Late-Breaking Science Oral Abstracts

Wednesday, February 12, 2014, 10:30 am - 12:00 noon

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: LB1

Publishing Title: The Urico-ictus Study: A Randomized Trial of Efficacy and Safety of Uric Acid Administration in Acute Stroke

Author Block: Angel Chamorro, Sergio Amaro, Hosp Clinic Barcelona, Barcelona, Spain; Mar Castellanos, Hosp Josep Trueta, Girona, Spain; Tomás Segura, Hosp de Albacete, Albacete, Spain; Juan Arenillas, Hosp Clínico de Valladolid, Valladolid, Spain; Joan Martí-Fàbregas, Hosp Sant Pau, Barcelona, Spain; Jaime Gállego, Hosp de Navarra, Pamplona, Spain; Jurek Krupinski, Hosp Mutua de Terrassa, Terrassa, Spain; Meritxell Gomis, Hosp Germans Trias i Pujol, Badalona, Spain; David Cànovas, Parc Taulí, Sabadell, Spain; Xavier Carné, Luis San Román, Laura Oleaga, Hosp Clinic Barcelona, Barcelona, Spain; Ferrán Torres, IDIBAPS, Barcelona, Spain; Anna M Planas, Ctr Superior Investigaciones Científicas, Barcelona, Spain; "URICO-ICTUS" Investigators

Abstract Body:

BACKGROUND Uric acid is an endogenous antioxidant molecule that is neuroprotective in experimental brain ischemia. We assessed whether it would improve functional outcome in patients with ischemic stroke.

METHODS The URICO-ICTUS was a double-blind, placebo-controlled trial of acute ischemic stroke patients treated with alteplase within 4.5 hours of symptoms onset in 10 Spanish sites. Patients were randomly assigned to receive in an 1:1 fashion an infusion of placebo or uric acid manufactured according to Good Manufacturing Procedures. The primary end point of the trial was the proportion of patients with a favorable outcome at 90 days, indicating a modified Rankin scale (mRS) of 0 to 1, or a mRS of 2 in patients with a prior qualifying mRS score of 2. Safety end points included death, symptomatic intracranial hemorrhage, and gouty attacks. All randomized patients defined the Intention To Treat population, and those with a correct diagnosis of stroke who had initiated the study medication, defined the modified Intention To Treat population, which was used for the main efficacy analysis. A Data Blind Review was performed before the lock of the database and the opening of randomization codes. Rates and Risk Ratios (RR) were estimated using a log-binomial regression model that included the treatment and the factors used to stratify the assignment (Stroke severity at baseline, and Center). Shift changes on the modified Rankin scale were also performed using a proportional odds model and non-parametric methods.

RESULTS Patients were enrolled into the study from July 1st, 2011, to April 30, 2013. Of 1129 thrombolysed patients screened during the trial, 421 were randomized, and 411 formed the modified Intention To Treat population, including 211 receiving uric acid, and 200 receiving placebo. Sixty patients died, and 7 were lost for follow up. Mean (standard deviation) age was 73.7 (11.8) year, median (interquartil range) admission NIHSS score was 13.00 (9.00, 18.00), and 50 percent were men. The two study groups were well balanced with respect to baseline prognostic variables. Results on the primary outcome, secondary outcomes, and relevant subgroup effects will be presented during the conference.

Author Disclosure Block:
LATE-BREAKING SCIENCE abstracts/studies presented at the INTERNATIONAL STROKE CONFERENCE 2014:
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Presentation Number: LB2

Publishing Title: Impact of Treatment Delay, Age and Stroke Severity on the Effects of Intravenous Thrombolysis With Alteplase in Acute Ischemic Stroke: An Individual-patient-data Meta-analysis

Author Block: Jonathan R Emberson*, Univ of Oxford, United Kingdom; Kennedy R Lees*, Univ of Glasgow, Glasgow, United Kingdom; Patrick Lyden*, Dept of Neurology, Los Angeles, CA; Lisa Blackwell, Univ of Oxford, Oxford, United Kingdom; Gregory W Albers, Stanford Univ, Stanford, CA; Erich Bluhmki, Boehringer Ingelheim, Ingelheim, Germany; Thomas G Brott, Mayo Clinic, Jacksonville, FL; Geoffrey Cohen, Univ of Edinburgh, Edinburgh, United Kingdom; Stephen Davis, Univ of Melbourne, Melbourne, Australia; Geoffrey Donnan, The Florey Inst of Neuroscience and Mental Health, Melbourne, Australia; James Grotta, The Univ of Texas Health Science Ctr at Houston, Houston, TX; George Howard, Univ of Alabama, Birmingham, AL; Markku Kaste, Helsinki Univresity Central Hosp, Helsinki, Finland; Masatoshi Koga, Natl Cerebral and Cardiovascular Ctr, Suita, Japan; Ruediger Von Kummer, Technische Univ, Dresden, Germany; Maarten Lansberg, Stanford Univ, Stanford, CA; Richard Lindley, Univ of Sydney, Sydney, Australia; Gordon Murray, Univ of Edinburgh, Edinburgh, United Kingdom; Jean Marc Olivot, Stanford Stroke Ctr, Stanford, CA; Mark Parsons, Univ of Newcastle, Newcastle, Australia; Barbara Tilley, Univ of Texas Health Science Ctr Sch of Public Health, Houston, TX; Danilo Toni, Sapienza Univ, Rome, Italy; Kazunori Toyoda, Natl Cerebral and Cardiovascular Ctr, Suita, Japan; Nils Wahlgren, Karolinska Inst, Clinical Neuroscience, Stockholm, Sweden; Joanna Wardlaw, William Whiteley, Univ of Edinburgh, Edinburgh, United Kingdom; Gregory J del Zoppo, Univ of Washington, Seattle, WA; Colin Baigent +, Univ of Oxford, Oxford, United Kingdom; Peter Sandercock #, Univ of Edinburgh, Edinburgh, United Kingdom; Werner Hacke #, Univ of Heidelberg, Heidelberg, Germany; for the Stroke Thrombolysis Trialists' Collaboration; *, # Equal contribution; + Corresponding author

Abstract Body:

Background: Intravenous recombinant tissue plasminogen activator (rt-PA) is effective in the treatment of acute ischemic stroke but there remains debate regarding its use at different times since stroke onset, as well as its use in older patients and patients who have had the least or most severe strokes.

Methods: Pre-specified independent individual-patient-data meta-analysis of 6756 patients from 9 randomized trials involving rt-PA versus placebo/open control. The primary outcome was no significant disability at 3-6 months (modified Rankin Score [mRS] 0-1). Secondary outcomes included symptomatic intracranial haemorrhage (sICH) and 90-day mortality.

Results: rt-PA significantly increased the odds of achieving mRS 0-1, including among patients treated within 3-4.5 hours, with earlier treatment associated with greater proportional benefits (delay ≤3 hours: 259 [33%] among rt-PA allocated patients vs 176 [23%] among control allocated patients, OR 1.75 [95% CI 1.35-2.27]; delay 3-4.5 hours: 485 [35%] vs 432 [30%], 1.26 [1.05-1.51]; delay >4.5 hours: 401 [33%] vs 357 [31%], 1.15 [0.95-1.40]). For mRS 0-1, the 95% confidence interval around the time at which there was no benefit had a lower limit of 5.0 hours. Proportional treatment benefits were similar irrespective of age or stroke severity. Despite an early 6-fold increase in sICH, much of which was fatal, there was no significant excess of mortality after 90 days (608 [17.9%] vs 556 [16.5%]; HR 1.11 [0.99-1.25]).

Conclusions: Irrespective of age or stroke severity, and despite the early risk from intracerebral hemorrhage, rt-PA significantly improves the odds of surviving with no significant disability when delivered within 4.5 hours of stroke onset.

Author Disclosure Block:

J.R. Emberson*: None. K.R. Lees*: Consultant/Advisory Board; Modest; DMC Chairman for trials conducted by Boehringer ingelheim, DMC Chairman for trial conducted by Grifols, DMC Chairman for trials conducted by
Lundbeck, DMC member for EU-FP7 Wake-Up trial, Speaker fee for Boehringer Ingelheim, DMC member for REVASCAT. **P. Lyden**: None. **L. Blackwell**: None. **G.W. Albers**: Research Grant; Significant; Lundbeck. Expert Witness; Modest; Expert witness. Ownership Interest; Modest; iSchemaView. Consultant/Advisory Board; Significant; Lundbeck, Covidien, Codman, Genentech. **E. Bluhmki**: Employment; Significant; Boehringer Ingelheim. **T.G. Brott**: None. **G. Cohen**: None. **S. Davis**: Honoraria; Modest; Boehringer Ingelheim, EVER Pharma, Sanofi. Consultant/Advisory Board; Modest; Boehringer Ingelheim, Sanofi. **G. Donnan**: Research Grant; Significant; NHMRC (Australia). Honoraria; Modest; Pfizer, Bristol-Myers Squibb. **J. Grotta**: Consultant/Advisory Board; Modest; Lundbeck. **G. Howard**: None. **M. Kaste**: None. **M. Koga**: None. **R. Von Kummer**: Speakers' Bureau; Modest; Penumbra, Lundbeck. Honoraria; Significant; Penumbra, Lundbeck. **M. Lansberg**: None. **R. Lindley**: Honoraria; Modest; Boehringer Ingelheim. **G. Murray**: None. **J. Olivot**: None. **M. Parsons**: Other; Modest; Travel support from Boehringer Ingelheim. **B. Tilley**: Honoraria; Modest; Pfizer. **D. Toni**: Speakers' Bureau; Modest; Boehringer Ingelheim, Bayer. Consultant/Advisory Board; Significant; Boehringer Ingelheim, Bayer. **K. Toyoda**: Research Grant; Significant; Grant from the Ministry of Health, Labour, and Welfare, JAPAN. Speakers' Bureau; Modest; Mitsubishi Tanabe Pharma. **N. Wahlgren**: None. **J. Wardlaw**: Research Grant; Significant; MRC IST main grant, BI support to UoE for research scanner>10 years ago. **W. Whiteley**: Research Grant; Significant; UK Medical Research Council. **G.J. del Zoppo**: None. **C. Baigent**: None. **P. Sandercock**: Honoraria; Modest; Lecture fees from Boehringer Ingelheim paid to department (2012/13). **W. Hacke**: Research Grant; Significant; Boehringer Ingelheim (Research Grant for study ECASS 4). Speakers' Bureau; Modest; Boehringer Ingelheim. Consultant/Advisory Board; Significant; Boehringer Ingelheim.
Presentation Number: LB3

Publishing Title: Blood Pressure Variability in INTERACT2: An Important Determinant of Outcome Following Acute Intracerebral Haemorrhage

Author Block: Lisa S Manning, Dept of Cardiovascular Sciences and NIHR Biomedical Res Unit in Cardiovascular Disease, Univ of Leicester, Leicester, United Kingdom; Youchiro Hirakawa, Xia Wang, The George Inst for Global Health, Univ of Sydney, Sydney, Australia; Thompson G Robinson, Dept of Cardiovascular Sciences and NIHR Biomedical Res Unit in Cardiovascular Disease, Univ of Leicester, Leicester, United Kingdom; John Chalmers, The George Inst for Global Health, Univ of Sydney, Sydney, Australia; Jiguang Wang, The Shanghai Inst of Hypertension, Rui Jin Hosp., Shanghai Jiaotong University, Shanghai, China; Yining Huang, Dept of Neurology, Peking Univ First Hosp, Beijing, China; Christian Stapf, Dept of Neurology, APHP - Hôpital Lariboisière and DHU NeuroVasc Paris - Sorbonne, Univ Paris Diderot, Paris, France; Mark Woodward, The George Inst for Global Health, Univ of Sydney, Sydney, Australia; Peter Rothwell, Stroke Prevention Res Unit, Univ Dept of Clinical Neurology, John Radcliffe Hosp, Oxford, United Kingdom; Craig S Anderson, Hisatomi Arima, The George Inst for Global Health, Univ of Sydney, Sydney, Australia

Abstract Body:

Objective: Recent evidence suggests that blood pressure variability (BPV), early after stroke, may be associated with worse prognosis, though the data for BPV following intracerebral haemorrhage (ICH) are limited. We examined the association of systolic BP (SBP) variability and maximum SBP on outcome in the INTERACT2 dataset.

Methods: INTERACT2 was an international, multicenter, blinded clinical trial of early rapid BP lowering in 2,839 acute hypertensive (SBP 150-220mmHg) ICH patients. Relationship of SBPV, defined by standard deviation (SD-SBP) of 5 measurements in the hyperacute phase (first 24 hours; n=2645) and 12 measurements in the acute phase (2-7 days; n=2,347), and outcome (death or dependency at 90 days) was determined using logistic regression models.

Results: Significant associations were found for SD-SBP on day 1, expressed as fifths, and poor outcome (OR for highest fifth SD-SBP 1.41, 95%CI 1.05-1.90; p for trend 0.017), and for SD-SBP on days 2-7 and poor outcome (OR for highest fifth SD-SBP 1.57, 95%CI 1.14-2.17; p for trend 0.012). Maximum SBP was also significantly associated with outcome in the hyperacute (P=0.03 for trend) and acute (P=0.02 for trend) phases. Interpretation: BPV in both hyperacute and acute periods after ICH is significantly associated with death or dependency, independent of mean BP. Effective BP lowering therefore involves early targeting and sustained control throughout the first 7 days.

Author Disclosure Block:

Presentation Number: LB4

Publishing Title: Effect of Chronic Blood Pressure Lowering on Cognition in Patients with Recent Lacunar Stroke. The Secondary Prevention of Small Subcortical Strokes (SPS3) Trial

Author Block: Oscar R. Benavente, Univ of British Columbia, Vancouver, BC, Canada; Lesly A. Pearce, Biostatistical Consultant, Minot, ND; Leslie A. McClure, Univ of Alabama at Birmingham, Birmingham, AL; Robert G. Hart, Univ of McMaster, Hamilton, ON, Canada; The SPS3 Investigators

Abstract Body:

Background: Hypertension and lacunar strokes are both associated with cognitive impairment. We aimed to determine if lower vs. higher blood pressure (BP) control and/or dual vs. mono antiplatelet (AP) therapy reduces cognitive decline in patients with recent lacunar stroke.

Methods: SPS3 was a multi-center randomized trial that enrolled MRI proven lacunar stroke patients. Primary endpoint was recurrent stroke; secondary endpoint was cognitive decline as measured by the Cognitive Abilities Screening Instrument (CASI). Patients were randomized in a factorial design to two interventions; a) antiplatelet therapy (aspirin vs. aspirin plus clopidogrel) and b) two targets of systolic blood pressure control (“higher” 130-149 mmHg vs. “lower” <130 mmHg). At study entry and annually thereafter, participants underwent neuropsychological testing by a certified examiner including the CASI and 7 other tests. Scores were normalized using published age, sex, education, and region-adjusted norms. Linear mixed models were fit to determine whether changes over time differed by AP group or BP group. Cognitive testing results after a recurrent stroke were excluded.

Results: After one year, the BP in the higher target group averaged 136 mmHg vs. 125 mmHg in the lower target group. On average, there were 3.3 assessments per patient (SD=1.83), with a range from 1-9. Average change in CASI z-score score from baseline to 1 year was 0.11 (SD=0.84) and from baseline to 3 years was 0.15 (SD=0.97). There were no significant differences in the changes over time by AP group (p=0.95), BP group (p=0.33) or by combinations of AP and BP group (p=0.27). Further, we observed no differences over time by either AP or BP group for any of the other cognitive outcomes.

Conclusion: In this well-characterized cohort of lacunar stroke patients, only modest decline in cognition was observed during a mean follow-up of 3.6 years. Neither aggressive BP lowering nor dual AP impacted the rate of cognitive decline.

Author Disclosure Block:

O.R. Benavente: Research Grant; Significant; NIH-NINDS. L.A. Pearce: Research Grant; Modest; NIH-NINDS. L.A. McClure: Research Grant; Modest; NIH-NINDS. R.G. Hart: Research Grant; Significant; NIH-NINDS.
Presentation Number: LB5

Publishing Title: Genomewide Association Study of Intracranial Aneurysm Identifies a New Association on Chromosome 7

Author Block: Joseph Broderick, Univ of Cincinnati, Cincinnati, OH; Dongbing Lai, Daniel Koller, Indiana Univ, Indianapolis, IN; Femke van't Hof, Univ Medical Ctr Utrecht, Utrecht, Netherlands; Mitja Kurki, NeuroCtr, Kuopio Univ Hosp, Kuopio, Finland; Craig Anderson, The George Inst for Global Health, Sydney, Australia; Robert D Brown, Mayo Clinic, Rochester, MN; E. Sander Connolly, Columbia Univ, New York, NY; Johan G. Eriksson, Univ of Helsinki, Helsinki, Finland; Paul deBakker, Univ Medical Ctr Utrecht, Utrecht, Netherlands; Matthew Flaherty, Univ of Cincinnati, Cincinnati, OH; Myriam Fornage, Univ of Texas Health Science Ctr, Houston, TX; Mikael von und zu Fraunberg, Kuopio Univ Hosp, Kuopio, Finland; Emilia I Gaal, Univ of Helsinki, Helsinki, Finland; Juha Hernesniemi, Helsinki Univ Central Hosp, Helsinki, Finland; John Huston, Mayo Clinic, Rochester, MN; Juha E Jaaskelainen, Riku Kivisaari, Helsinki Univ Central Hosp, Helsinki, Finland; Dawn Kleindorfer, Univ of Cincinnati, Cincinnati, OH; Charles Moomaw, Univ of Cincinnati, Cincinnati, OH; Thomas H Mosley, Univ of Mississippi, Jackson, MS; Mike Niemela, Helsinki Univ Central Hosp, Helsinki, Finland; Aarno Palotie, Univ of Helsinki, Helsinki, Finland; Joanna Pera, Jagiellonian Univ, Krakow, Poland; Stephan Ripke, Broad Inst, Boston, MA; Guy Rouleau, Montreal Neurologic Inst, Montreal, QC, Canada; Laura Sauerbeck, Univ of Cincinnati, Cincinnati, OH; Agnieszka Slowik, Jagiellonian Univ, Krakow, Poland; Daniel Woo, Univ of Cincinnati, Cincinnati, OH; Bradford B Worrall, Univ of Virginia, Charlottesville, VA; Tatiana Foroud, Indiana Univ, Indianapolis, IN; For the FIA Investigators

Abstract Body:

Objective: Intracranial aneurysm (IA) has a clear genetic contribution. Genomewide association studies have been performed to identify common variants contributing to IA susceptibility. Methods: We performed a genomewide association analysis in a Discovery Sample of Caucasian ancestry (2,644 IA cases; 2,548 controls). A case control analysis was performed and chromosomal regions with genomewide significance were identified. Two independent Replication Samples, one Dutch (717 cases; 3,004 controls) and the other Finnish (799 cases; 2,314 controls) were tested for association in the novel region that had been identified. Meta-analysis was performed combining results from the 3 studies in the key chromosomal region of interest. Results: Genomewide evidence of association was detected in the Discovery Sample on chromosome 9 in the gene CDKN2BAS (rs10733376; p< 1.0 x 10-11) which was reported previously to be associated with IA. A region on chromosome 7 not previously associated with IA was also detected (rs10230207; p= 6 x 10-8). This association was replicated in the Dutch sample (p=0.01) but was not replicated in the Finnish sample (p=.25). We speculate that the lack of association in the Finnish sample is due to their unique origins and genetic architecture. Meta-analysis of the three samples was also significant (p=8.5 x 10-9). Interpretation: We detected a novel region associated with IA susceptibility that was replicated in an independent Dutch sample. This region on chromosome 7 has been previously associated with ischemic stroke and large vessel stroke (including HDAC9) - suggesting a possible genetic link between this stroke subtype and IA.

Author Disclosure Block:

J. Broderick: Other Research Support; Modest; Novo Nordisk. Consultant/Advisory Board; Modest; Pfizer, Inc., D. Lai: None. D. Koller: None. F. van't Hof: None. M. Kurki: None. C. Anderson: None. R.D. Brown: None.
Presentation Number: LB6

Publishing Title: Safety Endpoints and Thromboembolic Events for the First 250 Patients Enrolled in the Clot Lysis: Evaluation of Accelerated Resolution of Intraventricular Hemorrhage Trial (CLEAR III)

Author Block: Wendy Ziai, Nichol McBee, Johns Hopkins Univ SOM, Baltimore, MD; Ken Butcher, Univ of Alberta, Edmonton, AB, Canada; Francois Aldrich, Univ of Maryland, Baltimore, MD; Jack Jallo, Thomas Jefferson Univ, Philadelphia, PA; Noeleen Ostapkovich, Johns Hopkins Univ SOM, Baltimore, MD; Charlene Aldrich, Univ of Maryland, Baltimore, MD; Ryan Snider, Stanford Univ, Stanford, CA; Carlos Kase, Boston Univ, Boston, MA; Ricardo Carhuapoma, Karen Lane, Johns Hopkins Univ SOM, Baltimore, MD; Issam Awad, Univ of Chicago, Chicago, IL; Daniel F. Hanley, Johns Hopkins Univ SOM, Baltimore, MD

Abstract Body:

Objective: The CLEAR III trial is a Phase III, randomized controlled trial comparing external ventricular drainage and either rt-PA or placebo in the management of subjects with small intracerebral hemorrhage (<30 cc) and large intraventricular hemorrhage (IVH) (blood obstruction of the 3rd or 4th ventricles). We report safety endpoints and use of heparin for the first 250 subjects.

Methods: We monitored pre-specified safety endpoint thresholds: symptomatic hemorrhage (i.e., hemorrhage extension, new hemorrhage, catheter tract hemorrhage) within 72 hours of study agent (35%) with daily CT scans; brain infections within 30 days of randomization (15%) with daily CSF cultures days 1-7; and 30-day mortality (30%) using systematic reporting of patient progress through day 30.

Results: Enrollment occurred over 34.63 months at 61 sites. Adjudicated safety events totaled three (1.2%) symptomatic hemorrhages within 72 hours of study agent, five (2.0%) cases of bacterial ventriculitis, 13 (5.2%) non-bacterial ventriculitis and 31 (12.4%) deaths at 30 days. At 30 days, brain hemorrhage had occurred in 48 subjects (19.2%)—6 (2.4%) were symptomatic; 42 (16.8%) were asymptomatic. Of the 48, there were 39 catheter tract, five ventricular, two parenchymal, and two subarachnoid hemorrhages. Of 35 intracranial hemorrhages within 72 hours post study agent, 23 (65.7%) occurred in the setting of prophylactic heparin; only one was symptomatic. There were 37 (14.8%) patients with DVT and eight (3.2%) with PE; in 16 patients (43.2%) prophylactic heparin had been started within an average of 231.04 hours of diagnosis. Of 213 patients without DVT, 151 (70.9%) received heparin; 62 (29.1%) did not. Additionally, there were 259 SAEs of which site investigators assessed 19 (7.3%) as possibly related to study agent. There were 13 ischemic strokes. Ventriculoperitoneal shunts were placed in 53 patients (21.2%).

Conclusion: None of the pre-specified safety thresholds have been crossed for the first 250 subjects. All three safety endpoints are lower than expected for patients with severe IVH and indicate that the study protocol is safe. The use of prophylactic heparin during and immediately post dosing may be associated with a higher risk of intracranial bleeding.

Author Disclosure Block:

Presentation Number: LB7

Publishing Title: Clopidogrel With Aspirin in Acute Minor Stroke or Transient Ischemic Attack and Intracranial Artery Stenosis: Subgroup-analysis of Chance

Author Block: Liping Liu, Yilong Wang, Xingquan Zhao, Beijing Tiantan Hosp, Beijing, China; David Wang, Illinois Neurological Inst Stroke Network, Sisters of the Third Order of St., Peoria, IL; Chunxue Wang, Xia Meng, Jing Jing, Hao Li, An-xin Wang, Xinying Zou, Beijing Tiantan Hosp, Beijing, China; S. Claiborne Johnston, Depts of Neurology and Epidemiology, Univ of California, San Francisco, CA; KS Lawrence Wong, Prince of Wales Hosp, Chinese Univ of Hong Kong, Hongkong, China; Yongjun Wang, Beijing Tiantan Hosp, Beijing, China

Abstract Body:

Background: In Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events (CHANCE) trial, clopidogrel plus aspirin reduced the risk of recurrent stroke for those Chinese patients with acute minor stroke or TIA at high risk for recurrence, we aim to investigate whether the efficacy and safety of clopidogrel plus aspirin is consistent among the subgroups of patients with and without intracranial artery stenosis (ICAS).

Methods: In this substudy we assessed the interaction of the treatment effects of clopidogrel plus aspirin among patients with and without ICAS which evaluated by 3D-TOF MRA. Efficacy analyses were by intention to treat and safety analyses were done in the on treatment population.

Results: 5170 patients were enrolled in CHANCE trial. Of those, 1089 subjects in 45 centers participated in imaging sub-analysis. 608(55.83%) patients with ICAS and 481(44.17%) without. patients with ICAS had higher rate of recurrent (12.47% vs 5.43%, P<0.0001) and poor outcome (mRS 0-2) (89.1% vs 97.02%, P<0.0001) at 90 days than the group without ICAS. The number of events for the primary endpoint in patient treated with combination compared with aspirin only was consistant among patients with ICAS ( 11.26% dual vs 13.60% aspirin; hazard ratio [HR] 0.79 , 95% CI 0.47- 1.32) and those without ICAS ( 5.33% dual vs 5.52% aspirin;HR1.12, 95% CI 0.56- 2.25; interaction p=0.5224). The number of any clinically relevant bleeding events in patients treated with dual compared with aspirin only was consistent among patients with ICAS ( 3.03 % dual vs 0.80% aspirin; HR 2.83, 95% CI 0.57- 14.11) and those without ( 5.33% dual vs 5.52% aspirin; HR 1.02, 95% CI 0.35- 2.97; interaction p=0.2769).

Conclusions: These evidence indicate the higher rate of recurrent stroke in minor stroke or high risk TIA patients who had intracranial artery stenosis, but no significant difference in the response to the dual anti-platelet treatment compare with aspirin only between patients who had ICAS and those without. Further analysis should be done to classify the mechanisms and efficacy of different treatments.

Author Disclosure Block:

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Presentation Number: LB8

Publishing Title: Dabigatran Provides Marked Protection from Hypertension-Carotid Artery Stenosis-Induced Vascular Cognitive Impairment

Author Block: Frank C Barone, Jie Li, Daniel M Rosenbaum, SUNY Downstate Medical CTR, Brooklyn, NY

Abstract Body:
Thrombin is involved in cerebrovascular inflammation and coagulation. Hypertension increases coagulation, vascular inflammation and cerebral injury. Vascular Cognitive Impairment (VCI) in rats occurs due to hypertension plus forebrain hypoperfusion. This “mixed-risk” model induces behavioral and forebrain pathology that mimics clinical VCI. We hypothesized that thrombin inhibition reduces VCI evolution in this model. Hypertensive rats (SHR) received bilateral carotid stenosis-reduced forebrain perfusion to produce VCI. VCI SHR were maintained on a control chow (VCI-Control) or a chow containing Dabigatran (VCI-Dabigatran). Clinically relevant Dabigatran levels and anticoagulant activity have been achieved using this chow. Sham stenosis of SHR maintained on control chow (Sham-VCI) was used for comparison. Animals were tested weekly for sensory motor-deficits using the modified Neurological Severity Score (mNSS) and Foot-Fault Test (FFT). Cognition Errors made in Active Place Avoidance (APA) were measured over 6 weeks. Baseline deficits were negligible and normal learning curves were achieved in all groups. Sham-VCI did not change from baseline. As expected, VCI-Control exhibited moderate sensory-motor and increasing cognitive deficits over 6 weeks. However, VCI-Dabigatran exhibited behaviors similar to Sham-VCI. The table lists results for all measures in the 3 groups at week 6 (** = p < 0.01). In summary, Dabigatran provides a dramatic protection from VCI in this translation-relevant mixed risk model. Although work is required to understand Dabigatran protective mechanisms, this model produces significant microvascular inflammation and forebrain fiber system injury responsible for cognitive loss. Additional work is required to further understand if atrial fibrillation with increased incidence of dementia observed in stroke and VCI evolution in high VCI risk patients might benefit from direct inhibition of thrombin using Dabigatran.

<table>
<thead>
<tr>
<th>Group (N)</th>
<th>mNSS</th>
<th>FFT</th>
<th>APA Errors</th>
</tr>
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<tr>
<td>Sham – VCI (5)</td>
<td>0.0 + 0.9**</td>
<td>0.2 + 0.2**</td>
<td>1.5 + 0.7**</td>
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<td>VCI – Dabigatran (7)</td>
<td>0.6 + 0.3**</td>
<td>2.5 + 0.5**</td>
<td>3.3 + 1.0**</td>
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<tr>
<td>VCI – Control (7)</td>
<td>2.9 + 0.8</td>
<td>6.3 + 1.0</td>
<td>35.9 + 3.9</td>
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Author Disclosure Block:
F.C. Barone: None. J. Li: None. D.M. Rosenbaum: None.
Presentation Number: LB9

Publishing Title: Intravenous Thrombolysis or Endovascular Therapy for Acute Ischemic Stroke Associated With Cervical Internal Carotid Artery Occlusion: The ICARO-3 Study

Author Block: Maurizio Paciaroni, Stroke Unit, Perugia, Italy; The ICARO Investigators

Abstract Body:

**Background and Purpose:** The benefit from intravenous (IV) thrombolysis in patients with acute ischemic stroke (AIS) attributable to the occlusion of extracranial internal carotid artery (ICA) remains unclear. The aim of the ICARO-3 study was to evaluate whether intra-arterial (IA) treatment, compared to IV thrombolysis, increases the rate of favourable functional outcome at three-months in AIS and extracranial ICA occlusion.

**Methods:** ICARO-3 was a prospective, case-control multicenter study. Patients treated with endovascular treatment within 6 hours from stroke onset (cases) were compared to matched patients treated with IV thrombolysis within 4.5 hours from symptom onset (controls). The efficacy outcome was disability at 90 days assessed by the modified Rankin Scale (mRS), dichotomized as favourable (score of 0-2) or unfavourable (score of 3-6). Safety outcomes were death and any intracranial bleeding.

**Results:** Included in the analysis were 324 cases and 324 controls: 105 cases (32.4%) had a favourable outcome as compared with 89 controls (27.4%) (adjusted odds ratio (OR), 1.25; 95% confidence interval [CI], 0.88-1.79; p=0.1). A total of 132 patients died: 57 cases (17.6%) and 75 controls (23.1%) (adjusted OR, 0.61; 95% CI, 0.40 -0.93; p=0.022). The rates of patients with severe disability or death (mRS 5-6) were similar in cases and controls (30.5% vs. 32.4%, p=0.67). An ordinal analysis showed a non-significant shift in mRS scores: common OR 1.15 (95% IC 0.86-1.54, p=0.33). There were more cases of intracranial bleeding (37.0% versus 17.3%; p=0.0001) in the IA procedure group than in the intravenous group.

**Conclusions:** Endovascular treatment of patients with acute ICA occlusion resulted in a non-significant improvement of efficacy and in a higher rate of intracranial bleeding. Overall mortality was significantly reduced in patients treated with endovascular treatment but the rates of patients with severe disability or death were similar.

Author Disclosure Block:

M. Paciaroni: None.
Presentation Number: LB10

Publishing Title: Transcranial Doppler is Superior to Echocardiography for Detection of Patent Foramen Ovale

Author Block: Joshua Tobe, Schulich Sch of Med & Dentistry, Western Univ, London, ON, Canada; Chrysi Bogiatzi, Claudio Munoz, Robarts Res Inst, Western Univ, London, ON, Canada; Arturo Tamayo, Brandon Health Sciences Ctr, Brandon, MB, Canada; J David Spence, Robarts Res Inst, Western Univ, London, ON, Canada

Abstract Body:

Background and purpose: Paradoxical embolism through a right-left shunt (RLS) such as a patent foramen ovale (PFO) accounts for ~ 5.5% of ischemic strokes. It has traditionally been diagnosed by echocardiography, but several reports suggest that transcranial Doppler saline studies (TCDSS) may be more sensitive. One reason is that sedation for trans-esophageal echocardiography may prevent an adequate Valsalva maneuver. Methods: We studied prospectively the frequency of detection of a RLS by echocardiography among patients with cryptogenic stroke suspected of paradoxical embolism, in whom a TCDSS detected a RLS. Results: Data were available in 340 patients, 61.5% female, mean (SD) age 53 (14) years, with a mean (SD) followup of 35 (27) months. Echocardiography failed to show a RLS in 43 (15.4%) of the patients; surprisingly, this occurred even in some patients with high-grade shunts (Spencer grade) on TCD. Among patients with a negative echo, 45.5% were grade 1, 32.2% grade 2, 13.3% grade 3, 7.1% grade 4 and 4.7% grade 5. Kaplan-Meier survival free of stroke or TIA was predicted significantly by TCDSS grade 3 or more (p=0.028), but not by RLS on echo (p=0.42). (Figures). Conclusion: TCD saline studies are superior to echocardiography in the diagnosis of PFO.
Author Disclosure Block:

J. Tobe: None. C. Bogiatzi: None. C. Munoz: None. A. Tamayo: None. J. Spence: None.
Presentation Number: LB11

Publishing Title: Cryptogenic Stroke and Underlying Atrial Fibrillation (CRYSTAL AF)

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Abstract Body:

Introduction:
Up to 30% of ischemic strokes have no identifiable cause despite extensive evaluation and are termed cryptogenic strokes (CS). Atrial fibrillation (AF) can be intermittent and asymptomatic and therefore may elude detection by routine evaluation after CS. Finding AF after CS prompts a change from anti-platelet therapy to oral anticoagulation (OAC). However, the optimal strategy for identifying intermittent AF after CS is unknown. We compared standard cardiac monitoring (Control) to the use of an insertable cardiac monitor (ICM) for detecting AF after CS. We hypothesized that more AF would be detected by ICM than Control.

Methods:
We randomized patients (pts) to ICM (Reveal® XT) or Control within 90 days of CS. The primary endpoint was AF detection (> 30 seconds) within 6 months of randomization as adjudicated by an independent committee. The secondary endpoint was AF detection by 12 months. All pts had vascular imaging, transesophageal echocardiography, and ≥24 hours of continuous cardiac monitoring. No pts were prescribed long term OAC prior to enrollment. Analysis was by intention to treat.

Results:
A total of 221 pts were randomized to ICM insertion and 220 to Control (mean age 61.5±11.3 years, 63% male). No relevant imbalances in race, geography, stroke risk factors, or virtual CHADS2 score were observed between arms. Pts were randomized a median of 32 (IQR 14-57) days after the index CS. The primary endpoint was reached in 8.9% of pts in the ICM arm compared to 1.4% of the Control arm [HR 6.4 (95% CI 1.9-21.7); p=0.0006]. At 12 months, AF was detected in 12.4% of pts in the ICM arm and 2.0% of the Control arm [HR 7.3 (95% CI 2.6-20.8, p<0.0001)]. By 36 months, AF was detected in 30.0% of pts in the ICM arm compared to 3.0% of the Control arm [HR 8.8 (95% CI 3.5-22.2, p<0.0001). Five device removals (2.2%) due to infection or pocket erosion occurred over 36 months. By 12 months, 97% of pts with AF detected were prescribed OAC.

Conclusion:
Continuous cardiac monitoring using an ICM was superior to standard cardiac monitoring for detecting AF after CS. Detection of AF changed clinical management in almost every case. Use of an ICM should therefore be considered in the evaluation of pts with CS.

Author Disclosure Block:

R.A. Bernstein: Speakers' Bureau; Significant; Medtronic, Inc. Consultant/Advisory Board; Significant; Medtronic, Inc. V. Di Lazzaro: Research Grant; Modest; Medtronic, Inc. M.M. Rymer: Consultant/Advisory Board; Modest; Medtronic, Inc. H. Diener: Honoraria; Significant; Medtronic, Inc. T. Sanna: Speakers' Bureau; Modest; Medtronic, Inc..
J. Brachmann: Research Grant; Significant; Medtronic, Inc.. Honoraria; Significant; Medtronic, Inc.. Consultant/Advisory Board; Significant; Medtronic, Inc.

R.S. Passman: Research Grant; Significant; Medtronic, Inc.. Speakers' Bureau; Significant; Medtronic, Inc.. Consultant/Advisory Board; Significant; Medtronic, Inc.

C. Morillo: Consultant/Advisory Board; Significant; Medtronic, Inc.

V.N. Thijs: Speakers' Bureau; Modest; Medtronic, Inc.. Other; Modest; Medtronic.

T.B. Rogers: Employment; Significant; Medtronic, Inc.

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K. Lindborg: Employment; Significant; Medtronic, Inc.
Presentation Number: LB12

Publishing Title: Improving Door-to-Needle Times in Acute Ischemic Stroke: Principal Results from the Target: Stroke Initiative

Author Block: Gregg C Fonarow, UCLA Medical Ctr, Los Angeles, CA; Xin Zhao, Duke Clinical Res Inst, Durham, NC; Eric E. Smith, Univ of Calgary, Calgary, AB, Canada; Jeffrey L. Saver, UCLA Neurology, Los Angeles, CA; Mathew J. Reeves, Michigan State Univ, East Lansing, MI; Deepak L. Bhatt, Brigham and Women's Hosp, Boston, MA; Ying Xian, Adrian Hernandez, Eric D. Peterson, Duke Clinical Res Inst, Durham, NC; Lee H. Swhwamm, Massachusetts General Hosp, Boston, MA

Abstract Body:

Background: The benefits of intravenous tPA in acute ischemic stroke are time-dependent and guidelines recommend a door-to-needle (DTN) time of ≤60 minutes, yet prior studies suggested fewer than 30% of patients in the US were meeting this goal. To address this shortfall, Target: Stroke, a national initiative organized by the AHA/ASA, was launched in 2010 to assist hospitals in increasing the proportion of patients with DTN times ≤60 minutes (initial goal of ≥ 50%).

Methods: Target: Stroke identified and disseminated 10 key best practice strategies associated with achieving faster DTN times, provided clinical decision support tools, and facilitated hospital participation, implementation of effective strategies, and sharing of best practices. Annual rates of DTN times ≤60 minutes and outcomes pre-TS 2003-2009 were compared to post-TS 2010-Sept 2013, including after adjustment for patient and hospital characteristics.

Results: There were 70,046 tPA treated patients (27,303 pre-TS; 42,743 post-TS) from 1029 GWTG-Stroke hospitals. Patient characteristics were similar in the pre- and post-TS periods. Median DTN time declined from 77 minutes pre-TS to 67 minutes post-TS (P<0.0001), with the % of patients with DTN times ≤60 minutes increasing from 29.6% immediately prior to the start of TS (Q4 2009) to 54.2% in Q3 2013. The annual rate of increase in patients with DTN times ≤60 minutes was 6.24% per year post-TS vs. 1.32% per year pre-TS (P<0.0001). Piecewise multivariable GEE analysis confirmed accelerated improvement post-TS independent of patient/hospital characteristics (P<0.0001). Clinical outcomes improved significantly in the post-TS period (Table).

Conclusions: The timeliness of tPA administration improved substantially in GWTG-Stroke hospitals after initiation of the AHA/ASA Target: Stroke quality initiative. This improvement was accompanied by lower in-hospital mortality and tPA complications.
Figure: Time Trend in DTN Times within 60 Minutes Pre- and Post-Target: Stroke

Table: Clinical Outcomes Pre- and Post-Target Stroke Implementation

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pre-Target Stroke (n=27,303)</th>
<th>Post-Target Stroke (n=42,743)</th>
<th>P value</th>
<th>Adjusted Hazard Ratios (95% CI)*</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-Hospital Mortality</td>
<td>9.93%</td>
<td>8.25%</td>
<td>&lt;0.0001</td>
<td>0.89 (0.83-0.95)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Discharge Home</td>
<td>37.7%</td>
<td>42.6%</td>
<td>&lt;0.0001</td>
<td>1.13 (1.08-1.19)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ambulatory Status</td>
<td>42.2%</td>
<td>45.3%</td>
<td>&lt;0.0001</td>
<td>1.03 (0.97-1.09)</td>
<td>0.3957</td>
</tr>
<tr>
<td>Symptomatic ICH</td>
<td>5.68%</td>
<td>4.70%</td>
<td>&lt;0.0001</td>
<td>0.84 (0.77-0.91)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>tPA Complications</td>
<td>6.68%</td>
<td>5.51%</td>
<td>&lt;0.0001</td>
<td>0.83 (0.77-0.90)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*adjusted for patient characteristics, including stroke severity (NIHSS), and hospital characteristics

Author Disclosure Block:

**G.C. Fonarow:** Employment; Significant; Dr. Fonarow is an employee of the University of California, which holds a patent on retriever devices for stroke. **X. Zhao:** Other; Modest; Dr. Zhao is a member of the Duke Clinical Research Institute which serves as the American Heart Association GWTG data coordinating center. **E.E. Smith:** None. **J.L. Saver:** Employment; Significant; Dr. Saver is an employee of the University of California, which holds a patent on retriever devices for stroke. Consultant/Advisory Board; Modest; CoAxia, Covidien, Grifols, Cygnis. **M.J. Reeves:** None. **D.L. Bhatt:** Research Grant; Modest; Amarin, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Medtronic, Sanofi Aventis, The Medicines Company. Other Research Support; Modest; FlowCo, PLx Pharma, Takeda. Honoraria; Modest; American College of Cardiology (Editor, Clinical Trials, Cardiosource), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), Population Health Research Institute (clinical trial steering committee), Slack Publications (Chief Medical Editor, Cardiology Today’s Intervention), WebMD (CME Steering committees). Consultant/Advisory Board; Modest; Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences, Board of Directors for Boston VA Research Institute, BOD, Society of Cardiovascular Patient Care, Chair, AHA GWTG Steering Committee. Other; Modest; Senior Associate Editor, Journal of Invasive Cardiology, Data Monitoring Committees, Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, Population Health Research Institute. **Y. Xian:** Other; Modest; Dr. Xian is a member of the Duke Clinical Research Institute which serves as the American Heart Association Get with the Guidelines data coordinating center. **A. Hernandez:** Research Grant; Modest; BMS, Janssen, Medtronic, Merck, Portola. Honoraria; Modest; Boston Scientific, BMS, Gilead, Janssen, Novartis. **E.D. Peterson:** Research Grant; Modest; American College of Cardiology, American Heart Association, Society of Thoracic Surgeons, Eli Lilly & Company, Janssen Pharmaceutical Products. Consultant/Advisory Board; Modest; Boehringer Ingelheim, Genetech, Eli Lilly & Company, Janssen Pharmaceutical Products, Merck & Co., Sanofi-Aventis. **L.H. Swhwammm:** Research Grant; Modest; NINDS, Genetech. Consultant/Advisory Board; Modest; Massachusetts Department of Public Health, The Joint Commission, Chair, GWTG Stroke Clinical Workgroup.