LATE-BREAKING SCIENCE abstracts/studies presented at the INTERNATIONAL STROKE CONFERENCE 2014:
For late-breaking science being presented at ISC 2014, the embargo lifts when the first presentation begins in the scientific session in which the abstract is being presented: either 11 am PT on Wednesday, Feb. 12; 6:15 pm PT on Wednesday, Feb. 12; 1:30 pm PT on Thursday, Feb. 13; or noon PT on Friday, Feb. 14). News media activities promoting late-breaking science are under embargo until the times noted above.

Presentation Number: LB P1

Publishing Title: Transcriptome Networks Change in Patients With Subarachnoid Hemorrhage Undergoing Remote Ischemic Conditioning

Author Block: Arthur Ko, Mark J Connolly, Marcus Alvarez, Elina Nikkola, Päivi Pajukanta, Nestor R Gonzalez, UCLA, Los Angeles, CA

Abstract Body:

Introduction: Despite advances in early aneurysm treatment and ICU care, the prognosis for patients with aneurysmal SAH remains grave, with 50% of patients suffering long-term morbidity or dying as a consequence of delayed ischemic events. Remote ischemic conditioning (RIC) has shown promising results against ischemic injury in animal models by inducing ischemic tolerance via genomic reprogramming of expression profiles. We performed a longitudinal cohort study using RIC in SAH patients to identify and compare transcript networks at baseline, immediately after, and one week after RIC. This is the first study investigating the impact of RIC on gene expression in human SAH patients.

Methods: We performed 3-timepoint transcriptome analysis of whole blood in 42 samples from 14 SAH patients undergoing IPC using paired-end, 100 bp RNA-sequencing. STAR and HTSeq were used to align and count reads, and edgeR to normalize counts. We used weighted gene co-expression network analysis (WGCNA) to identify transcript networks correlated with vasospasm and clinical outcomes in SAH applying Bonferroni correction for multiple testing. We also searched for functional categories in the trait-associated networks utilizing DAVID.

Results and Conclusions: 4 modules demonstrated statistically significant time-specific, down-regulation: at baseline a transcript network of 31 downregulated genes correlated with the diagnosis of vasospasm (-0.82, p=0.0005) and a second network correlated with discharge Glasgow Outcome Scale (GOS) (-0.85, p=0.0002) and was significantly enriched for cellular response to starvation and nutrient levels. Immediately after RIC, we detected significant correlation between a transcript network of 82 downregulated genes with discharge GOS (-0.78, p=0.0009), and one week after RIC a network of 49 genes correlated with the presentation Fisher grade of SAH (-0.79, p=0.0008). Taken together, our novel data implicate significant longitudinal transcriptome changes in SAH patients undergoing RIC, suggesting that RIC influences the biological processes in SAH.

Author Disclosure Block:

Presentation Number: LB P2

Publishing Title: Spontaneous Swallow Frequency and Dysphagia Outcomes in Acute Stroke

Author Block: Michael A Crary, Giselle D Carnaby, Lisa LaGorio, Swallowing Res Lab - Univ Florida, Gainesville, FL

Abstract Body:

Background: Spontaneous swallow frequency analysis (SFA) has been shown to identify dysphagia and is related to dysphagia severity in acute stroke patients. The relation of SFA to dysphagia related outcomes in acute stroke is unknown.

Purpose: To evaluate associations between SFA and dysphagia related outcomes in acute stroke.

Methods: 63 stroke patients received dysphagia screening via SFA within an average of 3 days following onset of symptoms. Dysphagia was identified via the Mann Assessment of Swallowing Ability (MASA) and Functional Oral Intake Scale (FOIS). Stroke severity was assessed with the National Institutes of Health Stroke Scale (NIHSS), Barthel Index (BI), and modified Rankin Scale (mRS). Dysphagia related outcomes were monitored via electronic medical record including: length of stay, infections, referral for dysphagia evaluation, dysphagia treatment, PEG placement, dysphagia at discharge, FOIS level at discharge, and death. Impact of rTPA on SFA was also assessed. Univariate statistics were used to investigate associations between SFA and dysphagia related outcomes.

Results: Dysphagia prevalence at baseline was 41%. Mean swallow frequency was 0.42 swallows per minute with lower rates in patients with dysphagia (0.51 vs. 0.27; p=< 0.0001). At baseline SFA was significantly correlated with MASA (r = 0.52, p = 0.0001), FOIS (r = 0.51, p = 0.0001), mRS (r = 0.51, p = 0.0001), and BI (r = 0.44, p = 0.0001), and NIHSS (r=-.39, p = .005) but not age, or time to screening. Baseline SFA rates were lower for those patients demonstrating dysphagia related morbidity at discharge from acute care. SFA was significantly associated with SLP dysphagia assessment (t = 2.14, p = 0.04), dysphagia (t = 1.99, p = 0.05), modified diet (t = 2.25, p = 0.02), mRS (t = 2.21, p = 0.03), and BI (t = 2.38, p = 0.02). Patients treated with rTPA demonstrated a descriptive trend toward higher swallow frequency rates.

Conclusions: As a dysphagia screening tool, SFA has high potential to identify dysphagia and is associated with dysphagia related outcomes in acute stroke. SFA may also be sensitive to outcome from acute stroke interventions such as rTPA.

Author Disclosure Block:

M.A. Crary: None. G.D. Carnaby: None. L. LaGorio: None.
Presentation Number: LB P3

Publishing Title: A Single Genetic Locus, Dce1, Causes Wide Variation in Pial Collateral Extent and Severity of Ischemic Stroke.

Author Block: James E Faber, Robert Sealock, Hua Zhang, Jennifer L Lucitti, Scott M Moore, Univ of North Carolina, Chapel Hill, NC

Abstract Body:

Severity of tissue injury in occlusive arterial disease depends, in large part, on the extent (number and diameter) of native collaterals (ie, those pre-existing before occlusion). We have recently found that collateral extent varies widely from naturally occurring differences in genetic background, eg, ~45-fold for pial collaterals among different mouse strains. This results in wide variation in their infarct volumes. Similar differences exist in their other tissues. Clinical studies suggest that native collateral extent in brain and other tissues may also vary significantly among healthy humans. Although the causative genetic elements are unknown, we recently reported that ~70% of the variation in mice, including the C57Bl/6J (B6, high collateral extent) and BALB/cByJ (Bc, low) strains, was linked to a QTL on chromosome 7 (Candq1). In the present study, we used congenic mapping to refine Candq1 and its candidate genes and create an “isogenic” strain-set with a large difference in collateral extent to assess its impact, alone, on ischemic injury. Six congenic strains possessing portions of Candq1 introgressed from B6 into Bc were generated and phenotyped. Candq1 was refined from 27 to 0.737 Mb with full retention of effect, ie, return/rescue of phenotypes from the poor values in Bc to nearly those of wildtype B6 in the B6/B6 congenic mice: 83% rescue of low pial collateral extent, and 4.5-fold increase in blood flow and 85% reduction of infarct volume after middle cerebral artery occlusion; 54% rescue of low skeletal muscle collaterals, and augmented recovery of perfusion (83%) and function after femoral artery ligation. Gene deletion and in-silico analysis further delineated the candidate genes. These results significantly refine Candq1 (now designated Determinant of collateral extent-1, Dce1), demonstrate that genetic background-dependent variation in collateral extent is a major factor underlying differences in ischemic tissue injury, and provide a congenic strain-set with wide, allele-dose-dependent variation in collateral extent for use in future investigations of the collateral circulation.

Author Disclosure Block:

Presentation Number: LB P4

Publishing Title: Delayed Administration of Perlecan Domain V Significantly Increases Neurogenesis and Functional Recovery after Experimental Ischemic Stroke

Author Block: Aileen Marcelo, Michael Kahle, Leon de Hoog, Gregory Bix, Univ of Kentucky, Lexington, KY

Abstract Body:

Stroke remains a major cause of significant morbidity and death with limited therapeutic options. In our attempt to develop novel stroke therapies, we have focused on exploiting the brain’s own neuroreparative potential with a particular focus on perlecan, a prominent proteoglycan in the brain’s extracellular matrix which is processed into the bioactive protein fragment domain V (DV) after stroke. DV is naturally neuroprotective and enhances angiogenesis (a key mechanism of neurorepair). In rodents, functional outcome can be significantly improved by administering DV 24 hours after experimental stroke. More recent studies have shown that DV also increases neurogenesis in vitro. As neurogenesis is another key, but ultimately insufficient (few new neurons survive) component of neurorepair, we studied the potential of delayed DV administration, initiated 7 days (to minimize confounding neuroprotective and angiogenic effects which initiate much sooner after stroke) after stroke, to increase neurogenesis and improve functional outcome in 3 month old C57BL6 male mice. After two doses of DV, mice subjected to transient middle cerebral artery occlusion had significant functional improvement as measured by rotor rod (significantly increased latency before falling off the rotor rod and in distance traveled on the device before falling off, n=6 each for control and DV treated groups per experiment, experiment repeated two separate times, p<0.05) as compared to vehicle treated stroked controls. Brain immunohistochemistry 21 days after stroke demonstrated that DV treated mice had many more cells that were positive for BrdU (a marker of cell division), doublecortin (a marker of immature neurons) and NeuN (another neuronal marker) in the infarct area. These results suggest that delayed DV treatment after experimental stroke increases neurogenesis, increases the number of new neurons that reach stroked brain regions and survive there, and improves functional outcome. Importantly, we are unaware of any other delayed stroke treatment, other than or combined with physical/occupational/speech therapy, that significantly improves functional outcome. Collectively, our data further support the promise of DV as a novel stroke therapy.

Author Disclosure Block:

A. Marcelo: None. M. Kahle: None. L. de Hoog: None. G. Bix: None.
Presentation Number: LB P5

Publishing Title: Stroke and ICH in 21,105 Patients with Atrial Fibrillation Randomized to Edoxaban vs Warfarin in the ENGAGE AF-TIMI 48 Trial

Author Block: Robert P Giugliano, Christian T. Ruff, Eugene Braunwald, Brigham & Women's Hosp, Boston, MA; Natalia Rost, Scott Silverman, Massachusetts General Hosp, Boston, MA; Stephen D. Wiviott, Cheryl Lowe, Naveen Deenadayalu, Sabina A. Murphy, Laura T. Grip, Brigham & Women's Hosp, Boston, MA; Joshua M Betcher, Quintiles, Morrisville, NC; Anil Duggal, Jay Dave, Minggao Shi, Michele Mercuri, Daiichi Sankyo, Edison, NJ; Elliott Antman, Brigham & Women's Hosp, Boston, MA

Abstract Body:

Background: Edoxaban is an investigational, oral, once-daily anticoagulant that specifically and reversibly inhibits factor Xa, has rapid onset, linear pharmacokinetics, and half-life 8-10h. In a phase 2 trial of 1146 patients with atrial fibrillation (AF) followed for 3 mths, bleeding was dose-related and lower with once-daily compared to twice-daily dosing.

Methods: ENGAGE AF-TIMI 48 (NCT00781391) was a randomized, double-blind, double-dummy, non-inferiority trial in 21,105 patients with moderate-to-high risk AF (mean CHADS2 score 2.8, prior stroke/TIA in 28%) comparing warfarin (goal INR 2.0-3.0) to two dose-regimens of edoxaban (high-dose, low-dose) followed for 2.8 years (median). Primary endpoints were: composite of stroke and systemic embolism (efficacy), and major bleeding (safety). Stroke was defined as an abrupt onset of focal neurologic deficit (generally single-artery distribution) due to infarction or bleeding with symptoms lasting >24h or fatal in <24h. Subdural and epidural bleeds were classified as intracranial hemorrhages (ICHs), but not strokes. Independent stroke neurologists unaware of treatment adjudicated all cerebrovascular events.

Results: Both edoxaban doses were non-inferior to warfarin (time-in-therapeutic range 68.4%) in the prevention of stroke or systemic embolism (high-dose edoxaban HR 0.79, low-dose edoxaban HR 1.07), and both edoxaban doses reduced major bleeding (HR 0.80 and 0.47). Edoxaban markedly reduced hemorrhagic stroke, but did not reduce ischemic compared to warfarin (Table). ICH was reduced by 53% and 70%, respectively, for high- and low-dose edoxaban compared to warfarin. Ischemic stroke and TIA were more frequent with low-dose edoxaban.

Conclusion: Once-daily edoxaban significantly reduces hemorrhagic stroke and ICH compared to warfarin in patients with AF. Ischemic stroke and TIA rates were similar with high-dose edoxaban and warfarin, while low-dose edoxaban was less effective than warfarin.
Author Disclosure Block:

R.P. Giugliano: Research Grant; Significant; Daiichi Sankyo Pharma Development, Merck, Johnson & Johnson, Sanofi, AstraZeneca. Honoraria; Modest; Bristol-Myers Squibb, Daiichi Sankyo Pharma Development, Merck, Sanofi. Consultant/Advisory Board; Modest; Daiichi Sankyo Pharma Development, Janssen Pharmaceuticals, Merck. C.T. Ruff: Research Grant; Significant; Daiichi Sankyo Pharma Development. Consultant/Advisory Board; Modest; Daiichi Sankyo Pharma Development, Boehringer Ingelheim, Bristol-Myers Squibb. E. Braunwald: Research Grant; Significant; Daiichi Sankyo Pharma Development, AstraZeneca. Honoraria; Modest; Eli Lilly, Menarini, Medscape, Bayer HealthCare. Consultant/Advisory Board; Modest; Sanofi, Genzyme, Amryocyte, Medicines Company, Cardiorentis. N. Rost: Other Research Support; Modest; Clinical Endpoint Committee. S. Silverman: Other Research Support; Modest; Clinical Endpoint Committee. S.D. Wiviott: Research Grant; Significant; Daiichi Sankyo Pharma Development, AstraZeneca, Bristol-Myers Squibb, Eisai, Arena Pharmaceuticals, Merck, Eli Lilly, Sanofi. Consultant/Advisory Board; Modest; AstraZeneca, Bristol-Myers Squibb, Eisai, Arena Pharmaceuticals, Eli Lilly, Daiichi-Sankyo, Aegerion, AngelMed, Janssen Pharmaceuticals, Xoma, ICON Clinical Research, Boston Clinical Research Institute. C. Lowe: Research Grant; Significant; Daiichi Sankyo Pharma Development. N. Deenadayalu: Research Grant; Significant; Daiichi Sankyo Pharma Development. L.T. Grip: Research Grant; Significant; Daiichi Sankyo Pharma Development. J.M. Betcher: None. A. Duggal: Employment; Significant; Daiichi Sankyo Pharma Development. J. Dave: Employment; Significant; Daiichi Sankyo Pharma Development. M. Shi: Employment; Significant; Daiichi Sankyo Pharma Development. M. Mercuri: Employment; Significant; Daiichi Sankyo Pharma Development. Other; Significant; Pending patent related to the clinical properties of edoxaban. E. Antman: Research Grant; Significant; Daiichi Sankyo Pharma Development.
Presentation Number: LB P6

Publishing Title: Microstructural White Matter Alterations Correlate With Cerebral Amyloid Angiopathy Burden and Cognitive Measures

Author Block: Yael D Reijmer, Panagiotis Fotiadis, Sergi Martinez-Ramirez, Aaron Schultz, Anne K. Reed, Alison M. Ayres, Kristin Schwab, Jonathan Rosand, Anand Viswanathan, Keith A. Johnson, Steven M. Greenberg, Edip Gurol, Massachusetts General Hosp, Boston, MA

Abstract Body:

Objectives: Cerebral amyloid angiopathy (CAA) is an important risk factor for dementia. We examined 1) whether diffusion tensor imaging (DTI) can detect microstructural white matter fiber tract alterations in patients with CAA compared to controls and 2) whether CAA-related white matter alterations are related to vascular amyloid burden and cognitive impairment.

Methods: Twenty-two non-demented patients with probable CAA without intracerebral hemorrhage (ICH) and 11 non-demented control participants underwent multimodal MRI and cognitive testing and 14 patients also had a PiB-PET scan. Whole-brain fiber tract reconstructions were parcellated into tracts projecting onto the frontal, parietal, occipital, and temporal lobes. The mean fractional anisotropy (FA) and mean diffusivity (MD) were averaged across all tracts of each lobe. PiB retention was expressed as the standardized uptake value. Analyses were adjusted for age, sex, education level and secondary for FLAIR white matter hyperintensity (WMH) volume.

Results: Patients with CAA had overall lower white matter FA and higher MD compared to controls (p<0.05). Between-group differences in FA and MD were most pronounced in tracts projecting on the occipital lobe (difference FA:-0.05±0.10, MD: 0.09±0.03 10-3 mm2/s, p<0.005), in line with the known posterior predominance of CAA pathology. Lower occipital-to-global FA ratio in patients was correlated with higher occipital PiB retention (r=-0.618, p<0.032) and with lower scores on executive functioning (r=0.601, p=0.007). These associations remained significant after adjusting for WMH load.

Conclusions: DTI can detect microstructural white matter abnormalities in patients with CAA without ICH. The associations between DTI measures, amyloid load, and cognition strengthen the view that vascular amyloid can contribute to cognitive impairment through microstructural white matter alterations even in patients without ICH.

Author Disclosure Block:

LATE-BREAKING SCIENCE abstracts/studies presented at the INTERNATIONAL STROKE CONFERENCE 2014:
For late-breaking science being presented at ISC 2014, the embargo lifts when the first presentation begins in the scientific session in which the abstract is being presented: either 11 am PT on Wednesday, Feb. 12; 6:15 pm PT on Wednesday, Feb. 12; 1:30 pm PT on Thursday, Feb. 13; or noon PT on Friday, Feb. 14). News media activities promoting late-breaking science are under embargo until the times noted above.

Presentation Number: LB P7

Publishing Title: The Serine Protease Cathepsin G is Detrimental in Low Reperfusion Subset of Ischemic Stroke

Author Block: Peter Y Cai, Saeed Ansari, Univ of Florida Coll of Med, Gainesville, FL; Nauder Faraday, Johns Hopkins Univ Sch of Med, Baltimore, MD; Sylvain Doré, Univ of Florida Coll of Med, Gainesville, FL

Abstract Body:

Introduction: Anti-inflammatory mechanisms are neuroprotective in stroke models and inflammatory markers are important determinants of clinical stroke outcomes. Cathepsin G (CG) is a serine protease that functions in chymotrypsin- and trypsin-like activity, cytokine modification, cell surface receptor regulation at inflammatory sites, and apoptosis.

Hypothesis: We hypothesized that (1) loss of CG expression is beneficial in the setting of both acute and long-term ischemic stroke outcomes and (2) high reperfusion is necessary for the detrimental effects of CG.

Methods: Two murine models were used: (1) transient middle cerebral artery occlusion (tMCAO) for acute outcomes and (2) permanent distal middle cerebral artery occlusion (pdMCAO) for long-term outcomes. Laser Doppler flowmetry was used to measure reperfusion after tMCAO. Neurological deficit, Rotarod, adhesive removal, and grip strength tests were performed. Infarct volume was assessed by Cresyl Violet staining.

Results: CG-/- mice [32.97±6.50%, n=16], compared to wildtype [43.49±7.41%, n=15], had significantly smaller infarct volume 24h after tMCAO (p=0.046). With less than 15% reperfusion, CG-/- mice [34.31±6.91%, n=10] had significantly smaller infarct volume than wildtype [53.60±6.99%, n=7] (p=0.003). With greater than 15% reperfusion, there was no significant difference in infarct volume (p=0.357). Wildtype mice [n=14], compared to CG-/- [n=16], performed worse on Rotarod (p=0.043) and neurological deficit scoring (p=0.040). CG-/- mice [2.81±0.87%, n=6] also showed significantly smaller infarct size than wildtype [5.27±1.12%, n=6] 7 days after pdMCAO (p=0.048).

Conclusions: CG is detrimental in ischemic stroke in two murine models. This study further supports previous evidence that inflammation plays a key role in ischemic stroke, but also suggests that anti-inflammatory stroke treatment modalities may be indicated for a subset of patients, similar to tPA. We propose that future clinical trials and basic science experiments of inflammatory inhibitors in ischemic stroke consider reperfusion as a key determinant of successful therapy.

Author Disclosure Block:

P.Y. Cai: None. S. Ansari: None. N. Faraday: None. S. Doré: None.
Presentation Number: LB P8

Publishing Title: Novel Mechanisms of Ischemic Stroke Injury

Author Block: James A Bibb, The Univ of Texas Southwestern Medical Ctr, Dallas, TX; Charles L Rosen, West Virginia Univ Sch of Med, Morgantown, WV

Abstract Body:

Identification of stroke injury mechanisms is critical to development of treatments that improve recovery. Ischemia triggers excitotoxicity and calpain activation. P35 activates the kinase Cdk5 and is cleaved by calpain. The resulting Cdk5/p25 is neurotoxic and causes neurodegeneration. We hypothesized that Cdk5/p25 is a primary perpetrator of ischemic neuronal death. Methods: For embolic strokes a fibrin clot was used to achieve middle cerebral artery occlusion (2 h) followed by tPA administration in aged rats or Cdk5 conditional knockout (cKO) mice. Volume, histopathology, and biochemical assessment of infarct were conducted. Also mouse brain slices were subjected to oxygen and glucose depravation (OGD). Excitotoxic effects OGD on tissue viability, neurophysiological activity and, neuronal signal transduction were assessed. OGD effects were also assessed in primary striatal neuron cultures. All data is S.E.M. (n<6). Results: MCAO caused an 18-fold increase in striatal p25, 6 h post-reperfusion, with comparable increases in calpain-cleaved fodrin, while phosphorylation of DARPP-32 by Cdk5 decreased 5-fold. In brain slices, OGD caused time-, Ca2+-, and calpain-dependent p25 generation, which was immunostained in OGD-treated striatal neurons. These effects again correlated with calpain-cleaved fodrin, and loss of phospho-DARPP-32. Cdk5 inhibition caused a 96-fold reduction in viability loss in response to 1 h OGD, with 70% of viability retained compared to untreated controls. Cdk5 inhibition also neuroprotected brain slices from OGD excitotoxic effects on dopamine neurotransmission and synaptic excitability. Consistently, Cdk5 cKO reduced striatal infarct size in response to MCAO 2.6-fold compared to wildtype littermates. Conclusions: We have shown Cdk5/p35 modulates NMDA receptors and dopamine neurotransmission. P35 conversion to p25 shifts Cdk5 to neurotoxic substrates, marks ischemic injury, and mediates excitotoxicity. Importantly, Cdk5 inhibition dramatically reduces neuronal death caused by OGD, and Cdk5 cKO profoundly reduces stroke injury. To improve stroke recovery it will be important to develop systemic Cdk5 inhibitors and identify effectors mediating injury.

Author Disclosure Block:

J.A. Bibb: None. C.L. Rosen: None.
Presentation Number: LB P9

Publishing Title: An ABCA1 Ligand Peptide that Stimulates Cellular Cholesterol Efflux with High Efficiency Increases Insulin Sensitivity and Reduces Blood Glucose in Metabolic and Genetic Mouse Models of Obesity and Diabetes

Author Block: John K Bielicki, Lawrence Berkeley Natl Lab, Berkeley, CA; Stefanie Bittner, Juveria Tabassum, GRECC, VA Palo Alto Health Care System, Stanford Univ, Palo Alto, CA; Anouar Hafiane, Jacques Genest, McGill Univ Health Ctr, Montreal, QC, Canada; Salman Azhar, GRECC, VA Palo Alto Health Care System, Stanford Univ, Palo Alto, CA; Jan Johansson, Artery Therapeutics, San Ramon, CA

Abstract Body:

Cholesterol accumulation in cells has been implicated in the development of diabetes, predisposing to atherosclerosis and stroke. Recently we developed a family of novel peptides based on apoE that stimulate cell cholesterol efflux with high potency. Presently we examined whether these peptides improved insulin sensitivity and lowered blood glucose in mouse models of diabetes. Two new peptides were identified from preclinical screens with drastically improved safety margins (NOAEL=500 mg/kg, mice and rats) and greatly reduced TG elevating effects common to other HDL mimetics. These peptides, CS6253 and T6991-2, stimulated ABCA1 cholesterol efflux from macrophages with high efficiency similar to the native apoE CT domain (Km= 0.33±0.14, 0.24±02, 0.21±0.02 μM, respectively). Administration of CS6253 at 30 mg/kg (SC) on alternate days for 6 weeks reduced atherosclerosis by 32% in apoE deficient (apoE-/-) mice fed high-fat, high-cholesterol diet for 14 weeks (15±2 vs. 22±4% plaque lesions, CS6253 vs. control, p<0.01). Low-dose (10 mg/kg) administration (SC, alternate days) of T6991-2 for 6 weeks in chow-fed ob/ob mice showed little effect on steady-state (basal) glucose levels compared to saline controls (126±22 vs. 135±11 mg/dl, respectively); however, the response following glucose challenge (1 g/kg BW) was greatly reduced with peptide vs. controls (1.8±0.5 vs. 2.8±0.4 fold increases in plasma glucose at 60 min, respectively, p<0.01). Treatment of C57BL/6J mice fed high-fat diet with T6991-2 (6 weeks, 30 mg/kg, SC, alternate days) also enhanced insulin sensitivity by 2.2±0.7 fold compared to vehicle controls (55±17 vs. 25±5% reduction in basal glucose levels, respectively, at 15 minutes post insulin, 0.75 Units/kg, p<0.01). The favorable anti-diabetes effects of T6991-2 were not associated with any changes in total body weight in mice. Our data suggest HDL mimetic peptides that efficiently stimulate ABCA1 cholesterol efflux may be useful therapeutically to ameliorate insulin resistance, treat diabetes and promote atherosclerosis regression and plaque stability. These novel observations are of high clinical significance, given that patients with diabetes are at much greater risk of developing cardiovascular disease including stroke.

Author Disclosure Block:

J.K. Bielicki: Research Grant; Modest; Artery Therapeutics. S. Bittner: None. J. Tabassum: None. A. Hafiane: None. J. Genest: None. S. Azhar: Research Grant; Modest; Artery Therapeutics. J. Johansson: Ownership Interest; Significant; Artery Therapeutics.
Presentation Number: LB P11

Publishing Title: Inpatient versus Outpatient Management of TIA or Minor Stroke: Clinical Outcomes

Author Block: John F Rothrock, Ivan Lopez, Peggie Smith, Univ of Nevada Sch of Med, Reno, NV

Abstract Body:

Background Current management of patients with acute transient ischemic attack (TIA) or minor stroke is highly variable. In this study we assessed the short-term clinical outcome associated with inpatient versus outpatient management of such patients.

Methods We evaluated a consecutive series of patients with acute TIA or minor ischemic stroke presenting to a single emergency department (ED) within 6 hours of symptom onset. We excluded stroke patients with an NIH Stroke Scale score >2. Patients with evidence of >69% stenosis involving a presumably symptomatic carotid artery also were excluded from participation, as were patients with evidence of major clinical instability. We randomized all eligible patients to be hospitalized or to be managed on an outpatient basis. All patients underwent brain computerized tomography scanning, magnetic resonance imaging or both. All patients received an antiplatelet agent and a statin. All patients were re-evaluated via direct interview and examination 7-10 days following the index event.

Results The study group included 100 patients, 48 with TIA and 52 with minor stroke. For the TIA patients, the mean ABCD2 scorer was 2.3; 16 (33%) had scores of 6 or 7. Fifty-two patients (24 with TIA; 28 with minor stroke) randomized to hospitalization, and the average length of stay was 2.2 days. Six (21%) of the stroke patients experienced neurologic worsening, and this occurred within 24 hours of admission in all 6. One (4%) of the 24 TIA patients experienced stroke, but that patient's deficit was considered too minor to require interventional treatment. Four (17%) of the hospitalized TIA patients experienced recurrent TIAs. All TIA patients were discharged to home. One (4%) stroke patient was transferred to an inpatient rehabilitation service.

Forty-eight patients (24 with TIA; 24 with minor stroke) randomized to outpatient management. Four (17%) stroke patients exhibited objective evidence of increased neurologic deficit 7-10 days following presentation; none required hospitalization. None of the TIA patients experienced stroke, and 3 (13%) experienced recurrent TIAs.

Conclusion These findings suggest that hospitalization of patients with TIA or minor ischemic stroke does not positively affect short-term clinical outcome.

Author Disclosure Block:

J.F. Rothrock: None. I. Lopez: None. P. Smith: None.
Presentation Number: LB P12

Publishing Title: T1128C NPY Polymorphism is Associated With Dyslipidemia as a Stroke Risk Factor

Author Block: Seyed Navid Yahyazadeh Mashhadi, Mobin Mohaddes Najafi, Science and Res branch, Islamic Azad Univ, Tehran, Iran, Islamic Republic of; Mohammad Mahdi Forghanifard, Dept of Biology, Damghan Branch, Islamic Azad Univ, Damghan, Iran, Islamic Republic of; Ali Masoudi Kazemabad, Science and Res branch, Islamic Azad Univ, Tehran, Iran, Islamic Republic of; Raheleh Dehghan Manshadi, Dept of Biology, Payamenoor Univ, Mashhad, Iran, Mashhad, Iran, Islamic Republic of

Abstract Body:

Objectives
Stroke is a major cause of human morbidity and mortality. Dyslipidemia is an independent predictor of coronary artery disease (CAD) as well as the stroke. The risk of stroke in patients with CAD is more than twice than healthy people. New investigations suggest that neuropeptide Y (NPY) gene may be a main candidate for ischemic stroke. The aim of this study was to investigate the association between T1128C NPY polymorphism and dyslipidemia as a stroke risk factor in CAD patients.

Method
A total of 485 CAD patients were recruited in this study including 380 dyslipidemia and 105 non-dyslipidemia patients. Also we enrolled 327 healthy subjects as control in two dyslipidemia and non-dyslipidemia groups. All DNA samples were extracted using salting out method followed by T1128C polymorphism analysis with PCR-RFLP technique.

Results
The results demonstrated that the prevalence of T1128C polymorphism was higher in dyslipidemia compared to non-dyslipidemia patients. TC genotype (OR: 1.699, 95% CI: 1.124-2.567, P=0.011) and the C allele (OR: 1.254, 95% CI: 1.031-1.524, P=0.023) $\chi^2$ (df =2) =8.11 p= 0.017. There was no significance correlation between T1128C polymorphism and non-dyslipidemia in healthy subjects. $\chi^2$ (df =2) =2.6 p>0.05.

Conclusion
Dyslipidemia promotes stroke in patients with CAD and is distinguished as a related high risk factor. This study indicates that the T1128C NPY polymorphism is significantly correlated with dyslipidemia and therefore can be considered as an independent predictor for stroke in CAD patients.

Author Disclosure Block:

Presentation Number: LB P13

Publishing Title: Health Utility in Patients Receiving OnabotulinumtoxinA (BOTOX®) for the Treatment of Adult Focal Spasticity: Final Results from MOBILITY®, A Prospective Observational Cohort Study

Author Block: Theodore Wein, Montreal Neurological Hosp, Montreal, QC, Canada; Farroq Ismail, West Park Healthcare Ctr, Toronto, ON, Canada; Meetu Bhogal, Grace Trentin, Allergan Inc., Markham, ON, Canada

Abstract Body:

Background: Many studies have shown the clinical benefit of BOTOX® for the treatment of adult focal spasticity (AFS); however few have comprehensively addressed its effect on patient-reported health utility. **Objective:** MOBILITY® is a multi-centre, observational study designed to capture data on the impact of BOTOX® on health utility over time in patients initiating (naïve) or receiving ongoing (maintenance) treatment for one of several approved indications, including AFS. **Methods:** In addition to collecting baseline demographics as well as dosing patterns, the SF-12v2 Health Survey was administered at baseline, week four post-BOTOX® treatment (W4) and up to five subsequent injection visits (SV) thereafter. Physical (PCS) and mental (MCS) component scores were derived from the self-reported SF-12v2 and health utility was measured via the SF-6D. Analysis of final data from the study will compare the change from baseline in SF6D, PCS and MCS scores at week four and all SVs, in stroke patients with AFS. **Results:** An interim analysis was previously conducted based on 333 patients with AFS. The most common etiologies of AFS reported were stroke (62%), multiple sclerosis (MS; 14%) and spinal cord injury (SCI; 13%). Data from the analysis had shown that baseline SF-6D scores were higher in stroke compared to MS and SCI patients. In addition, SF-D scores were lower in BOTOX®-naïve versus maintenance patients. Improvements from baseline in SF-6D scores were seen in both naïve and maintenance patients at subsequent visits 1 and 2. **Conclusion:** Interim data has suggested that improvements in health utility may develop over time with BOTOX® treatment in stroke patients with AFS. Final data presented at the conference will demonstrate whether these early trends were significant and continued over the longer term.

Author Disclosure Block:

**T. Wein:** Consultant/Advisory Board; Modest; Part of the MOBILITY Project Scientific Advisory Committee. **F. Ismail:** Consultant/Advisory Board; Modest; Part of the MOBILITY Project Scientific Advisory Committee. **M. Bhogal:** Employment; Significant; Employee of Allergan Inc. **G. Trentin:** Employment; Significant; Employee of Allergan Inc.
Presentation Number: LB P14

Publishing Title: Ischemic Stroke in Patients with Mechanical Heart Valve off Anticoagulation After Intracranial Hemorrhage

Author Block: Jay Z Yao, Holly Hinson, Helmi Lutsep, Oregon Health and Science Univ, Portland, OR

Abstract Body:

Introduction
The management of anticoagulation in patients with one or more mechanical heart valves who suffer an intracranial hemorrhage poses a difficult dilemma. Thromboembolism and hemorrhage are the most frequent overall complications of mechanical valves. Current guidelines advocate immediate reversal of anticoagulation for life-threatening hemorrhage. However, the duration anticoagulation should be held remains unclear. To date, very few studies have addressed this issue directly.

Methods
We compiled a retrospective cohort of patients admitted to OHSU Medical Center between January 1, 2009 and October 1, 2013. Patients were identified from the electronic medical record by ICD-9 codes for epidural hematoma (EDH), subdural hematoma (SDH), and/or intracerebral hemorrhage (ICH) who also had a mechanical valve in the aortic and/or mitral position. The medical record was reviewed for ischemic strokes as well as additional hemorrhage.

Results
We identified 35 intracranial hemorrhages in 31 unique patients in the setting a mechanical valve. There were 17 cases of ICH, 15 SDH, and three mixed hemorrhages. All but three patients were on anticoagulation at the time of hemorrhage. At presentation, 18 patients were subtherapeutic, five were supratherapeutic. In 29 cases (83%), the patient received reversal of anticoagulation, 15 with factor VII and/or PCC. The average duration off anticoagulation was 9.6 days. During the time off anticoagulation, three cases (9%) suffered new ischemic strokes, totaling five discrete infarcts. Two of the three cases were symptomatic. Eleven cases (31%) had additional hemorrhage, though only one case was symptomatic. There were six deaths.

Conclusion
The present study echoes previous investigations, indicating that the risk of additional hemorrhage outweighs the risk of ischemic stroke in the acute period after intracranial hemorrhage. However, our cohort showed a higher incidence of both ischemic stroke and hemorrhage than previous studies. The cause is unclear. Our study is limited by its retrospective nature. However, holding anticoagulation for a short time, 14 days, might be safe and reasonable.

Author Disclosure Block:

J.Z. Yao: None. H. Hinson: None. H. Lutsep: None.
Presentation Number: LB P15

Publishing Title: Application of MicroRNA in Treating Acute Ischemic Stroke

Author Block: Suh-Hang H. Juo, Yung-Song Wang, Hsin-Yun Cheng, Kaohsiung Medical Univ, Kaohsiung, Taiwan; Yi-Chu Liao, Taichung Veterans General Hosp, Taichung, Taiwan

Abstract Body:

microRNAs are endogenous, non-coding small RNAs with a length of 21-23 nucleotides. A microRNA can use its sequence complementarity to bind to the 3’ untranslated region (UTR) of several messenger RNAs (mRNAs) leading to an inhibition of protein translation or mRNA degradation. We have identified a microRNA (called it microRNA-X for the confidential reason) that is abundant in the brain and it possesses neuroprotective, anti-inflammatory and anti-apoptotic effects while neural cells are damaged. From the cellular and functional studies, microRNA-X can block a Sema protein to bind to its receptor and therefore it decreases Cdc42, FasL, caspase-3, but increases expression of bcl-2. Thus results can reduce the neuron apoptosis when neural cells are damaged. In addition, microRNA-X inhibits the NFkB pathway to reduce inflammatory reaction leading to a decrease of IL-1b, IL-6 and IL-8. Transfection of microRNA-X to neural cells under oxygen-glucose deprivation significantly reduces the neural death. We used middle cerebral artery occlusion (MCAO) to induce stroke in rats and injected microRNA-X encapsulated by a nanoparticles to the tail vein. When microRNA-X was injected in 30 min after the induction of stroke, the infarction volume can be reduced by 40% at 24h; when injected in 3 hours after stroke, the reduction was still by 30% at 24h (Fig). Since microRNA-X can be simply synthesized and since it is an endogenous microRNA, there is no observable side effect from our initial toxicity test. We demonstrate a promising treatment for acute ischemic stroke.

Figure. Representative brain slices. The rats were sacrificed at 24 hours after the treatment. Rt panel: placebo; Lt panel: microRNA-X treatment.

Author Disclosure Block:

Presentation Number: LB P16

Publishing Title: TARGET Intracranial Aneurysm Coiling Prospective Multicenter Study: Initial Periprocedural Results

Author Block: Osama O Zaidat, Alicia C Castonguay, Medical Coll of Wisconsin, Milwaukee, WI; Ajit S Puri, Univ of Massachusetts, Worcester, MA; Ansaar T Rai, West Virginia Univ Hosp, Morgantown, WV; Aamir Badruddin, Provena Saint Joseph Medical Ctr, Joliet, IL; William J Mack, Univ of Southern California, Los Angeles, CA; Amer Alshekhlee, SSM Neuroscience Inst, DePaul, MN; Qaisar A Shah, Abington Memorial Hosp, Abington, PA; Syed I Hussain, Michigan State Univ, East Lansing, MI; Mouhammed R Kabbani, Gundersons Lutheran, La Crosse, WI; Ketan R Bulsara, Yale Univ, New Haven, CT; Muhammad A Taqi, Desert Regional Medical Ctr, Palm Springs, CA; Vallabh Janardhan, Texas Stroke Inst, Plano, TX

Abstract Body:

Background/Purpose: To describe the periprocedural results of the TARGET study, an on-going, prospective, non-randomized, multicenter study of patients with ruptured or unruptured intracranial aneurysms that are embolized with the new generation TARGET Coils.

Methods: Patients with de novo untreated ruptured or unruptured intracranial aneurysms were embolized with either TARGET 360° or Helical coils in 13 US centers. The primary outcome, aneurysm packing density (PD), was assessed at immediate post-procedure. Analysis was by per protocol. The secondary outcomes were modified Rankin's Scale (mRS) at discharge and the influence of use of 100% 360 coils on clinical and angiographic outcomes. Core lab adjudicated angiographic outcomes, and independent medical monitor reviewed all procedural related adverse events. JMP statistical software was used for analysis. Results: 52/53 patients enrolled to date were eligible for this per protocol analysis. 31 patients with unruptured and 21 with recently ruptured aneurysms were treated using TARGET 360° or Helical Coils. Mean age was 58.8±13.3 years; 71.1% female, 76.9% white. Of those treated, 57.7% were embolized with TARGET 360° coils, 9.6% with TARGET Helical Coils, and 32.7% with 360° and Helical Coils. Primary outcome: mean PD of 27.1 ± 18.1%. In a multivariate analysis for predictors of PD and adjusting for maximum aneurysm size, neck size, rupture status, type of coil used, balloon and stent assisted coiling; only maximum aneurysm size (p value 0.007) was associated with PD with a trend for stent assisted coil embolization (0.09). PD was the main predictor of complete occlusion (mean PD 32.6±20.2 in those with complete aneurysm occlusion vs 17.5±7.1 p-value 0.003). No difference was found in those treated with 100% 360 coils vs. mixed coils. In-hospital mortality was 1.9% (1/52), and the predictors of clinical outcome included aneurysm size and rupture status, occlusion rate, PD, and procedural perforation.

Conclusion: In this prospective and core lab adjudicated multicenter Target aneurysm study, the PD was 27.1 ± 18.1% and was the main predictor of aneurysm occlusion. Predictor of poor outcome included aneurysm size and rupture status, occlusion rate, PD, and procedure related perforation.

Author Disclosure Block:

LATE-BREAKING SCIENCE abstracts/studies presented at the INTERNATIONAL STROKE CONFERENCE 2014:
For late-breaking science being presented at ISC 2014, the embargo lifts when the first presentation begins in the scientific session in which the abstract is being presented: either 11 am PT on Wednesday, Feb. 12; 6:15 pm PT on Wednesday, Feb. 12; 1:30 pm PT on Thursday, Feb. 13; or noon PT on Friday, Feb. 14). News media activities promoting late-breaking science are under embargo until the times noted above.

Presentation Number: LB P17

Publishing Title: International Survey of Acute Stroke Imaging Capabilities

Author Block: Max Wintermark, Univ of Virginia, Dept of Radiology, Charlottesville, VA; Marie Luby, Natl Inst of Neurological Disorders and Stroke (NINDS), Natl Insts of Health (NIH), Bethesda, MD; Natan Bornstein, Dept of Neurology, Elias Sourasky Medical Ctr, Sackler Faculty of Med, Tel Aviv, Israel; Andrew Demchuk, Univ of Calgary, Dept of Neurology, Calgary, AB, Canada; Jens Fiehler, Univ Medical Ctr Hamburg-Eppendorf, Hamburg, Germany; Kohsuke Kudo, Dept of Diagnostic Radiology, Hokkaido Univ Hosp, Sapporo, Japan; David Liebeskind, UCLA Stroke Ctr, Los Angeles, CA; Patrik Michel, Ctr Hospier Univire Vaudois (CHUV) and Univ of Lausanne, Lausanne, Switzerland; Raul Nogueira, Emory Univ Sch of Med, Atlanta, GA; Mark W. Parsons, Hunter Medical Res Inst, Univ of Newcastle, Australia, Australia; Makoto Sasaki, Inst for Biomedical Sciences, Iwate Medical Univ, Yahaba, Japan; Joanna M. Wardlaw, Brain Res Imaging Ctr, Div of Neuroimaging Sciences, Ctr for Clinical Brain Sciences, Univ of Edinburgh, Edinburgh, United Kingdom; Ona Wu, Massachusetts General Hosp and Harvard Medical Sch, Boston, MA; Weiwei Zhang, Guangming Zhu, Military General Hosp of Beijing PLA, Beijing, China; Steven J. Warach, Seton/UT Southwestern Clinical Res Inst of Austin, Dept of Neurology and Neurotherapeutics, UT Southwestern Medical Ctr, Austin, TX

Abstract Body:

PURPOSE: To assess the differences across continental regions in terms of stroke imaging workflow and how imaging is used for making acute revascularization therapy decisions.

METHODS: Stroke Imaging Repository (STIR) and Virtual International Stroke Trials Archive (VISTA)-Imaging circulated an online survey through its website, through the websites of national professional societies from multiple countries as well as through email distribution lists from STIR and the above mentioned societies.

RESULTS: We received responses from 223 sites (2 from Africa, 38 from Asia, 9 from Australia, 101 from Europe, 5 from Middle East, 55 from North America, 13 from South America). In combination, the sites surveyed administered acute revascularization therapy to a total of 25,326 acute stroke patients in 2012. Seventy-three percent of these patients received intravenous tPA, and 27%, endovascular treatments. CT is the routine modality for the acute imaging work-up. Seventy-two percent (139/192) of sites are equipped to perform hyperacute MRIs. Vascular imaging is routinely obtained as part of standard IV tPA treatment decisions in 46% (92/198) of sites, and in 79% (152/193) of sites for endovascular recanalization decisions. Perfusion CT imaging is routinely performed as part of standard of care for stroke patients in 30% (66/223) of sites while PWI MR imaging is performed in 17% (37/223) of sites. There were significant differences in terms of stroke imaging work-up amongst the different geographical areas.

CONCLUSION: CT is the mainstay for the imaging work-up of acute stroke patients. The use of multimodal CT and MR imaging varies considerably from site to site and amongst geographical regions. Vascular imaging is routinely obtained and used to make recanalization treatment decisions in a significant proportion of sites, including in the intravenous tPA window.

Author Disclosure Block:

Presentation Number: LB P18

Publishing Title: Long-term Changes of Perivascular Matrix After Juvenile Brain Injury: Possible Relation with Amyloid-beta Accumulation

Author Block: Amandine Jullienne, Loma Linda Univ, Loma Linda, CA; Jill Roberts, Sanders-Brown Ctr on Aging, Univ of Kentucky, Lexington, KY; Viorela Pop, Loma Linda Univ, Loma Linda, CA; M. Paul Murphy, Elizabeth Head, Gregory Bix, Sanders-Brown Ctr on Aging, Univ of Kentucky, Lexington, KY; Jerome Badaut, Loma Linda Univ, Loma Linda, CA

Abstract Body:

Perivascular matrix and angiogenesis are very important during brain disorders like stroke and traumatic brain injury (TBI). TBI is a leading cause of death and disability in pediatric populations. At the cellular level, it induces dysfunction in the neurovascular unit (NVU). Phenotypic transformation of endothelial cells is associated with accumulation of amyloid beta (Aβ) and cognitive dysfunctions 2 months after juvenile TBI (jTBI). Perlecan and fibronectin, two proteins of the basal lamina, have a dual role of promoting Aβ fibrillization that decreases perivascular drainage; and contributing to neuroprotection and angiogenesis by activation of endothelial α5β1 integrin. We investigated whether perlecan and fibronectin expression is changed in association with Aβ in a rat model of juvenile (j) TBI. A controlled cortical impact was given to 17-day-old rats; immunohistochemistry and western blot (WB) were carried out after 2 and 6 months.

Aβ accumulation was increased 6 months after jTBI (0.06±0.02 vs 0.78±0.15 % Aβ load, p<0.05), and paralleled an increase of perlecan (2.41±0.77 and 1.81±0.60 fold, p<0.05) and fibronectin (3.70±0.67 and 2.67±0.27 fold, p<0.05) at 2 and 6 months in the perivascular space. WB showed an increase in the number of low molecular weight bands for fibronectin in jTBI animals, suggesting its degradation. Immunostaining for α5 integrin was observed in neurons and astrocytes in both groups but did not show any changes, however we see morphometric changes of blood vessels with a decrease of its diameter after jTBI. Angiogenesis quantification is in process.

Our results suggest that a juvenile brain injury could accelerate neurodegenerative processes like Aβ deposition, changes that may be associated with long-term cognitive dysfunctions and NVU phenotypic transformation. Furthermore, increases in perlecan and fibronectin staining are observed up to 6 months after jTBI. The role of the long-term changes of these proteins in cognitive impairment associated with brain injury requires further investigation, which can uncover novel molecular pathways suitable as targets of repair and TBI treatment.

Author Disclosure Block:

Presenting Number: LB P19

Publishing Title: Superselective Intra-arterial Administration of Verapamil is Profoundly Neuroprotective in Experimental Ischemic Stroke

Author Block: Michael Maniskas, Jill Roberts, Gregory J Bix, Justin F Fraser, Univ of Kentucky, Lexington, KY

Abstract Body:

While intravenous and intra-arterial thrombolysis are mainstays in ischemic stroke therapy, clinical outcomes lag behind improving rates of revascularization. As such, we explore adjunctive, targeted pharmacotherapy for reducing ischemic injury. Prior neuroprotective studies failed due to long intervals between symptom onset and drug administration, lack of concordant thrombolytic revascularization, and lack of targeted administration to the affected vessel. Despite known neuroprotective properties, verapamil, a calcium channel blocker (CCB) already safely injected intra-arterially (IA) in patients for vasospasm, has never been rigorously studied as a stroke therapy, and is not used as a neuroprotectant. To determine whether verapamil might be an effective stroke therapy when administered in this fashion, we have developed a novel method to mimic the clinical condition of superselective (directly to the stroke-affected cerebral vessel) IA pharmacotherapy administration after vessel recanalization in a rodent model of ischemic stroke (transient middle cerebral artery occlusion, MCAO). Specifically, after 1 hour MCAO and recanalization in three month old male C57/B16 mice, we examined the potential neuroprotective effects of verapamil administered via the external carotid artery (10mg/kg) to the internal carotid artery or intraperitoneal injection (IP, 15mg/kg). On post stroke day three (3), Tetrazolium chloride (TTC) staining of sectioned brains and subsequent infarct volume measurement with NIH Image J software demonstrated a significant reduction in infarct volume with IP verapamil that was even further reduced with IA administration, both as compared to IA or IP saline-injected controls. These results support administration of IA verapamil immediately following acute recanalization of a large vessel occlusion stroke as an effective neuroprotective stroke therapy that could be readily employed in human ischemic stroke patients.

Author Disclosure Block:

M. Maniskas: None. J. Roberts: None. G.J. Bix: None. J.F. Fraser: None.
Presentation Number: LB P20

Publishing Title: Prospective Observational Study of Avoiding Early DNR in Intracerebral Hemorrhage

Author Block: J Claude Hemphill III, Univ of California, San Francisco, San Francisco, CA; Darin B. Zahuranec, Brisa N. Sánchez, Univ of Michigan, Ann Arbor, MI; Kyra J. Becker, Univ of Washington, Seattle, WA; Madeleine C. Geraghty, Providence Sacred Heart Medical Ctr, Spokane, WA; Gregory Norris, Wayne State Univ, Detroit, MI; Lewis B. Morgenstern, Univ of Michigan, Ann Arbor, MI

Abstract Body:

Background and Objective: Prior retrospective studies have found that Do-Not-Resuscitate (DNR) orders within the first day of hospital admission are independently associated with worsened outcome in intracerebral hemorrhage (ICH). We studied whether ICH outcome is better than predicted at centers that avoid early DNR orders.

Methods: We performed a prospective multi-center observational cohort study in ICH patients in whom the initial treatment plan was to avoid the use of DNR orders for the first 5 days after hospital admission. Other aspects of care followed the AHA ICH Guidelines. Eligible subjects included adults (age >18) with a GCS of 12 or less who did not have pre-existing DNR orders. If a patient surrogate initiated a request for DNR orders after enrollment, then this was honored. Elements of the ICH Score were determined. The primary pre-specified outcomes were 30 day mortality and 90 day score on the modified Rankin Scale (mRS). The study tested the hypothesis that the observed mortality at 30 days was lower than predicted from the original ICH Score publication, and that this did not result in an unacceptable rate of patients with 90 day mRS scores of 5. The sample size was calculated a priori.

Results: 109 subjects were enrolled. Mean age was 62 years; median GCS was 7, and mean hematoma volume was 39 cc. Based on benchmarking each patient with their predicted mortality risk from the original ICH Score publication, the expected overall 30 day mortality rate was 50%. Observed mortality was substantially lower at 20%. The absolute average difference was 30% (95% CI: 21%-37%) and each level of the observed ICH Score had lower than predicted mortality (figure). At the time of abstract submission, 90 day outcomes were pending for some patients.

Conclusion: Avoidance of early DNR orders along with guideline concordant ICH care results in substantially lower mortality than predicted. Ninety-day functional outcomes will be available for inclusion in this presentation at ISC 2014.
Author Disclosure Block:

**J.C. Hemphill:** Honoraria; Modest; AAN for speaking on prognostication in neurocritical care, NINDS for serving on ATACH II DSMB. **D.B. Zahuranec:** Research Grant; Significant; NIH Grant K23AG03873; Overall for study: Michigan Institute for Clinical & Health Research grant support(CTSA: UL1RR024986). Honoraria; Modest; AAN for speaking on end-of-life treatment in stroke. **B.N. Sánchez:** None. **K.J. Becker:** None. **M.C. Geraghty:** None. **G. Norris:** None. **L.B. Morgenstern:** None.
LATE-BREAKING SCIENCE abstracts/studies presented at the INTERNATIONAL STROKE CONFERENCE 2014:
For late-breaking science being presented at ISC 2014, the embargo lifts when the first presentation begins in the scientific session in which the abstract is being presented: either 11 am PT on Wednesday, Feb. 12; 6:15 pm PT on Wednesday, Feb. 12; 1:30 pm PT on Thursday, Feb. 13; or noon PT on Friday, Feb. 14). News media activities promoting late-breaking science are under embargo until the times noted above.

Presentation Number: LB P21

Publishing Title: Spontaneous Swallowing Frequency is an Index of Stroke Severity and Dysphagia

Author Block: Giselle D Carnaby, Arnaldo Velez, Ganesh Asaithambi, Anna Khanna, Michael Crary, Univ of Florida, Gainesville, FL

Abstract Body:
Background: Spontaneous swallowing is a protective reflex involved in airway protection. Reductions in spontaneous swallowing have been shown to be associated with stroke and the presence of dysphagia post stroke.
Purpose: This study evaluated the relationship between spontaneous swallowing frequency, stroke severity and stroke lesion characteristics.
Method: In a cohort of 62 acute stroke patients spontaneous swallowing frequency rate was compared to stroke severity, handicap, clinical diagnosis, stroke pathogenesis, and CT /MRI lesion characteristics. Mean differences between patients with and without dysphagia as identified by swallow frequency rate were reviewed.
Results: Lowered spontaneous swallowing frequency was significantly associated with more severe stroke identified by; lower modified Rankin score (t=3.022, P<.004), higher NIHSS score (r=-.362, P<.01); and higher modified Barthel score (r=.421, P<.001). Swallowing frequency was also linearly related to dysphagia severity (r = .52; p< .0001). Moreover, swallowing frequency was significantly lower in cardio-embolic stroke (F (3, 57) = 5.8, P<.002), and those presenting with greater midline shift (t=2.2, P<.02).
Conclusion Spontaneous swallowing frequency is a robust biologic signal that identifies subjects with significant deficit from stroke. This metric may be a sensitive and objective index of stroke severity and dysphagia in stroke populations.

Author Disclosure Block:

Imatinib Reduces Blood-Brain-Barrier Degeneration and Infarct Volume After Ischemic Stroke in a Rat Model

Zamir Merali, Jackie Leung, Andrea Kassner, Univ Of Toronto, Toronto, ON, Canada

BACKGROUND and PURPOSE: Recent studies indicate that the platelet-derived growth factor receptor-alpha inhibitor, Imatinib Mesylate, may attenuate blood brain barrier (BBB) degeneration and neuronal death after an ischemic insult. The therapeutic potential for Imatinib in ischemic stroke, however, has not been fully explored. In this study we hypothesized that Imatinib would have therapeutic benefit after ischemic stroke.

METHODS: Adult male Sprague Dawley rats (n=25) were randomized into treatment and control groups and underwent transient middle cerebral artery occlusion for 1-hour. In the treatment group Imatinib (100mg/kg) was administered 1-hour and 21-hours after reperfusion. BBB integrity was assessed in two ways: in-vivo at 5-hours and 24-hours with dynamic contrast enhanced MRI and model-based permeability analysis, and ex-vivo by quantifying Evans Blue extraversion into CNS tissue. MRI was also used to quantify infarct volume, assess vasculature patency, and assess diffusion characteristics at 5-hours and 24-hours. Western blots and immunohistochemistry were performed on CNS tissue. Neurologic testing was performed to assess functional deficit.

RESULTS: MRI measures indicated that Imatinib treatment reduced BBB permeability at 24-hours (1.22+/-0.07 treatment vs. 1.45+/-0.16 control, p<0.05). This was supported by tissue analysis of Evans Blue Extraversion (p<0.05). Furthermore, Imatinib treatment reduced infarct volume at 24-hours (226mm³ +/- 38.6 treatment vs. 288mm³ +/- 38.6 control, p<0.05), and reduced neurologic deficit (10.5+/-1.34 treatment vs. 9+/-1.23 control, p<0.05). Tissue analysis revealed that rats treated with Imatinib had significantly reduced NF-kB activation, and increased levels of the neuroprotective protein GAD2 (p<0.05). Finally, Imatinib treatment resulted in reduced neutrophil infiltration into the CNS tissue at 24-hours (p<0.05).

CONCLUSIONS: Imatinib is both neuroprotective and BBB stabilizing after ischemic stroke in a rat model. These effects may partially result from an attenuation of the inflammatory response and up-regulation of neuroprotective proteins. In conclusion, Imatinib may be a candidate neuroprotectant worth investigating in further translational studies.

Author Disclosure Block:

Z. Merali: None. J. Leung: None. A. Kassner: None.
Presentation Number: LB P23

Publishing Title: Brain Peptidase Neurolysin as an Endogenous Mechanism for Self-Preservation and Repair After Stroke

Author Block: Naomi J Wangler, Mamoon Rashid, Vardan T Karamyan, Sch of Pharmacy, TTUHSC, Amarillo, TX

Abstract Body:

The aim of this study was to obtain preliminary information on functional significance of endopeptidase neurolysin (Nln) in the brain after ischemia. It is important, in our opinion, to study function of Nln in the post-stroke brain because there is a sustained functional upregulation of Nln in the mouse brain for at least 7 days after stroke, which is not transcriptionally or translationally regulated, but rather depends on translocation of cytosolic Nln to the plasma membrane. In addition, Nln is known to inactivate several neurotoxic and to generate three cerebro-protective/regenerative peptides. To study the functional significance of Nln upregulation in the post-stroke brain we utilized a specific inhibitor of Nln, Agaricoglyceride A, in a mouse MCAO model of stroke. Administration of Agaricoglyceride A to mice 1 h after reperfusion (1 h occlusion) aggravated stroke injury in a dose-dependent manner at 24 h after stroke, providing the first evidence that Nln may have a protective function in the post-stroke brain. To further address our question, we developed an adeno-associated virus serotype 5 vector encoding mouse Nln driven by chicken β-actin promoter (AAV5-CBA-Nln) to overexpress Nln in the mouse brain prior to stroke. Applicability of AAV5-CBA-Nln to transduce functional Nln was confirmed in mouse primary cortical neurons. Four weeks after in vivo transduction using the AAV5-CBA-Nln, or a control AAV5-CBA-eGFP vector (intrastriatal administration; 1.5 x 10^11 genome copies) the mice were subjected to MCAO (1 h occlusion followed by 72 h reperfusion). The results of these experiments revealed that abundance of Nln in the brain protects animals from stroke injury. Based on these preliminary observations and the knowledge about endogenous substrates of Nln, we view this peptidase as one of brain’s self-protective mechanisms directed towards preservation and recovery of brain after stroke.

Author Disclosure Block:

N.J. Wangler: None. M. Rashid: None. V.T. Karamyan: None.
**Presentation Number:** LB P24

**Publishing Title:** The Western States Stroke Consortium Telestroke Study

**Author Block:** Gene Y Sung, Univ of Southern California, Los Angeles, CA; Bart Demaerschalk, Mayo Clinic-Scottsdale, Scottsdale, AZ; Christopher Fanale, Swedish Medical Ctr, Denver, CO; Jennifer Majersik, Univ of Utah, Salt Lake City, UT; Nobl Barazangi, California Pacific Medical Ctr, San Francisco, CA; Matt Grantz, Univ of Utah, Salt Lake City, UT; Dan Capampangan, Mayo Clinic - Scottsdale, Scottsdale, AZ; David Liebeskind, Univ of California-Los Angeles, Los Angeles, CA

**Abstract Body:**

Abstract:

Background: Telemedicine is rapidly expanding in the U.S. and has proven to be useful in the delivery of health care to rural and underserved areas. Though approved for use since 1996, rates of iv-thrombolysis remain low, especially where there is no 24/7 neurological presence to guide diagnosis and treatment. This study of telestroke utilizes four networks within the Western States Stroke Consortium (WSSC), encompassing rural and underserved areas in four states.

Objectives:
The objectives are to determine whether telemedicine consultations for stroke patients will improve care per guidelines compared to stroke patients treated at control hospitals and to determine whether the care provided via telemedicine consultations will be similar to care per guidelines provided to stroke patients treated at hub hospitals.

Design:
Prospective observational study recruiting from four networks with a 500 subject goal. Subjects with stroke onset within 12 hours are consecutively enrolled and followed 90 days. Data entered on-line utilizing a common case report form. Each site will be divided into three cohorts:

- Hub hospitals: JCAHO-certified Primary Stroke Centers providing telemedicine support;
- Spoke hospitals: non-stroke center certified sites, where patients are treated with consultation using telemedicine technology from hub hospital physicians;
- Control hospitals: non-stroke center certified sites with no telemedicine services

Results:
Data from 507 subjects were entered into the secure, on-line database. Initial results revealed that reperfusion therapy with thrombolysis was 20% in the control cohort, 36% in the hub cohort and 53% in the spoke cohort, which was statistically significant. No significant differences were seen in the accuracy of the choice to treat with thrombolysis between the three cohorts.

Discussion:
This study of telestroke across four networks is unique; previously published telestroke studies have been single network data with common technological underpinnings. Telemedicine did improve the rate of acute stroke therapy.

**Author Disclosure Block:**

- **G.Y. Sung:** Research Grant; Significant; National Stroke Association. Other Research Support; Significant; NIH.
- **B. Demaerschalk:** None.
- **C. Fanale:** None.
- **J. Majersik:** None.
- **N. Barazangi:** None.
- **M. Grantz:** None.
- **D. Capampangan:** None.
- **D. Liebeskind:** None.