We assessed the hypothesis that intra-arterial autologous BMMC transplantation is safe and feasible in acute ischemic stroke. **Methods:** This phase I open label trial involved patients with an ischemic stroke in the territory of the middle cerebral artery (MCA) with a NIHSS between 4 and 20 and with spontaneous recanalization confirmed transcranial Doppler (TCD) and magnetic resonance angiography. Between the third and the seventh day after stroke onset, bone marrow cells were aspirated from the posterior iliac crest. On the same day, 30 million BMMC were injected in the MCA via catheter angiography. The procedure was monitored by TCD and electroencephalography. Brain perfusion with 99mTc-ECD SPECT, PWI/DWI-MRI and brain PET-FDG were performed at baseline and 7 days, 3 and 6 months after BMMC injection. Clinical examination

was quantified by the NIHSS, Barthel Index (BI) and modified Rankin Scale (mRS). 10 patients are programmed to be enrolled in the active group, and 5 in the control group. **Results:** We report the results of the first 5 patients of the active group (enrolment should be completed until December, 2005). Mean age was 51.8±6 years old and 3 were male. No EEG abnormalities or significant micro-embolic signals were observed during BMMC injection. Median NIHSS; BI and mRS were 12, 25 and 4 at baseline; 8, 55, 3 at 1 week and 7, 85 and 3 at 1 month after procedure, respectively. Interestingly, one week after cell transplantation, PET-FDG showed a marked increase in glucose metabolism in the infarcted area in one of the patients. **Conclusion:** These initial data suggests that intra-arterial injection of autologous BMMC in the MCA is feasible and safe in acute stroke. If these initial results are confirmed, phase II studies will be required to evaluate the efficacy of BMMC transplantation using different ways of administration (e.g. intravenous, intra-arterial) and doses.

25

Intracranial Stent-Assisted Angioplasty in Symptomatic Intracranial Stenosis

Wei-Jian Jiang, Thomas W Leung, Xiao-Tong Xu, Bin Du, Yong-Jun Wang; Beijing Tiantan Hosp, Beijing, China

Objective: To investigate the safety and feasibility of stent-assisted angioplasty in symptomatic intracranial arterial stenosis. Methods: Consecutive patients who had transient ischemic attack (TIA) or stroke attributed to an intracranial arterial stenosis that measured more than 50 % by digital subtraction angiography were approached for consent to participate in the study. Results: 175 patients (with 189 stenoses) were recruited and had stent-assisted angioplasty from September 2001 to November 2004. 160 patients (91.4 %), or 174 attempted lesions (92.1 %), had stent deployment-success (residual stenosis $\leq$20 %). Thirteen of the 15 stent deployment-failure cases were related to failed negotiation of guiding catheter (n=1), microwire (n=4) or stent-system (n=8) through the difficult vascular access. Cerebrovascular complications (adverse events within 30 days) occurred in 20 (10.6%) attempted lesions. 6 patients (3.4 %) had 'not recovered' stroke (NIHSS on day-30 $\geq$ pre-operative rating) and 2 patients (1.1%) died (both from intracranial hemorrhage). 152 patients (86.9 %) or 166 stenoses (87.8 %) had treatment-success (stent deployment-success plus day-30 NIHSS same or less than pre-operative rating). During follow-up of 170 patients (422.4 days ± SD 315.1, all $\geq$ 180 days; 3 patients lost to follow-up after day-30 assessment), the nonfatal stroke and fatal stroke recurred in 2 patients and one patient, respectively; in whom, two were stent deployment-failure cases and one of them died. Angiographic follow-up of 61 treated stenoses (in 55 patients) revealed re-stenosis (stenosis $\geq$ 50%) in 14 lesions (23.0 %). By Location, Morphology and Access (LMA) classification, type I access had significantly higher stent deployment-success; whereas type III access was a risk factor for stent deployment-failure. Conclusion: Stent-assisted angioplasty is a feasible and promising treatment option for symptomatic intracranial stenosis. LMA classification is useful in pre-operative evaluation.

26

Prognostic Value of Glucose Levels in Acute Stroke Outcome: GLIA Study

Blanca Fuentes, Exuperio Díez-Tejedor, Hosp Univ La Paz, Madrid, Spain; José Castillo, Hosp Clínico Univ, Santiago de Compostela, Spain; Antonio Dávalos, Hosp Can Ruti, Badalona, Spain; Antonio Gil Nuñez, Hosp Univ Gregorio Marañon, Madrid, Spain; José Vivancos, Hosp Univ La Princesa, Madrid, Spain; José Egido, Hosp Clínico Univ San Carlos, Madrid, Spain; on Behalf of the Stroke Project Cerebrovascular Diseases Study Group Spanish Society of Neurology

Objetive: To evaluate the prognostic influence of hyperglycemia in acute stroke outcome, adjusting for other known prognostic factors and to establish the glucose level associated to poor outcome. **Methods:**Multicentre, observational study. We include acute ischemic stroke patients (<24 h), excluding patients unconsciousness on admission, previous stroke with modified Rankin Scale (mRS)$\geq$2, other symptomatic intracranial lesion, severe concomitant disease or impossibility to complete a 3-months follow-up. Capillary glucose, blood pressure, body temperature, and neurological state were determined on admission and 3 times a day during the first 48h. Outcome at 3 months was determined by mRS. Statistical analysis: χ-square, t-student, Spearman and Pearson correlations, ROC-analysis, multivariate stepwise logistic regression. **Results**: 476 patients. Mean age 70.78±10.5; time stroke-onset to inclusion: 6.8±5.7 h. Mean glucose on admission (glu adm): 137.2±57.2 mg/dl. Both glu adm and maximum glucose in the first 48h (glumax 48h) correlated to lesion volume (r0.204 and 0.189) and mRS 3m (r0.213 y 0.282). Glumax 48h= 155.5 mg/dl was the point of maximum specificity and sensibility for outcome at 3m in ROC analysis. Multivariate logistic analysis pointed out as independent prognostic factors for death or dependence at 3m: glumax 48h > 155 mg/dl (OR 2.1; 95%IC 1.2–3.7), age (OR 1.05;95%IC 1.01–1.08) and CSS on admission (OR 0.1; 95%IC 0.4–0.5). HbA1c correlated to glu adm (r 0.541), glumax 48h (r0.676), CSS 3m (r0.222) and mRS 3m (r0.352). In all the series, patients with not previously known diabetes had poor outcome than those with diagnosed diabetes and both poor than non-diabetic patients (p<0.001). However, in the group of patients with glumax 48h >155 mg/dl no differences in outcome at 3 months were found with regards to history of diabetes. **Conclusions**: Both hyperglycaemia >155 mg/dl within the first 48 h and HbA1c>6% are independent predictive factors for death or dependence at 3m. Patients with not previously known diabetes had poor outcome than those with diagnosed diabetes and both poor than non-diabetic patients. Acute stroke hyperglycaemia clearly determines poor outcome at 3 months in both diabetic and non-diabetic patients.

27

Influence of Statin Withdrawal on Acute Ischemic Stroke Outcome: A Randomized Prospective Study

Florentino Nombela, Hosp Univ de la Princesa, Madrid, Spain; Miguel Blanco, Hosp Clínico Univ, Santiago de Compostela, Spain; M A Moro, Sch of Med, Univ Complutense, Madrid, Spain; Manuel Rodríguez-Yáñez, Rogelio Leira, Hosp Clínico Univ, Santiago de Compostela, Spain; Ignacio Lizasoain, Sch of Med, Univ Complutense, Madrid, Spain; Mónica Millán, Hosp Germans Trias i Pujol, Badalona, Spain; Joaquin Serena, Hosp Dr Josep Trueta, Girona, Spain; Jose Vivancos Mora, Hosp Univ de la Princesa, Madrid, Spain; Jose Castillo; Hosp Clínico Univ, Santiago de Compostela, Spain

BACKGROUND AND PURPOSE Retrospective, uncontrolled data suggest that the withdrawal of statin therapy may have deleterious effects on ischemic brain injury. In this prospective, open-labeled, randomized study of 215 patients with acute ischemic stroke we sought to investigate the influence of statins withdrawal after the onset of symptoms on stroke outcome MATERIALS and METHODS Patients were admitted in a single center within 24 hours from symptoms onset. A total of 89 patients (41,4%) on current statin treatment were randomized to statin withdrawal (n=46) during the first 3 days (Group A), or to continue on statin therapy (n=43) (Group B); 126 patients who were not taken statins at stroke onset were also evaluated (Group C). All patients initiated atorvastatin 20 mg/day after day 3. Outcome variables were early neurological deterioration (END) defined as a fall $\geq$ 4 points in NIHSS between admission and 48 hours, infarct volume on CT at day 4–7, and poor functional outcome defined as a modified Rankin scale score > 2 at 3 month. Informed consent was obtained, and the trial was approved by the local Ethics Committee. The effect of statin withdrawal was analyzed by logistic regression and lineal models, adjusted by stroke severity and related variables in bivariate analyses. RESULTS Baseline clinical characteristics were well balanced between groups A and B, but a cardioembolic source was found more frequently in group C, and large artery atherosclerotic disease in group A and B. Group A had the higher frequency of END (A: 65.2%; B: 20.9; C: 27.8%; p<0.0001) and poor outcome (A: 58.7% ; B: 37.2%; C: 42.1%; p=0.001), and the greater infarct volume (A: 74[45–126]; B: 26[12–70]; C: 53[14–117] c.c.; p<0.0001). The OR (95%CI) of END and poor outcome for statins withdrawal were 9.93 [3.97–24.86] and 3.57 [1.47–8.69]. Statins withdrawal was associated with an increase of 20.8 cc [4.19–37.51] in the mean of estimated infarct volume. CONCLUSION This prospective study confirms that statins withdrawal in the acute phase of ischemic stroke is associated with poor neurological outcome and larger brain injury

28

Use of Lipid-Lowering Agents During Acute Ischemic Stroke Decreases In-Hospital Mortality

Norrina B Allen, Lawrence M Brass, Yale Univ, New Haven, CT; Julie Cerese, Jackie Dostal, Joanne Cuny, Univ HealthSystem Consortium, Oak Brook, IL; Judith H Lichtman; Yale Univ, New Haven, CT

Background/Objective: In addition to lipid lowering, statins may have a protective effect in ischemic injury. Clinical data suggests a beneficial effect in acute coronary syndromes. There are limited clinical data for stroke. Our objective was to look for an association between the use of statins and clinical outcome in a well-characterized cohort of patients hospitalized with acute ischemic stroke. **Methods**: Charts were abstracted on consecutive patients admitted with ischemic stroke among 32 academic medical centers from January through June, 2004 as part of the University HealthSystem Consortium Ischemic Stroke Benchmarking Project. We examined the use of lipid-lowering agents (LLA) within the first 48 hours of hospitalization. Multivariate logistic regression was used to identify the association between LLA use and in-hospital mortality adjusting for potential confounders. **Results**: The study included 1256 patients (49% women; mean age 66.6 yrs; 56% white), of whom 41% (513/1256) were treated with LLA during the hospitalization. Patients treated with LLA had decreased stroke severity on admission (p<0.01) and a shorter length-of-stay (p<0.05). These patients had a greater prevalence of comorbidities (CAD, HTN, hyperlipidemia, DM, p<0.001 respectively; MI, CVA, smoking, p<0.01 respectively). Patients receiving LLA had a lower unadjusted mortality (1.4% vs 7.9%; p <0.001), and LLA use was associated with an 80% decrease in mortality in risk adjusted analyses (OR 0.17, 95% CI 0.07–0.39). **Conclusions**: This study represents the largest, multi-center study of LLA use during hospitalization for acute ischemic stroke. Use of lipid lowering agents during the acute phase of ischemic stroke is associated with reduced in-hospital mortality. Our results fill an important gap in the data which is required to justify and inform future clinical trials in the setting of acute ischemic stroke.

Outcomes

29

Lipoprotein-Associated Phospholipase A2 and C-Reactive Protein as Predictors of Stroke Recurrence and Death: The Northern Manhattan Study

Mitchell S Elkind, Kristen Coates, Wanling Tai, Ralph L Sacco; Columbia Univ , New York, NY

Background: Inflammatory markers have been associated with first ischemic stroke risk and prognosis after cardiac events. Their relationship to risk of recurrence after first stroke is unsettled. We hypothesized that levels of high-sensitivity C-reactive protein (hsCRP), an acute phase protein, and lipoprotein-associated phospholipase A_2 (LP-PLA2), a macrophage-derived enzyme involved in metabolism of low-density lipoprotein to pro-inflammatory mediators, would predict risk of recurrence. **Methods:** In the population-based Northern Manhattan Study (NOMAS), first ischemic stroke patients $\geq$40 years were followed for recurrent stroke. Levels

of Lp-PLA2 and hsCRP were measured in 467 patients, and categorized by quartile. Cox proportional hazard models of recurrent stroke, and of death, were used to calculate hazard ratios and 95% confidence intervals (HR, 95% CI) associated with marker quartiles after adjusting for demographics and vascular risk factors. Mortality models were further adjusted for stroke severity using a derived NIH Stroke Scale. **Results:** Mean age was 68.9 ± 12.7 years; 54.6% were women, 53.3% Hispanic, 27.2% black, and 17.8% white. Median follow-up was 4.0 years, and there were 80 recurrent strokes. LP-PLA2 and hsCRP levels were not strongly correlated (R=0.09, p=0.051). HsCRP, but not LP-PLA2, was strongly associated with stroke severity. Compared to the lowest quartile of LP-PLA2, those in the highest (Q4) had an increased risk of recurrent stroke (HR 2.3, 95% CI 1.2–4.4). After adjusting for demographics, hypertension, diabetes, hyperlipidemia, smoking, atrial fibrillation, and coronary disease, this effect attenuated slightly (HR 2.0, 95% CI 1.0–4.0). LP-PLA2 was not significantly associated with mortality (adjusted HR for Q4: 1.5, 0.9–2.4). HsCRP was not associated with risk of recurrent stroke (adjusted HR for Q4: 0.7, 95% CI 0.4–1.4), but was associated with risk of death (adjusted HR for Q4: 2.0, 1.2–3.5). **Conclusion:** Inflammatory markers predict prognosis after first ischemic stroke, and may offer complementary information. LP-PLA2 may be a stronger predictor of recurrent stroke risk. HsCRP, an acute phase reactant, increases with stroke severity, and may predict mortality better than recurrence.

30

Elevated White Blood Cell Count and Increased Risk for Stroke and Vascular Death in Patients with Symptomatic Intracranial Disease

Bruce Ovbiagele, UCLA Sch of Med, Los Angeles, CA; Michael J Lynn, Emory Univ Sch of Public Health, Atlanta, GA; Jeffrey L Saver, UCLA Sch of Med, Los Angeles, CA; Marc I Chimowitz, Emory Univ Sch of Med, Atlanta, GA; for the WASID Study Group

Background: Atherogenesis is a chronic inflammatory process characterized by early white blood cell (WBC) recruitment, but there are few data about the prognostic value of serum WBC count among patients with symptomatic cerebrovascular disease. We investigated the relationship between baseline serum WBC count and vascular risk in persons with symptomatic intracranial disease. **Methods:** The Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) Study was a clinical trial in which 569 patients with TIA or stroke due to 50–99% stenosis of a major intracranial artery were randomized to warfarin or aspirin. For this analysis, WBC was treated as a binary variable with subjects categorized into 2 groups based on the median serum WBC count (7.2 10E3μL). The univariate association between WBC and baseline demographic and clinical data was assessed using a chi-square test (for categorical variables) or t-test (for continuous variables). The relationship between WBC and the WASID primary endpoint (the time to first stroke or vascular death) was evaluated using the log-rank test and Cox proportional hazards regression. **Results:** Among 567 subjects with baseline WBC levels measured, mean follow-up was 1.8 years. WASID subjects in the higher WBC category were younger (mean: 62 vs. 65 years, p = 0.0026), less likely to be Black (25% vs. 36%, p = 0.034), more likely to be diabetic (43% vs. 33%, p = 0.014) or on statin treatment (67% vs. 55%, p = 0.0044), and had higher mean BMI (29.2 vs. 28.1, p =0.012) and lower mean triglycerides (157.9 vs. 180.2 mg/dl, p = 0.026). The rate of the primary endpoint was greater among WASID subjects in the higher WBC category (28% vs. 16%, hazard ratio = 1.7; 95%CI = 1.2–2.5, p = 0.003). In a multivariate analysis, after adjusting for baseline factors significantly related to the time to primary endpoint, higher WBC was independently associated with a greater risk for the primary endpoint (hazard ratio of 1.5; 95% CI = 1.06 - 2.2, p=0.024). **Conclusions:** An elevated baseline WBC count is associated with an increased risk of stroke and vascular death in patients with symptomatic intracranial atherosclerotic disease.

31

Hemorrhagic Transformation Is Associated with Hyperthermia in Patients with Acute Stroke

Rogelio Leira, Hosp Clínico Univ, Santiago de Compostela, Spain; Mar Castellanos, Hosp Dr Josep Trueta, Girona, Spain; Javier Arenillas, Hosp Germans Trias i Pujol, Badalona, Spain; Florentino Nombela, Hosp de la Princesa, Madrid, Spain; Tomás Sobrino, Hosp Clínico Univ, Santiago de Compostela, Spain; Yolanda Silva, Hosp Dr Josep Trueta, Girona, Spain; Javier Abella, Hosp Clínico Univ, Santiago de Compostela, Spain; Salvador Pedraza, Hosp Dr Josep Trueta, Girona, Spain; María Ángeles Moro, Univ Complutense, Madrid, Spain; José Vivancos, Hosp de la Princesa, Madrid, Spain; Joaquín Serena, Hosp Dr Josep Trueta, Girona, Spain; Antonio Dávalos, Hosp Germans Trias i Pujol, Badalona, Spain; José Castillo; Hosp Clínico Univ, Santiago de Compostela, Spain

PURPOSE AND METHODS: Hyperthermia is a prognostic factor of poor outcome in acute stroke, and increases blood-brain barrier (BBB) permeability in experimental stroke models. In this study we sought to investigate the relationship between hemorrhagic transformation (HT), body temperature and markers of endothelial damage in 208 patients admitted within 12 hours from onset of ischemic stroke. Patients treated with tPA (n=47), and those who died within the first 72 hours (n=8) were excluded. A multimodal MRI was performed on admission and at 72h. HT was evaluated in the 2nd MRI and was analyzed according to SITS-MOST criteria. Plasma matrix metalloproteinase 9 (MMP-9) and cellular fibronectin (cFN) levels were determined by ELISA in samples obtained on admission. The effect of the mean tympanic temperature during the first 24 hours was analyzed by logistic regression models. Continuous variables are expressed as median values. RESULTS: Out of 153 patients, 53 (34.4%) showed HT (IH1 26; IH2 18; PH1 6; PH2 3). HT was associated with a cardioembolic source (64.2% vs 23.0%; p<0.001), higher body temperature during the first 24h (36.9 vs 36.5 °C; p<0.001), stroke severity (NIHSS score, 14 vs 10; p<0.001) and greater DWI lesion volume (22.5 vs 13.3 cc; p<0.001) on admission. Plasma MMP-9 (185.1 vs 45.1 ng/mL; p<0.001) and cFN (15.2 vs 7.4 μg/mL; p=0.006) concentrations were higher in patients with HT. Body temperature correlated with MMP-9 (r=0.34; p<0.001) and cFN (r=0.29; p<0.001). Mean body temperature during the first 24h was independently associated with HT (OR, 7.4; 95%CI, 2.5–21.9; p<0.0001) after adjustment for cardioembolic source, baseline NIHSS score and DWI lesion volume. This effect remained unchanged after controlling for MMP-9 and cFN. CONCLUSIONS: These findings suggest that high body temperature within the first day after ischemic stroke is a risk factor of HT in patients not treated with tPA. The effect is independent of the biological signatures of endothelial damage.

32

Antiplatelet Use Is Associated with Less Severe Stroke in Patients with No Prior History of Stroke or TIA

Nerses Sanossian, Jeffrey L Saver, Tannaz Razinia, Doojin Kim, Bruce Ovbiagele; UCLA, Los Angeles, CA

Background: Conflicting results exist as to the efficacy of antiplatelet agents in reducing ischemic stroke severity. We aimed to evaluate the independent effect of premorbid antiplatelet use on incident ischemic stroke severity and outcome at discharge. **Methods:** Consecutive patients presenting within 24hours of ischemic stroke over a one-year period were studied. NIHSS score at presentation was used as index of stroke severity and a modified Rankin scale of 0 to1 at discharge as index of good functional outcome. Patients were categorized according to their pre-morbid antiplatelet use. Age, risk factor history (hypertension, atrial fibrillation, tobacco use and diabetes), admission glucose, premorbid statin use, premorbid ACE inhibitor/angiotensin receptor blocker use, history of prior stroke or TIA, and stroke subtype were controlled for across the two groups using multivariate logistic regression. **Results:** 260 individuals met study criteria. 92 patients were on antiplatelet agents prior to admission, 168 were on no antiplatelets. Pre-treatment with antiplatelet was associated with lower presenting median NIHSS (4.5 vs. 7, p=0.005). Antiplatelet use was associated with less severe stroke at presentation in those having no history of stroke or TIA (4.8 vs. 8.0, p=0.03) but not in those with a prior history of stroke or TIA (4.9 vs. 4.9, p=0.987). The likelihood of a good outcome was increased in those on antiplatelets after adjusting for other variables (OR 2.105, p= 0.0073). **Conclusions:** Pre-stroke use of antiplatelet is associated with reduced severity of incident ischemic strokes in those with no prior history of stroke or TIA, and with an increased likelihood a good discharge outcome regardless of prior cerebrovascular event history. Antiplatelet agents may be less effective in attenuating the extent of ischemic injury in a brain which has developed its own internal mechanisms to combat ischemia.

UNADJUSTED, AND ADJUSTED MEDIAN NIHSS SCORE FOR THE BOTH STUDY GROUPS

Proportions	Antithrombotic Category	NIHSS*(IQR)	p value
Unadjusted			
	On Antiplatelets (n=92)	4.5 (2–9)	0.005
	No Antiplatelets (n=168)	7 (3–15)	
Adjusted			
	No History of Stroke or TIA		
	On Antiplatelets (n=48)	4.8	0.03
	No Antiplatelets (n=38	8	
	History of Stroke or TIA		
	On Antiplatelets (n= 44	4.91	0.987
	No Antiplatelets (n=130)	4.86	

33

Trends in 30-Day and Long-Term Survival After First-Ever Ischemic Stroke: The Greater Cincinnati/Northern Kentucky Stroke Study, 1993–1994 vs 1999

Yong-Jin Cho, Ilsan Paik Hosp, Inje Univ, Goyang, Republic of Korea; Dawn Kleindorfer, Jane C Khoury, Charles J Moomaw, Kathleen Alwell, Daniel Woo, Matthew L Flaherty, Pooja Khatri, Joseph P Broderick, Brett M Kissela; Univ of Cincinnati College of Med, Cincinnati, OH

Background: A decline in stroke mortality has been reported in the United States for several decades. More recent studies have suggested a substantial deceleration in the rate of decline during the 1980s. However, no population-based studies have examined mortality trends in the 1990s. **Methods:** All patients ≥ 18 years old hospitalized with first-ever ischemic stroke in the Greater Cincinnati/Northern Kentucky region were identified retrospectively using ICD-9 codes between 7/1/93–6/30/94 (cohort 1) and between 1/1/99–12/31/99 (cohort 2). All cases were verified by physician review. Vital status information for the cohorts was obtained through 6/30/97 for cohort 1 and through 12/31/02 for cohort 2. Kaplan-Meier survival curves were constructed, and cumulative survival rates were compared by log-rank test. Odds ratios (ORs) for comparing the survival of the two cohorts were obtained through multiple logistic regression. **Results:** A total of 3,205 patients, 1,534 cases in cohort 1 and 1,671 cases in cohort 2, met study criteria. Mean age (72.3 vs. 72.0), proportion of females (57.0% vs. 56.8%), and proportion of African-Americans (16.6% vs. 16.5%) were not significantly different between the two cohorts. Cumulative survival rates at 30 days, 1 year, 2 years, and 3 years were 87.6%, 74.8%, 67.1%, and 60.7% for patients in cohort 1, respectively, and 87.6%, 75.3%, 67.8%, and 61.6% for cohort 2 (p=0.90 for 30-day survival, p=0.65 for 3-year survival). Comparison of survival, by gender and race after adjusting for age, is presented in Table 1. **Conclusion:** Thirty-day and long-term survival after first-ever ischemic stroke did not change in the 1990s. Further advances in acute stroke therapy and long-term rehabilitative care are necessary to improve post-stroke survival.

AGE ADJUSTED ORS AND 95% CIS FOR SURVIVAL BY GENDER AND RACE IN COHORT 2, WITH COHORT 1 AS REFERENCE

Follow-up duration	Male (n=1384)	Female (n=1821)	Whites (n=2674)	Blacks (n=531)
30 days	1.02(0.73–1.42)	0.99(0.75–1.31)	1.00(0.79–1.25)	1.20(0.63–2.30)
1 year	1.05(0.81–1.37)	1.01(0.81–1.25)	1.01(0.84–1.20)	1.24(0.78–1.98)
2 years	1.00(0.79–1.27)	1.06(0.86–1.30)	1.02(0.86–1.20)	1.19(0.79–1.81)
3 years	1.08(0.85–1.36)	1.02(0.83–1.24)	1.04(0.89–1.23)	1.08(0.73–1.60)

34

An Improved Prediction Model for Acute Ischemic Stroke

Karen C Johnston, Douglas P Wagner, Univ of Virginia, Charlottesville, VA; George C Newman, Univ of Wisconsin, Madison, WI; Vincent Thijs, Univ Hosp Leuven, Leuven, Belgium; Souvik Sen, Univ of North Carolina, Chapel Hill, NC; Steven Warach, NIH-NINDS, Bethesda, MD; for the GAIN and Citicoline Investigators

Background: We have previously developed and validated prediction models using clinical information and delayed head CT imaging data. These models accurately predict outcome but cannot be used in an acute stroke setting. The purpose of this study was to combine clinical and DWI volume data in the acute stroke setting to determine if the acute DWI data improves clinical prediction. Methods: All subjects in the GAIN Americas, GAIN International, Citicoline 010 and Citicoline 018 trials with acute DWI scans were included. Treatment groups were combined as there was no treatment effect. Logistic regression was used to estimate the models. Independent variables were prespecified and limited to avoid over fitting the models. Three month outcomes included excellent outcome by NIHSS (0,1), BI (95,100), mRankin (0,1) and devastating outcome by NIHSS (>=15, dead), BI (<<26>60, dead), mRankin (5,6). Models with and without imaging data were compared for each outcome using a prespecified acceptable area under the ROC curve (AUC) of 0.8. Internal validation using bootstrap techniques provided bias corrected AUC estimates. Calibration curves were generated. Results: A total of 382 subjects were included in this analysis. The baseline NIHSS score and age contributed significantly to all models. For models that included DWI infarct volume, this variable also contributed significantly. History of DM, previous stroke, tPA, time to DWI and DWI/time interaction did not consistently contribute significantly to the models. Internally validated AUC for the models w/ and w/o DWI infarct volume are below:

Bias Corrected AUC

	NIHSS excellent	NIHSS devastating	BI excellent	BI devastating	RANKIN excellent	RANKIN devastating
Full model w/DWI	0.802	0.837	0.803	0.808	0.795	0.811
Fulll model w/o DWI	0.761	0.825	0.794	0.792	0.776	0.790

Conclusions: Acute DWI infarct volume adds substantial predictive information to our clinical models for all outcomes. The clinical models, however, perform at or very near the model performance required for individual prediction (AUC = 0.8). The prospective validation data set has completed enrollment (N=300) and these data will be externally validated.

35

Cross-Validation of a Simple 3-Point Prediction Rule to Stratify 7-Day Stroke Risk After TIA

S Claiborne Johnston, UCSF Med Ctr, San Francisco, CA; Peter M Rothwell, Stroke Prevention Rsch Unit, Univ of Oxford, Oxford, United Kingdom; Mai Nguyen-Huynh, UCSF Med Ctr, San Francisco, CA; Matthew Giles, Stroke Prevention Rsch Unit, Univ of Oxford, Oxford, United Kingdom; Jacob S Elkins, UCSF Med Ctr, San Francisco, CA; Stephen Sidney; Kaiser-Permanente Med Care Plan, Oakland, CA

Background: Distinct but similar prediction rules for short-term risk of stroke after TIA have been published previously by groups in Northern California and Oxford, England. We sought to create a single prediction rule by combining results from these two populations and testing them in distinct cohorts to generate a more robust model of stroke risk in the 7 days after TIA. Methods: We used two cohorts to derive the rules: patients with TIA diagnosed in 16 hospitals in Northern California (Johnston et al JAMA 284:2901) and a population-based sample of referrals with possible TIA in Oxfordshire (Rothwell et al Lancet 365:256). Significant ($p<0.05$) independent predictors from both cohorts of stroke at 7 days in multivariable logistic regression models were selected for inclusion in the final prediction rule. This rule was then validated using four distinct cohorts from Northern California and Oxford. Receiver-operator curves (c statistics) were used to compare the new prediction rule to other proposed rules. Results: Independent predictors of stroke within 7 days after TIA in both populations were diabetes mellitus, symptom duration >60 min, and focal weakness. A total score of one point for each of these factors (final score 0–3) was strongly predictive of subsequent stroke risk (Table). C statistics for the new rule in the validation cohorts were generally comparable to those for previously proposed models of Johnston and Rothwell, and the rule was simpler. Conclusions: A simple prediction rule–scoring one point for diabetes, symptom duration >60 minutes, and focal weakness with the event–is highly predictive of 7-day stroke risk after TIA in multiple, large, distinct populations.

Table. Seven-Day Stroke Risk by Prognostic Score, No. (%)

	California ED Derivation Cohort		Oxford Population-based Derivation Cohort		California ED Validation Cohort		California Clinic Validation Cohort		Oxford Population-based Validation Cohort		Oxford Clinic Validation Cohort	
	No. Patients	Stroke Risk <7 Days	No. Patients	Stroke Risk <7 Days	No. Patients	Stroke Risk <7 Days	No. Patients	Stroke Risk <7 Days	No. Patients	Stroke Risk <7 Days	No. Patients	Stroke Risk <7 Days
Overall	1707 (100)	103 (6.0)	378 (100)	20 (5.3)	1084 (100)	71 (6.5)	982 (100)	29 (3.0)	209 (100)	18 (8.6)	208 (100)	14 (6.7)
Score												
0	319 (19)	4 (1)	131 (35)	0 (0)	152 (14)	5 (3)	250 (26)	0 (0)	69 (33)	1 (1)	73 (35)	0 (0)
1	665 (39)	32 (5)	154 (41)	3 (2)	452 (42)	20 (4)	407 (42)	11 (3)	84 (40)	10 (12)	69 (33)	4 (6)
2	595 (35)	52 (9)	85 (22)	15 (18)	399 (37)	37 (9)	256 (27)	14 (5)	56 (27)	7 (13)	61 (29)	9 (15)
3	128 (7)	15 (12)	8 (2)	2 (25)	81 (7)	9 (11)	49 (5)	4 (8)	0 (0)	0 (0)	5 (3)	1 (20)
C statistic	0.65 (0.60-0.70)		0.85 (0.78-0.92)		0.62 (0.56-0.68)		0.71 (0.64-0.79)		0.66 (0.55-0.77)		0.77 (0.67-0.87)	

Pathophysiology/Thrombosis

36

Synergistic Effects of Statins and Dipyridamole on Stroke Protection: Mechanisms Beyond Lipid Lowering and Platelet Inhibition

Hyung-Hwan Kim, Brigham and Women's Hosp, Boston, MA; Zhipeng Zhou, Michael A Moskowitz, Massachusetts General Hosp, Boston, MA; James K Liao; Brigham and Women's Hosp, Boston, MA

Anti-platelet therapy has been the principal therapy for stroke prevention. However, in the MATCH trial, addition of aspirin (ASA) to clopidogrel did not confer additional stroke protection compared to clopidogrel alone, suggesting that further platelet inhibition beyond that of ASA is not beneficial. In contrast, addition of dipyridamole (DIP) to ASA in the European Stroke Prevention Study (ESPS)-2 decreased the relative risk of stroke by about 20% compared to ASA alone. These findings suggest that DIP may exert stroke protection beyond platelet inhibition. By inhibiting cGMP phosphodiesterase, DIP may also potentiate the vascular protective effects of nitric oxide (NO). Indeed, the upregulation of endothelial NO synthase (eNOS) by statins mediate some of their neuroprotective effects, independent of cholesterol lowering. To determine whether the combination of statins and DIP can produce syngergistic stroke protection, we pre-treated mice with simvastatin (SIM, 1 mg/kg/d, 7 d, i.p.), DIP (60 mg/kg/d, 3 d, p.o.), alone or in combination, before transient intraluminal middle cerebral artery occlusion. Treatment with sub-therapeutic dose of activated SIM alone increased aortic eNOS expression and activity by 40–56%, but did not confer stroke protection ($P>0.05$ vs. saline, $n=7$). Similarly, treatment with sub-therapeutic dose of DIP alone resulted in a plasma DIP level of 0.32 Â± 0.1 ug/ml (therapeutic plasma DIP level in humans is 1.3 ug/ml), which did not confer stroke protection ($P=0.065$ vs saline, $n=6$). However, the combination of SIM and DIP decreased stroke volume by 54 Â± 7% ($P<0.001$, $n=7$). These findings correlated with no changes in absolute cerebral blood flow (CBF) with either SIM or DIP ($P>0.05$ for both, $n=5$–7), but a substantial 50% increase in absolute CBF in mice treated with the combination of SIM and DIP (226 Â± 20 vs 152 Â± 18 ml/100 g/min, $P=0.02$, $n=8$). However, SIM, DIP, alone or in combination, did not affect serum cholesterol levels, absolute CBF or decrease stroke volume in eNOS KO mice ($P>0.05$ for all conditions, $n=4$–6). These results indicate that DIP can exert stroke protective effects beyond platelet inhibition and suggest that the combination therapy of statins and DIP may be a novel treatment strategy for vascular and stroke protection.

37

C-Reactive Protein Induced Disruption of the Blood Brain Barrier Is Prevented by Statins: Involvement of Oxidative Stress, Endothelial Contractile Machinery, and Nitric Oxide

Christoph R Kuhlmann, Heiko J Luhmann; Inst of Physiology, Johannes Gutenberg Univ, Mainz, Germany

Background: The formation of brain edema is an outcome determinant of stroke. Since high plasma levels of c-reactive protein (CRP) are associated with increased mortality, the aim of the present study was to examine the effects of CRP on blood brain barrier (BBB) opening and to determine possible beneficial effects of statins. Methods and Results: C6- and endothelial like ECV cells were co-cultured and measurements of Trans-Endothelial-Electrical-Resistance (TEER) were performed as a model of BBB integrity. CRP (1–20 μg/ml) disrupted BBB in a time dependent manner (maximum after 60 minutes). The significant decrease of TEER values (64.7 % of control; $p<0.001$, $n=6$) was antagonized by the application of the following inhibitors: apocynin (500 μmol/l; NAD(P)H-oxidase), ML-7 (10 μmol/l; myosin light chain (MLC) kinase), cerivastatin and fluvastatin (0.01–0.25 μmol/l and 1–25 μmol/l, respectively; HMG-CoA-reductase). Increasing CRP concentrations (10 and 20 μg/ml) caused an increase of intracellular oxidative stress in ECV cells, as determined by DCF-fluorescence imaging. Actin fibers and MLC-phosphorylation were analyzed by immunocytochemistry using a confocal laser-scanning microscope. CRP caused an increase of MLC-phosphorylation and induced the formation of actin stress fibers. DAF-fluorescence imaging revealed an increase of intracellular nitric oxide (NO) generation after statin treatment. Interestingly, the BBB protective effect of the statins was inhibited, if the NO-synthase was blocked by L-NMMA (300 μmol/l). Conclusions: CRP-induced oxidative stress causes an activation of the endothelial contractile machinery that results in BBB disruption. This effect is antagonized by statins involving NO-dependent mechanisms.

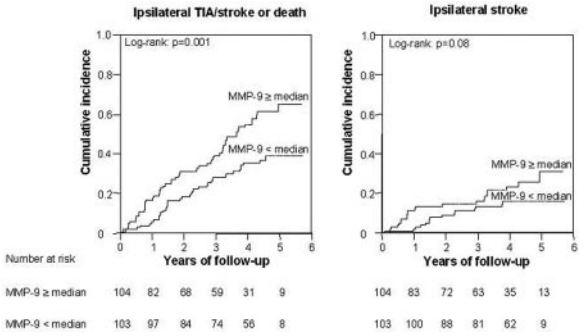
38

Elevated Matrix Metalloproteinase-9 Associated with Transient Ischemic Attack, Stroke, or Death in Patients with Carotid Stenosis

Nikolaj Eldrup, Marie-Louise Grønholdt, Henrik Sillesen, RigsHospet, Copenhagen, Denmark; Børge Nordestgaard; Herlev Univ Hosp, Herlev, Denmark

Background Matrix metalloproteinase-9 could exhibit an important role in destabilisation of atherosclerotic carotid plaques. We hypothesized that in patients with carotid stenosis, elevated levels of plasma matrix metalloproteinase-9 predict transient ischemic attack(TIA), ischemic stroke or death. **Method and Results** We followed 207 patients with ≥ 50% carotid stenosis for up to 6 years, during which 97 patients developed ipsilateral TIA/stroke or death. Cumulative incidence of ipsilateral TIA/stroke or death was higher in those with matrix metalloproteinases-9 above versus below the median of 41.9 ng/mL (Log-rank: $p=0.001$). Matrix metalloproteinases-9 above versus below the median had a hazard ratio for ipsilateral TIA/stroke or death of 2.0(95%CI 1.3–3.0). The absolute risk of ipsilateral TIA/stroke or death at 4.4 years was 57% and 37% in those with matrix metalloproteinases-9 above versus below the median. Elevated matrix metalloproteinase-9 and an echolucent plaque on B-mode ultrasound versus a low matrix metalloproteinase-9 and an echorich plaque had a hazard ratio for ipsilateral TIA/stroke or death of 2.9(1.6–5.6) and for ipsilateral stroke of 3.7(1.3–11.2).

Conclusion Elevated levels of matrix metalloproteinase-9 in patients with ≥50% carotid stenosis was associated with a 2-fold risk of ipsilateral TIA/stroke or death. Combining elevated matrix metalloproteinase-9 and plaque echolucency was associated with a 4-fold risk for ipsilateral stroke.



39

Phosphodiesterase 4 as Regulator of Brain Infarction and Brain Endothelial Fibrinolysis

Dong Xue, Fan Yang, Shur-Jen Wang, Jeong Kim, Steven Schreiber, Mark Fisher; UCI, Irvine, CA

Introduction: Genetic studies have implicated the phosphodiesterase 4 (PDE4) pathway, specifically PDE4D, in stroke pathogenesis. While initial work has shown low expression of PDE4D isoforms in subjects with the at risk genotype (Nature Genetics 2003), the mechanism linking PDE4D and stroke remains uncertain. Hypothesis: We hypothesized that PDE4 regulates both infarction in experimental stroke and fibrinolysis in brain endothelial cells. Methods: We investigated PDE4 in an experimental stroke model and in cell culture studies. Fisher-344 rats were treated with the PDE4 inhibitor rolipram (3mg/kg ip) 30 minutes prior to onset of focal cerebral ischemia, induced by ligation of the middle cerebral artery and transient occlusion of both common carotid arteries. In cell culture studies, we incubated human brain microvascular endothelial cells for 48 hours with rolipram and measured tissue plasminogen activator (tPA) protein in conditioned media by enzyme immunoassay. The effect of PDE4D siRNA on tPA expression was measured using quantitative PCR. Results: After 24 hours, cortical infarct volume was increased 42% ($p<.05$) in rolipram treated animals (27±12%) compared to vehicle(19±7%). In cell culture studies, endothelial cells incubated with rolipram exhibited 48% reduction in release of tPA protein. Studies using siRNAs to inhibit transcription of PDE4D in human brain microvascular endothelial cells showed 62–69% ($p<.005$) decrease of PDE4D mRNA. Downregulation of PDE4D expression was associated with 46–59% ($p<.005$) reduction of tPA mRNA. Conclusion: Inhibition of PDE4 enhances focal cerebral ischemia in an experimental stroke model. In vitro inhibition of PDE4 produces reduced release of endothelial tPA protein, while siRNA-mediated downregulation of PDE4D produces reduced expression of tPA mRNA by brain microvascular endothelial cells. These findings demonstrate a link between PDE4/PDE4D and brain endothelial fibrinolysis, and support a role for the PDE4 pathway in stroke pathogenesis.

40

Variations in Blood-Brain Barrier Opening in Stroke Demonstrated by Magnetic Resonance Imaging with Contrast Agents of 2 Different Sizes

Tavarekere N Nagaraja, Richard L Croxen, Polly A Whitton, Kelly A Keenan, Joseph D Fenstermacher, Robert A Knight; Henry Ford Health System, Detroit, MI

Background and Purpose: Gadolinium-diethylenetriaminepentaacetic acid (Gd-DTPA) contrast-enhanced magnetic resonance imaging (MRI) is the most commonly used technique for assessing blood-brain barrier (BBB) function in stroke. However, with a molecular weight of ~550 Da and Stokes-Einstein radius of ~0.7 nm, Gd-DTPA cannot differentiate between small and large openings. But, such openings in stroke have been shown by some studies employing different sized tracers. Therefore, we hypothesized and tested that MR contrast agents of dissimilar sizes enhance differently when openings vary in size using a rat stroke model. Methods: Male Wistar rats (275–300 g; n=5) were subjected to focal cerebral ischemia using suture occlusion of the right middle cerebral artery for 3 hr followed by reperfusion via suture withdrawal. Gd-DTPA and Gd-DTPA linked to bovine serum albumin (Gd-BSA) were synthesized in-house. Gd-BSA was then linked to the vital, fluorescent dye Evans blue (Gd-BSA-EB; 68 kDa and 3.7 nm). Status of the BBB at 21 hr of reperfusion was assessed for 21 min first with Gd-DTPA-MRI and then Gd-BSA-EB-MRI in a 7 Tesla magnet. Immediately thereafter, brains were immersion fixed in 10% paraformaldehyde and 100 μm sections were studied by fluorescence microscopy for imaging Gd-BSA-EB distribution. Results and Conclusions: Extravascular Gd-DTPA enhancement (249.8±166.5 pixels) was observed in all 5 rats during MRI indicating BBB opening in the ischemic regions. The Gd-BSA-EB distribution was within the Gd-DTPA enhancing region, but spanned a smaller area (89.0±29.4 pixels; p=0.06) for all studies. Considering the size difference of the two tracers, this relationship was attributed to the presence of larger BBB openings and greater BBB damage in such regions. The Evans blue staining patterns mimicked those of Gd-BSA-EB enhancement and confirmed the MRI findings. Because of this dissimilarity between the Gd-DTPA and Gd-BSA-EB contrast patterns, we conclude that the apparent size of BBB openings after ischemia varies among tissue sites, thus providing the first, on-line, in vivo evidence for it. The causes of such 'small' and 'large' BBB openings in stroke and their relative effects on cellular pathology in the surrounding area merit further investigation.

41

Plasminogen Activator Inhibitor Type-1 Expression in Vascular Smooth Muscle and Microvascular Endothelial Cells Is pp60$^{c\text{-}src}$/Mitogen-Activated Kinase/Upstream Stimulatory Factor Dependent and a Potential Target for Stroke Therapy

Paul J Higgins; Albany Med College, Albany, NY

Plasminogen activator inhibitor type-1 (PAI-1) is the major physiologic inhibitor of fibrinolysis. High PAI-1 levels are associated with cardiovascular disease risk, ischemic stroke and interference with tPA-induced recanalization in stroke patients. PAI-1 targeting may be important in the design of multi-modality approaches to stroke therapy. Pharmacologic agents that inhibit MEK (PD98059, U0126) or *src* family (PP1) kinases attenuated TGF-beta1-induced PAI-1 transcription in smooth muscle and microvascular endothelial cells. PP1 also blocked ERK1/2 phosphorylation/nuclear accumulation placing the *src* kinase upstream of ERK1/2. Transfection of a dominant-negative pp60$^{c\text{-}src}$ reduced TGF-beta1-induced PAI-1 expression levels to that of unteated controls or PP1-pretreated cells. The EGF receptor (EGFR) co-immunoprecipitated with activated pp60$^{c\text{-}src}$ in TGF-beta1-stimulated cells. Pretreatment with the EGFR-specific inhibitor AG1478 attenuated EGFR activation and eliminated TGF-beta1-dependent PAI-1 synthesis. Co-localization and co-immunoprecipitation analyses indicated that the TGF-beta1-activated src-MEK-ERK pathway targeted upstream stimulatory factor (USF), a member of the Myc family of transcription factors. An intact USF-binding consensus E box motif (CACGTG) at the PAI-1 promoter HRE-2 site was required for TGF-beta1-induced expression. Mutation of CA to TC at position -165/-164 in a reporter construct driven by 764 bp of PAI-1 promoter sequence attenuated TGF-beta1-stimulated CAT activity by >80%. The same CA→TC substitution eliminated USF binding to an 18-bp HRE-2 target probe highlighting the importance of site occupancy to transcriptional activation. Transfection of a dominant-negative USF construct, moreover, completely inhibited formation of USF/HRE-2 DNA complexes, attenuated PAI-1 promoter-driven luciferase activity and reduced TGF-beta1-dependent endogenous PAI-1 expression to that approximating quiescent controls. These data indicate that TGF-beta1 target gene transcription [e.g., PAI-1]) requires pp60$^{c\text{-}src}$ kinase activity and MEK signaling and involves activation of the EGF) receptor. Targeted manipulation of this pathway may have therapeutic usefulness in stroke treatment.

42

3-Dimensional High-Resolution Magnetic Resonance Direct Thrombus Imaging: Detection of Carotid AHA Type VIb/c Plaque

Richard Bitar, Univ of Toronto, Sunnybrook and Women's College HSC, Toronto, Canada; General Leung, Susan Crisp, Sunnybrook and Women's College HSC, Toronto, Canada; Sean Symons, Univ of Toronto, Sunnybrook and Women's College HSC, Toronto, Canada; Corwyn Rowsell, Univ of Toronto, Toronto, Canada; Jagdish Butany, Univ of Toronto, Univ Health Network, Toronto, Canada; David Gladstone, D J Sahlas, Regional Stroke Ctr, Sunnybrook and Women's College HSC, Toronto, Canada; Alexander Kiss, Inst for Clinical Evaluative Sciences, Toronto, Canada; Andrew Nelson, Sunnybrook and Women's College HSC, Toronto, Canada; Robert Maggisano, Sunnybrook and Women's College HSC, Toronto, Canada; Alan R Moody; Univ of Toronto, Sunnybrook and Women's College HSC, Toronto, Canada

Background: Intraplaque hemorrhage/thrombus (IPH/T) is increasingly being recognized as one of the markers that defines atherosclerotic plaques as being at increased risk of causing symptomatic disease, as well as being a potential stimulus for the progression of atherosclerosis. The purpose of this study was to develop a high-resolution 3-dimensional (3D) technique that exploits the T1-shortening effects of methemoglobin, directly visualizing IPH/T and therefore complicated atherosclerotic plaques (AHA type VIb/c). **Methods:** Thirteen patients (11 male, 2 female, mean age 72.7 ± 4.5 years [64–80 years]) undergoing carotid endarterectomy for symptomatic or asymptomatic carotid artery stenosis were imaged at 1.5T (GE Twin Speed MR scanner, USA) using high-resolution Magnetic Resonance Direct Thrombus Imaging (hiresMRDTI). The scanning parameters were: TR/TE/flip angle/spatial resolution 11.2/3.3/15^0/0.5mm^3. Fat suppression was achieved using *SPECIAL* (*SPEC*tral *I*nversion *A*t *L*ipids), a GE proprietary technique. A total of 160 MRI images were acquired for each patient, and were available for matching with the corresponding histology slices. Endarterectomy specimens were fixed, decalcified, sectioned and stained with Hematoxylin & Eosin. Matching of MRI and histology slices employed the distance from the bifurcation, and vessel/plaque morphology. A 16-segment template was used for MRI/histology correlation. Agreement between MRI and histology was measured by calculating Cohen's kappa. **Results:** A total of 910 segments were matched between hiresMRDTI and histology. Good-to-very good agreement was seen (kappa=0.7). The sensitivity / specificity / positive predictive value / negative predictive value were: 73% / 93% / 85% / 87%. **Conclusion:** hiresMRDTI allows very good delineation of the exact location of intraplaque hemorrhage/ thrombosis in the plaque, resulting in good-to-very good agreement between imaging and histology. Being a 3D technique, hiresMRDTI allows multiplanar reformations, as well as providing a large number of images for analysis. These features of hiresMRDTI could be useful to gain a better understanding of plaque pathophysiology, and to monitor the effects of therapy on atherosclerotic plaques

Experimental Ischemia

43

Upregulation of Tumor Necrosis Factor-α and Integrins After Exercise Preconditioning Enhances Cerebrovascular Integrity in Ischemic Rats

Yun H Ding, Wayne State Univ Sch of Med, Detroit, MI; William W Davis, Yuchuan Ding; Univ of Texas HSC at San Antonio, San Antonio, TX

There is increasing evidence that physical activity prior to transient middle cerebral artery (MCA) occlusion in rats reduces the extent of brain damage. We hypothesized that exercise

preconditioning strengthens brain microvascular integrity against ischemia/reperfusion injury by causing TNF-α up-regulation which is temporally associated with increased integrin expression. Adult male Sprague Dawley rats (n=30) were divided into 3 experimental groups: 1) exercise (the animals run on a treadmill 30 minutes each day) for 3 weeks, 2) exercise for 3 weeks plus 3 week rest, and 3) non-exercised. In order to induce brain edema and modulate vascular integrin levels, five animals from each of the 3 groups (n=15) were subjected to stroke, the remaining animals from each group served as experimental controls (n=5x3). Brain edema and integrin as well as TNF-α expression were determined by Nissl and immunochemistry. An additional 26 animals in 6 experimental groups were used to evaluate the TNF-α expression by real-time reverse transcriptase-polymerase chain reaction: Groups 1,2,3,4) exercise for 0, 1, 2 and 3 weeks (n=4x4); Groups 5,6) exercise for 3 weeks (n=4x2) and non-exercise (n=4x2) subjected to 2 hour MCA occlusion followed by 6 or 12 hour reperfusion. In addition, we used human umbilical vein endothelial cell (HUVEC) and flow cytometry to address the causal role of TNF-α in inducing the expression of integrins. The study demonstrated that physical activity reduces brain infarction and brain edema. This neuroprotection is continued even after cessation of exercise. Expressions of integrin subunit α_1, α_6, β_1 and β_4 were increased after exercise. Exercise preconditioning reversed stroke-reduced integrin expression. The ultimately high but slowly elevated TNF-α during exercise was associated with the significantly increased integrins. An *in vitro* study revealed a causal link between the gradual up-regulation of TNF-α and cellular expression of integrins. These results suggest that integrin upregulation altered by TNF-α during exercise enhances neurovascular integrity after stroke. This type of exercise-induced endogenous neuroprotection could be an effective strategy to ameliorate ischemia/reperfusion injury in brain.

44

Oxygen-Glucose Deprivation Causes Necroptosis in Neurons and Endothelial Cells

Sean I Savitz, Beth Israel Deaconess Med Ctr/Harvard Med Sch, Boston, MA; Alexei Degterev, Junying Yuan, Harvard Med Sch, Boston, MA; Michael Moskowitz; Massachusetts General Hosp/Harvard Med Sch, Boston, MA

Background: Emerging studies support the existence of a regulated type of necrosis called necroptosis, which is caspase-independent. Our lab has designed small molecule compounds (necrostatins), which selectively inhibit necroptosis but not apoptosis, and necrostatin-1 (Nec-1) reduces infarct volumes in mice subjected to MCAo. However, it is unknown which types of brain cells undergo necroptosis and which cells may be protected by necrostatins in ischemic stroke. **Methods**: We studied the effects of Nec-1 or the caspase inhibitor, Z-VAD, on cultures of cortical neurons and a brain-derived endothelial cell line (bend.3) exposed to oxygen-glucose deprivation (OGD). Neuronal viability was assessed using MAP2 cytoblot, and bend3 cell viability was quantitated by assessing efflux of LDH or trypan blue staining. **Results**: OGD for 90 min followed by 24 hr re-oxygenation led to widespread neuronal death largely mediated by glutamate receptors. Nec-1 (30μM) attenuated neuronal death ($p<0.05$) while an inactive analogue failed to rescue neurons. There was no protection by 100μM Z-VAD, which is consistent with prior studies, nor was there enhancement of Nec-1 protection in the presence of Z-VAD. Exposure of bend.3 cells to OGD for 5 hr followed by 24 hr of reoxygenation caused about 50% cell death. Addition of 30μM Nec-1 attenuated neuronal death by about 50% ($p<0.05$). In contrast, the addition of 100μM Z-VAD reduced cell death by only 10%. There was a mild additive protective effect from the combination of Z-VAD and Nec-1 compared with Nec-1 alone. Exposure of bend.3 cells to 100nM staurosporine, which causes a primarily caspase-dependent death, for 24 hr induced death characterized by cell body shrinkage. Addition of 100μM Z-VAD but not 30μM Nec-1 significantly reduced cell loss ($p<0.05$). **Conclusions**: This study supports the significance of necroptosis as a separate caspase-independent process, which may be a primary mode of cell death in both neurons and endothelial cells in OGD. Our data suggests that necrostatins may protect multiple brain cell types in stroke and may represent a novel class of anti-necrosis compounds for the treatment of acute ischemic injury.

45

Vasoprotective Effect of Inducible Nitric Oxide Synthase in Ischemic Tolerance

Alexander Kunz, Laibaik Park, Josef Anrather, Ping Zhou, Costantino Iadecola; Weill Cornell Med College, New York, NY

Background: Application of a sublethal stimulus confers tolerance toward a subsequent lethal ischemic insult, a phenomenon termed ischemic preconditioning. Cerebrovascular expression of iNOS is crucial for the tolerance produced by the proinflammatory agent lipopolysaccharide (LPS), but the mechanisms of the effect are not known. Because NO improves post-ischemic cerebral blood flow (CBF), we studied whether iNOS-derived NO contributes to ischemic tolerance by improving the post-ischemic CBF and CBF reactivity. Methods: C57Bl6/J or iNOS-null mice were treated with LPS (0.5 mg/kg; i.p.) and subjected to transient middle cerebral artery occlusion (MCAO) 24 hrs later. CBF was monitored in the lesion's core and penumbra by laser-Doppler flowmetry. CBF reactivity to whisker stimulation, hypercapnia (pCO2: 50–60 mmHg), and neocortical application of acetylcholine (ACh; 10 μM), was tested 1–3 hrs after MCAO. Results: LPS improved CBF in the penumbra (CBF reduction: vehicle: 35$\pm$1%; LPS: 51$\pm$2%; n=6/group; $p<0.05$). MCAO attenuated CBF reactivity (n=6/group) to whisker stimulation (Sham: 25$\pm$3%; MCAO: 11$\pm$3%; $p<0.05$), hypercapnia (Sham: 68$\pm$8%; MCAO: 42$\pm$5%; $p<0.05$) or ACh (Sham: 22$\pm$4%; MCAO: 8$\pm$2%; $p<0.05$). LPS fully reversed the impairment in post-ischemic CBF reactivity (whisker stim.: 23$\pm$2%; hypercapnia: 60$\pm$4%; ACh: 21$\pm$4%; $p>0.05$ from Sham; n=6/group). Treatment with the iNOS inhibitor aminoguanidine abolished the beneficial effects of LPS preconditioning on penumbral CBF (CBF reduction: 34$\pm$2%) and post-ischemic CBF reactivity (ACh: 10$\pm$2%). The beneficial CBF effects of LPS were not observed in iNOS null mice (MCAO: ACh: 10$\pm$4%; MCAO+LPS: 13$\pm$3%; $p>0.05$). Discussion: LPS preconditioning is associated with preservation of microvascular flow in regions of the ischemic penumbra. The improved CBF can be attributed to a salutary effect of LPS on post-ischemic CBF reactivity. The vasoprotective effect of LPS is mediated by iNOS-derived NO. Thus, cerebrovascular iNOS expression contributes to the beneficial effects of LPS preconditioning by counteracting the CBF dysregulation produced by cerebral ischemia and improving post-ischemic microvascular perfusion.

46

Angiotensin II Type 2 Receptor Stimulation Enhances Neural Differentiation and Affects Cognitive Function Through MMS2-Upregulation After Stroke

Masaki Mogi, Jian-Mei Li, Jun Iwanami, Kana Tsukuda, Li-Juan Min, Masaru Iwai, Masatsugu Horiuchi; Ehime Univ Sch of Med, Tohon, Ehime, Japan

Introduction: Angiotensin II type 1 receptor blockers (ARB) have been widely used as antihypertensive drugs, and proved to be effective to prevent cognitive decline by major clinical studies; however the detail mechanism of the brain protection by ARB is unclear. Recently, angiotensin II type 2 (AT_2) receptor signaling has been highlighted in ARB treatment. We examined the roles of AT_2 receptor signaling in neural differentiation and cognitive function after middle cerebral artery (MCA) occlusion employing AT_2 receptor-deficient (*Agtr2*$^-$) mice. **Hypothesis:** We assessed the hypothesis that AT_2 receptor stimulation contributes to neural differentiation and affects cognitive function after stroke. **Methods:** *Agtr2*$^-$ mice and age-matched wild-type littermate were subjected to passive avoidance task just before and 3 days after MCA occlusion. Real-time PCR was performed with extracted brain-mRNA. Neural differentiation was evaluated using neural stem cells isolated from rat fetal cortex. ARB, valsartan was administrated intra-peritoneum by osmotic mini-pump at a non-hypotensive dose of 3 mg/kg/day. **Results:** *Agtr2*$^-$ mice exhibited a significant impairment of avoidance-rate after focal ischemia compared to wild-type mice. In wild-type mice, treatment with valsartan ameliorated avoidance-rate. The expression of AT_2-mRNA was increased in ischemic area. Moreover, in ischemic brain area, the expression of MMS2, which is one of the ubiquitin converting enzyme variants, was increased in wild-type mice but not in *Agtr2*$^-$ mice. Treatment with valsartan increased MMS2 expression in not only ischemic but also non-ischemic area. In culture model, angiotensin II promoted neural differentiation and increased mature neural cells which were expressed neural-marker, MAP2 and βIII tubulin. Valsartan enhanced such effects, whereas an AT_2 receptor specific blocker, PD123319 inhibited them. Gene knockdown of MMS2 in neural stem cells by siRNA could not form neurospheres and failed in Ang II-induced neural differentiation, indicating that MMS2 plays a pivotal role in neural differentiation. **Conclusions:** In conclusion, cognitive decline after stroke partially depends on AT_2 receptor signaling, involving a neural differentiation associated gene, MMS2.

47

Atypical Pkc ζ Mediates Neuroblast Migration from the Subventricular Zone Toward the Ischemic Boundary Regions

Zg Zhang, Y Letourneau, Rl Zhang, S R Gregg, A Hozeska, Y Wang, D Morris, M Chopp; Henry Ford Hosp, Detroit, MI

Neuroblasts in the subventricular zone (SVZ) of adult brain migrate to the olfactory bulb via rostral migratory stream. Stroke redirects neuroblast migrating towards the ischemic boundary regions. Molecules that mediate neuroblast migration are not fully known. We hypothesized that atypical PKC zeta regulates neuroblast migration after stroke. Using a time-lapse microscope, we dynamically tracked neuroblast migration on coronal brain slices. Neuroblast migration was limited within the SVZ of non-stroke rats with a speed of 3 $\pm$ 0.5 μm/h (n=17 cells of 2 rats), whereas many neuroblasts migrated from the SVZ towards the ischemic striatum (17 $\pm$ 2.1 μm/h, n=45 cells of 3 rats, $p<0.01$). To examine the effects of PKC on neuroblast migration, neurospheres derived from stroke SVZ cells were incubated in matrigel in the presence or absence of isoform-specific inhibitory myristoylated peptides of PKC beta (10 μM), epsilon (10 μM) and zeta (10 μM). PKC zeta significantly ($p<0.01$) blocked cell migration (17 $\pm$ 6.7 μm, n=24 spheres) compared with the control group (213 $\pm$ 22.3 μm, n=24), while PKC beta (221 $\pm$ 32.7 μm, n=8) and epsilon (164 $\pm$ 31.7 μm, n=8) did not reduce cell migration, indicating that PKC zeta specifically inhibits neuroblast migration. To examine whether PKC zeta affects matrix metalloproteinase (MMP), we imaged degradation of a quenched fluorescent derivative of type IV collagen by living neurospheres in matrigel using 3D laser confocal microscope. PKC zeta significantly reduced fluorescent intensity released by neurospheres and MMP2 activity measured by zymography. Real-time PCR and zymography showed that SVZ cells did not express MMP9. Neuroblasts from MMP9 null mice did not exhibit reduction of migration. Therefore, reduction of MMP2 by PKC zeta contributes to inhibition of neuroblast migration. In addition, mRNA levels of stromal cell-derived factor 1α and its receptor CXCR4, tenacin C, TIMP1 were substantially reduced in SVZ cells treated with PKC zeta, suggesting that inhibition of PKC zeta downregulates many genes that are involved in cell migration. Our data demonstrate that atypical PKC zeta mediates adult neural progenitor cell motility, which is through many downstream target genes involved in cell migration.

48

Poly(ADP-ribose) Glycohydrolase Limits Focal Cerebral Ischemic Damage

Raymond C Koehler, Judith A Klaus, Zhenfeng Xu, David W Koh, Ted M Dawson, Valina L Dawson; Johns Hopkins Univ, Baltimore, MD

Inhibition of poly(ADP-ribose) polymerase (PARP) or gene deletion of PARP-1 reduces infarct volume after middle cerebral artery occlusion (MCAO). Potential mechanisms of PARP-mediated injury include energy depletion and stimulation of apoptosis-inducing factor translocation to the nucleus by polymers of ADP-ribose (PAR). In the latter mechanism, degradation of PAR by poly(ADP-ribose) glycohydrolase (PARG) should act to limit focal ischemic injury. Alternatively, PARP is capable of limiting its own activity by self-ADP ribosylation. In this case, PARG activity may worsen ischemic injury by disinhibiting PARP activity through removal of PAR on PARP. To test the role of PARG, transgenic male mice overexpressing PARG (PARG Tg) and heterozygous knockdown male mice (PARG+/-) were generated and subjected to transient MCAO by the filament technique. (PARG gene knockout is embryonic lethal.) Compared to wild-type (WT) littermates (n = 10), PARG Tg mice (n = 11) subjected to 2 h MCAO had significantly smaller infarct volume in striatum (28 $\pm$ 30% vs 60 $\pm$ 33%), cerebral cortex (17 $\pm$ 20% vs 42 $\pm$ 26%)

and hemisphere (13 ± 13% vs 33 ± 23%) (% of contralateral structure corrected for swelling; ±SD). In contrast, PARG+/- mice (n = 16) subjected to 1.5 h MCAO had significantly larger infarcts in striatum (58 ± 22% vs 37 ± 20%), cortex (39 ± 18% vs 24 ± 15%) and hemisphere (39 ± 18% vs 24 ± 15%) compared to WT littermates (n = 15). The reduction in laser-Doppler flow (80–85%) during MCAO was similar among groups. Thus, increasing PARG expression decreases damage, and decreasing PARG expression increases damage. Hence, PARG activity normally limits focal ischemic injury. Results are consistent with the hypothesis that signaling by PAR contributes to ischemic damage.

49

Microglia-Derived Reactive Oxygen Species Potentiate Blood-Brain Barrier Disruption After Stroke

Xian N Tang, UCSF, San Francisco VAMC, and Stanford Univ, San Francisco and Stanford, CA; Lijun Xu, Yanli Qiao, Rona Giffard, Stanford Univ, Stanford, CA; Midori A Yenari; UCSF and San Francisco VAMC, San Francisco, CA

Following ischemic stroke, microglia are activated and may potentiate ischemic injury by enhancing blood-brain barrier (BBB) disruption. In this study, we investigated the influence of microglia on BBB disruption both in vitro and in vivo, and the effect of minocycline on reversing it by inhibiting microglial activation. *In vitro,* astrocytes (G), endothelial cells (E) and microglia (M) were isolated from postnatal Swiss Webster mice. Primary EG or EGM mixed cultures were prepared. Cultures were subjected to 8 h oxygen & glucose deprivation followed by 18 h reperfusion. *In vivo,* 28 C57BL/6J male mice (25~30 grams) were subjected to 1.5 h middle cerebral artery occlusion followed by 24 h reperfusion. Mice were treated with minocycline (to inhibit microglial activation) (n=16) or vehicle (n=12). When microglia were added to EG cocultures, cell death nearly doubled compared to the cocultures lacking microglia ($P<0.01$). The increase in EG cell death in the presence of microglia could be completely reversed by minocycline ($P<0.05$). As NADPH oxidase is the primary enzyme system by which inflammatory cells (including microglia) generate superoxide, EGM cultures were treated with the NADPH oxidase inhibitor, apocynin and injury was similarly reduced. Minocycline and apocynin also reduced generation of superoxide ($P<0.01$), and apocynin reduced generation of hydrogen peroxide ($P<0.05$) in EGM cultures. Infarct volume ($P<0.01$), neurological deficit scores ($P<0.01$) and Evans blue extravasation ($P<0.01$) decreased significantly in the minocycline treated mice compared with the vehicle treated group. Minocycline also reduced the occurrence of gross cerebral hemorrhage ($P<0.05$) and microglial recruitment to cerebral vascular structures. Microglia potentiate injury to BBB components. This damage can be reversed by preventing microglial activation by minocycline or NADPH oxidase-induced microglial generation of superoxide by apocynin. These observations suggest that anti-inflammatory treatments in acute stroke might be useful in preserving BBB components, and may be useful as an adjunct to thrombolytics.

Recovery

50

The Hematopoietic Factor G-CSF Drives Neurogenesis and Improves Long-term Functional Outcome After Cerebral Ischemia

Armin Schneider, Axaron Bioscience, Heidelberg, Germany; Tobias Steigleder, Univ, Heidelberg, Germany; Carola Krueger, Axaron Bioscience, Heidelberg, Germany; Georg Kuhn, Neuroscience, Gothenburg, Sweden; Wolf R Schäbitz; Univ, Münster, Germany

Granulocyte-colony-stimulating factor (G-CSF) is a potent hematopoietic factor that enhances survival and drives differentiation of myeloid lineage cells resulting in the generation of neutrophilic granulocytes. We have shown that G-CSF passes the intact blood-brain-barrier, is neuroprotective in acute stroke models, and is expressed in a broad variety of brain regions together with its receptor. Surprisingly, the G-CSF receptor was also expressed by adult neural stem cells in vitro and in vivo. By using a number of assays to quantify mature cell markers we show that G-CSF strongly induces neuronal differentiation in vitro. In vivo, G-CSF markedly improved long-term behavioural outcome after cortical ischemia while stimulating neural progenitor response, providing a link to functional recovery. Thus, G-CSF is a novel neurotrophic factor that appears beneficial both for acute neuroprotection, as well as for long-term recovery after cerebral ischemia.

51

Elevated Homocysteine Accelerates Cognitive Decline After Ischemic Stroke

Syed I Hussain, George C Newman, Univ of Wisconsin Hosp & Clinics, Madison, WI; Heejung Bang, Weill Med College of Cornell Univ, New York, NY; James F Toole; Wake Forest Univ, Winston-Salem, NC

Introduction: Elevated homocyst(e)ine (HCY) has been linked to increased oxidative injury in animal stroke models and to degenerative neuropsychiatric conditions in humans. Angiotensin receptor activation may also increase oxidative stress. Our objectives were to test the hypotheses that: 1) elevated HCY impairs cognition, 2) high dose B vitamins slow cognitive decline, and 3) ACE inhibitors (ACE-I) slow cognitive decline. **Methods:** The NIH-funded Vitamin Intervention for Stroke Prevention (VISP) multi-center study failed to demonstrate benefit of high dose B6, B12 and folate in patients with non-disabling stroke followed for 2 years, despite a significantly reduced HCY. We extracted relevant information from this rich database in order to test our *post hoc* hypotheses. The Mini-mental Status Exam (MMSE) and modified Rankin (mRS) scores at baseline, 1 and 2 years were obtained for 3680 study subjects. Linear regression and mixed effects models assessed the influence of patient demographics, laboratory values, stroke localization and medical treatment on the MMSE and mRS at baseline and longitudinally, respectively. Final regression models included variables significant at the $p<0.05$ level as well as specific variables of interest, which were selected *a priori*. **Results:** Elevated baseline HCY was associated with progressively worsening MMSE ($p=0.03$) and mRS ($p=0.003$). However, high dose B vitamins had no effect on MMSE or mRS. Unexpectedly, ACE-I were associated with increased mRS at baseline ($p<0.001$) and longitudinally ($p=0.006$). Increasing age, black or other non-white race and low HDL were consistently associated with poorer baseline and longitudinal MMSE and mRS. Left hemisphere and right cortical lesions lowered MMSE scores while right hemisphere and brainstem lesions worsened mRS. **Conclusion:** Elevated HCY is associated with worsening cognition and disability following stroke. Treatment with B vitamins or ACE-I does not mitigate this decline. Cognitive impairment and functional disability after stroke were associated with different lesion locations.

52

Short-Term Recovery of Aphasia After Acute Ischemic Stroke Results from Restoration of Blood Flow to Specific Brain Regions

Argye E Hillis, Melissa Newhart, Sangeetha Vimal, Eric Aldrich, Jennifer Heidler-Gary, Lynda Ken; Johns Hopkins Univ Sch of Med, Baltimore, MD

Background and Purpose: Improvement of language in the first few days of ischemic stroke is common, but the mechanisms of recovery are unclear. Previous studies indicate that ischemic and hypoperfused regions visualized with MRI perfusion-weighted imaging (PWI) and diffusion-weighted imaging (DWI) contribute to language deficits after acute stroke. Therefore, spontaneous or treatment-induced reperfusion might be responsible for improvement. We tested the hypothesis that reperfusion of specific brain regions in the first days of stroke account for improved naming and comprehension. **Methods:** 54 right-handed patients with acute, left hemisphere ischemic stroke were studied at Day 1 and Day 3–5 with tests of naming and spoken word comprehension, and DWI, PWI and conventional MRI. Technicians blinded to language test scores examined 12 regions in left frontotemporal parietal cortex for dense ischemia on DWI, hypoperfusion on PWI at Day 1, and reperfusion at Day 3–5. Areas where reperfusion contributed to improved naming and word comprehension were identified by step-wise linear regression analysis. **Results:** Improved naming was best predicted by the following model, where RP = "reperfusion of"; PITG = posterior inferior temporal gyrus; BA = Broca's area; and WA=Wernicke's area: *RP PITG x .76 + RP BA x .43 + RP WA x .39 + 0 (r =.76; p <.0001)* Reperfusion of posterior inferior temporal gyrus, Broca's area, and Wernicke's area contributed to improved naming within 5 days of onset. Improved word comprehension was best predicted by: *RP WA 22 x .82 + 0 ($p<.0001$)* Only reperfusion of Wernicke's area was significantly associated with improved word comprehension. **Conclusion:** Recovery of naming and word comprehension by Day 3–5 after stroke onset depends on reperfusion of posterior inferior temporal gyrus, Broca's and Wernicke's areas. Improvement in word comprehension depends on reperfusion of Wernicke's area. Results provide insights into mechanisms of recovery in acute stroke, and confirm the essential role of these areas in naming.

53

Effects of a Single Dose of Methylphenidate on Motor Deficits After a Subcortical Stroke: Behavioral and Cerebral Correlates

Jean Tardy, Isabelle Loubinoux, Sophie Dechaumont, Anne Léger, Jean-François Albucher, Angelique Gerdelat-Mas, Jeremie Pariente, Philippe Marque, Christophe Cognard, François Chollet; INSERM U455, Toulouse, France

Objective We hypothesized that a single dose of methylphenidate MPH (Ritalin®), a catecholaminergic drug which inhibits dopamine and noradrenaline reuptake, could modulate cerebral activation and performances in subcortical stroke patients. ***Material and methods*** 8 men (median age: 60 years, [46–69], 7 right-handed) with a single stroke (7 ischemic, 1 hemorragic, 4 left lesions) on the corticospinal tract and a pure motor hemiparesis were prospectively included in a cross-over, double-blind, placebo-controlled study. Patients were first evaluated 19 days after stroke onset by valid neurological scales and performed motor tests. Then they received 20 mg MPH or placebo and underwent a 2x 10 min passive training (electrical stimulation of the paretic arm). At peak plasma concentration, 2 hours later, they performed all tests again and underwent an fMRI motor of the paretic hand. Seven days later, patients received the other drug MPH/Placebo and were also evaluated. fMRI data were processed with SPM2. 10 healthy age-matched subjects (6 men; median age: 50 years, [47–62], right-handed) served as controls. ***Results*** Placebo intake combined with training did not change performance. MP compared to placebo elicited a significant improvement of motor performance of the affected hand at the finger tapping test. The motor activation of patients compared to that of healthy subjects was diminished in the upper part of the S1M1 hand area, increased in the lower part of the S1M1 hand area and in the cingulum. The S1M1 face area was also recruited. MP induced a hyperactivation of the ipsilesional S1M1 including the motor face area, the contralesional premotor cortex. MP minimized the overactivation of the ipsilesional anterior cingulum. Hyperactivation in the face motor area and in the contralesional premotor cortex correlated positively with the improvement of performances. ***Discussion*** The anterior cingulum over-activation in patients compared to controls suggests that patients need additional attention/effort to perform the active movement and that the effect of MPH might partly rely on an improvement in attention/effort through cingulum modulation. We demonstrated that the reorganized network and especially the face motor area was efficiently targeted by the drug.

54

Amphetamine-Enhanced Stroke Recovery Trial: Effect of Statins on Poststroke Recovery

Larry B Goldstein, Duke Univ Med Ctr and Durham VAMC, Durham, NC; Laura Lennihan, Helen Hayes Hosp, West Haverstraw, NY; Merhoz Rabadi, Burke Rehabilitation Hosp, White Plains, NY; AESR Investigators

Purpose: AESR is a pilot clinical trial designed to collect data critical for the design of a full-scale clinical trial testing the efficacy of d-amphetamine combined with physical therapy to facilitate motor recovery following hemispheric ischemic stroke. Data collected in the first phase of the AESR trial was analyzed to determine whether there was an effect of HMG-CoA reductase inhibitors (statins) on poststroke recovery. Background: Experiments in laboratory animals suggest that statins may improve poststroke recovery unrelated to their cholesterol-lowering effects. Methods: Statin use at the time of rehabilitation admission or started during rehabilitation hospitalization was recorded. Stroke severity was measured with the NIH Stroke Scale (NIH-SS) at rehabilitation admission, discharge, and after 3 months. Results: The study population included 72 subjects (mean age 65+/-2 yr; 56% male; 79% White, 15% Black) of whom 39% had lacunar, 58% partial anterior, and 3% total anterior circulation ischemic strokes (Oxfordshire); 49% of patients were receiving a statin at the time of rehabilitation admission with an additional 6% started during the hospitalization; none had statins discontinued. Stroke severity was less in patients receiving a statin at admission (mean NIH-SS 11.6+/-0.7 vs. 15.1+/-1.6; p=0.015). Stroke severity was also lower at discharge (NIH-SS 7.3+/-0.8 vs. 12.4+/-1.9, p=0.007) and after 3 months (NIH-SS 6.5+/-0.7 vs. 10.8+/-2.3, p=0.007) among those who received a statin during rehabilitation. However, there was no statin X time interaction (repeated measures ANOVA, p=0.661). Conclusion: Statin use was associated with lower stroke severity at the beginning of rehabilitation, but no change in the rate of subsequent recovery.

55

Depression After Lacunar Stroke: Results from the Secondary Prevention of Small Subcortical Strokes Study

Carole L White, Univ of Texas Health Sciences Ctr, San Antonio, TX; Alice Liskay, MetroHealth Med Ctr, Cleveland, OH; Patricia Wallace, ViaHealth Rochester General Hosp, Rochester, NY; Janet Braimah, Grady Memorial Hosp, Atlanta, GA; Janyna Mercado, Univ of Texas Health Sciences Ctr, San Antonio, TX; Leslie McClure; Univ of Alabama at Birmingham, Birmingham, AL

Background: Depression is a serious but treatable problem after stroke. Controversy remains about the relationship between stroke and depression and its determinants which may, in part, be related to the diverse group of strokes included in previous studies. The SPS3 cohort is an MRI-defined group of subcortical strokes. The trial is testing two targets of blood pressure control and two antiplatelet regimens. Using data from this cohort, our purpose is to determine the prevalence and treatment of depression at 3 months after study entry, and to examine the relationship between stroke severity, gender, age, education, ethnicity, stroke risk factors, and depression. **Methods:** The presence of depressive symptoms is evaluated quarterly using the Patient Health Questionnaire (PHQ), a 9-item scale that assesses the 9 DSM-IV depression criteria for frequency of occurrence in the past two weeks (range 0 to 27). Depression was defined as a score $\geq$ 9. A multivariate logistic regression model was fitted to examine the relationship between each of the covariates of interest and depression, adjusted for all of the other covariates and for time between the qualifying stroke and the 3 month follow-up. **Results:** Of the initial 519 subjects with a 3-month follow-up, the prevalence of depression was 20% and the majority of those depressed (65%) was not receiving antidepressant medications. In the fully adjusted model, for each one year increase in age, the odds of depression decreased by approximately 0.95 (95% CI: 0.93, 0.98) times. Additionally, those with a Rankin of 2–3 were 1.61 (95% CI: 0.97, 2.67) times more likely to exhibit depressive symptoms, as compared to those with a Rankin of 0–1. With each increase in number of stroke risk factors, the odds of depression increased by 1.3 (95% CI: 1.03, 1.58). Finally, those without any college education were 1.84 (95% CI: 1.14, 2.30) times more likely to exhibit depressive symptoms, as compared to those with any college, even after adjustment for other factors. **Conclusions:** In this largest study of post-stroke depression in an MRI-defined cohort of small subcortical stroke, the risk of poststroke depression is substantial and treatment rates are low. Recognition of risk factors for depression is critical for optimizing poststroke care.

56

Incidence and Frequency of Falling Accidents Among Persons With and Without Stroke: Health and Retirement Study Survey 2002

Afshin A Divani, Amardeep Hoonjan, Abu Nasar, Siatta Dunbar, Jarrett Hesselbrig; Zeenat Qureshi Stroke Res Ctr, UMDNJ, Newark, NJ

Background: Falling accidents among patients with history of stroke is a concern. Loss of balance, sensory deficit, weakness, and neglect secondary to stroke may predispose the patients to falling accidents that can lead to further complications thus augmenting disability. **Methods:** We determined the incidence and frequency of falling accidents among stroke patients using the Health and Retirement Study (HRS) in 2002. HRS is a national longitudinal study that focuses on persons born between the years 1931 and 1941 and their health, retirement, and economic status. The HRS participants were interviewed in 1992 and every two years thereafter. Data sets included in the HRS are: demographics, health, cognition, housing, family structure, employment, disability, income, and health Insurance **Results:** There were 17,992 participants in the year 2002 survey. A total of 1273 (7.07%) reported a previous history of stroke. The incidence of falling accidents in the past two years prior to the survey among subjects with history of stroke verses those with no history of stroke were 36% vs. 16% (P< 0.05), respectively. The mean and standard deviation of number of falling accidents were 7.6±19.7 verses 5.4±16.8 (P< 0.05), respectively. The percentage of injury due to the falling accident was 14.1 verses 5.5 (P<0.5), respectively. The percentage of hip fraction due to the injury was 2.6 verses 0.9 (P<0.05), respectively. **Conclusions:** The present study provides the incidence of falling accident and associated injury among subjects with history of stroke compared with those without previous stroke. The study revealed a higher incidence of falling accident and associated injury among subjects with history of stroke that may warrant further rehabilitation strategies for stroke survivors.

Nursing and Rehabilitation

57

Best versus Actual Practices in Stroke Rehabilitation: Results of the Canadian National Survey

Nicol Korner-Bitensky, Sharon Wood-Dauphinee, McGill Univ, Montreal, Canada; Robert Teasell, Univ of Western Ontario, London, Canada; Johanne Desrosiers, Univ de Sherbrooke, Sherbrooke, Canada; Francine Malouin, Univ Laval, Quebec, Canada; Aliki Thomas, McGill Univ, Montreal, Canada; Margaret Harrison, Univ of Ottawa, Ottawa, Canada; James Hanley, McGill Univ, Montreal, Canada; Franceen Kaizer, Jewish Rehabilitation Hosp (McGill Univ), Laval, Canada; Eva Kehayia, McGill Univ, Montreal, Canada; Anita Menon-Nair, Univ of Toronto, Toronto, Canada; Annie Rochette, Chantal Dumoulin; McGill Univ, Montreal, Canada

INTRODUCTION: The quality of stroke care is known to impact on survival and function. Yet, little is known about actual practices in stroke rehabilitation. OBJECTIVES: This Canada-wide survey examines problem identification, the assessments and interventions used in the treatment of individuals with stroke, and the relationship between explanatory variables and variations in practice. In addition, we explored practice styles of clinicians and the impact of these on best practice. SUBJECTS: In 2004/05, 1804 rehabilitation specialists {664 occupational therapists (OT); 655 physical therapists (PT); 50 physiatrists; and 435 speech-language pathologists (SLP)} working across stroke care (acute, in-patient rehabilitation, community) were interviewed. METHODS: Prompted by case vignettes of typical patients with stroke, clinicians described their "usual practices". Information on frequency and timing of assessments/interventions was also elicited. RESULTS: Participation was excellent (over 90%). Identification of some critical problems such as dysphagia was high by physiatrists and SLP but lower, 58% and 54%, respectively by OT and PT. Important social concerns such as driving and family support were rarely identified. Type of urinary incontinence (urge, stress, functional) was almost never correctly identified and behavioural interventions aimed at this problem were rare. Standardized assessment practices varied greatly; PT commonly used the Berg Balance Scale. Using a standardized measure, a sub-group of 243 OT and PT were classified as: seekers (characterized by a willingness to diverge from traditional practice if evidence-based sources support this change); receptives (evidence-oriented, but likely to rely on clinical judgment of respected authorities); traditionalists (views clinical experience/authority as the most reliable) and pragmatists (focuses on practicality). The largest proportion, 55%, was pragmatic. Seekers were significantly more likely to choose assessment tools based on reliability and validity, whereas pragmatics looked for practicality. CONCLUSION: Extreme variations in practice behaviours were found, raising concern for the quality of care that some individuals with stroke are receiving.

58

The Effect of Electro-Acupuncture on Upper Limb Spasticity in Chronic Stroke Survivors

Mukul Mukherjee, Lisa McPeak, John Redford, Chao Sun, Wen Liu; Univ of Kansas Med Ctr, Kansas City, KS

The Effect of Electro-acupuncture on Upper Limb Spasticity in Chronic Stroke Survivors
Background and Purpose: Spasticity is a characteristic feature of stroke and is a potential obstacle for improvements in motor control and functional ability through sensorimotor training. The efficacy of acupuncture in reducing spasticity has not been systematically studied. The purpose of this study is to quantitatively assess the change in spasticity of the impaired wrist joint in chronic stroke patients after electro-acupuncture treatment. Methods: A cross-over design was used in which 8 chronic stroke subjects received either a combined electro-acupuncture and muscle strength training or only the strength training twice a week for 6 weeks, and then switched over to the other treatment for another 6 weeks. Quantitative measurements of wrist joint strength and spasticity were conducted using the Biodex System3 (Biodex Medical Systems Inc., New York). Outcome measures included Velocity sensitivity of Averaged Speed dependent Reflex Torque (VASRT); regression slope of the baseline ASRT; modified Ashworth scores, and EMG integral of wrist flexor during passive stretch. Results: VASRT and modified Ashworth scores reduced significantly in the experimental group ($p<0.05$) after the combined treatment, but not with muscle strengthening alone. Regression slope of the baseline ASRT at a very slow passive stretch (5 deg/s) showed significant reduction after both treatments ($p<0.05$). Integral EMG of wrist flexors during passive wrist extension showed significant reduction ($p<0.05$). Conclusions: a combination of electro-acupuncture and muscle strengthening exercise can significantly reduce spasticity over a 6-week period of application. A neural mechanism of spasticity reduction through electro-acupuncture is implicated as shown in reduced EMG activities in the antagonistic muscles.

59

A New Measure of Paretic Leg Contribution in Hemiparetic Walking

Steven A Kautz, Brain Rehabilitation Res Ctr, Malcom Randall VA Med Ctr, and Univ of Florida, Gainesville, FL; Mark G Bowden, Brain Rehabilitation Res Ctr, Malcom Randall VA Med Ctr, Gainesville, FL; Chitralakshmi K Balasubramanian, Univ of Florida, Gainesville, FL; Richard R Neptune; Univ of Texas, Austin, TX

Walking after stroke is characterized by slow speed, poor endurance, changes in the quality and adaptability of the walking pattern, and an inability to coordinate the two legs. Estimates based on mechanical work calculations have suggested that the paretic leg does 30–40% of the total mechanical work over the gait cycle, and this percentage does not vary with stroke severity. Much of this paretic leg contribution may be related to supporting body weight during single support, with little contribution to propelling the body forward. We propose to use the anterior-posterior ground reaction forces (A-P GRF) as a measure of forward propulsion in order to quantify the contribution of the paretic leg to the task of walking. Forty-seven participants with chronic hemiparesis were bilaterally instrumented with surface EMG electrodes and walked at self-selected speeds over an instrumented walkway and embedded force platforms to provide their 3-dimensional GRFs. The percentage of paretic propulsion (PPP) was calculated by dividing the net propulsion performed by the paretic leg by the sum of the propulsion done by both legs. The PPP was 16% for those with Brunnstrom 3, 36% for those with Brunnstrom 4 or 5, and 49% for those with Brunnstrom 6, providing a strong linkage between the PPP measure and stroke severity. Furthermore, 5 participants with the most severe stroke were able to walk at least 0.8 m/s while each had a PPP of $<$ 25%, illustrating a compensation to produce normal speeds with an impaired contribution of the paretic leg. EMG data from the period of double limb support prior to paretic swing suggests that decreased PPP is more associated with increased flexor muscle activity than it is with decreased extensor muscle activity. PPP less than 25% demonstrates substantial force production asymmetry and suggests that compensatory patterns are required by the non-paretic leg (i.e. $>$ 75% of propulsion) to maintain steady-state movement, such that the PPP may be effective in distinguishing functional compensation from physiological restitution. We believe that the PPP is useful in providing a quantitative measure of the coordinated output of the paretic leg.

60

Area of Tissue Dysfunction Associated with Impaired Sentence Comprehension in Acute Stroke

Pushpa Raja, Melissa Newhart, Jennifer Heidler-Gary, Argye E Hillis; Johns Hopkins Univ Sch of Med, Baltimore, MD

OBJECTIVE: To identify brain regions crucial to auditory sentence comprehension, using DWI, PWI, and sentence comprehension tests in acute left hemisphere stroke. **BACKGROUND**: Aphasic patients often have a graded disruption of sentence comprehension, with better performance on simple compared to complex sentence structures. Associations between infarcted and/or hypoperfused regions on MRI studies auditory sentence comprehension deficits may reveal areas essential for processing simple and complex sentence structures. **DESIGN/METHODS**: Patients with acute left hemisphere ischemic stroke (n=86) underwent DWI, PWI and an auditory comprehension test consisting of 10 questions, 4 "complex" (e.g. Is a horse larger than a dog?) and 6 "simple" (e.g. Are limes sour?). Patients were directed to answer questions with a "yes" or "no" depending on veracity of the sentence. For each patient, 10 left hemisphere Brodmann's areas (BAs) were evaluated for infarct and/or hypoperfusion. Chi-square tests with Bonferroni correction for multiple comparisons ($p<.005$ was considered significant) were used to identify associations between regions of hypoperfusion/infarct and sentence comprehension deficits. **RESULTS**: Impairment in simple sentence comprehension was associated only with infarct and/or hypoperfusion of BA 39 ($p = .0001$). Impairment in complex sentence comprehension was associated with infarct/hypoperfusion of BA 6 ($p = .0006$), 39 ($p = .0009$), and 44 ($p = .003$). **CONCLUSIONS**: Infarct/hypoperfusion of left BA 39 (angular gyrus) results in deficient comprehension of simple sentences, while infarct/hypoperfusion of BAs 6, 39 and 44 independently contribute to deficient comprehension of complex sentences. These results support the proposed function of BA 39 in semantic processing, required for comprehension of both simple and complex sentences. Results are consistent with functional imaging and lesion studies that provide independent evidence that BA 6 (dorsolateral prefrontal cortex) is necessary for working memory and BA 44 (Broca's area) is essential for syntax processing - two processes critical for comprehension of complex sentences but not simple sentences.

61

Stroke Survivor and Caregiver Congruence of Depressive Symptom Appraisal

N Jennifer Klinedinst, Sarah Blanton, Steven L Wolf, Emory Univ, Atlanta, GA; Patricia C Clark; Georgia State Univ, Atlanta, GA

The purposes of this study are to determine stroke survivor (SS) and caregiver (CG) congruence of the appraisal of depressive symptoms in the SS and to examine the influence of CG and clinical characteristics of stroke recovery on the congruence of symptom appraisal. Methods: Baseline data from a multi-site caregiving study, complementary to a clinical trial testing constraint-induced therapy in SS, were used to examine congruence of depressive symptom appraisal (n=130 family caregiver/ first-time SS dyads). Five items from the Mood/Emotion subscale of the Stroke Impact Scale were used to measure of SS depressive symptoms (SSDS) (α=.72). Five items from the Memory and Behavior Problems Checklist were used to measure of caregiver appraisal of SS depressive symptoms (CADS) (α=.61). A single item 'feel sad' from each scale was also compared. CG depressive symptoms were measured using the CES-D (α=.90). SS functional ability was measured using the upper extremity portion of the Fugl-Meyer (FM). A bivariate dyad congruence variable was calculated using the SSDS and CADS scores. An absolute value of the difference in scores of 10 or less (range 0–100; higher = less depressive symptoms) was considered congruent. Results: Mean score for the SSDS was 79.7 $\pm$ 15.8, and for the CADS was 70.64 $\pm$ 18.85. Using the bivariate congruence variable, 75% of CG and SS were discordant in their depressive symptom appraisal. On the single 'feel sad' item, 73% of the dyads were discordant (Cohen's Kappa =.074; p=.09). CG and clinical characteristics were dichotomized and compared for the level of congruence on the single item. Dyads with female CGs (k=.10, p=.04), CGs with low depressive symptoms (CES-D $<$16) (k=.12, p=.02), and dyads with SS who were not on an antidepressant (k=.15, p=.008) were significantly congruent in their assessment of the SS feeling sad; their counterparts were discordant. Dyads were congruent primarily when they perceived that the SS rarely felt sad or had an absence of symptoms (79–71%). Discussion: Overall, SS/CG dyads were not congruent in their appraisal of depressive symptoms in the SS. Health care providers may need to educate and talk with both SS and CG to obtain better symptom assessment.

62

Changes in Sense of Coherence and Depression Symptoms Among Informal Caregivers of Stroke Survivors Across 2 Years

Neale R Chumbler, Maude Rittman, Haijing Qin, Samuel Wu; Rehabilitation Outcomes Res Ctr, North Florida/South Georgia Veterans Health System, Gainesville, FL

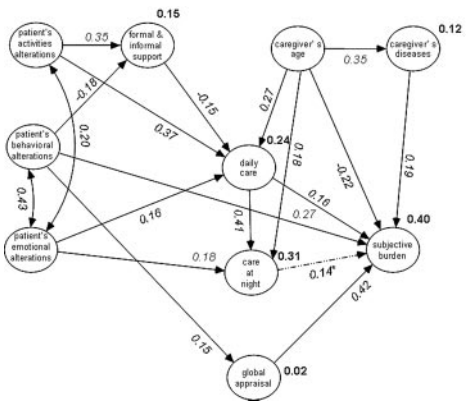
Introduction: An individual's sense of coherence (SOC), which takes into account one's ability to respond to stressors by the use of adaptive coping resources, is presumed crucial in coping with stressful life events such as caring for friends or family members. **Hypothesis:** We assessed the hypothesis that caregivers with a stronger SOC would have lower levels of depression two years following a stroke. We also examined the extent to which stroke survivor characteristics (functional status, cognitive function, and depression) were predictive of caregiver depression two years following a stroke, adjusting for SOC. **Methods:** One-hundred fifteen veterans hospitalized after experiencing an acute stroke from one of five Veterans Affairs Medical Centers in the Southeast and their informal caregivers were enrolled prior to discharge. Data were collected via face-to-face in-home interviews at 1-, 6-, 12-, 18-, and 24-months after discharge. Data were analyzed using linear mixed models, which allowed random and fixed effects to be considered. **Results:** The majority of caregivers were female (88%), spouses (66%), and had attained less than a high school education (56%). The prevalence of caregiver depression was 21% at 1-month, but was 11% at 24-months. Based on the mixed models, there were four significant variables associated with lower levels of caregiver depression at 24-months: 1) caregivers with a stronger SOC ($p < .0001$); 2) caregivers who rated their health as good to excellent ($p = .0005$); 3) caregivers caring for patients with a higher Functional Independence Measure Motor score ($p = .03$); and 4) caregivers with more than a high school education ($p = .05$). There was also a significant time effect, indicating that caregiver depression at 24-months was significantly lower than at one-month ($p = .01$). **Conclusions:** A stronger SOC appears to be an important predictor of lower levels of depression among caregivers two-years following a stroke. Caregivers for patients with higher functional independence reported fewer depressive symptoms. In conclusion, given the increasing pressures on families and friends to provide care for stroke survivors, the SOC may be tailored for interventions in developing some assistance for informal caregivers.

63

Caregivers to Stroke Patients: Predictors of Burden

Wolfgang Hasemann, Annemarie Kesselring, Inst of Nursing Science, Basel, Switzerland; Markus Stoecklin, Inst of Psychology, Univ of Basel, Basel, Switzerland; Elmar Graessel; Clinic for Psychiatry and Psychotherapy, Univ of Erlangen, Erlangen, Germany

Background and Purpose: From the 63% of stroke patients who survive their first-ever-in-a-lifetime-stroke, only 17% to 33% are able to independently perform their activities of daily life after hospital discharge. Relatives who care for stroke survivors at home provide extensive emotional, social and physical care, which might be perceived as a burden. A recent review of the literature revealed inconsistencies in predicting caregivers' subjective burden. The purpose of this secondary analysis was to test the validity of various known predictors of caregiver burden. Methods: We analyzed data from a subsample of caregivers of stroke patients (N=481) from a larger cross sectional German study. We built a structural equation model (SEM), including patient, caregiver and situation characteristics as predictor variables and subjective burden as outcome variable. Subjective burden was measured with the Burden Scale for Family Caregivers. Results: The poor fit of the initial SEM reflected the inconsistencies in the literature. In the refined final SEM the strongest predictor of caregiver burden was the caregivers' appraisal (β=0.42) of the caregiving situation. Next best predictors, in descending order of standardized path coefficient significance, were: behavioral alterations of the patient (γ=0.27), caregiver age (γ=-0.22), caregiver health status (β=0.19), and the workload associated with daily care (β=0.16). The predictor nocturnal workload was unstable, the variables patient cognition, drive, and age were insignificant. Conclusions: Professional interventions need to focus on the caregiver's appraisal of the situation.



Community/Risk Factors

64

FLAP and Ischemic Stroke and Subtypes of Ischemic Stroke Among Whites and Blacks

Daniel Woo, Ritesh Kaushal, Kathleen Alwell, Mary Haverbusch, Brett Kissela, Dawn Kleindorfer, Matthew Flaherty, Prodipto Pal, Ranajit Chakraborty, Ranjan Deka, Joseph Broderick; Univ of Cincinnati, Cincinnati, OH

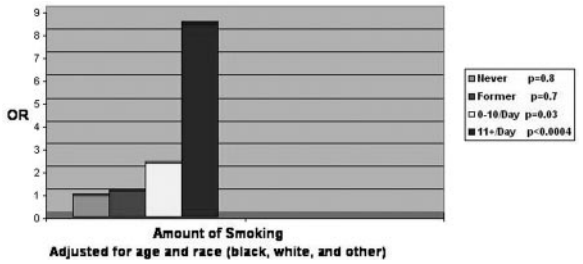
Introduction: The 5-lipoxygenase activating protein (FLAP or ALOX5AP) gene has been reported to confer risk of stroke in European populations. Few studies have examined the association in a US population or among blacks. We examined genotype and haplotype association of the FLAP gene in cases and controls from the same population. **Methods**: Single nucleotide polymorphisms (SNPs) were selected based on prior association studies. Cases were recruited from a population-based stroke study and controls were matched by age (+/- 5 years), race and gender. Genotyping was performed using TaqMan and genotype association, Hardy-Weinberg Equilibrium (HWE), linkage disequilibrium (LD) and haplotype association were performed using HELIXTREE. **Results**: Of 451 cases, genotyping results were available for 357 cases of ischemic stroke and 303 matched controls. All SNPs were found to be HWE. The rs4769874 SNP was associated (after multiple testing corrections) with ischemic stroke, cardioembolic, large vessel and ischemic stroke of unknown cause among whites. Other associations were not significant after multiple testing corrections. No association was observed among blacks and the allele frequencies for markers rs9579646 and rs10507391 had inverse proportions to whites. Significant haplotype association (after multiple testing corrections) was observed for all ischemic stroke and ischemic stroke subtypes among whites. Haplotypes inferred using rs10507391 and rs4769874 (that were part of the HapA haplotype) were associated with all ischemic stroke and all subtypes except for small vessel ischemic stroke among whites. Haplotype associations among blacks were not significant after multiple testing corrections. **Conclusions**: FLAP is significantly associated with ischemic stroke and ischemic stroke subtypes among whites, but not blacks.

65

A Gene-Environment Interaction Between Phosphodiesterase 4D Genotype and Cigarette Smoking Influences Stroke Risk: The Stroke Prevention in Young Women Study

John W Cole, Univ of Maryland Sch of Med, Baltimore, MD; Qing Song, Morehouse Sch of Med, Atlanta, GA; Jeffrey R O'Connell, Oscar C Stine, Univ of Maryland Sch of Med, Baltimore, MD; Margaret Gallagher, Wayne H Giles, Ctrs for Disease Control and Prevention, Atlanta, GA; Braxton D Mitchell, Marcella A Wozniak, Barney J Stern, John D Sorkin, Laurie J Reinhart, Univ of Maryland Sch of Med, Baltimore, MD; Qin Xu, Gary H Gibbons, Morehouse Sch of Med, Atlanta, GA; Steven J Kittner; Univ of Maryland Sch of Med, Baltimore, MD

Background: Previous studies demonstrated *PDE4D* polymorphisms are associated with ischemic stroke. Using data from the SPYW Study, we sought to further explore these associations by performing analyses stratified by standard risk factors. **Methods:** A population-based case-control study of stroke among women aged 15–49 (~50% black) identified 300 cases of first ischemic stroke and 225 age-comparable control subjects. Single nucleotide polymorphisms (SNPs) were genotyped in the population and assessed for association with stroke. Significant SNPs underwent analyses stratified by standard risk factors (age, oral contraceptive use (OCP), smoking, hypertension (HTN), diabetes, and history of angina or myocardial infarction). Tests for interaction were performed. **Results:** A screening analysis (adjusted for age and race) of 24 genotyped SNPs revealed a 5' SNP (risk allele frequency = 0.4) to be significantly associated with stroke (OR=1.5, p=0.005). Risk factor stratified analyses demonstrated that this SNP is highly associated with stroke among smokers (OR=2.98, p<0.0005) but not associated with stroke among nonsmokers (OR=1.04, p=0.836). The smoking by genotype interaction term was significant (p=0.03) in a model including the covariates of age, race, HTN, diabetes, and OCP. The figure below suggests that amount of current smoking influences the *PDE4D*-associated stroke risk.



Conclusions: This is the first study to identify a gene-environment interaction between *PDE4D* and smoking. Our results confirm *PDE4D* as a stroke-susceptibility locus, with further analyses demonstrating a 5' SNP that confers risk among smokers, but not among non- or former-smokers.

66

A Prospective Evaluation of Advanced Glycosylation End Product-Specific Receptor Gene Polymorphisms with the Risk of Incident Myocardial Infarction and Ischemic Stroke

Robert Y Zee, Jose R Romero, Jessica J Gould, Dennis A Ricupero, Paul M Ridker; Brigham and Women's Hosp, Harvard Med Sch, Boston, MA

Background: A role for advanced glycosylation end product-specific receptor (AGER, a.k.a. RAGE) in the development of cardiovascular disease has been reported. Genetic variation of AGER has recently been implicated in human coronary atherosclerosis. However, to date, no prospective, genetic-epidemiological data have been reported relating AGER with the development of athero-thrombotic events. Methods and Results: Using a prospective, nested case-control approach, we evaluated three AGER gene polymorphisms (dbSNP rs1800625, rs1800624, and rs2070600) amongst 610 Caucasian individuals who subsequently developed an athero-thrombotic event (incident myocardial infarction or ischemic stroke) and amongst 610 age- and smoking-matched Caucasian individuals who remained free of reported vascular disease during follow-up (controls). Genotype distributions for the polymorphisms tested were in Hardy-Weinberg equilibrium. The polymorphisms tested were in strong linkage disequilibrium (Lewontin's normalized D'>0.90). Haplotype-based conditional logistic regression, adjusting for age, smoking status, BMI, hypertension, diabetes, and randomized treatment assignment, showed that haplotype C-T-Gly (myocardial infarction: OR=0.61, 95%CI 0.41–0.90, p=0.013), and haplotype T-A-Gly (ischemic stroke: OR=0.61, 95%CI 0.39–0.96, p=0.031) were associated with reduced risk of atherothrombotic events. Conclusion: In this large, prospective cohort of apparently healthy Caucasian men, we found evidence of an association between polymorphisms in the AGER gene and reduced risk of atherothrombosis. These findings support the hypothesis that AGER plays a role in the development of cardiovascular diseases.

67

Antiphospholipid Antibody Portfolio Predicts a High-Risk Subgroup of Ischemic Stroke Patients for Subsequent Events: Preliminary APASS-WARSS Results

Steven R Levine, Mount Sinai Sch of Med, New York, NY; Robin L Brey, Univ of Texas HSC, San Antonio, San Antonio, TX; Barbara C Tilley, Y Lin, Med Univ of South Carolina, Charleston, SC; J L Thompson, Ralph L Sacco, J P Mohr, Columbia Univ, New York, NY; and the APASS Investigators

Data from the APASS-WARSS study (JAMA 2004;291:576) suggested that ischemic stroke patients positive for *both* anticardiolipin antibodies (aCL) and lupus anticoagulant (LA) had greater risk for subsequent thrombo-occlusive events (TOE) than antiphospholipid antibody (aPL) negative patients. We investigated the predictive value of positivity on >1 aPL assay using new aPL assays in the same cohort. A random sample of 200 of the 1,770 subjects from the APASS-WARSS Cohort (stratified by aCL/LA status and yr. of enrollment) underwent further aPL testing for antibodies to phosphatidylserine (aPS, REEADS®) and $\beta_2$glycoprotein-I (β_2GPI, ELISA, Innova Diagnostics) from stored (-70ºC) baseline sera. Treatment groups were combined based on no treatment x TOE interaction. Of patients who were LA+/aCL+, 66% (95%CI 51,79) were either aPS+ or β_2GPI+ compared to 29% (17,44) of LA-/aCL- patients, OR 4.69 (1.92,11.81, p = 0.0006). Correlation coefficients among assay of the same isotype ranged from 0.028 for aCL and β_2GPI (IgA) to 0.592 for β_2GPI and aPS (IgM). Subjects who were positive for both β_2GPI and any of the other aPL (a 2nd aPL: aCL, aPS, and/or LA) had a 2-fold higher TOE rate than β_2GPI- subjects (Table 1). This combination of assays also had one the best overall performances regarding all of the predictive value indicators (Table 2).

TABLE 1. APL AND TOE RATE

aPL+ Definition	aPL+ (N)	aPL- (N)	TOE Rate + vs. -	RR	95% CI	P value
aCL+ &/or LA+	145	48	+22.8 -20.8	1.11	0.55,2.25	0.78
aPS+ or β_2GPI+	94	104	+26.6 -18.3	1.52	0.84,2.76	0.17
aCL or LA+ & aPS+ or β_2GPI+	77	115 (aPS- & β_2GPI-)	+29.9 -17.4	1.78	0.97, 3.24	0.06
β_2GPI+ & 2nd aPL+	45	147 (β_2GPI-)	+31.1 -19.7	2.03	1.03, 3.98	0.04

TABLE 2. APL PREDICTIVE VALUES (ADJUSTED FOR HTN)

Assay	Sensitivity	Specificity	PPV	NPV	Efficiency
Hypertension	67	34	23	78	42
aCL or LA+ & aPS+ or β_2GPI+	54 (38,69)	64 (56,72)	30 (20,42)	82 (74,89)	62 (54,69)
β_2GPI+ & aPL+ on a 2nd assay	33 (19,49)	80 (72,86)	32 (19,48)	80 (73,86)	69 (62,75)
LA+ & 2nd aPL+	26 (14,41)	24 (17,32)	9 (5,15)	52 (40,65)	24 (18,31)
Any IgG aPL+	18 (7,33)	87 (80,92)	28 (12, 49)	79 (71,85)	72 (64,78)

Correlation between aCL/LA and aPS/β_2GPI is substantial and significant, however > ¼ of LA-/aCL- subjects were aPS+ or β_2GPI+. β_2GPI+ with a 2nd aPL+ assay conferred a doubling of the subsequent TOE rate (adjusted absolute increase 11.4%) compared to β_2GPI-. An aPL portfolio correctly classifies subjects having a TOE at 2 yrs. about 50% better than hypertension.

68

Parental Occurrence of Stroke and Risk of Stroke in Their Children: The Framingham Study

Sudha Seshadri, Alexa Beiser, Margaret Kelly-Hayes, Carlos S Kase, Philip A Wolf; Boston Univ Sch of Med, Boston, MA

Background: Parental CHD <65 years is accepted as a marker of increased CHD risk in their offspring. Data regarding stroke risk and parental occurrence of ischemic stroke are sparse. **Objective:** To determine if prospectively documented parental occurrence of stroke increases the risk of ischemic stroke in the children in the community-based Framingham Study. **Methods:** 1925 Framingham Offspring study participants, free of baseline stroke who attended the 1st, 3rd, 5th or 7th offspring examinations were followed for up to 8 years or until the start of the next follow-up period (4504 observation periods). Participants whose parents were enrolled in the Original cohort were included if a parent had sustained a prospectively identified and verified clinical stroke by age 65 or was known to be stroke-free at this age. Cox proportional hazards models were used to determine the risk of offspring developing a completed stroke by age 65 years. Increased risk conferred by parental occurrence of stroke was computed after adjusting for stroke risk factors and for sibship among offspring. Risks were determined for maternal and paternal stroke, and for stroke subtypes in parent and offspring. **Results:** 542 parental and 33 offspring strokes were directly documented. Parental stroke, total as well as ischemic, were associated with a significant increased risk of stroke in the offspring by age 65 years and this applied to both maternal and paternal stroke. **Conclusion:** Documented parental stroke by age 65 years was associated with a significantly increased risk of offspring stroke by age 65. This increased risk was present even after adjusting for known stroke risk factors strongly suggesting a hereditary propensity for ischemic stroke.

		Parent HR**	Offspring P value	Parent Cases	Offspring Cases/N*
All stroke	All stroke	542	33/4504	3.02	0.004
All stroke	Ischemic stroke	542	24/4504	4.04	0.002
All stroke	Cardioembolic stroke	542	5/4504	1.07	0.955
All stroke	Atherothrombotic infarct	542	19/4504	4.69	<0.001
Ischemic stroke	All stroke	411	32/4458	2.39	0.040
Ischemic stroke	Ischemic stroke	411	23/4458	2.86	0.032

*N= Number of discrete 8-year observation periods.
**adjusted for stroke risk factors: systolic blood pressure, hypertension treatment, current smoking, diabetes, atrial fibrillation, ECG-LVH, prior cardiovascular disease and sibship.

69

Lipid Levels and the Risk of Hemorrhagic Stroke in Women

Tobias Kurth, Brigham and Women's Hosp, Boston, MA; Carlos S Kase, Boston Univ Med Ctr, Boston, MA; Julie E Buring, J Michael Gaziano; Brigham and Women's Hosp, Boston, MA

Background-Several observational studies have suggested that low lipid levels are associated with increased risk of hemorrhagic stroke (HS) but randomized trials showed no effect of lipid lowering drugs on HS risk. **Objectives-**To prospectively evaluate the association between total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides (TG), and the ratio of TC:HDL, and the risk of HS in apparently healthy women. **Methods-**Prospective cohort study among 27,937 US women participating in the Women's Health Study who provided blood samples and were free of stroke at baseline. Stroke occurrence was self-reported and confirmed and classified into ischemic or hemorrhagic stroke (including intracerebral and subarachnoid hemorrhage) by detailed medical record review. We categorized plasma lipid measures into quintiles. To control for age, cholesterol lowering treatment, alcohol consumption, smoking, history of hypertension, and antihypertensive treatment, we used the Cox proportional hazards model. We tested linear and nonlinear relationships by using the likelihood ratio test, with lipid quintile as a continuous variable and its quadratic term. **Results-**After 10 years of follow-up, a total of 65 HS occurred. Compared to women in the 3rd quintile, women in the first quintile had adjusted hazard ratios (HRs) for hemorrhagic stroke of 2.04 (95% CI, 0.90–1.64) for TC, 2.18 (1.01–4.70) for LDL, 1.12 (0.57–2.21) for TG, and 2.93 (1.33–6.44) for the TC:HDL ratio. The highest quintile of HDL was associated with a HR for HS of 2.22 (1.00–4.94). We observed statistically significant inverse linear trends for TG (P=0.046) and the TC:HDL ratio (P=0.031) but not for TC (P=0.33), HDL (p=0.22), and LDL (P=0.12). We observed a statistically significant U-shape association between HDL and HS (P=0.025). **Conclusion-**Our data suggest that low TC, LDL, TG, and TC:HDL as well as high HDL measures were associated with increased risk of HS. Low numbers of HS and potential residual confounding should caution the interpretation of our data. Further observations in larger cohorts of subjects with HS will be needed to determine whether cholesterol measures are a marker or risk factor for increased risk of HS in women.

70

Genomic Susceptibility Loci for Leukoaraiosis and Brain Atrophy in Hypertensive European (White) and African-American Sibships

Stephen T Turner, Mayo Clinic, Rochester, MN; Myriam Fornage, Univ of Texas Health Science Ctr, Houston, TX; Clifford R Jack, Mayo Clinic, Rochester, MN; Thomas H Mosley, Univ of Mississippi Med Ctr, Jackson, MS; Sharon L Kardia, Univ of Michigan, Ann Arbor, MI; Eric Boerwinkle, Univ of Texas Health Science Ctr, Houston, TX; Gary L Schwartz, Mariza de Andrade; Mayo Clinic, Rochester, MN

Hypertension in midlife contributes to cognitive dysfunction late in life, largely due to ischemic brain injury. Genetic susceptibility to hypertension-related ischemic brain injury has been demonstrated, but locations of the genes responsible are largely unknown. We conducted a genomewide search for loci contributing to ischemic damage to the subcortical white matter (leukoaraiosis) and brain atrophy in 680 European non-Hispanic white Americans (279 men, 401 women from 334 sibships; mean age [± standard deviation] 62±9 years; 75% hypertensive) and 594 African-Americans (188 men, 406 women from 402 sibships; mean age =64±9 years; 79% hypertensive) enrolled in the Genetic Epidemiology Network of Arteriopathy study, which recruited sibships with >=2 members with essential hypertension diagnosed before age 60. The volume of leukoaraiosis was quantitated by MRI and the difference between intracranial and brain volumes provided a measure of brain atrophy. Blood pressure (BP) was measured by random zero sphygmomanometer, and the calculated mean arterial pressure (=[systolic BP + 2*diastolic BP]/3) and pulse pressure (=systolic BP - diastolic BP) provided measures of steady-state-level and pulsatile components of BP. After adjustment for sex and age, variance components models estimated greater heritability of leukoaraiosis in European than African-Americans (0.62 vs. 0.29, respectively; both *P*'s <0.01) and similar heritability of brain atrophy in both groups (0.48 and 0.54, respectively; both *P*'s <0.0001). In univariate linkage analyses, the multipoint maximum LOD scores (MLS) were observed for brain atrophy on chromosome 17 in European Americans (MLS =3.0 at 52 cM, *P* =0.0001), and for leukoaraiosis on chromosome 22 in African-Americans (MLS =2.3 at 29 cM, *P* = 0.0006). Bivariate linkage analyses of each brain & BP measure provided evidence of a region with pleiotropic effects on brain atrophy & pulse pressure on chromosome 11 in European Americans (bivariate MLS =4.3 at 15 cM, *P* =0.00005). These results suggest that multiple genes influence susceptibility to hypertension-related ischemic brain injury and their contributions to genetic predisposition may differ between European and African-Americans.

Acute Management

71

MRI-Based Thrombolysis in Acute Stroke Patients with Unclear Onset Time is Safe and Feasible

A-Hyun Cho, Deok H Lee, Jong S Kim, Choong G Choi, Sun U Kwon, Dae Chul Suh, Jimi Choi, Sang-Beom Chun, Sang J Kim, Jae-Young Koh, Dong-Wha Kang; Asan Med Ctr, Seoul, Democratic People's Republic of Korea

Background: Standard selection criteria for thrombolysis typically exclude acute stroke patients with unclear onset time, e.g., those with deficits on awakening. MRI may provide a tissue clock replacing the currently used time clock when deciding whether to initiate thrombolytic therapy. We hypothesized that safety and outcomes of MRI-based thrombolysis in patients with unclear onset time would not be inferior to those in patients with clear onset time. Methods: In this prospective study during 15-month period, 213 acute ischemic stroke patients within 6 hours of stroke awareness were considered for intravenous (IV) or intra-arterial (IA) thrombolysis. Patients within 6 hours from last known normal time (n=182) were considered for conventional CT or MRI-based thrombolytic therapy. For patients with unclear onset time and more than 6 hours from last known normal time (n=31), additional MRI specific eligibility criteria (i.e., positive perfusion-diffusion mismatch, and no more than subtle T2 changes of acute diffusion lesions) were applied. Early neurologic improvement was defined as reduction by ≥ 4 points in National Institutes of Health Stroke Scale (NIHSS) score at 24 hours after treatment. Symptomatic intracranial hemorrhage (ICH) was defined as ICH on CT performed within 48 hours after treatment with ≥ 4 point increase of NIHSS. Long-term outcome was the modified Rankin Scale (mRS) obtained at 3-month. Results: Of 213 patients screened for thrombolysis, 70 (38.5%; group A) of patients with clear onset time (IV in 35, IV+IA in 13, IA in 22) and 10 (32.3%; group B) of those with unclear onset time (IV in 2, IV+IA in 2, IA in 6) received thrombolysis. Demographics, baseline stroke severity, stroke subtypes, and door-to-needle times were comparable between two groups. Early neurologic improvement (30% in group A vs. 40% in group B), symptomatic ICH (5.8% vs. 0%), 3-month outcomes (mRS 0–1, 26% vs. 20%; mRS 0–2, 42% vs. 40%; mortality, 24.6% vs. 10%) did not differ between two groups. Conclusion: These data suggest that thrombolysis based on MRI criteria may safely be applied to acute stroke patients with unclear onset time.

72

Comparison of Perfusion-CT/CT Angiography and MRI in the Selection of Stroke Patients for Acute Treatment

Max Wintermark, Univ of California, San Francisco, San Francisco, CA; Patrick Michel, Marc Reichhart, Patrick Browaeys, Reto Meuli, Pierre Schnyder, Julien Bogousslavsky; Univ Hosp, Lausanne, Switzerland

PURPOSE: Diffusion- (DWI) and perfusion-weighted imaging (PWI) have been used in several drug trials to select stroke patients for acute treatment. The purpose of this study was to evaluate how perfusion-CT (PCT) and CT-angiography (CTA) compare with MRI for the evaluation of the criteria used for treatment decision. MATERIAL&METHODS: 42 acute stroke patients underwent successive CT and MRI examinations in the 3–9 hour time window following symptom onset, 14 being eventually selected for acute stroke treatment based on clinical and MRI criteria. The PCT/CTA and MRI examinations obtained in the 42 patients were independently reviewed by 2 observers for the following criteria: infarct core (PCT infarct or DWI abnormality) <1/3 of the MCA territory, ischemic penumbra (PCT penumbra or DWI/PWI mismatch) exceeding the infarct core by >20%, and ischemic involvement of the cortex. The PCT infarct and ischemic penumbra were automatically computed using cerebral blood volume (CBV) and mean transit time (MTT) thresholds reported in the literature. Evaluations of the above-mentioned criteria, and final treatment decision based on these criteria, were compared using Pearson's khi square statistics (alpha). RESULTS: Agreement between PCT/CTA and MRI was excellent regarding infarct size (alpha=0.89) and cortical involvement (alpha=0.84), and substantial regarding the penumbra/infarct ratio (alpha=0.79). Agreement for treatment decision was excellent (alpha=0.95). Only one patient would have been treated based on MRI,

and not treated based on CT. In this patient, the penumbra/infarct ratio was eyeballed as >20% on DWI/PWI, and not fulfilling this condition on PCT. Quantitative PCT measurements revealed that the penumbra/infarct ratio (23%) actually exceeded 20%. The discordance resulted from the eyeballing approach used in the review rather than from the PCT technique itself. CONCLUSION: Similar acute stroke treatment decisions would have been made using a PCT/CTA or a MRI approach to assess criteria regarding the arterial occlusion site and the extent of infarct and ischemic penumbra. For the infarct/penumbra ratio evaluation, a quantitative assessment of the PCT results may be more reliable than subjective eyeballing.

73

Maintaining Euglycemia Following Stroke: The Hypotensive Effect of Glucose Potassium Insulin Infusions Upon Blood Pressure—the Glucose Insulin in Stroke Trial Experience

Chris S Gray, Anthony J Hildreth, Janice E O'Connell, Newcastle Univ, Sunderland, United Kingdom; Donna E Johnston, Sunderland Royal Hosp, Sunderland, United Kingdom; Kurt G Alberti; Newcastle Univ, Sunderland, United Kingdom

The effect of maintaining euglycaemia following acute stroke upon blood pressure; the Glucose Insulin in Stroke Trial experience Background GIST-UK is a multi-centre randomised controlled trial that seeks to determine the benefit of glucose/potassium/insulin (GKI) infusions to maintain euglycaemia in acute stroke patients with post stroke hyperglycaemia (PSH). The effect of GKI upon blood pressure was examined as part of the ongoing safety monitoring of the trial. **Methods** Acute stroke patients (cerebral infarction CI or intracerebral haemorrhage ICH) presenting with plasma glucose 6.1–17.0 mmol/l within 24 hours symptom onset are randomised to receive variable dose insulin GKI infusion (treatment) or saline (control) as a continuous intravenous infusion (100mls per hour for 24hours). The aim of GKI is to maintain capillary glucose between 4–7mmol/l, there being no intervention in the control group to modify plasma glucose concentrations. Blood pressure (BP) and pulse rate is measured in the unaffected limb on admission, start of treatment and 4 hourly intervals thereafter. Plasma glucose, urea and electrolytes are measured on admission, 24 and 48 hours. **Results** The first 848 patients recruited are included in this analysis, median age 76.0, range 40 to 97 years. A previous history of diabetes mellitus was found in 16.5%. Both systolic and diastolic BP fell within the first 4 hours of treatment and remained significantly lower throughout treatment; overall mean GKI SBP for the 24 hour period was 12.4mmHg less than saline, diastolic BP 5.41mmHg less than saline ($p<0.001$ and $p<0.05$ respectively). Maximal reductions in SBP (19.53mmHg) and DBP (9.3mmHg) were observed in patients with total anterior circulation syndromes $p<0.001$ and $p<0.05$ respectively) with further significant reductions confined to lacunar syndromes (SBP only). A significant hypotensive effect of GKI was observed both in patients with CI and ICH. Significant reductions in BP were confined to patients with no previous history of DM. **Conclusion** Treatment with GKI compared with saline resulted in a significant hypotensive effect independent of stroke pathology and maximal in those most severely affected (TACS). This effect was not observed in patients with a previous history of DM.

74

Plasma Biomarkers Distinguish Acute Ischemic Stroke Patients at Risk to Develop Intracerebral Hemorrhage After Thrombolytic Therapy

Edward C Jauch, Univ of Cincinnati College of Med, Cincinnati, OH; Gary F Ross, Ciphergen Biosystems, Freemont, CA; Shauna Beiler, Christian Beiler, Tina Choudhri, Kenneth R Wagner; Univ of Cincinnati College of Med, Cincinnati, OH

Objective: Thrombolytic therapy for acute ischemic stroke offers significant promise for patient improvement but is not without risk of inducing intracerebral hemorrhage (ICH). A diagnostic plasma biomarker panel that would assign risk for tissue plasminogen activator (rt-PA) associated ICH would be a valuable adjunct in clinical decision making. Presently, we examined the plasma protein profiles of acute stroke patients who developed ICH after rt-PA (seen on 24 hr CT or MRI) versus those who did not. **Methods:** Plasma was obtained from patients who presented with acute ischemic stroke and were enrolled in the NINDS-sponsored Combination Approach to Lysis utilizing Eptifibatide And rt-PA (CLEAR) trial. Patient plasmas were collected prior to administration of fibrinolytic therapy (baseline) and at 24 hours post-admission. We characterized plasma protein profiles by Surface Enhanced Laser Desorption/Ionization (SELDI) analyses. Specifically, we fractionated the samples using Q Hyper D spin columns, applied aliquots to H50 and CM10 Protein Chip array surfaces, and performed SELDI analysis using Ciphergen Biosystems PBS IIc Reader. Spectra were normalized and compared between CLEAR patients who developed ICH (N=5) versus a matched set of non-bleed stroke patients (N=5) using Ciphergen's Biomarker Wizard and Expression Difference Mapping Software. **Results:** The intensities of 11 protein peaks in the low molecular weight spectra (under 20,000 Daltons) were significantly different ($p = 0.009$ to 0.047) in the plasmas from ICH versus non-bleed patients at 24 hours. Eight peaks were increased and 3 peaks were decreased. Additionally, at baseline, these same peaks were present with several intensities trending towards differences. One peak (4412.979 m/z) was already significantly increased in ICH versus non-bleed patient plasmas. **Conclusions:** These results demonstrate several plasma biomarkers may potentially identify patients at risk to develop ICH after tPA administration for acute ischemic stroke prior to treatment. To confirm the validity of these results, analyses of plasmas from a larger cohort of patients will be required. Identification of the specific proteins with different expression intensities between the two patient groups is ongoing.

76

Association of Early Recanalization with Reperfusion and Clinical Outcome Following Intravenous tPA at 3 to 6 Hours: Results of the DEFUSE Study

Michael P Marks, Stanford Stroke Ctr, Palo Alto, CA; Vincent N Thijs, UZ Gasthuisberg, Leuven, Belgium; Wataru Kakuda, Stanford Stroke Ctr, Palo Alto, CA; Lawrence Wechsler, Univ of Pittsburgh, Pittsburgh, PA; Roland Bammer, Stephanie Kemp, Gregory W Albers, Stanford Stroke Ctr, Palo Alto, CA; On behalf of the DEFUSE Investigators

Background: The rate of early recanalization associated with iv tPA therapy, as well as the relationships between early recanalization, tissue reperfusion and clinical outcomes, are not well established. *Methods:* In this prospective, 7 center, NIH-funded study, magnetic resonance angiography (MRA), diffusion imaging (DWI), and perfusion imaging (PWI) were obtained in 70 consecutive acute ischemic stroke patients (NIHSS $\geq$ 6) immediately prior to, and 3–6 hrs after, treatment with iv tPA in the 3–6 hr window. A neuroradiologist (MM) blindly assessed the MRAs and rated vessels as occluded, partially occluded, normal or unreadable. *Results:* The baseline MRA was of adequate quality to interpret in 64 patients. Of these, 44 (69%) had a complete (N=22) or partial (N=22) occlusion of an intracranial vessel appropriate to the stroke symptoms. The follow-up MRA (median time from tPA bolus, 4.25 hours) was readable in 41 of these 44 patients (93%). Complete early recanalization occurred in 9 (22%) and partial recanalization in 9 (22%) for an overall recanalization rate of 44%. Patients with complete recanalization had an 80% reduction in PWI volume compared with a 57% reduction among those with partial recanalization and a 9% increase if no recanalization occurred (ANOVA <0.001). For lesions involving the M1 segment of the MCA (alone or in conjunction with the ICA), the recanalization rate was 46% (partial recanalization 23% [9/39], complete recanalization 23% [9/39]). For patients with an isolated M1 segment MCA occlusion (no ICA involvement) the recanalization rate was 40% (partial in 2/15 [13%] and complete in 4/15 [27%]). Despite being significantly older (76 vs 65 yrs, p= 0.016) and having slightly higher baseline NIHSS scores (14 vs 13), 44% of the patients with early recanalization had favorable clinical outcomes (NIH 0–1 / $\geq$ 8 pt improvement) compared to 26% of those without early recanalization, p=0.22. *Conclusion*s: Early MRA-documented recanalization following iv tPA therapy in the 3–6 hr treatment window correlates with significantly improved cerebral perfusion and better clinical outcomes. Reperfusion rates differ for individual vessels; however, the overall rate of early complete recanalization is modest (22%).

77

Hospital Notification by EMS in Acute Stroke Is Associated with Shorter Door-to-CT Time and Increased Likelihood of tPA Administration

Abdul R Abdullah, Eric E Smith, Paul Biddinger, Deidre Kalenderian, Lee H Schwamm; Massachusetts General Hosp, Boston, MA

Background: Rapid CT acquisition and interpretation are a critical step in facilitating use of IV tPA or catheter-based thrombolysis. In 2000, we initiated protocols to obtain rapid CT in all acute stroke patients presenting within 6 hours, regardless of NIHSS score. We hypothesized that prehospital notification would further shorten ED arrival to CT time and increase use of thrombolysis. **Methods**: We analyzed data on all acute stroke patients transported from the scene to our facility by EMS arriving within six hours of symptom onset from 4/1/04 to 6/30/05. We reviewed digital voice recordings of all EMS communications to our hospital (recorded using the ASC Marathon software system), and in-hospital time intervals and outcomes from our Get With the Guidelines-Stroke database. Comparisons of proportions were done by Fisher's exact test, continuous variables by t-test or Wilcoxon-Rank Sum, and multivariate analysis by linear regression. **Results**:There were 118 patients transported by EMS during the study interval. There were no significant differences between those with notification (n=44) and those without (n=74) in terms of age, gender, history of prior stroke, or duration of symptoms prior to ED arrival. There was a trend toward higher median NIHSS scores (8.5 vs. 6, p=0.09) and a lower proportion of mild strokes (defined as NIHSS $\leq$4, 55% vs. 70%, p=0.12) among the patients with notification compared to those without notification. Median door to CT time was 23% shorter (39 vs. 48 min, p=0.009) in the notification group, and thrombolysis, intravenous (n=32) and intra-arterial alone (n=2), occurred twice as often (41% vs. 21%, p=0.03). Reduced door to CT time was also correlated with increased NIHSS (Pearson r =-0.36, p<0.0001); a linear regression model showed that both notification (p=0.01) and increased NIHSS (p=0.002) were independent predictors of more rapid door to CT time. **Conclusions**: Advanced notification of patient arrival further shortened time to CT and increased the use of thrombolysis at our hospital to 41%, even in the setting of rapid CT access protocols. Further research is needed to understand how to increase prehospital notification in potential tPA candidates and to study the generalizability of our findings.

Diagnosis

78

Results of the Diffusion-Weighted Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) Study

Gregory W Albers, Stanford Stroke Ctr, Palo Alto, CA; Vincent N Thijs, UZ Gasthuisberg, Leuven, Belgium; Lawrence Wechsler, Univ of Pittsburgh Med Ctr, Pittsburgh, PA; Stephanie Kemp, Stanford Stroke Ctr, Palo Alto, CA; Gottfried Schlaug, Beth Israel Deaconess Hosp, Boston, MA; Elaine Skalabrin, Univ of Utah, Salt Lake City, UT; Roland Bammer, Micheal P Marks, Wataru Kakuda, Maarten Lansberg, Stanford Stroke Ctr, Palo Alto, CA; Ashfaq Shuaib, Univ of Alberta, Edmonton, Canada; William Coplin, Wayne State Univ, Detroit, MI; Micheal Moseley, Stanford Stroke Ctr, Palo Alto, CA; On behalf of the DEFUSE Investigators

Background: It is hypothesized that specific MRI patterns can identify patients who are most likely to benefit from early reperfusion. *Methods:* In this prospective, open-label, 7 center,

NIH-funded study, an MRI was obtained in 74 consecutive acute ischemic stroke patients (NIHSS ≥ 6) immediately prior to, and 3–6 hrs (median 4.25 hr) after, treatment with iv tPA in the 3–6 hr window. A mismatch (MM) was defined as a PWI volume 20% larger than the baseline DWI volume. Early reperfusion (ER) required a ≥30% and ≥ 10 cc reduction in PWI. The malignant MRI pattern (Malignant MP) was a baseline DWI ≥100 cc or severe PWI lesion (≥8 seconds delay on Tmax) of ≥100 cc. Target mismatch (TMM) excluded patients with the Malignant MP. Small baseline lesion (Small lesion) was defined as a baseline DWI and PWI volume both ≤10 cc. The primary endpoint was the "clinical response" defined as an NIHSS 0–1 / ≥ 8 pt improvement at 30 days. Major symptomatic intracranial hemorrhage (SICH) required an NIHSS increase ≥ 4 pt. *Results*:

	N	Age	Baseline NIHSS	SICH	Clinical Response	Rankin 0–2	Rankin 4–6
All patients	74	70.6	13.0	7%	41%	45%	45%
MM / ER	17	78.6	14.6	18%	53%*	47%	47%
TMM / ER	14	79.9	13.6	0%	64%**	57%**	36%**
MM / no ER	16	67.4	12.8	0%	19%	19%	75%
No MM / ER	5	67.0	13.0	20%	20%	40%	60%
No MM / no ER	7	71.3	12.1	0%	57%	43%	43%
Small lesion	19	71.1	9.8	0%	58%	74%‡	16%‡
Malignant MP	6	62.8	17.5	50%†	17%	17%	67%

*p< 0.05 compared with MM / no ER
**p< 0.05 compared with TMM / no ER †p= 0.00001 and ‡ p<0.01 compared with all other MRI patterns

Early reperfusion was associated with a favorable clinical response in mismatch patients, particularly those with a target mismatch. Patients without mismatch did not appear to benefit from early reperfusion. The malignant pattern was highly predictive of SICH, particularly for patients with early reperfusion (p=0.003 compared with early reperfusion patients who did not have the malignant pattern). Patients with small baseline lesions had favorable outcomes. *Conclusions*: The DEFUSE results support the concept that MRI patterns can differentiate patient subgroups that benefit from early reperfusion from those who do not benefit, or may be harmed.

79

Bleeding Risk Analysis in Stroke by T2*-Weighted Imaging Before Thrombolysis (BRASIL): A Multicenter Study of 600 Patients of the MR Stroke Collaborative Group

Jens Fiehler, Neuroradiology, Hamburg, Germany; Jean-Martin Boulanger, Foothills Med Ctr, Univ of Calgary, Calgary, Canada; Wataru Kakuda, Stanford Stroke Ctr, Stanford, CA; Jong S Kim, Univ of Ulsan, Seoul, Republic of Korea; David S Liebeskind, UCLA Stroke Ctr, Los Angeles, CA; Tobias Neumann-Haefelin, Univ Hosp Goethe-Univ, Frankfurt/Main, Germany; Norbert Nighoghossian, Cerebrovascular Disease Ctr, Lyon-I Univ, Lyon, France; Salvador Pedraza, Hosp Univ Doctor Josep Trueta, Girona, Spain; Alex Rovira, Inst Hosp Vall d'Hebron, Barcelona, Spain; Peter D Schellinger, Univ of Heidelberg, Heidelberg, Germany; Joachim Rother, Klinikum Minden, Minden, Germany; for the MR STROKE Collaborative Group

Introduction Symptomatic intracranial hemorrhage (SICH) is the most feared adverse event after thrombolytic therapy in ischemic stroke patients. Based on preliminary case series, it has been hypothesized that the presence of small hypointense lesions (HLE, "microbleeds") in T2*-weighted magnetic resonance imaging (T2*w MRI) might be predictive for a higher risk of hemorrhagic transformation and thus for SICH. **Patients and Methods** We analyzed 600 patients from nine centers in Europe, North America and Asia with ischemic stroke and MRI within six hours after symptom onset. Multiparametric MRI including a T2*w MRI was performed immediately after clinical evaluation and before intravenous and/or intraarterial thrombolysis (I.V. n=468, I.V.+I.A. n=40, or I.A. n=92). Initial T2*w imaging was rated for the presence of HLE smaller than 5 mm. SICH was defined as clinical deterioration with increase in NIH-SSS by two or more points, temporally related to a hemorrhage confirmed by CT or MRI. **Results** We observed HLE in 109 patients (18.2%) and SICH in 46 patients (7.6%). There was no difference in the rate of SICH between the patients with HLE (9/109, 8.3%) and without HLE (37/491, 7.5%) (p=0.800, Fisher's exact test). Number of HLEs in the individual patient ranged from 0 to 77. A higher rate of patients presenting with a pre-treatment NIH-SSS >10 was observed in the SICH group (p=0.017, Fisher's exact test) whereas no difference in age and onset to treatment time was observed between both groups (p=0.564 and p=0.263, Mann Whitney U-test). **Discussion** The data from this large study do not support the hypothesis that patients with HLE are at higher risk for SICH after thrombolysis therapy. A final analysis will be presented after additional data from two more centers have been evaluated. For the time being, our data do not support the exclusion of patients from thrombolysis therapy due to the presence of HLE.

80

Temporal Profile of Recanalization After Intravenous tPA: Selecting Patients for Rescue Reperfusion Techniques

Marc Ribo, José Alvarez-Sabín, Francisco Romero, Joan Montaner, Pilar Delgado, Marta Rubiera, Raquel Delgado-Mederos, Carlos A Molina; Hosp Vall d'Hebron, Barcelona, Spain

Background Intravenous thrombolysis in stroke achieves arterial recanalization in around 50% of cases. Determining temporal profile of recanalization may address patient selection and potential benefits of further rescue reperfusion techniques. **Methods** We studied 179 consecutive intravenous t-PA treated patients with intracranial artery occlusion. Transcranial doppler assessed recanalization (none-partial-complete) at 60 (early), 120 (delayed) minutes post t-PA bolus and 6 hours (late) from symptoms onset. Outcomes were determined: NIHSS (48hNIHSS), three months modified Rankin Scale (mRS). **Results** On admission 70% of patients presented proximal and 30% distal MCA occlusion, median NIHSS 17. Recanalization rates were, early: complete 17%, partial 28%, none 55%, delayed: complete 31%, partial 22%, none 47%. While early flow improvement was observed in up to 45% of patients, only 19% of patients with persistent occlusion (11% of total) presented delayed recanalization (OR delayed/early recanalization: 0.16, 95%CI 0.085–0.304;p<0.001). Among patients with persistent occlusion at 2 hours only 15% (7% of total) presented late flow improvement (OR late/early recanalization: 0.09, 95%CI 0.043–0.196;p<0.001). The few patients with late recanalization presented comparable median 48hNIHSS to those with early/delayed recanalization (3Vs4.5;p=0.9) and much lower than those with persistent occlusion after 6 hours (3Vs15,p=0.005). At three months the rate of mRS≤2 was similar between patients with early/delayed versus late recanalization (55%Vs86%;p=0.12) but lower if occlusion persisted six hours after onset (22%;p<0.001). **Conclusion** The majority of t-PA-induced recanalizations occur during the first hour post-treatment. Recanalizations during following hours are rare but still related to clinical improvement if achieved within 6 hours from onset. Rescue reperfusion techniques should be considered if flow improvement is not observed 60 minutes after t-PA bolus.

81

Early Decrease in Blood Pressure Predicts DWI Lesion Growth in Stroke Patients Treated with Intravenous tPA

Raquel Delgado-Mederos, Alex Rovira, Marc Ribo, Marta Rubiera, Esteban Santamarina, Joan Montaner, Elena Huerga, José Alvarez-Sabin, Carlos A Molina; Hosp vall d'Hebron, Barcelona, Spain

Background: There is controversy regarding the influence of blood pressure (BP) changes in the course of acute ischemic stroke, particularly in the setting of thrombolysis. We aimed to evaluate the impact of BP changes in the evolution of acute DWI lesion volume in tPA-treated stroke patients. Methods: We studied 35 consecutive acute stroke patients due to an intracranial artery occlusion treated with iv tPA who were imaged with multiparametric MRI before and 24–36 hours after tPA bolus. DWI volume change (ΔDWI: DWI final-initial) was measured. Recanalization was assessed by TCD during the first 6 hours of treatment. Maximum , minimum, mean, variability (ΔBP) values of systolic (SBP), diastolic (DBP) and mean (MBP) BP were obtained on admission and serially monitored during 12 hours after tPA bolus. BP drop was defined as the maximal BP decrease between baseline and minimal BP values during 12-hour monitoring. Clinical improvement was defined as a decrease of ≥4 points on the NIHSS score at 48 hours from baseline. Results: 18 (51.4%) patients had previous history of hypertension. Mean SBP, DBP and MBP on admission were 155±32.4, 82.5±18.7 and 106.7±21 mmm Hg. Mean ΔSBP and ΔDBP were 58.8±27 and 36.3±17.3 mm Hg, respectively. Recanalization on TCD occurred in 20 (57.1%) patients. DWI lesion growth was strongly correlated with the decrease of SBP (r=0.520, p=0.002) and DBP (r=0.562, p=0.001) during the first 12 h. For every 10 mmHg decrease of SBP and DBP, DWI increased in 6.95 and 12.01 cc, respectively. The impact of BP drop on DWI lesion growth varied depending on the occurrence of recanalization: SBP (r=0.545, p=0.044) and DBP (r=0.653, p=0.011) decrease were significantly correlated with DWI growth in non-reperfused, but not in reperfused tPA- treated patients. Similarly, clinical improvement at 48 hours was associated with a lesser degree of SBP drop only in patients who did not recanalized (p=0.039). Conclusion: BP decrease during stroke thrombolysis is associated with greater DWI lesion growth and worse clinical course. The deleterious role of BP drop is higher in patients who did not achieve recanalization. Avoiding BP drop may limit infarct expansion and improve outcome after thrombolysis

82

Extent of Ischemic Edema on CT before Thrombolysis: Prognostic Value of the Alberta Stroke Program Early CT Score in ECASS II

Imanuel Dzialowski, Michael D Hill, Shelagh B Coutts, Andrew Demchuk, Univ of Calgary, Calgary, Canada; David M Kent, Tufts-New England Inst, Boston, MA; Olaf Wunderlich, Ruediger Von Kummer; Univ of Dresden, Dresden, Germany

Objective: The significance of early ischemic changes on computed tomography (CT) to triage patients for thrombolysis has been controversial. The Alberta Stroke Program Early CT Score (ASPECTS) semi-quantitatively assesses EIC within the middle cerebral artery territory using a10-point grading system. Dichotomizing ASPECTS by 7 has been shown to predict response to intraarterial thrombolysis in selected patients. We hypothesized that dichotomized ASPECTS predicts response to intravenous thrombolysis and incidence of parenchymal hematoma within 6 hrs of stroke onset. Methods: Data from the ECASS II study were used in which 800 patients were randomized to recombinant tissue Plasminogen Activator (rt-PA) or placebo within 6 hrs of symptom onset. We retrospectively assessed all baseline CT scans by randomly assigning them to 2 groups of each 3 experienced CT-readers. Each group scored APECTS by consensus. We dichotomized ASPECTS at 7 and defined favorable outcome as modified Rankin Scale score 0–2 after 90 days. Secondary hemorrhage was defined as parenchymal hematoma (PH-1 or PH-2) as assessed by the ECASS expert panel. We performed a multivariable logistic regression analysis to adjust for age and baseline NIHSS and to assess for an interaction between rt-PA treatment and baseline ASPECTS score. Results: We scored ASPECTS > 7 in 557 and <<26> 7 in 231 patients. In both groups, patients treated with placebo and rt-PA were evenly distributed (p=.39). There was no treatment interaction with dichotomized ASPECTS (p=.3). This also applied for the 0–3 and 3–6 hrs subcohorts. However, effect modification by ASPECTS <<26> 7 was seen in predicting parenchymal hematoma (p=0.0085 for the interaction term, likelihood ratio test) Secondary hemorrhage (RR 18.9 CI95 2.6–138.5) was much more common with ASPECTS <<26> 7. Conclusion: In ECASS II, the effect of rt-PA on functional outcome is not influenced by baseline ASPECT score despite an increased risk of thrombolytic-related parenchymal hematoma in patients with extensive EIC.

83

A Spatial Component to the Risk of Infarction in Acute Ischemic Stroke

Hakan Ay, AA Martinos Ctr for Biomed Imaging, Stroke Service, Massachusetts General Hosp, Boston, MA; Walter J Koroshetz, Stroke Service, Massachusetts General Hosp, Boston, MA; Chloe J Lopez, Nina M Menezes, Mingwang Zhu, Thomas Benner, Christopher Melinosky, Ethem M Arsava, Ona Wu, A G Sorensen; AA Martinos Ctr for Biomed Imaging, Massachusetts General Hosp, Boston, MA

Background: Brain infarcts often appear to expand from the core to the periphery in a centrifugal pattern, suggesting that there is a spatial organization within the ischemic region. This may in turn mean the risk of tissue proceeding to infarction changes as a function of distance from the core. We sought to quantify the risk of developing infarction in each ischemic zone surrounding the DWI lesion. **Methods:** We studied 46 consecutive acute stroke patients with a demonstrated occlusive lesion in one of the major intracranial arteries. In each patient, diffusion- and perfusion-weighted images were obtained within the first 12 hours of symptom onset (5.7±2.6 hours) and a follow-up imaging on day 5 or later. The region visually abnormal on the mean transit time map (MTT) was segmented into the DWI lesion (zone 1), as well as 2 mm zones (one-voxel size) surrounding the DWI lesion (zones 2,3. . .n). For a given zone, the proportion of voxels that were infarcted on follow-up examination was calculated and averaged across all patients. These probabilities were then used in a predictive model in which the probabilities measured in (n-1) patients for each zone is applied to the remaining patient to produce voxel-based predictions of tissue outcome, as either infarcted or not-infarcted. **Results:** The proportion of voxels in the MTT lesion that were infarcted monotonically decreased in a zonal pattern from the center towards the periphery. This trend was highly statistically significant compared to a distribution that assumed the probabilities were the same across all zones ($p<0.0001$). The area under the ROC curve to evaluate the predictive ability of these zonal probability values was 0.837. At the optimal operating point on the curve (43%), voxels that proceeded infarction was predicted with 77% sensitivity and 79% specificity. **Conclusion:** In acute human stroke the likelihood of tissue proceeding to infarction in the region with abnormal perfusion depends on its proximity to the core, and predictive algorithms using such spatial information are feasible. Further studies in more diverse populations are needed to assess the reliability and dependence on time from onset as each zone may have different times of survival and therefore different time windows of therapeutic opportunity.

84

Gradient-Echo MRI Phase Mismapping Reveals Angiographic Correlates in Acute Ischemic Stroke

David S Liebeskind, Nerses Sanossian, Jeffry R Alger, Doojin Kim, Sidney Starkman, Bruce Ovbiagele, Amelia L Laughton, Noriko Salamon, Reza Jahan, Gary R Duckwiler, Fernando Vinuela, J P Villablanca, Jeffrey L Saver; UCLA, Los Angeles, CA

Background: Gradient-echo (GRE) MRI is used principally in acute stroke for the detection of hemorrhage or intraluminal thrombus, yet these sequences are exquisitely sensitive to flow. Phase mismapping (PM) is a common artifact produced by flowing blood evident as increased signal intensity at the luminal margins indicative of flow direction. We investigated whether PM can predict hemodynamic features demonstrated on concurrent conventional angiography. **Methods:** GRE sequences acquired immediately prior to conventional angiography for acute stroke were reviewed in blinded fashion. Presence of blooming artifact (BA) associated with thrombus, flow voids, and PM were examined. Catheter angiography findings including clot location, direction of flow, and collaterals (graded on a 5-point scale) were recorded. Descriptive and correlative analyses were used to corroborate GRE predictors of cerebral hemodynamics. **Results:** Concurrent GRE MRI and angiographic correlates were analyzed in 66 patients (33 men, 33 women; mean age 63 years, SD 19 years). BA was noted in 38/66 (58%) cases, associated with discontinuity of PM in all 38. PM discontinuity or segmental loss of this artifact was noted in an additional 6 cases, corresponding to the site of thrombus at angiography. Prominent PM was appreciated in 18 cases proximal to GRE-identified site of thrombus, whereas distal PM was evident in only 5 cases. In 41 cases of proximal MCA occlusion at angiography, asymmetry of PM in sylvian branches was noted in 37 (90%) with diminished flow voids in 32 (78%) and BA in only 25 (61%). In the 5 cases with PM distal to the occlusion, the direction of PM was reversed corresponding to retrograde collateral flow on angiography. **Conclusions:** GRE MRI phase mismapping provides important noninvasive depictions of angiographic findings and critical hemodynamic variables. Flow direction in intracranial arteries, including retrograde collateral perfusion, may be discerned with recognition of phase mismapping.

Outcomes

85

The Association Between Socioeconomic Status and Stroke Care Delivery: An Analysis of Data from the Registry of the Canadian Stroke Network

Crystal Chan, Geoffrey M Anderson, Univ of Toronto, Toronto, Canada; Jiming Fang, Inst for Clinical Evaluative Sciences, Toronto, Canada; David A Alter, Univ of Toronto, Toronto, Canada; Susan E Bronskill, Inst for Clinical Evaluative Sciences, Toronto, Canada; Michael D Hill, Univ of Calgary, Calgary, Canada; Douglas G Manuel, Inst for Clinical Evaluative Sciences, Toronto, Canada; Jack V Tu, Moira K Kapral, Univ of Toronto, Toronto, Canada; Investigators of the Registry of the Canadian Stroke Network

Background: Previous research has shown that socioeconomic status is inversely associated with stroke mortality. To account for this finding, we undertook a study to determine whether socioeconomic status is associated with the quality of stroke care delivery. Methods: We analyzed data from Phase 3 of the Registry of the Canadian Stroke Network, which contains data on all stroke patients treated at 11 selected Ontario tertiary care institutions between July 1, 2003, and March 31, 2004. Socioeconomic status for each patient was inferred on the basis of median neighbourhood income from the 2001 Canadian Census. We assessed for linear trends in patient characteristics as well as in various processes of stroke presentation, care, and outcomes across income quintiles. Secondary analyses compared the risk of death at 30 days and 1 year. Results: The study cohort consisted of 3210 patients. There were no differences in stroke type or severity based on socioeconomic status. Patients in the lowest income quintile were less likely to receive neurological consultation in hospital (60% vs. 88%, $p<0.001$), to receive thrombolysis (3.3% vs. 8.4%, $p<0.001$), and to be admitted to a designated stroke unit (28% vs. 31%, $p=0.005$), and were less likely to be referred to stroke prevention clinics after discharge (28% vs. 40%, $p<0.001$). Each $10,000 increase in median neighbourhood income was associated with a 23% reduction in the risk of death at 30 days (adjusted hazard ratio 0.77, 95% confidence interval 0.62 to 0.96) and a 14% reduction in the risk of death at 1 year (adjusted hazard ratio 0.86, 95% confidence interval 0.73 to 1.01). Conclusions: Socioeconomic status adversely affects stroke care and outcomes, despite Canada's universal health insurance program.

86

Hospital Characteristics and the Quality of Acute Stroke Care: Findings from the Paul Coverdell National Acute Stroke Prototype Registry

Mathew J Reeves, Michigan State Univ, East Lansing, MI; Charles J Moomaw, Rosie Miller, Univ of Cincinnati, Cincinnati, OH; Gengxin Li, Michigan State Univ, East Lansing, MI; Joseph P Broderick, Univ of Cincinnati, Cincinnati, OH; Michael Frankel, Emory Univ, Atlanta, GA; Lee Schwamm, Massachusetts General Hosp, Boston, MA; Kenneth A LaBresh, MassPro, Waltham, MA; Paul Coverdell Prototype Registries Writing Group

Introduction: The purpose of the Paul Coverdell National Acute Stroke Registry is to monitor and improve the delivery of care to acute stroke patients. We believe quality of care is influenced by both patient-level (e.g., age and stroke severity) and hospital-level characteristics (e.g., size and geographic location). We examined the relationship of hospital size and location to 8 pilot stroke-specific care performance measures established by JCAHO (see Table). Methods: During 2001–2002, data were collected on 6,867 acute stroke admissions treated at 97 hospitals from 4 statewide prototype registries (GA, MA, MI, OH). Information on hospital size (i.e., bed size divided into 4 groups) and location (i.e., inclusion within a Metropolitan Statistical Area vs. not) was obtained. The proportion of eligible subjects who met the criteria for each pilot measure was calculated. Chi-square analysis was used to determine the association between the hospital characteristics and the proportion of subjects meeting the criteria for each measure. Results: Statistically significant ($p < 0.05$) linear trends were found between bed size and 4 performance measures. In each case, the larger the hospital, the greater the level of compliance. Hospital location was associated ($p < 0.05$) with 3 measures. In each case, compliance was higher in the urban hospitals.

	Bed Size (% of subjects meeting criteria)				Mantel-Haenzel chi-square for trend p value	MSA (% of subjects meeting criteria)		Chi-square p value
Pilot Performance Measure	27–145	146–263	264–499	500–970		No	Yes	
1. Antithrombotic medication within 48 hrs of hospitalization	94	94	93	94	0.56	89	94	<0.0001
2. DVT prophylaxis	48	62	70	79	<0.0001	56	73	<0.0001
3. Lipid testing	19	31	41	45	<0.0001	26	41	<0.0001
4. Dysphagia screening	37	38	45	47	<0.0001	44	44	0.94
5. Smoking cessation	23	36	20	24	0.22	31	23	0.06
6. Discharged on antithrombotics	99	98	98	98	0.42	99	98	0.07
7. Discharged on anticoagulants	47	58	61	49	0.50	59	54	0.50
8. Discharged to rehabilitation	39	36	51	53	<0.0001	51	48	0.46

Conclusions: For certain measures, quality of care was associated with hospital size and/or geographic hospital location. Both size and location are likely proxy variables for the level of organization of acute stroke care within each hospital. Further analyses are required to identify other hospital level factors and how they can be used for quality improvement once JCAHO performance measures have been finalized.

87

Frequency and Predictors of Readmission in the First Year After Stroke

Irene L Katzan, MetroHealth Med Ctr, Cleveland Clinic Foundation, Cleveland, OH; Patrick K Murray, Charles Thomas; MetroHealth Med Ctr, Cleveland, OH

Background: Hospital readmissions contribute to the large public health burden from stroke. We evaluated the one year hospital readmission rates and clinical factors associated with readmission in a community-based cohort of patients with stroke. Methods: Our cohort included all 14293 Medicare patients admitted with stroke to 28 Cleveland hospitals 1991 -1997. Readmissions and deaths within one year of discharge were identified by linking hospital data with MEDPAR files. Detailed patient-level information was obtained from the chart-abstracted data of Cleveland Health Quality Choice. Lifetable analysis, censoring out-of-hospital deaths, was performed to calculate readmission rate. Extended Cox hazard regression models were used to evaluate the effects of patient and hospital factors on hazard for readmission. Results: The one year readmission rate of the 12,790 pts alive at hospital discharge was 44.4%. The risk declined over time, with 30% of 1st readmissions occurring $\leq$ 30 days and 53.6% occurring $\leq$ 90 days of discharge. Median LOS for 1st readmissions was 6 days [IQR 3, 10], similar to the LOS for initial stroke hospitalization [6, IQR 4,10]. 41.3% (1981/4797) of readmitted patients had $\geq$2 readmissions in the 1st year. Blacks (HR 1.14 [95%CI 1.04 - 1.26]) and men (HR 1.06 [95%CI 1.0 - 1.3]) had higher adjusted risks for readmission. Among the clinical predictors were motor weakness (HR 1.13 [95%CI 1.03 -1.25]), creatinine $>$ 2 (HR 1.24 [95%CI 1.11 - 1.38]), hemodialysis (HR1.34 [95%CI 1.05 - 1.72]), and low serum albumin (HR 1.10 [95%CI 1.03 - 1.17]. Discharge with requirements for extended care was associated with a risk that became less pronounced with increasing time from discharge (HR 1.30 at 30 days, HR 1.04 at 180 days). Conclusions: Readmission after stroke is a significant problem, occurring in almost half of survivors during the 1st year postdischarge and resulting in similar LOS as the initial stroke admission. Renal dysfunction

and nutritional deficits, important risk factors for readmission, could be a focus of preventive efforts. Differences in adjusted risks for readmission by gender and race may be due to differences in aggressivity of care, patterns of postdischarge management, or complication rates and merit further evaluation.

88

Racial Differences in Risk Factor Management in the Warfarin vs Aspirin for Symptomatic Intracranial Disease Trial

Salina Waddy, George Cotsonis, Michael Lynn, Michael Frankel, Emory Univ, Atlanta, GA; Seemant Chaturvedi, Wayne State Univ, Detroit, MI; Marc Chimowitz, Emory Univ, Atlanta, GA; for the WASID investigators

Background and Objective: Differences in the effectiveness of risk factor management in blacks v. whites in multicenter stroke trials has not been studied extensively. **Methods:** We analyzed differences in the frequency and treatment of risk factors and the effectiveness of this treatment among blacks and whites at enrollment and one year in the Warfarin vs. Aspirin for Symptomatic Intracranial Disease (WASID) trial. **Results:** At baseline, blacks were significantly more likely to have a history of hypertension (95% v. 85%, p=0.01), be on antihypertensive medication (81% vs. 68%, p=0.02), and use > 1 antihypertensive medication (16% v. 8%, p=0.02). Despite these differences, there was no significant difference in blacks v. whites (53% v. 50%) in measured hypertension (systolic pressure >140 or diastolic pressure >90). At one year, blacks were on antihypertensive therapy more commonly (89% vs. 76%, p=0.01) and used multiple agents more commonly (20% vs. 13%, p=0.01). Nevertheless, both groups had a similar frequency of measured hypertension at 1 year (52 blacks % v. 49% whites). Active smoking was higher in blacks at baseline (27% blacks v. 18% whites, p= 0.01) and at 1 year (20% v. 14%, p=0.17). At baseline, 57% blacks and 46% of whites had a history of hyperlipidemia or cholesterol > 200mg / dl (p=0.10), and 57% of blacks and 61% of whites (p=0.61) were on statins. At 1 year, 59% blacks and 76% whites were on a statin (p=0.01) and 45% blacks and 36% whites had cholesterol > 200 mg/dl (p=0.15), **Conclusion:** Antihypertensive therapy was commonly used in both blacks and whites in WASID, however, almost 50% of both groups had measured hypertension at 1 year. Statins were used significantly less in blacks than whites despite a significantly higher frequency of hyperlipidemia in blacks. While some progress was made in smoking cessation in both groups, it was limited. These data suggest that stroke prevention trials should incorporate formal protocols for managing risk factors in study patients

89

Race, Surgeon Specialty, and Appropriateness of Carotid Endarterectomy After the RCTs

Ethan A Halm, Stanley Tuhrim, Jason Wang, Mary Rojas, Edward L Hannan, Mark R Chassin; Mt Sinai Med Ctr, New York, NY

Background: A large national Medicare study of carotid endarterectomy (CEA) in 1981 found that 32% were done for inappropriate indications. Since then several large RCTs were done to clarify the indications for and efficacy of CEA. The New York Carotid Artery Surgery (NYCAS) Study is the first to assess in a population-based, clinically detailed manner the appropriateness of CEA in the US since publication of the major RCT results. It also examines the patient (Pt) and surgeon characteristics associated with inappropriate surgery. Methods: Detailed clinical data were abstracted on all Medicare Pts undergoing CEA from 1/98 to 6/99 in NY State (N=9588). We assessed appropriateness using a previously validated list of 1557 indications for CEA generated by national experts using the RAND appropriateness method. Appropriateness was based on neurologic symptoms (type, severity, recency, frequency), % carotid stenosis, comorbidity risk, and surgeons' complication rates. We used multiple logistic regression to identify Pt and surgeon characteristics associated with inappropriate surgery. Results: Nearly three-quarters of Pts (72.3%) underwent CEA for asymptomatic stenosis. Overall, 87.1% of operations were done for appropriate reasons, 4.3% for uncertain reasons, and 8.6% for inappropriate reasons. Among procedures considered inappropriate, the most common reasons were: high comorbidity among asymptomatic Pts (62.1%), operating after a major stroke (14.1%), or for minimal stenosis (13.7%). Blacks and Hispanics had higher adjusted odds of inappropriate surgery compared with Whites (OR=1.58; CI, 1.09–2.30 and OR=2.14; CI, 1.50–3.06) largely because higher proportions of these minority Pts had high levels of comorbidity. Neurosurgeons had lower adjusted odds of inappropriate surgey (OR=.70; CI, .50 to .97). Patients >85 years old and those operated on by the highest volume or most junior surgeons also had higher adjusted odds of inappropriateness (p<.05). Conclusions: Since publication of the RCTs, the rate of inappropriate surgery in Medicare Pts has dropped from 32% to 8.6% and most patients are now asymptomatic. Further work is needed to understand why some non-clinical Pt and surgeon characteristics were associated with inappropriate surgery.

90

Case Management of Poststroke Depression: The Results of the AIM Trial

Linda S Williams, Roudebush VA Med Ctr, Indianapolis, IN; Tamilyn Bakas, Indiana Univ, Indianapolis, IN; Laura Plue, Roudebush VA Med Ctr, Indianapolis, IN; Ed Brizendine, Wanzhu Tu, Hugh Hendrie, Kurt Kroenke; Indiana Univ, Indianapolis, IN

Background: Post-stroke depression (PSD) is prevalent and is associated with increased morbidity and mortality. Although effective depression treatments exist, they have been infrequently evaluated in randomized trials in stroke. We conducted a randomized controlled trial to evaluate the effectiveness of a case management strategy vs. usual care for PSD. **Methods:** Patients with ischemic stroke and no significant language or cognitive deficits were screened for PSD between one and two months post-stroke. Depressed patients were randomized to the AIM intervention vs. usual care. The intervention consisted of Activating and educating the patient about depression, Initiating antidepressant treatment, and Monitoring symptoms. Antidepressants were chosen based on a standardized algorithm. Usual care subjects received antidepressants at the discretion of their provider. All subjects received biweekly phone calls; intervention calls focused on depression symptoms and compliance and control calls on stroke symptoms. The primary outcome was PSD remission at 12 weeks, defined as score < 8 on the Hamilton Depression Inventory (HAM-D). Secondary outcomes were mean 12-week HAM-D and Patient Health Questionnaire (PHQ)-9 scores. **Results:** 188 depressed patients were randomized (94 intervention; 94 usual care). Characteristics at study entry were similar between study groups: race (61% white; 35% black), age (mean 60), sex (46% male), HAM-D depression severity (18.7) and NIH Stroke Scale (mean 2.7). 41% of control subjects did not take any antidepressants. A significantly greater proportion of intervention subjects had remission of depression at 12 weeks than did control subjects. (40% vs. 23%, p = 0.02). Mean 12-week depression scores were significantly lower in intervention than control subjects (HAM-D 10.7 vs. 13.7, p = 0.009 and PHQ-9 6.0 vs. 9.5, p < 0.001). **Conclusion:** Case management of PSD including antidepressant treatment and monitoring is more likely than usual care to result in PSD remission. Although some patients may improve with antidepressants alone, the addition of patient activation and monitoring via telephone support may be critical to successful treatment of PSD.

91

How Reliable Is the NIH Stroke Scale? An Analysis of Video Ratings

S A Josephson, Nancy K Hills, S C Johnston; Univ of California, San Francisco, San Francisco, CA

Background and Purpose: The National Institutes of Health Stroke Scale (NIHSS) is widely used in stroke clinical trials. Variance in scale scoring may reduce power of these trials. In order to further investigate the reliability of the NIHSS, we analyzed a large database of video certification examinations. **Methods**: The analysis involved all 7,405 unique raters who each completed one of two multiple patient videotaped certification examinations through the National Stroke Association. For each item on the NIHSS, a total of 38,148 individual responses were included. **Results**: Total NIHSS scores varied widely between raters; scoring for six of the 11 patients (55%) had a four or more point difference in NIHSS score from the 5th to 95th percentile. Variance was greater with increasing mean total NIHSS score (P<0.0001). Modified kappa values showed that the aphasia (0.596) and facial palsy (0.652) items on the test contributed most to the variance in the total NIHSS score. Nurses tended to agree with the most common response on scoring more frequently than physicians and other healthcare specialists. Taking the certification examination multiple times did not improve agreement. **Conclusions**: Although inter-rater reliability for individual elements of the NIHSS on videotaped vignettes was generally good, overall scoring was inconsistent, particularly for patients with substantial impairment. Whether additional training, modification of examination elements, or clearer definitions for scoring could improve reliability requires further study.

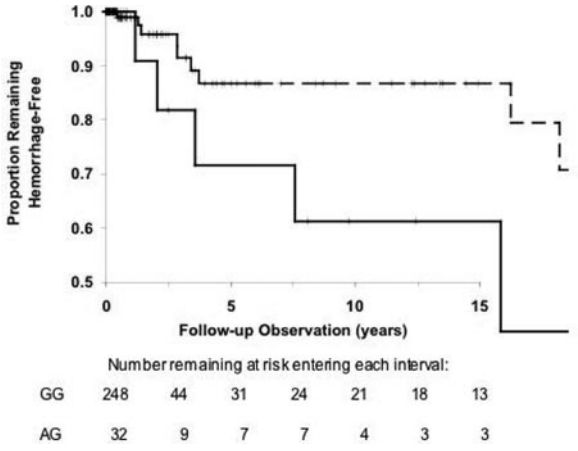
Hemorrhage

92

TNFα-238G>A Promoter Polymorphism Is Associated with Increased Risk of New Hemorrhage in the Natural Course of Patients with Brain Arteriovenous Malformations

Achal S Achrol, Ludmila Pawlikowska, Charles E McCulloch, K Y Trudy Poon, Connie Ha, Jonathan G Zaroff, S Claiborne Johnston, Chanhung Lee, Michael T Lawton, Univ of California, San Francisco, San Francisco, CA; Stephen X Sidney, Kaiser-Permanente Med Care Program, Oakland, CA; Douglas A Marchuk, Duke Univ Med Ctr, Durham, NC; Pui-Yan Kwok, William L Young, Univ of California, San Francisco, San Francisco, CA; for the UCSF BAVM Study Project

BACKGROUND AND PURPOSE. Patients with brain arteriovenous malformation (BAVM) are at life-threatening risk of intracranial hemorrhage (ICH). Identification of single nucleotide polymorphisms (SNPs) associated with increased risk of *new* ICH after diagnosis would facilitate risk stratification as well as identify potential targets for therapeutic intervention. METHODS. Patients with BAVM evaluated at University of California, San Francisco or Kaiser Permanente Northern California were longitudinally followed. Primary outcome was *new* ICH after diagnosis; censoring events were last follow-up or any BAVM treatment. Patients were genotyped for four previously reported promoter SNPs in two inflammatory cytokine genes, interleukin 6 (*IL6*-174G>C; *IL6*-572G>C) and tumor necrosis factor-alpha (*TNF*α-238G>A, *TNFa*-308G>A). Association of genotype with risk of *new* ICH was screened using c^2; SNPs found to be associated with *new* ICH were further characterized using Cox proportional hazards. RESULTS. We genotyped 280 patients with BAVM (50% female, 59% White, mean$\pm$SD age at diagnosis 37$\pm$17 years, 40% *presenting* with ICH). *TNF*α-238G>A was associated with increased risk of *new* ICH after diagnosis (c^2, P=0.003). After adjusting for age, race-ethnicity and clinical presentation, the risk of *new* ICH was increased for patients with *TNFa*-238 AG genotype (hazard ratio: 4.01, P=0.015). No other SNP was found to be associated with *new* ICH. CONCLUSION. A polymorphism in the inflammatory cytokine *TNF*α was associated with increased risk of *new* ICH in the natural course of BAVMs. The role of inflammatory cytokines in the pathogenesis of BAVM hemorrhage merits further study.



93

Incidence of Recurrent Subarachnoid Hemorrhage After Clipping for Ruptured Intracranial Aneurysms

Marieke J Wermer, Paut Greebe, Ale Algra, Gabriel J Rinkel; Univ Med Ctr Utrecht, Utrecht, The Netherlands

Background and Purpose - Since intracranial aneurysms develop during life, patients with subarachnoid hemorrhage (SAH) and successfully occluded aneurysms are at risk for a recurrence. We studied the incidence of and risk factors for recurrent SAH in patients who regained independence after SAH and in whom all aneurysms were occluded by means of clipping. **Methods -** From a cohort of patients with SAH admitted between 1985 and 2001, we included those patients who were discharged home or to a rehabilitation facility. We interviewed these patients about new episodes of SAH. We retrieved all medical records and radiographs in case of reported recurrences. If patients had died we retrieved the cause of death. We analyzed the incidence of and risk factors for recurrent SAH by Kaplan-Meier curves and Cox regression analysis. **Results -** Of 752 patients with 6016 follow-up years (mean follow-up 8.0 years), 18 had a recurrence. In the first 10 years after the initial SAH the cumulative incidence of recurrent SAH was 3.2% (95% CI 1.5–4.9%) and the incidence rate 286/100.000 patient-years (95% CI 160–472/100.000). Risk factors were smoking (HR 6.5; 95% CI 1.7–24.0), age (HR 0.5 per 10 years; 95% CI 0.3–0.8) and multiple aneurysms at the time of the initial SAH (HR 5.5; 95% CI 2.2–14.1). **Conclusions -** After SAH the incidence of a recurrence within the first 10 years is 22 times higher than expected in a population with comparable age and sex. Whether this increased risk justifies screening for recurrent aneurysms in patients with a history of SAH requires further study.

94

Aneurysmal Hemorrhage After the Procedure to Treat an Unruptured Aneurysm

David Wiebers, Mayo Clinic, Rochester, MN; James Torner, Univ of Iowa, Iowa City, IA; Robert Brown, Irene Meissner, David Piepgras, John Huston, David Kallmes, Mayo Clinic, Rochester, MN; ISUIA Investigators (International Study of Unruptured Intracranial Aneurysms)

This study was undertaken to define the risk of subsequent hemorrhage among a cohort of patients who underwent treatment of an unruptured intracranial aneurysm. Post-procedure hemorrhage following treatment of an unruptured aneurysm may reflect selection of the aneurysm for treatment, degree of aneurysmal obliteration, and/or new aneurysm development. Patients were part of the NIH-sponsored International Study of Unruptured Intracranial Aneurysms. In 61 centers patients were entered in a prospective cohort study of unruptured aneurysms, with a mean follow-up of 4 years. Hemorrhage was determined by clinical, radiologic and pathologic observation. Central adjudication of endpoints was performed. Hemorrhagic events within 24 hours of the treatment procedure and any others clearly associated with the original procedure were excluded. Among 451 patients treated with endovascular occlusion of the aneurysm, 10 patients (2.2%) had a post-procedure hemorrhage. Five hemorrhages (1.1%) were from the treated aneurysm, 1 from an untreated aneurysm, 1 from a de novo aneurysm, and 3 were of uncertain etiology. Three of the hemorrhages occurred within 30 days of the procedure. Among the 1917 surgically treated patients, 11 (0.6%) had post-procedure hemorrhages. Seven (0.4%) occurred from the treated aneurysm, 1 from a de novo aneurysm and 3 were of uncertain etiology. Five hemorrhages occurred within 30 days. The risk of post-procedure aneurysmal rupture is greatest in the acute period. In over half the cases the treated aneurysm hemorrhaged and, in all of these cases, treated aneurysms were 15mm or greater in diameter.

95

Prediction of Symptomatic Vasospasm After Subarachnoid Hemorrhage: The Modified Fisher Scale

Jennifer A Frontera, Jan Claassen, Michael Schmidt, Katja E Wartenberg, Richard E Temes, E S Connolly, Columbia Univ, New York, NY; Robert L Macdonald, Univ of Chicago, Chicago, IL; Stephan A Mayer; Columbia Univ, New York, NY

Objective: We developed a modification of the Fisher computed tomography (CT) rating scale and compared it to the original Fisher scale to determine which scale best predicts symptomatic vasospasm after subarachnoid hemorrhage (SAH). **Methods:** We analyzed data from 1355 SAH patients in the placebo arm of four randomized, double-blind, placebo-controlled studies of tirilazad. Modified Fisher CT grades were calculated based the presence of cisternal blood and intraventricular hemorrhage (IVH). Crude odds ratios (OR) reflecting the risk of developing symptomatic vasospasm were calculated for each scale level, and adjusted ORs expressing the incremental risk for each scale were calculated after controlling for known predictors of vasospasm. **Results:** Of 1355 patients, 451 (33%) developed symptomatic vasospasm. For the modified Fisher scale, compared to grade 0–1 patients, the crude OR for vasospasm was 1.6 (95% CI 1.0–2.5) for grade 2, 1.60 (95% CI 1.1–2.2) for grade 3 and 2.2 (95% CI 1.6–3.1) for grade 4 patients. For the original Fisher scale, referenced to grade 1, the OR for vasospasm was 1.3 (95% CI 0.7–2.2) for grade 2, 2.2 (95% CI 1.4–3.5) for grade 3 and 1.7 (95% CI 1.0–3.0) for grade 4. Early angiographic vasospasm, history of hypertension, neurologic grade, and elevated admission mean arterial pressure were identified as risk factors for symptomatic vasospasm. After adjusting for these variables, the modified Fisher scale remained a significant predictor of vasospasm (adjusted OR 1.28, 95% CI 1.06–1.54) while the Fisher scale was not. **Conclusions:** The modified Fisher scale predicts symptomatic vasospasm more accurately than original Fisher scale.

RISK OF SYMPTOMATIC VASOSPASM ACCORDING TO THE ORIGINAL AND MODIFIED FISHER CT RATING SCALES

	Percent classified to grade	Percent within grade with symptomatic vasospasm	*Odds ratio**	*95% confidence interval*	P
Modified Fisher Scale					
1† Focal or diffuse thin SAH, no IVH	21.6	24	-	-	-
2 Focal or diffuse thin SAH, with IVH	10.8	33	1.58	1.02–2.46	0.042
3 Thick SAH present, no IVH	33.9	33	1.59	1.14–2.22	0.006
4 Thick SAH present, with IVH	33.7	40	2.20	1.58–3.05	<0.001
Adjusted odds ratio for incremental risk of symptomatic vasospasm for each scale level			*1.28*	*1.06–1.54*	*0.010*
Fisher Scale					
1 Focal thin SAH	8.1	21	-	-	-
2 Diffuse thin SAH	10.9	25	1.26	0.70–2.23	0.442
3 Thick SAH present	67.7	37	2.18	1.35–3.51	0.001
4 Focal or diffuse thin SAH, with significant ICH or IVH	13.3	31	1.71	0.98–2.98	0.060
Adjusted odds ratio for incremental risk of symptomatic vasospasm for each scale level			*1.1*	*0.84–1.43*	*0.488*

* Adjusted values were calculated controlling for other significant predictors of vasospasm (early angiographic vasospasm, history of hypertension, neurologic grade, and mean arterial pressure).

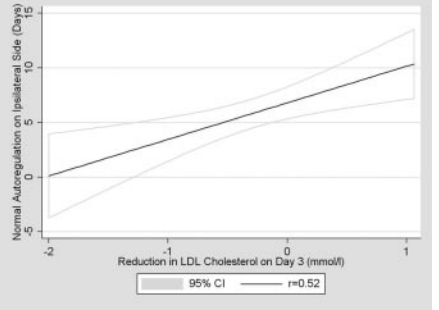
† Includes 20 patients classified to modified Fisher 0 (no SAH or IVH present).

96

Biological Effects of Acute Pravastatin Therapy on Cerebral Vasospasm, Delayed Ischemic Deficits, and Outcome in Patients Following Aneurysmal Subarachnoid Hemorrhage: A Randomized Controlled Trial

Ming-Yuan Tseng, Marek Czosnyka, Hugh Richards, John Douglas Pickard, Peter John Kirkpatrick; Neurosurgery, Cambridge, United Kingdom

Introduction: We have demonstrated that acute treatment with Pravastatin after aneurysmal subarachnoid haemorrhage (aSAH) can ameliorate vasospasm, improve autoregulation and reduce delayed ischemic deficits (DID). **Hypothesis:** We assessed the hypothesis that these effects were mediated through anti-inflammatory and anti-thrombogenic mechanisms. **Methods:** Eighty adult aSAH patients (<72 hours from ictus) were randomised equally to receive oral Pravastatin (40mg) or placebo daily for up to 14 days. Laboratory data, including C-reactive protein (CRP), fibrinogen, d-dimer, and lipid profiles, were measured every 3 days. Data were compared between the two groups, and between patients with/without vasospasm, DID, or unfavourable outcome using the t-test. **Results:** Baseline laboratory data were similar in both groups. Low-density lipoprotein (LDL) cholesterol levels were significantly reduced in the Pravastin group (-0.6 mmol/L, $p<0.001$) from Day 3, which seemed to relate to the anti-vasospamic property ($p = 0.08$). Only in the placebo group, the reduction in LDL cholesterol level on Day 3 correlated with the duration of normal autoregulation ($\gamma = 0.52$, $p = 0.002$, Figure). The increments in fibrinogen (+1.02g/L, $p=0.07$) and CRP levels (+27.7mg/L, $p = 0.02$) on Day 3 and decrements in d-dimer level on Day 6 (-502.9 ugFEU/L, $p=0.09$) in the Pravastatin group were less pronounced. When patients with/without vasospasm were compared, all these laboratory changes correlated significantly with the duration of vasospasm, DID, and unfavourable outcome. **Conclusions:** These data support the anti-inflammatory and anti-thrombogenic mechanism of Pravastatin therapy on aSAH patients.



97

A Shortened Baseline NIH Stroke Scale Predicts 3-Month Outcome After Subarachnoid Hemorrhage

Enrique C Leira, Patricia H Davis, Coleman O Martin, Bongin Yoo, James Torner, Julie Weeks, Bradley Hindman, Michael Todd, Univ of Iowa, Iowa City, IA; and the IHAST Investigators

The World Federation of Neurological Surgeons (WFNS) score has been used to predict outcome after subarachnoid hemorrhage (SAH). The NIH Stroke Scale (NIHSS), a predictor of outcome in ischemic stroke, has not been validated for SAH. The objective was to determine if the NIHSS improved the ability of WFNS to predict outcome. We analyzed data from 1000 participants in the Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST). The study was intended to determine the impact of intraoperative hypothermia (33ºC) on Glasgow Outcome Scale (GOS) in good-grade (WFNS I, II or III) SAH patients. We assessed the baseline NIHSS as a predictor of GOS and Rankin scores obtained 3 months after surgery. We performed a stepwise logistic regression to identify individual NIHSS items with independent predictive value after adjustment for age, gender and baseline WFNS. We then constructed a shorter version of the NIHSS using only those significant components and tested it in a logistic regression model for predicting a favorable outcome (Rankin 0 or 1). At baseline, 535 patients (53%) had a NIHSS of 0, and 34 (3%) had a score over 7. There was a correlation between GOS and Rankin scores ($p<0.001$). Baseline NIHSS scores strongly correlate with GOS ($p<0.001$) and Rankin ($p<0.001$) at 3 months. The baseline NIHSS independently predicted outcome after adjusting for WFNS. The significant baseline NIHSS components included in the logistic regression model were orientation, dysarthria, visual fields and total motor score for the arms. These were used to construct a shortened version (SAH-NIHSS). Baseline SAH-NIHSS independently predicts 3-month Rankin ($p<0.001$) in a linear fashion ($c=0.68$). A favorable outcome was observed in 72%, 53% and 30% for baseline SAH-NIHSS scores of 0, 1 and 2 respectively. The odds ratio for an unfavorable outcome at 3-months with a baseline SAH-NIHSS above 0 was OR=2.15 (95% CI:1.51–3.4). A short form of NIHSS including orientation, dysarthria, visual fields and the total arm motor score predicts outcome at 3 months after SAH independently of WFNS. This scale detects more subtle focal findings associated with poor outcome after SAH, improving the present predictive ability of WFNS. It could be used in future SAH clinical trials and clinical practice.

98

Elevated BNP Levels Predict Cerebral Vasospasm and Death in Subarachnoid Hemorrhage

Pam Rajendran, Univ of Washington, Seattle, WA; Nerissa Ko, Alan Wu, Sirisha Yarlagadda, Alexander Kopelnik, William Young, Jonathan Zaroff; UCSF, San Francisco, CA

Background: Elevated B-type natriuretic peptide (BNP) levels are associated with cardiac injury and dysfunction in patients with subarachnoid hemorrhage (SAH), consistent with a cardiac source of BNP release. Cardiac dysfunction has been associated with cerebral vasospasm after SAH. The objective of this study was to test the hypothesis that elevated BNP levels are associated with an increased risk of cerebral vasospasm and inpatient mortality after SAH. **Methods:** This was a prospective cohort study. In 150 SAH patients, a blood sample was obtained for measurement of plasma BNP levels as soon as possible after admission, using the Bayer Centaur BNP assay. Patients with myocardial infarction or congestive heart failure were excluded. The neurological outcome variables included cerebral vasospasm requiring neurointerventional treatment (angioplasty or intra-arterial verapamil) and inpatient mortality. A BNP level $>$ 600 pg/ml was used as the predictor variable in logistic regression models predicting vasospasm and death, reporting odds ratios (OR) and 95% confident intervals (CI). The covariates included in these models were: age, gender, Hunt-Hess score, presence or absence of fever, mechanical ventilation, neosynephrine dose, and time from SAH symptom onset. **Results:** BNP levels were obtained at a mean of 5.1 $\pm$3.5 days after SAH symptom onset. The mean BNP level was 245 $\pm$ 454 pg/mL (median = 94, IQR = 35 - 275 pg/mL). Fourteen patients (9%) had a BNP level $>$ 600 pg/ml. Fifty (40%) patients required neurointerventional treatment for vasospasm and 15 (10%) died during the hospitalization. In the multivariate logistic regression models, a BNP level $>$ 600 pg/mL was strongly associated with both death (OR 37.7, 95% CI 5.0 - 286.2, $P<0.001$) and vasospasm requiring interventional treatment (OR 5.1, 95% CI 1.1–22.5, $P=0.034$). **Conclusions:** Elevated BNP levels ($>$ 600 pg/mL) observed early after SAH are independently predictive of adverse neurological outcomes after SAH. Because BNP is likely released from the heart, BNP may be a useful biomarker that heralds both cardiac and neurologic dysfunction after SAH. These findings support the hypothesis that cardiac injury and dysfunction may contribute to the extensive morbidity and mortality suffered by SAH patients.

Pediatric Stroke

99

Pediatric NIHSS as a Predictor of Neurological Outcome in Childhood Stroke

Adam Kirton, The Hosp for Sick Children, Toronto, Canada; Gabrielle deVeber, The Hosp for Sick Children, Population Health Sciences Program, The Hosp for Sick Children Res Inst, Toronto, Canada; Ophelia Yeboah, Faculty of Medicine, Univ of Toronto, Toronto, Canada; Rebecca Ichord, Children's Hosp of Philadelphia, Philadelphia, PA; Mubeen F Rafay, The Hosp for Sick Children, Population Health Sciences Program, The Hosp for Sick Children Res Inst, Toronto, Canada; Daune MacGregor, Rosalind Curtis, The Hosp for Sick Children, Toronto, Canada; Sharon Friefeld; Univ of Toronto, Toronto, Canada

Background: The National Institutes of Health Stroke Scale (NIHSS) is a clinical measure of acute stroke severity which predicts neurological outcome and aids in treatment decisions. Retrospective scoring has been validated in adults. A pediatric modification of the NIHSS (PedNIHSS) has not yet been tested in a large cohort of children with arterial ischemic stroke (AIS). The pediatric stroke outcome measure (PSOM) is an established tool in childhood AIS. Hypothesis: PedNIHSS predicts neurological outcome in pediatric AIS. Methods: PedNIHSS was retrospectively scored for 41 children aged 2–18 years with confirmed AIS. Reliability of this method was evaluated on 6 consecutive children who had the PedNIHSS scored both prospectively and retrospectively by separate observers. Neurological outcome was evaluated by PSOM at 6–24 (mean 13.7+/-5.1) months and classified as good (absent or mild deficits) or poor (moderate or severe deficits). The ability of the PedNIHSS to predict outcome was assessed with logistic regression and an ROC curve was constructed. Results: Excellent agreement was demonstrated between retrospective and prospective PedNIHSS scores (interclass correlation coefficient = 0.98 (95% CI 0.87–1.00). Total PedNIHSS and PSOM scores were well correlated (Spearman's correlation coefficient = 0.31, $p=0.02$). Evaluation of the PedNIHSS as a predictor of neurological outcome generated an area under the ROC curve of 0.72. A PedNIHSS score $\geq$ 12 predicted a poor neurological outcome with a specificity of 93% but was only 50% sensitive. Conclusions: PedNIHSS predicts neurological outcome following childhood AIS and can be scored retrospectively. Poor outcome is strongly predicted by a PedNIHSS score $\geq$ 12 but is not well excluded by lower scores. A multi-centre study is currently underway to further define the clinical utility of the PedNIHSS.

100

Childhood Cerebral Sinovenous Thrombosis: A Study of Clinical and Radiographic Outcomes

Mahendranath Moharir, The Hosp for Sick Children and the Population Health Sciences Program, The Hosp for Sick Children Res Inst, Toronto, Canada; Manohar Shroff, The Hosp for Sick Children, Toronto, Canada; Margaret Adams, Pheroze Bharucha, Population Health Sciences Program, The Hosp for Sick Children Res Inst, Toronto, Canada; Anthony Chan, The Hosp for Sick Children, Toronto, Canada; Gabrielle deVeber; The Hosp for Sick Children and the Population Health Sciences Program, The Hosp for Sick Children Res Inst, Toronto, Canada

Background: Childhood cerebral sinovenous thrombosis (CSVT) is increasingly seen. No clinical trials or outcome studies have been done to date. Based on adult trials children are anticoagulated for 3–6 months. Understanding extent & timing of thrombus recanalization would help establish rational duration of therapy & assist clinical trial design. Outcome studies would be useful for prognosis. Objective: To determine extent/rate of recanalization, safety of anticoagulants & outcome in childhood CSVT. Methods: We conducted a consecutive cohort study of children (excluding neonates) with CSVT diagnosed with CT/MR venogram between January 1992-July 2004 at our institution. Children without contraindications received anticoagulation based on published institutional protocols. A study neuroradiologist assessed extent of thrombosis & hemorrhage on initial & follow-up neuroimaging studies & documented propagation or recanalization. Clinical outcome was assessed with the validated Pediatric Stroke Outcome Measure (PSOM). Results: Analysis of 39 children showed that 82% received anticoagulants, 72% for median 16wks (range 1–85wks), 25% lifelong. No new or increased hemorrhage or thrombus propagation was seen in treated children. Thirty three children had long-term follow-up, 2 died from unrelated causes & were excluded. On follow-up of 31 children (mean 3.5y, range 0.25–14.5y), CSVT recurred in 1, residual neurological deficits were none (58%), mild (19%), moderate (13%) & severe (10%). In analyses to date, there was no association between recanalization extent & neurological outcome. Analysis of recanalization rates at additional time intervals & predictor testing for recanalization & outcomes is underway. Conclusions: In childhood CSVT, at least partial recanalization seems to occur in many by 6weeks of therapy & continues for up to 6 months. Current anticoagulation protocols appear safe. Neurological outcome in most children with CSVT is excellent.

# with f/u imaging at this timepoint	No Recanalization	Partial Recanalization	Full Recanalization
6 wks, N=27	17(62.5%)	8(30.0%)	2(7.5%)
3 mo, N=30	17(56.6%)	6(20.0%)	7(23.4%)
6 mo, N=35	9(25.7%)	14(40.0%)	12(34.3%)
Overall, N=39	3(7.7%)	13(33.3%)	23(59.0%)

101

Emergency Room Presentation of Childhood Arterial Ischemic Stroke: A Prospective Cohort Study

Rebecca Ichord, Univ of Pennsylvania Sch of Med and Children's Hosp Philadelphia, Philadelphia, PA; S E Smith, N Abend, R Shellhaas, S Agner, E O'Tool, D Licht; Univ of Pennsylvania, Children's Hosp Philadelphia, Philadelphia, PA

Background Treatment of children with acute arterial ischemic stroke (AIS) with interventions such as thrombolysis is limited by delays in diagnosis. There are few detailed reports of the initial clinical presentation collected in a prospectively defined consecutive cohort of children with AIS. Objective To characterize timing and nature of presenting symptoms and signs in a prospectively defined cohort of children with AIS. Methods This single center prospective consecutive cohort study included children age 2–18 yr presenting to an emergency room for acute AIS between Mar 2003-Nov 2004. Patients with stroke due to head trauma, meningitis or as complications of other illness or procedures were excluded. Data were extracted from charts on nature and timing of symptoms, and intervals from symptom onset to presentation, diagnostic testing and treatment. Results The study included 12 patients, mean age 10 yr (range 2–17), 7 males. Median interval from symptom onset to presentation for medical care was 5.6 hrs, range 30 min to 5 days. Six of 12 patients were brought to medical attention in $<$ 3 hrs after symptom onset. Median time interval from symptom onset to initiation of stroke-specific treatment (IV fluids, antithrombotics) was 23 hrs, and to specific imaging confirmation of diagnosis was 36 hrs. Primary symptoms prompting presentation for medical care included acute hemiplegia (5), ataxic gait (5), chorea (1), vertigo (1). Neurologic deficits were associated with headache in 4 cases, and seizures in 2 cases. Interval to presentation was not associated with age or pre-existing known stroke risk factor (3 cases). Conclusion In this small cohort, the majority of children with AIS were brought to medical attention promptly after symptom onset, but experienced delays approaching 24 hrs in definitive diagnosis and initiation of emergency stroke-specific treatment. The clinical features of AIS in children are frequently assumed to be symptomatic of other common diseases of childhood such as

migraine, acute cerebellar ataxia and epilepsy. Improved knowledge and management of stroke syndromes in children among primary care providers could improve outcomes.

102

Recurrence Risk of Hemorrhagic Stroke in Children

Heather J Fullerton, Yvonne W Wu, Univ of California, San Francisco, San Francisco, CA; Stephen Sidney, Kaiser Permanente Med Care Program, Oakland, CA; S Claiborne Johnston; Univ of California, San Francisco, San Francisco, CA

Background: Although hemorrhagic strokes (HS) account for half of all strokes in children, rates and predictors of recurrence after HS have not been studied. *Methods:* We collected data on all documented cases of HS (intracerebral hemorrhage, subarachnoid hemorrhage, and intraventricular hemorrhage [IVH], excluding neonatal IVH), among all children (<20 years) enrolled in the 16 hospital Kaiser Permanente Medical Care Program from 1/93 to 12/04. Using Kaplan-Meier survival analyses censoring at death or loss to follow-up, we determined rates of recurrent HS after initial stroke. Cox proportional hazards models were used to analyze predictors of recurrent HS. Multivariate models were based on univariate screening (cut-off of p<0.10). *Results:* Of 106 children who suffered HS, 100 had follow-up data (3 died, 3 lost to follow-up). HS etiologies included structural lesions (54%), trauma (21%), idiopathic (17%), and "other" (8%). Within a median follow-up of 3.7 years (range 6 days to 12 years), 8 (8%) had a recurrent HS at a median of 1.9 months after the initial event (range 7 days to 5.7 years). Two of the 8 had multiple recurrences. The underlying HS etiology was structural in 7 of the 8 (2 arteriovenous malformations, 2 cavernous malformations, 2 brain tumors, and 1 cerebral aneurysm), and multifactorial (hypertension and anticoagulation) in one. Recurrence rates varied by underlying etiology (Table), and gender (16% for girls, 3% for boys, p=0.04), but not HS sub-type. In the multivariate model, female sex was a predictor of recurrent hemorrhage (HR 5.17, p=0.045), while there were non-significant trends for neurological deficits at discharge (7.16, p=0.067) and structural etiology (5.01, p=0.14). The gender difference persisted when traumatic HS cases were excluded (HR 5.35, p=0.041). *Conclusions*: Childhood HS due to structural lesions recurs frequently, while idiopathic and traumatic HS rarely recurs. Girls may be more likely to suffer a recurrence than boys.

TABLE: CUMULATIVE HEMORRHAGIC STROKE RECURRENCE RATE BY ETIOLOGY

	Structural		Traumatic		Other		Idiopathic	
Time*	No.**	%	No.**	%	No.**	%	No.**	%
0	54	0	21	0	8	0	17	0
1 month	52	5.6	20	0	8	12.5	17	0
3 months	51	7.4	20	0	7	12.5	17	0
12 months	43	9.3	16	0	6	12.5	17	0
3 years	36	11.5	8	0	4	12.5	13	0
6 years	14	17.4	5	0	0	12.5	5	0

*Time from initial hemorrhage stroke
**Number of at risk subjects in the analysis at that time point

103

Potential rtPA Eligibility in Children: A Population-Based Study

Pooja Khatri, Jane C Khoury, Kathleen Alwell, Daniel Woo, Brett M Kissela, Charles J Moomaw, Rosie Miller, Univ of Cincinnati, Cincinnati, OH; Yong-Jin Cho, Ilsan Paik Hosp, Inje Univ, Goyang, Republic of Korea; Dawn Kleindorfer; Univ of Cincinnati, Cincinnati, OH

Background: In the Greater Cincinnati/Northern Kentucky (GCNK) 1993–94 epidemiological cohort, 8% of adults who presented to emergency departments were eligible for rt-PA. As safety studies of rt-PA in children are being developed, eligibility rates for children become relevant. **Methods**: All adult and childhood strokes from 7/93–6/94 and 1999 were identified in the GCNK Stroke Study region, a biracial population of 1.3 million. Strokes were found by screening ICD-9 stroke diagnosis codes of all inpatient and emergency department visits. Only ischemic stroke patients less than 18 years of age were included. Cases were deemed eligible for rt-PA based on Brain Attack Coalition guidelines, with the exception of the relative contraindications of recent gastrointestinal/urinary hemorrhage, lumbar puncture, and arterial puncture, for which data were not available. **Results**: There were 10 childhood ischemic strokes in 1993–94 and 11 in 1999. The distribution of contraindications is shown in the table below.

	Patients to ED ≤ 3 hours (n=4)	Patients to ED > 3 hours or unknown (n=17)
ABSOLUTE CONTRAINDICATIONS		
ICH/SAH/IVH	0 (0%)	0 (0%)
SBP>185 or DBP>110	0 (0%)	0 (0%)
INR>1.5	0 (0%)	1 (5.9%)
PTT>40 sec	0 (0%)	1 (5.9%)
Platelet<100,000	0 (0%)	3 (17.6%)
Stroke, intracranial surgery, or serious head trauma within 3 months	0 (0%)	1 (5.9%)
Aneurysm/AVM/brain tumor	0 (0%)	1 (5.9%)
Eligible by absolute criteria	**4 (100%)**	**11 (64.7%)**
RELATIVE CONTRAINDICATIONS		
Seizure*	3 (75.0%)	10 (58.8%)
Glucose < 50 or >400	0 (0%)	1 (5.9%)
NIHSSS <5	2 (50.0%)	5 (29.4%)
Major surgery/trauma within 14 days	0 (0%)	0 (0%)
Recent MI or post-MI pericarditis	0(0%)	0(0%)
Eligible by absolute and relative criteria	**1(25.0%)**	**2(11.8%)**

* This variable includes all seizures at <24 hours and is likely an overestimate of seizures at presentation.

Conclusions: Within our population, 5–19% of children with ischemic stroke were eligible for rt-PA, depending on how relative contraindications are interpreted. Public education emphasizing early arrival may substantially increase eligibility. Based on an age-, sex-, and race-adjusted ischemic stroke incidence rate of 3.4 childhood strokes per 100,000 from the same cohort, approximately 2,000 strokes occur annually and 100–400 of these currently would be eligible for rt-PA in the United States. However, these interpretations should be made with caution given the small number of ascertained cases. Furthermore, whether rt-PA is safe and efficacious in the <18-year-old age group remains to be determined.

104

Early Cognitive Outcome After Neonatal Stroke

Angela McLinden, Univ of Windsor, Windsor, Canada; Peter E Anderson, The Hosp for Sick Children and Children's Hosp of Eastern Ontario, Ottawa, Canada; Anne D Baird, Univ of Windsor, Windsor, Canada; Robyn Westmacott, The Hosp for Sick Children, Toronto, Canada; Gabrielle deVeber; The Hosp for Sick Children and Population Health Sciences Program, The Hosp for Sick Children Rsch Inst, Toronto, Canada

Pediatric stroke is often associated with long-term neurological deficits, including cognitive and motor impairments. These deficits can adversely affect a child's ability to function in all settings, including home and school. Objective: To examine early cognitive outcome for survivors of neonatal arterial ischemic or cerebral sinovenous thrombosis (i.e., stroke before 28 days of age) with minimal neurological impairment. Methods: A cross-sectional design was used, following children included in the Canadian Pediatric Ischemic Stroke Registry at 12 and 24 months post stroke (the number of participants varied across these testing points). The Bayley Scales of Infant Development were used to measure cognitive development. Scores were compared with standardized normative data of healthy children. Neurologic impairment was assessed using the validated Pediatric Stroke Outcome Measure. Results: We assessed the cognitive development of 29 children with neonatal ischemic and cerebral sinovenous thrombosis with minimal neurologic impairment at 12 and 24 months post-stroke.Although the mean cognitive scores of the group of children were generally within the average range, children with neonatal stroke obtained significantly lower scores than the normative sample on the Bayley PDI at 12 months (p=0.02), the Bayley MDI at 24 months post-stroke (p=0.01) and Bayley PDI at 24 months post-stroke (p=0.02). Outcome did not differ based on gender, stroke type, or presence of infarction. Conclusion: This study was the first of its kind to study cognitive outcome longitudinally in stroke confined to the neonatal period. Evidence of subtle cognitive impairment in children was found within the first two years post-stroke, despite ratings of minimal neurological impairment. Further research is required to confirm whether cognitive impairments in these children resolve, remain in the low average range, or increase with development as more complex skills are learned.

105

Reduced Preoperative Cerebral Vascular Reactivity in Infants with Severe Congenital Heart Defects Is Associated with Periventricular Leukomalacia

Daniel J Licht, The Children's Hosp of Philadelphia, Philadelphia, PA; Jiongjiong Wang, The Hosp of the Univ of Pennsylvania, Philadelphia, PA; David W Silvestre, Shannon C Agner, Sarah Tabbutt, Susan C Nicolson, Lisa M Montenegro, Gil Wernovsky, David M Shera, Thomas L Spray, Robert A Zimmerman, J W Gaynor, Robert R Clancy, The Children's Hosp of Philadelphia, Philadelphia, PA; John A Detre; The Hosp of the Univ of Pennsylvania, Philadelphia, PA

OBJECTIVE: Poor neurocognitive outcome in survivors of early heart surgery has become a major focus for study as surgical survival rate increases. Periventricular leukomalacia (PVL) is implicated as a possible risk factor for poor neurocognitive development and has been demonstrated to occur in pre-operative infants with severe forms of congenital heart defects (CHD). The central hypothesis is that pre-operative cerebral blood flow (CBF) and CO2 reactivity (rCO2, deltaCBF/deltapCO2) are reduced and are risk factors for PVL. METHODS: To understand risk factors for PVL, we studied cranial MRIs in pre-operative full-term infants with CHD. CBF was measured in baseline and hypercarbic conditions using pulsed arterial spin labeling perfusion MRI (PASL-pMRI). All patients were ventilated and sedated in similar fashion. 16 different CHD diagnoses were studied; hypoplastic left heart syndrome (n = 21) was the most common diagnosis. In our statistical model stepwise selection procedures were conducted to identify strong predictors, adjusting for weaker predictors. RESULTS: 60 term infants were studied (32 male, average weight 3.19 + 0.53 kg, average head circumference 33.7 + 1.6 cm). Baseline CBF for the entire cohort was 18.0 + 9.7 ml/100g/min, below the expected 50 + 3.4 for term newborns. Baseline CBF varied linearly with systolic blood pressure and inversely with hemoglobin concentration and arterial oxygen saturations (all p < 0.01). rCO2 was 1.02 + 0.64ml/100g/min/mmHg and varied with birth weight, hemoglobin concentration and diastolic blood pressure (all p < 0.01). PVL was present in 12 patients and was associated with low rCO2 (p = 0.03). CONCLUSION: CO2 reactivity, and not baseline CBF, is associated with the finding of PVL on neuroimaging in the pre-operative neonate with severe CHD.

Community/Risk Factors

106

White Matter Hyperintensity Volume Is Associated with Motor Performance and Delayed Recall: The Northern Manhattan Study

Clinton B Wright, Yaakov Stern, Ralph L Sacco, Columbia Univ, New York, NY; Charles Decarli; UC Davis, Sacramento, CA

BACKGROUND: White matter hypertensities (WMH) are often found on brain MRI scans but the mechanism is unclear. The relationship of WMH to cognitive function and the importance of

vascular disease are important, especially in minorities at higher risk of cerebrovascular disorders. METHODS: The Northern Manhattan Study (NOMAS) is a population-based prospective cohort of 3,298 stroke-free subjects identified by random digit dialing. To date 478 have undergone brain MRI with quantitative measurement of WMH volume (WMHV) as well as neuropsychological testing. We categorized WMHV; those above one age-corrected standard deviation had WMHV-large, and used multivariate logistic regression to estimate the association between WMHV-large and the following tests: grooved pegboard, color trails (A and B), California Verbal Learning Test (recognition and delayed recall), adjusting for sociodemographic variables and vascular risk factors. We also analyzed WMHV as a continuous variable. RESULTS: The study sample (mean age 71; 57% women; 58% Hisp, 22% black, 19% white) and the prevalence of vascular risk factors was similar to the overall cohort. The mean WMHV was 0.6 mL (SD 0.7, range 0.02–4.7 mL) and the prevalence of WMHV-large was 17%. Older age, female gender, and Hispanics and blacks compared to whites had a larger prevalence of WMHV-large and greater WMHV. Diastolic but not systolic blood pressure and total homocysteine (tHcy) were positively associated with WMHV in a linear fashion. Worse performance on delayed recall (OR=1.3 95% CI=1.1–1.4) and the grooved pegboard (OR=2.3, 95% CI=1.0–5.4) were independently associated with WMHV-large, adjusting for sociodemographic variables and vascular risk factors. Color trails A and recognition memory were not associated with WMHV. Blacks and Hispanics had higher WMHV and a greater prevalence of WMHV-large than whites. CONCLUSIONS: WMHV detected by MRI were associated with worse performance on tests of delayed recall and motor speed, suggesting a pathological process. Simple tests of processing speed and recognition memory were not associated with WMHV but delayed recall requires strategic mental operations. Thus, our findings support the concept that WMH are related to impaired executive function.

107

Preeclampsia and the Risk of Ischemic Stroke Among Young Women: Results from the Stroke Prevention in Young Women Study

David W Brown, Ctrs for Disease Control and Prevention, Atlanta, GA; Nicole Dueker, Univ of Maryland Sch of Med, Baltimore, MD; Denise J Jamieson, Ctrs for Disease Control and Prevention, Atlanta, GA; John W Cole, Marcella A Wozniak, Barney J Stern, Univ of Maryland Sch of Med and Baltimore Dept of Veterans Affairs Med Ctr, Baltimore, MD; Wayne H Giles, Ctrs for Disease Control and Prevention, Atlanta, GA; Steven J Kittner; Univ of Maryland Sch of Med and Baltimore Dept of Veterans Affairs Med Ctr, Baltimore, MD

Background. Preeclampsia is a pregnancy-specific systemic syndrome with unknown cause that may affect 3%–8% of pregnancies in the United States. While pre/eclampsia is known to be an important risk factor for pregnancy-associated stroke, few data exist with regard to its association with stroke not occurring during pregnancy or the post-partum period. **Methods.** Using data from the Stroke Prevention in Young Women Study, a population-based case/control study of risk factors for ischemic stroke in women aged 15–44 years, we examined the independent association between preeclampsia and the risk of ischemic stroke. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were estimated using logistic regression. Cases (n=261) were women hospitalized for stroke in the greater Baltimore-Washington area, and controls (n=421) were women free of a history of stroke identified by random digit dialing. Women who were pregnant at the time of stroke, those whose stroke occurred within 42 days postpartum, and nulligravida women were excluded from the analysis. **Results.** The prevalence of preeclampsia among cases and controls was 15% (SPYW-1: 16%; SPYW-2: 15%) and 10% (SPYW-1: 10%; SPYW-2: 11%), respectively. Preeclampsia was associated with an increased risk of ischemic stroke (crude OR: 1.59; 95% CI: 1.00–2.52). After multivariable adjustment for age, race, education, and number of pregnancies, women with a history of preeclampsia remained at increased risk for ischemic stroke (OR: 1.63; 95% CI: 1.02–2.62). Similar patterns were observed for reported symptoms of preeclampsia (elevated blood pressure and proteinuria). **Conclusion.** These results suggest an association between a history of preeclampsia and ischemic stroke remote from pregnancy. A better understanding of the factors mediating this association will be important for developing effective and efficient efforts to prevent stroke in young women.

108

Incidence of Stroke Is Not Declining: Temporal Trends in the Framingham Study

Raphael Carandang, Sudha Seshadri, Alexa Beiser, Margaret Kelly-Hayes, Carlos Kase, Philip Wolf; Boston Univ Sch of Med, Boston, MA

BACKGROUND: Long-term trends in the incidence of stroke and survival after stroke are not well characterized. Prior studies have reported both a stable and declining incidence. Estimates vary depending on the population and time-period studied. We have over 50 years of community-based, prospectively collected data on incident stroke. **METHODS**: We determined temporal trends in the incidence, lifetime risk, severity and 30-day mortality of all-strokes and ischemic stroke over 3 consecutive time periods: 1950–78; 1978–90; 1990–2004 using data gathered from the Framingham Original and Offspring cohorts. Participants have been under active surveillance for incident stroke; stroke risk factor data is measured biennially. We estimated age-specific and age-adjusted incidence. Lifetime risk was estimated using modified Kaplan-Meier analyses, assuming subjects were stroke-free at age 55. We compared subjects by age, mean systolic blood pressure (SBP) and risk factor prevalence across the three time periods using analysis of variance, and compared stroke severity and 30-day mortality using the χ-square test. **RESULTS**: Framingham participants (n=8,636) contributed a total of 155,118 person-years. There were 1030 first-ever completed strokes (454 in men, 885 ischemic strokes). Mean SBP, frequency of treatment and prevalence of smoking decreased over time, while the prevalence of diabetes increased. Results are:

	1950–1978		1978–1990		1990–2004	
Outcome Measure	men	women	men	women	men	women
Incident Strokes	176	184	134	191	144	201
Incidence per 1000 person-yrs (age-adjusted)	7.9	6.3	6.2	5.9	7.0	6.5
Lifetime Risk (at age 55 years)	19.4	18.7	15.8	19.2	16.1	18.8
Moderate and Severe stroke (% of total)	47%	41%	47%	60%	48%	57%
30-day mortality	22%	21%	20%	21%	14%	19%

CONCLUSION: Incidence, lifetime risk and severity of stroke remained stable over the three time periods studied. Mortality decreased, especially in men. Divergent trends in risk factor prevalence may explain the absence of a decline in stroke incidence.

109

Unrecognized Myocardial Infarction and Risk of Stroke: The Rotterdam Study

Arfan M Ikram, Monika Hollander, Michiel J Bos, J A Kors, Peter J Koudstaal, Albert Hofman, Jacqueline C Witteman, Monique M Breteler; Erasmus MC, Rotterdam, The Netherlands

Background: Persons with myocardial infarction have an increased risk of cardiovascular morbidity and mortality. However, the relationship between unrecognized myocardial infarction and the risk of stroke is not well documented. We investigated this relation in a population-based cohort study. **Methods:** We followed 6,439 participants from the Rotterdam Study for stroke until January 2002. Participants were free from stroke and presence of myocardial infarction was assessed at baseline (1990–1993). We calculated hazard ratios (HR) of stroke for persons with unrecognized or recognized myocardial infarction as compared to persons without myocardial infarction. Analyses were adjusted for age, sex and additionally for cardiovascular risk factors. **Results:** A total of 505 strokes occurred. Recognized myocardial infarction was only borderline associated with an increased risk of stroke. Unrecognized myocardial infarction increased the risk of stroke by 75% (age and sex adjusted HR 1.76, 95% confidence interval (CI) 1.31 to 2.37). After adjusting for cardiovascular risk factors at baseline, the risk remained significantly increased (HR for stroke 1.80, 95%CI 1.32 to 2.47). Stratification for sex showed that the increased risk was only found in men (HR men 2.53, 95%CI 1.68 to 3.81, HR women 1.27, 95%CI 0.82 to 1.96). Subtyping of strokes revealed that unrecognized myocardial infarction was associated with infarcts, particularly cortical infarcts (HR in men 3.22, 95%CI 1.96 to 5.28 for total infarcts and 3.57, 95%CI 1.79 to 7.12 for cortical infarcts). **Conclusions:** Men with unrecognized myocardial infarction have an increased risk of stroke, independent of the presence of other cardiovascular risk factors.

110

A Comparison of Blood Pressure Parameters in Assessing Risk of Total, Ischemic, and Hemorrhagic Stroke in Apparently Healthy Men

Thomas Bowman, Tobias Kurth, J Michael Gaziano; Brigham and Women's Hosp, Boston, MA

Background and purpose: While elevated blood pressure is an established risk factor for stroke, it remains unclear which parameter is the best predictor for stroke. Therefore, we compared blood pressure parameters in the prediction of total, ischemic and hemorrhagic stroke. **Methods:** We used a prospective cohort study design with 11,467 men followed for incident stroke during a median of 19.4 years in the Physicians' Health Study. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were collected at baseline and after 2 years. We calculated relative risks (RRs) and 95% confidence intervals (CI) for total, ischemic, and hemorrhagic stroke using Cox proportional hazard models adjusting for major risk factors. Model fit was compared using the χ^2 test statistic from likelihood ratio tests. **Results:** A total of 508 strokes occurred during follow-up (411 ischemic, 89 hemorrhagic and 8 of unknown etiology). For each 10 mm Hg increase in SBP, the multivariable RRs for total, ischemic, and hemorrhagic stroke were 1.30 (95% CI, 1.20–1.42), 1.27 (95% CI, 1.16–1.40), and 1.38 (95% CI, 1.13–1.68). DBP, PP and MAP were not superior parameters to SBP alone, and adding DBP did not significantly improve the model fit of SBP alone for any type of stroke (all P>0.05). **Conclusion:** In this large cohort of healthy men, SBP was a consistent and significant predictor of total, ischemic, and hemorrhagic stroke. SBP alone was the only parameter necessary to predict risk of total stroke or its major subtypes, and our results support the continuing emphasis on using SBP to predict risk of stroke.

111

Causes and Severity of Stroke in Patients with Symptomatic Intracranial Stenosis

Bolanle M Famakin, Michael J Lynn, Mary G George, Marc I Chimowitz, Emory Univ Sch of Med, Atlanta, GA; for the WASID Investigators

Background: There are limited data on the causes and severity of stroke in patients with intracranial stenosis. We sought to determine the location, type (lacunar vs. non-lacunar), cause, and severity of stroke in patients who had an ischemic stroke in the Warfarin Aspirin Symptomatic Intracranial Disease (WASID) trial. **Methods:** WASID was a multicenter clinical trial in which 569 patients with TIA or ischemic stroke due to 50–99% stenosis of a major intracranial artery were randomized to warfarin or aspirin. Patients with a cardiac source of embolism and tandem carotid stenosis > 50% were excluded. This analysis focuses on the 106 patients who suffered an ischemic stroke in the trial. **Results:** Stroke occurred in the territory of the symptomatic artery in 77 (73%) of 106 patients. Of these 77 strokes, 70 (91%)

were non-lacunar and 34 (44%) were disabling. Potential causes of stroke other than the symptomatic intracranial artery were identified in 15 (19%) of 77 patients: 7 penetrating disease (1 also had extracranial vertebral artery stenosis), 4 extracranial carotid stenosis, 3 cardioembolism, 1 extracranial vertebral artery stenosis. Stroke out of the territory of the symptomatic artery occurred in 29 (27%) of 106 patients. Among these 29 strokes, 24 (83%) were non-lacunar and 9 (31%) were disabling. Potential causes of the 29 strokes out of the territory were: 10 stenosis of a previously asymptomatic intracranial artery (3 of which were also associated with another potential cause e.g. cardioembolism), 5 penetrating artery disease, 1 extracranial vertebral artery stenosis, 1 intraluminal thrombus of an intracranial artery, and 12 of undetermined cause. **Conclusions:** Most strokes in patients with symptomtic intracranial artery stenosis are in the same territory and non-lacunar, and nearly half of the strokes in the territory are disabling. The most commonly identified cause of stroke out of the territory was a previously asymptomatic intracranial stenosis. Penetrating artery disease was responsible for a surprisingly low number of strokes, and carotid stenosis and cardioembolism developed uncommonly in this population.

112

Carotid Plaque Surface Irregularity Predicts Ischemic Stroke: The Northern Manhattan Study

Shyam Prabhakaran, Tatjana Rundek, Xiaodong Luo, Rajinder Singh, Palma Gervasi-Franklin, Romel Ramas, Ralph L Sacco; New York Presbyterian Hosp–Columbia Univ Med Ctr, New York, NY

Background and objective: Degree of carotid stenosis is a known risk factor for stroke. Evidence regarding carotid plaque number and surface irregularity and ischemic stroke risk is less convincing. Using a prospective cohort design, we assessed their impact on ischemic stroke risk in a multi-ethnic population. **Methods**: High-resolution B-mode ultrasound of the carotid arteries was performed in 1917 stroke-free subjects (mean age 69 +/- 10.0 years; 59% women; 53% Hispanic, 25% black, 22% white). Plaque was defined as a focal protrusion 50% greater than the surrounding area and localized to common carotid artery or internal carotid artery/bifurcation bilaterally. Subjects with carotid stenosis >60% (1.7%) were excluded from analysis. Plaque surface was categorized as regular or irregular. Plaque number was categorized as 0, 1, or >1 plaque. Cox proportional hazard models were used to assess the impact of surface features and number of plaques in predicting ischemic stroke. **Results**: Among 1885 subjects, carotid plaque was visualized in 55.3% (1 plaque in 21.9%, >1 plaque in 33.4%; irregular plaque in 4.5%). During a mean follow-up of 6.3 years after ultrasound examination, 60 ischemic strokes occurred. Unadjusted cumulative 5-year risks of ischemic stroke were: 1.1%, 2.7%, and 5.4% for no plaque, regular plaque, and irregular plaque, respectively. After adjusting for traditional vascular risk factors (age, sex, race-ethnicity, education, hypertension, diabetes, hyperlipidemia, coronary artery disease, and current smoking), presence of irregular plaque (vs. no plaque) predicted ischemic stroke (adj. HR 3.3, 95% CI 1.1–9.5). Presence of any plaque (vs. no plaque) [adj. HR 1.7, 95% CI 0.9–3.2] and plaque number (>1 vs. 0) [adj. HR 1.5, 95% CI 0.7–3.1] were less predictive of ischemic stroke. **Conclusions**: The presence of non-stenotic irregular carotid plaque independently predicted ischemic stroke in a multi-ethnic elderly stroke-free cohort. Presence of plaque alone or multiple plaques were less predictive. Plaque surface irregularities assessed by B-mode ultrasonography may help stratify risk among stroke-free individuals. The pathophysiology underlying unstable carotid plaque and its management need further study.

Diagnosis

113

Diagnosis of Symptomatic Carotid Plaques with T1-Weighted Magnetic Resonance Imaging and Ultrasonography

Naoki Oyama, Naoaki Yamada, Kazuyuki Nagatsuka, Susumu Miyamoto, Kazuo Minematsu, Hiroaki Naritomi; National Cardiovascular Ctr, Osaka, Japan

Background and Purpose: Substantial fractions of cerebrovascular events are associated with vulnerable carotid plaques and unrelated to the severity of carotid stenosis. We aimed to characterize unstable carotid plaques using magnetic resonance (MR) imaging and ultrasonography (US). **Methods**: We studied 208 atherosclerotic carotid plaques (181 patients) with 50–99% stenosis on MR angiography. MR plaque imaging was performed using three-dimensional inversion-recovery based T1-weighted imaging (MPRAGE) on a 1.5-T clinical system, and carotid plaque was categorized to be high if peak signal of the plaque exceeded 200% of adjacent muscle intensity. Plaque echogenicity on B-mode US was evaluated with the gray-scale median (GSM) in 128 carotid plaques after exclusion of 80 cases with severe calcification, deep lesions or long interval (more than 30 days) between MPRAGE and US studies. Carotid plaque was categorized to be low echoic in the case of GSM<32 and high in the case of GSM≥32. Ischemic events were judged to be positive if cerebral infarction, transient ischemic attack, or retinal ischemia occurred in the ipsilateral carotid territory within the preceding 6 months. The relationships of ischemic events with the MPRAGE and US findings were studied. **Results**: In the MPRAGE study, ipsilateral ischemic events were significantly more frequent in high signal plaque group than in low signal plaque group (40% versus 21%, P<0.005). In the US study, GSM of carotid plaque was significantly lower in ischemic group (n=46) than in non-ischemic group (n=82) (mean GSM, 30 versus 43, P<0.005). In the combined study, ischemic events were significantly more frequent in group of MPRAGE high signal with low US echogenicity (n=45) than in group of MPRAGE low signal with high US echogenicity (n=30) (51% versus 13%, P=0.0005) and somewhat more frequent than in group of MPRAGE high signal with high US echogenicity (n=37) (51% versus 30%, P<0.05). **Conclusions**: MPRAGE has a potential to identify vulnerable plaques and may be more useful than US in cases of severe calcified plaques or deep lesions. The combined use of MPRAGE and US makes the evaluation of symptomatic plaques highly accurate.

114

High-Dose Atorvastatin Improves Cerebral Vasoreactivity in Patients with High-Grade Carotid Stenosis

Theodoros Karapanayiotides, Ioanna Zaloni, Georgios Aposporos, Konstantinos Lianos, Adriano Margerita, Thomas Thomaides; "Pammakaristos" Hosp, Athens, Greece

Objectives : Data suggest that statins improve cerebral vasoreactivity in patients with small vessel disease by propagating NO-mediated vasodilation. Hitherto, it is not known whether this benefit occurs : a) independently from the lipid lowering properties of statins and b) in patients with high-grade carotid stenosis. We investigated the influence of short-term high-dose atorvastatin treatment on cerebral vasomotor reactivity in patients with high-grade carotid stenosis. **Methods :** We evaluated cerebral vasoreactivity (CVR) in 21 patients with >70% carotid stenosis (S)(women=12, mean age=61±8.2, symptomatic=15) by recording with trancranial Doppler (DWL, Doppler-box) the MCA ipsilateral to the stenosis before and after iv. administration of 1 g acetazolamide and by calculating the relative increase (%) of the MCA mean velocity. The test was performed at baseline and after 3 days of administation of 80 mg atorvastatin/day. Results were compared with a control group (C) of 15 healthy age- and sex-matched individuals that received the same regimen. **Results :** Baseline CVR was clearly lower in S compared to C (median [quartiles]: 21.3 [12.7, 35.1] vs 41.4 [18.8, 61.3]; Mann-Whitney p<0.001). Baseline cholesterol values were higher in S (median [quartiles] mg/dl : 171.3 [122.5, 245.6] vs 149.1 [109.9, 181.6]; Mann-Whitney p<0.005) and were not influenced by atorvastatin treatment (Wilcoxon signed rank, p=0.88). Atorvastatin improved VSR in S (29.3 [13.5, 44.2]; Wilcoxon signed rank p<0.008) but only tended to improve VSR in C (49.3 [18.5, 74.2]; Wilcoxon signed rank p=0.057). The degree of vasoreactivity improvement in S was higher compared to C (relative increase %: 38.5 [13.8, 53.2] vs 17.3 [6.9, 28.7]; Mann-Whitney p<0.002). **Conclusions:** Our results suggest that high doses of atorvastatin administered for very short periods can improve the impaired cerebral vasomotor reactivity in patients with high-grade carotid stenosis through other mechanisms than lowering blood lipids. The potential benefits of routine statin administration prior to carotid endarterectomy should be investigated in further studies.

115

Cerebral Microhemorrhages Predict New Disabling or Fatal Strokes in Patients Presenting with Acute Ischemic Stroke or Transient Ischemic Attack

Jean-Martin Boulanger, Michael Eliasziw, Shelagh B Coutts, Alexis J Gagnon, Jessica E Simon, Suresh Subramaniam, Chul-Ho Sohn, James Scott, Andrew M Demchuk; Univ of Calgary, Calgary, Canada

Background: Cerebral microhemorrhages (MH) are relatively common among patients presenting with acute ischemic stroke and may predict both subsequent ischemic and hemorrhagic strokes. *Methods*: We prospectively studied patients with and without MH presenting within 12 hours of their ischemic stroke or transient ischemic attack (TIA). All had a premorbid modified Rankin scale score ≤ 3. A magnetic resonance (MR) scan was performed within 24 hours of symptom(s) onset. The primary outcome was disabling or fatal stroke. Secondary outcomes included all strokes and deaths from any cause. *Results*: A MR scan with gradient-echo or perfusion-weighted echo-planar imaging was done in 236 patients with acute ischemic stroke or TIA. Forty five (19.1%) patients had microhemorrhage(s) on a baseline MR. After adjustment for confounding factors (age, confluent white matter disease), patients with MH were 2.8 times (10.8% vs 4.0%; p= 0.036) more likely to have a subsequent disabling or fatal stroke within 18 months of their ischemic symptoms than patients without a microhemorrhage. The hazard ratio (HR) for all deaths was 3.1 (16.5% vs 5.6%; p = 0.015). The risk of symptomatic intracerebral hemorrhage was not statistically significant among MH and non MH patients (3.3% vs 0.8%; p=0.31) while the risk of ischemic stroke was higher in the MH group (20.3% vs 8.7%, p= 0.039). *Conclusions*: The presence of cerebral microhemorrhage(s) in patients with acute ischemic stroke or TIA predicts recurrent disabling and fatal strokes. This risk is mainly assumed by recurrent ischemic strokes.

116

Noninvasive Imaging of Inflammation/Apoptosis with ^{99m}Tc-Annexin A5 Reveals Plaque Instability in Patients with Significant Carotid Artery Stenosis

Sander L Wolters, Maastricht Univ and Hosp, Maastricht, The Netherlands; Steven Appleby, Univ of California, Irvine, CA; Bas L Kietselaer, Esther Lutgens, Hendrikus H Boersma, Jan H Tordoir, Jaap Teule, Chris P Reutelingsperger, Maastricht Univ and Hosp, Maastricht, The Netherlands; Jagat Narula, Univ of California, Irvine, CA; Leonard Hofstra; Maastricht Univ and Hosp, Maastricht, The Netherlands

Introduction Apoptosis and inflammation constitute important substrates of atherosclerotic plaques that are vulnerable to result in acute events. Apoptosis and inflammation can be imaged non-invasively with ^{99m}Tc-Annexin A5 (TAA5). We evaluated the role of TAA5 imaging in patients who had suffered from recent or remote cerebrovascular accidents, scheduled for carotid endarterectomy (CEA). We hypothesized that TAA5 uptake would correlate with histology findings in carotid artery plaque. **Methods** Sixteen patients underwent radionuclide imaging. All patients had ultrasonic evidence of significant carotid artery stenosis and had CEA one day after imaging. SPECT imaging of the cervical region was performed after IV administration of 15–30 mCi TAA5. CEA specimens were collected during surgery and analyzed for AA5 content, and plaque histology. **Results** Significant TAA5 uptake was observed in culprit carotid vessel in 4 patients. In all these cases, histologic characteristics were suggestive of plaque instability, including large necrotic cores, macrophage infiltration, and presence of AA5. In 10 patients no TAA5 uptake was seen, which correlated in 9 cases with the histologic characteristics of stable atherosclerotic disease, characterized by smooth muscle-rich lesions. In 2 cases with equivocal TAA5 uptake, unstable histologic features were observed. **Conclusion** These data indicate that enhanced uptake of TAA5 in the carotid artery region

reflects plaque instability. Therefore, non-invasive imaging with TAA5 could offer a valuable tool for the detection of plaque instability in carotid artery disease.

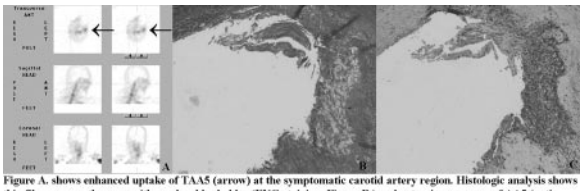


Figure A. shows enhanced uptake of TAA5 (arrow) at the symptomatic carotid artery region. Histologic analysis shows thin fibrous cap atheroma with a vulnerble sholder (EVG staining, Figure B.) and extensive presence of AA5 (anti Annexin A5 staining, Figure C.)

117

Early Ischemic Lesion Recurrence on Diffusion-Weighted Imaging in Atherosclerotic Intracranial Disease

Dong-Wha Kang, Sun U Kwon, Sung-Hee Yoo, Jong S Kim; Asan Med Ctr, Seoul, Republic of Korea

Background and Purpose: Prior observations identified frequent ischemic lesion recurrence on diffusion-weighted imaging (DWI) within the first week after ischemic stroke. However, the differential pattern of early ischemic lesion recurrence among stroke subtypes, particularly in atherosclerotic intracranial arterial disease, remains unknown. **Methods**: We reviewed consecutive acute ischemic stroke patients who underwent initial DWI within 24 hours of onset and subsequent DWI between 1 and 7 days after onset. Recurrent lesions were defined as new ischemic lesions on follow-up DWI separate from the index stroke lesion. Patients with intracranial large-artery atherosclerosis (IC-LAA), extracranial LAA (EC-LAA), cardioembolism (CE), or small-vessel occlusion (SVO) were included. We excluded those who had tandem IC-LAA and EC-LAA, other determined or undetermined etiology, or who underwent invasive diagnostic or therapeutic procedures between DWI scans. Vascular territory (VT) of recurrent lesions and associations between lesion recurrence and degree of stenosis and recanalization were compared among stroke subtypes. **Results**: Of 175 patients included in this analysis, recurrent ischemic lesions were observed in 29/55 (52.7%) of IC-LAA, 9/19 (47.4%) of EC-LAA, 26/59 (44.1%) of CE, and 3/42 (7.1%) of SVO. Recurrent lesions in IC-LAA occurred 1) mostly in the pial or cortical border-zone of the same VT of index stroke (28/29, 96.6%), 2) without subsequent recanalization, and 3) more frequently in severe stenosis or occlusion than in milder stenosis (29/42 vs. 0/13, $p<0.001$). On the contrary, recurrent lesions in the same VT in CE (16/26, 61.5%) were mostly associated with subsequent recanalization (9/16), and recurrent lesions in the same VT in EC-LAA (7/9, 77.8%) were not related with stenosis degree. Recurrent lesions in IC-LAA were associated with clinical recurrent symptoms compared to other stroke subtypes (7/29 vs. 1/38; $p=0.017$). **Conclusions**: IC-LAA has different patterns of early ischemic lesion recurrence from EC-LAA or CE. These data have implications for the design of stroke prevention trials in atherosclerotic intracranial disease.

118

Absence of a Diffusion-Weighted Imaging Lesion in Minor Stroke/Transient Ischemic Attack Events Predicts Future Transient Ischemic Attacks But Not New Strokes

Jean-Martin Boulanger, Michael Eliasziw, Shelagh B Coutts, Suresh Subramaniam, James Scott, Andrew M Demchuk; Univ of Calgary, Calgary, Canada

Background: Recurrence of stroke or transient ischemic attack (TIA) is a major concern in clinical practice. Among patients presenting with a TIA or a minor stroke, some clinical features predispose to recurrent TIA while others predispose to subsequent strokes. Nevertheless, the implication of a baseline magnetic resonance (MR) scan in predicting the pattern of recurrent events has never been studied. *Methods*: We prospectively studied patients presenting in the emergency department within 12 hours of their TIA or minor stroke, defined as a National Institutes of Health Stroke Scale (NIHSS) score <4. All patients had a MR scan within 24 hours of the index event. The primary outcomes were stroke and transient ischemic attack within 12 months of study entry among patients with and without diffusion-weighted imaging (DWI) lesions on the baseline MR scan. *Results*: A total of 152 patients with a minor stroke or a TIA had a MR scan, among which 88 patients (57.9%) had DWI lesions at study entry. The mean time from symptoms onset to MR scan was 12.6 hours in both the DWI lesions group and the DWI lesion absent group. Patients without a DWI lesion on baseline MR were 4.3 times (13.7% versus 3.2%; $p=0.05$) more likely to have a subsequent TIA at 12 months rather than a stroke. In contrast, patients with a DWI lesion were 2.9 times (21.5% versus 7.3%; $p=0.008$) more likely to have a subsequent stroke rather than a TIA. The difference in risk ratios was statistically significant ($p = 0.002$). Patients with a DWI lesion were 6.7 times more likely to have a subsequent stroke ($p=0.0015$) and about half as likely to have a subsequent TIA ($p=0.30$) when compared to patients without DWI lesions. *Conclusion*: A baseline MR scan is useful in predicting the pattern of future cerebrovascular ischemic events among patients presenting with a minor stroke or TIA. In this population, the presence of a DWI lesion on a baseline MR scan predicts subsequent stroke(s) while its absence is a risk factor of future TIA(s).

119

The Utility of Diffusion-Weighted Imaging to Predict Neurologic Outcome in Comatose Patients After Cardiac Arrest

Michael Mlynash, Stanford Stroke Ctr, Stanford Univ, Palo Alto, CA; Amie W Hsia, NINDS, Stroke Branch, Bethesda, MD; Anna C Finley-Caulfield, Irina Eyngorn, Stanford Stroke Ctr, Stanford Univ, Palo Alto, CA; Roland Bammer, Michael Moseley, Lucas MRS/I Ctr, Stanford Univ, Palo Alto, CA; Christine A Wijman; Stanford Stroke Ctr, Stanford Univ, Palo Alto, CA

Background: Early accurate prediction of neurologic outcome is challenging in a substantial proportion of patients who remain comatose after cardiac arrest. In this pilot study we assessed the utility of brain diffusion-weighted MRI (DWI) in predicting neurologic outcome in these patients. Methods: Forty-one comatose survivors after cardiac arrest were prospectively enrolled. Patients who met criteria of any one of 3 outcome groups and who had technically satisfactory DWI scans within 8 days after the arrest were included in this analysis. Group 1 (poor outcome): bilateral absent cortical responses by somatosensory evoked potentials and/or clinical evidence of brainstem dysfunction after 72 hours, or persistently vegetative after 3 months. Group 2A (good outcome): alive at 3 months with GOS 4/5 or mRS 0/1/2, Group 2B (intermediate outcome): alive at 3 months but not comatose and not in group 2A. Mean brain ADC values and the percent of total brain volume below an ADC cutoff value of 650 x 10^{-6} mm^2/sec were measured. Results: Twenty patients with a mean age of 54 ± 17 years and mean arrest duration of 20 ± 12 minutes are included in this report. Nine patients were in group 1, five in group 2A, and six in group 2B. Age and arrest times did not differ between the 3 groups. Mean brain ADC values and the percentage of brain volume with an ADC value below 650 x 10^{-6} mm^2/sec were found to distinguish group 1 from group 2 (A and B combined) when the MRI was performed more than 24 hours after the arrest: 902 ± 43 and 10 ± 6%, respectively, for group 2, and 770 ± 61 and 33 ± 13% for group 1 (both $p<0.001$). There also was a strong trend for the cutoff of 650 x 10^{-6} mm^2/sec to differentiate group 2A from group 2B: 6 ± 4% and 13 ± 6% respectively ($p=0.07$). The optimal time window for DWI to differentiate between the 3 groups appeared to be between day 3 and 5 after the cardiac arrest. Conclusions: DWI may be useful in the prediction of neurologic outcome in the first week after cardiac arrest. Both mean brain ADC values and the percentage of brain volume below an ADC cutoff of 650 x 10^{-6} mm^2/sec appear to distinguish poor outcome patients (dead or persistently vegetative at 3 months) from survivors when the MRI is performed more than 24 hours after the arrest.

Experimental Ischemia

120

A Differential Regulation of Mutant *EAAT2* Promoter Accounts for Higher Glutamate Concentrations and Brain Injury in Stroke Patients with Mutant Genotype

M A Moro, Sch of Med, Univ Complutense, Madrid, Spain; J Mallolas, Hosp Univ Dr Josep Trueta, Girona, Spain; O Hurtado, Sch of Med, Univ Complutense, Madrid, Spain; M Castellanos, Hosp Univ Dr Josep Trueta, Girona, Spain; T Sobrino, M Blanco, Hosp Clínico Univ, Santiago de Compostela, Spain; J Vivancos, Hosp de la Princesa, Madrid, Spain; J Castillo, Hosp Clínico Univ, Santiago de Compostela, Spain; J Serena, Hosp Univ Dr Josep Trueta, Girona, Spain; I Lizasoain, Sch of Med, Univ Complutense, Madrid, Spain; A Davalos; Hosp Univ Germans Trias i Pujol, UAB, Badalona, Spain

Aim: A novel polymorphism in the promoter region of the *EAAT2* gene (-181A/C) that is associated with higher glutamate plasma levels and neurological deterioration in patients with acute stroke has been recently identified. Our aim was to investigate the role of this polymorphism by analysing its effects on the EAAT2 promoter activity. ***Methods***: Bioinformatics analysis of wild type (WT) and mutant EAAT2 promoter was performed using the SIGSCAN 4.05. A 773 bp fragment from WT and mutant promoter were cloned into the pGL3-basic luciferase reporter vector and co-transfected with pRL-KT. Transcriptional activity was investigated in cultured rat astrocytes, by luciferase assay. GCF2 expression was studied by immunoblotting using a specific anti-GCF2 antibody, in homogenates of ipsilateral cortices and striata from rats sacrificed 2, 24 and 48 h after a permanent middle cerebral artery occlusion (MCAO) or sham procedure. ***Results***: The polymorphism abolished the putative activator transcription factor-binding element AP-2, and created a new consensus sequence corresponding to the GCF2, a transcriptional repressor expressed in human tissues showing low expression in brain. In astrocytic cultures, the mutant EAAT2 construct showed a 30% reduction in promoter activity compared to the WT. Cotransfection with AP2 enhanced EAAT2-WT but not mutant-EAAT2 activity. In contrast, cotransfection with GCF2 decreased expression of mutant promoter whereas WT promoter expression was not affected. GCF2 expression in brain samples from sham animals was not detected, but MCAO increased GCF2 expression in both cortex and striatum at all times examined. ***Conclusions:*** The mutation in the *EAAT2* gene is associated with decreased promoter activity. Co-transfection with AP-2 and GCF2 yielded a different pattern of regulation in WT and mutant promoter. We also show a GCF2 overexpression in ischemic brain suggesting a highly repression of glutamate uptake in individuals with the mutant genotype after stroke, consistent with the higher glutamate concentrations found in these patients. GCF2 could be a new therapeutic target in acute ischemic stroke for patients with -181A/C polymorphism.

121

Unraveling Genetic Susceptibility by the Construction of 8 Consomic Strains Derived from the Stroke-Prone Spontaneously Hypertensive Rat

Hyoe Inomata, Yi-Qiang Liang, Kazuyuki Yanai, International Med Ctr of Japan, Tokyo, Japan; Mitsuaki Isobe, Tokyo Med and Dental Univ, Tokyo, Japan; Norihiro Kato; International Med Ctr of Japan, Tokyo, Japan

The incident of stroke increases in parallel with the degree of blood pressure elevation, whereas the pathophysiological relevance of dyslipidemia remains controversial. It has been also argued that there are primary, blood-pressure independent genetic factors predisposing to stroke. To investigate these issues, the stroke-prone spontaneously hypertensive rat (SHRSP), characterized by severe hypertension, dyslipidemia and the propensity for stroke, is considered a unique model organism. We performed genome-wide linkage analysis of quantitative trait loci (QTLs) for blood pressure, its associated metabolic traits and the stroke incident in experimental crosses involving SHRSP and its control strain, the Wistar Kyoto rat (WKY). A total of six QTLs for blood pressue were found to account for 40 to 50% of the variance (R-square), among which rat chromosome (RNO) 1 QTL appeared to be a major determinant. Moreover, this RNO1 region overlapped with the one previously reported as a stroke QTL, STR1. Three QTLs and one QTL were further identified for total cholesterol and triglyceride levels, respectively. Next, to evaluate the genetic impacts on individual target phenotypes, we constructed eight consomic rat strains by recombining the relevant chromosomes between SHRSP and WKY. Here, we adopted a speed-congenic strategy which could shorten the construction period to less than a half, i.e., 1.5 to 2 years. A number of QTLs were shown to exist in the recombined chromosomal regions as originally detected by the linkage analysis. For example, blood pressure QTLs were verified in six consomic strains with each showing 10–30 mmHg of changes as compared to progenitor strains. Towards the identification of causative genes, we are currently narrowing down the target regions by developing a series of subcongenic lines as well as by performing DNA microarray analysis. Thus, we have constructed a panel of eight consomic rat strains in which principal QTLs for blood pressure, dyslipidemia and stroke are successfully trapped. These strains should constitute useful molecular tools for the dissection of complex genetic interplay.

122

Imaging Apoptosis by ^{99m}Tc-Labeled Annexin V Spect After Stroke

Xian N Tang, UCSF and San Francisco VAMC, San Francisco, CA; Francis Blankenberg, Danye Cheng, Stanford Univ, Stanford, CA; Midori A Yenari; UCSF and San Francisco VAMC, San Francisco, CA

Programmed cell death (apoptosis) is thought to play a role in brain injury following stroke. There are obvious advantages to being able to image apoptosis and the progression of stroke noninvasively. Annexin V is an endogenous protein with high affinity to phosphatidylserine (PS). Externalization of membrane PS is an early sign of apoptosis. We previously showed that radiolabeled Annexin V can be used to noninvasively detect apoptosis in stroke models, and that Annexin V binding occurs primarily in ischemic neurons. In this study we explored whether ^{99m}Tc-annexin V imaging using SPECT (single photon emission computed tomography) could be used to monitor a potential treatment response to minocycline, a tetracycline antibiotic with both antiapoptotic and anti-inflammatory properties, in experimental stroke. 40 CB6/F1 adult male mice underwent unilateral distal middle cerebral artery occlusion (dMCAO) and were survived 1 &3 d. Animals were given 22.5 mg/kg minocycline (or vehicle) i.p. 30 min and 12 hour after dMCAO, then 22.5 mg/kg twice daily up to the time of sacrifice. In each group, mice were injected with 5–10 mCi of ^{99m}Tc annexin V 2 hours before undergoing SPECT on days 1 & 3. After imaging, brains were collected for histology and assessed for apoptosis using TUNEL stain and activated microglia using isolectin B4 (IB4). There was marked multifocal uptake of ^{99m}Tc labeled annexin V in both cerebral hemispheres, hind brain, and cervical spinal cord as confirmed by SPECT that was significantly decreased 2–7 fold by minocycline. This was correlated to reduced infarct size ($P<0.01$), numbers of TUNEL ($P<0.05$) & IB4 ($P<0.01$) positive cells among treated mice. We show that radiolabeled annexin V SPECT imaging may be a novel way to monitor the progression stroke and response to therapy.

123

Real-Time Bioluminescent Imaging of Neural Stem Cell Transplant Survival in the Brains of Mice: Assessing the Impact of Immunity and Ischemia

Dong-Eog Kim, Dongguk Univ International Hosp, Goyang, Republic of Korea; Kiyoshi Tsuji, Neuroprotection Res Lab, Charlestown, MA; Young Ro Kim, NMR Ctr, Charlestown, MA; Franz-Josef Mueller, Developmental and Regenerative Cell Biology, The Burnham Inst, La Jolla, CA; Hyeon-Seok Eom, National Cancer Ctr, Goyang, Republic of Korea; Evan Y Snyder, Developmental and Regenerative Cell Biology, The Burnham Inst, La Jolla, CA; Eng H Lo, Neuroprotection Res Lab, Charlestown, MA; Ralph Weissleder, Ctr for Molecular Imaging Res, Charlestown, MA; Dawid Schellingerhout; MD Anderson Cancer Ctr, Houston, TX

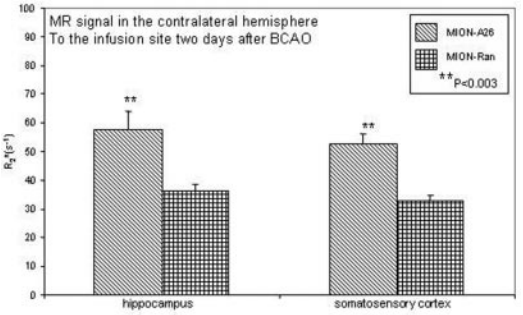
Purpose: A major concern in translating stem cell biology to clinical practice, is the inability to follow grafted cells in real-time in order to detect survival, anatomic location, rejection or even the emergence of stem-cell derived abnormalities. We describe the use of bioluminescent imaging in a murine transplant model to monitor the *in vivo* responses of transplanted neural progenitor cells (NPC) containing the luciferase marker gene to host immunity and ischemia. **Materials & Methods:** A cranial window was created in C57BL6 (C57), nude and CD-1 mice, and C17.2-Luc-GFP-gal (C17.2-Luc) NPC were transplanted into the right basal ganglia. At D9 after transplantation, C57 mice underwent 18 minutes of transient forebrain ischemia by means of temporary bilateral carotid occlusions. Controls underwent sham surgery. Bioluminescence imaging was performed at days 7, 9, 11, and 14. Similar imaging was performed on C57, nude, and CD-1 mice, with subsequent sacrifice and histological analysis. **Results:** *In vivo* cell tracking demonstrated: 1) C17.2-LUC NPC survived and proliferated better in the T-cell deficient nude mice than in the immunocompetent C57 or CD-1 mice, in which they showed progressive immune mediated cell loss. 2) Transient forebrain ischemia appeared, unexpectedly, to act as a short term stimulus to transplanted NPC growth/survival in immunocompetent mice. **Conclusion:** Our findings demonstrate that differences in the host environment can powerfully influence graft survival between strains and individuals. Assessment of NPC survival using serial non-invasive imaging technology will likely increase our understanding of the complex physiology of NPC transplantation.

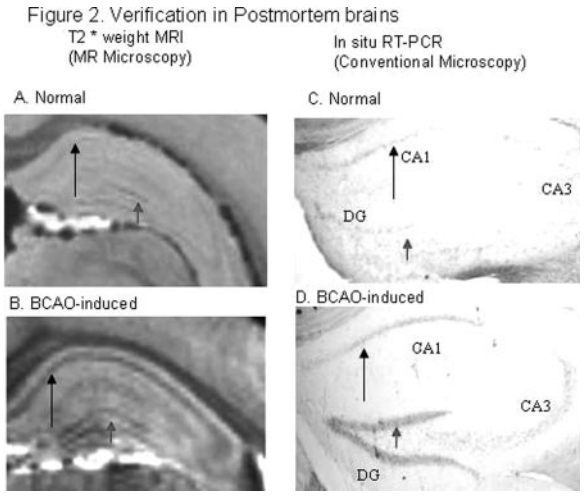
124

Cerebral Ischemia-Induced Gene Expression in the Brain of Live Animals Can Be Imaged Using MRI

Christina H Liu, Young R Kim, Bruce R Rosen, Philip K Liu; Massachusetts General Hosp, Charlestown, MA

The expression of immediate early genes is thought to be associated with cell repair/viability of the brain after stroke and heart attack. Currently gene expression is detected using postmorten samples. We tested the hypothesis that endougenous gene expression at the transcription level using MR imaging will provide significant clinical benefits. We labeled short phosphorothioate-modified oligo-DNA (s-ODN) with monocrystalline iron oxide nanoparticles (MION, an MR T2 contrast agent). We infused male C57black6 mice intracerebroventricularly with one of two conjugates of MION: (1) MION-A26, a targeting conjugate which contains an s-ODN of 26 bases with sequence complementary to c-fos mRNA, and (2) MION-Ran, a non-targeting conjugate of s-ODN with a random sequence as a negative control. We selected c-fos mRNA as the target, because its product, Fos protein is an essential component of activator protein-1 (AP-1) which regulates many genes (one of them is mRNA of nerve growth factor). We demonstrated that MION-A26 significantly increased MR susceptibility relaxation rate (R_2*) after cerebral ischemia by 30-min bilateral carotid occlusion (BCAO). The elevation was observed in brain regions of the somatosensory cortex and the hippocampus, corresponding to elevation in c-fos mRNA, but not b-actin mRNA, using molecular assay in post mortem samples. We conclude this ODN-based contrast probes may be used to explore the potential of MRI for real-time detection of transcripts, offering a new approach to direct, minimally invasive molecular assessment of gene expression in the brain under normal or neurologic disease states. (NSR01045845, P41RR14075 & the MIND Inst)





125

Flow Cessation Induces Leukocyte-Mediated MMP/TIMP Release at the BBB: Role of Proinflammatory Cytokines in Differential Regulation of TIMP-1 and TIMP-2

Ljiljana Krizanac Bengez, Mohammed Hossain, Vincent Fazio, Cleveland Clinic Foundation, Cleveland, OH; Marc R Mayberg, Seattle Neuroscience Inst, Seattle, WA; Damir Janigro; Cleveland Clinic Foundation, Cleveland, OH

The substantial evidence links blood-brain barrier (BBB) failure during ischemia to inflammatory processes involving cytokines (TNF-α and IL-6) and membrane metalloproteinases (MMP). BBB may be affected by loss of shear stress under normoxia/normoglycemia, as shown by cardiopulmonary bypass studies. The present study used a dynamic *in vitro* BBB model (DIV-BBB) to analyze the individual contributions of flow, cytokine levels and blood cells on BBB

under normoxia/normoglycemia. Using DIV-BBB, we showed previously that exposure to normoxic/normoglycemic flow cessation/reperfusion with blood leukocytes in the luminal perfusate led to a significant increase in TNF-α and IL-6, accompanied by biphasic BBB opening. In current study we analyzed the effect of flow cessation on the release (ELISA) and activity (zymography) of MMP-2 and MMP -9. The presence of blood leukocytes in the luminal perfusate under normoxic/normoglycemic flow cessation/reperfusion significantly increased baseline MMP-9 levels; activity of both MMP-2 and MMP-9; and induced partial reduction of TIMP-1 and complete reduction of TIMP-2 levels. None of the changes were observed after normoxic/normoglycemic or hypoxic/hypoglycemic flow cessation/reperfusion without blood cells in the luminal perfusate. Addition of an anti-IL-6 or anti-TNF- α antibody in the lumen prior to the reperfusion, suppressed the release of MMP-9 and activity of MMP-9 and MMP-2. Blockade of IL-6 proved to be more effective. Blockade of both cytokines had no effect on TIMP-1, while re-storing the levels of TIMP-2 to the baseline values. The data implicate that blood leukocytes and loss of flow are major players in (1) release of MMP-2 and MMP-9, and in (2) cytokine-mediated differential regulation of TIMP-1 and TIMP-2, involved in blood-brain barrier failure. *Supported By: AHA SDG 0230015N, NIH NS046513*

126

Involvement of Neuronal NOS, Poly (ADP-Ribose) Polymerase and Apoptosis-Inducing Factor in Gender Selective Cell Death

Zhiyuan Zeng, Univ of Connecticut Health Ctr, Farmington, CT; Scott Pin, Kathleen Blizzard, Johns Hopkins Univ, Baltimore, MD; Louise D McCullough; Univ of Connecticut Health Ctr, Farmington, CT

Background: We have shown previously that female-derived (XX) hippocampal slice cultures are protected after oxygen-glucose deprivation (OGD) compared to males (XY). Differential gender responsiveness is also seen after focal stroke which is linked to neuronal NOS (nNOS) and poly(ADP-Ribose) polymerase-1 (PARP). In males loss of nNOS or PARP is neuroprotective. In contrast, loss of nNOS or PARP increases stroke damage in females. The objectives of this study were to determine 1) if gender differences exist after OGD in cortical neurons 2) if this effect is related to nNOS/PARP 3) if gender differences exist in the downstream effector molecule, apoptosis inducing factor (AIF) after stroke. **Methods:** Cortical cultures were derived from E17 nNOS-/-, PARP-/- and wild-type (WT) mice. Embryos were sexed with Sry (XY) genotyping. Neurons were exposed to OGD (90 min) at day 10 and cell death was determined (PI/Calcein) at 24hrs. Reversible middle cerebral artery occlusion (MCAO-2hrs) was performed in PARP-/- and WT mice (n=5/gp) and AIF translocation assessed by Western blot at 2, 6 and 24 hours. PARP activity (R & D systems) was measured in WT mice 24 hours after stroke (n=5/gp). **Results:** Female WT neurons had less cell death (% death) after OGD than males (XX 29.9$\pm$2.6 vs. XY 46.6$\pm$3.5; $p<.001$, n=17). Both nNOS-/- and PARP-/-derived XX neurons showed an enhanced sensitivity to OGD compared to nNOS-/- and PARP-/- XY neurons (nNOS XX 55$\pm$2.7 vs. XY 37.0$\pm$3.8,$p<.001$,n=19:PARP XX 56.6$\pm$5.1 vs. XY 32.5$\pm$5.1, $p<.001$,n=21). PARP activity was higher in female WT brains (0.18mg/ml,n=5/gp) after ischemia compared to males (0.09mg/ml). AIF translocation was seen in both WT and PARP-/- mice 6 and 24 hrs after stroke. Nuclear AIF levels were significantly lower in PARP-/- mice of both genders, and were lowest in PARP-/- females. **Conclusions:** Female neurons are protected against OGD. Reversal of this effect occurs in nNOS and PARP deficient XX neurons. Female PARP-/- mice demonstrate exacerbation of stroke damage compared to WT, despite a dramatic reduction in AIF translocation. The nNOS/PARP/AIF pathway is a major mediator of cell death in the male, but not the female brain. Strategies targeted at inhibiting this sexually dichotomous pathway will likely exacerbate damage in females.

Oral Presentations

Stroke. 2006;37:619-646
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628