Late-Breaking Science Oral Abstracts

Thursday, February 18, 2016, 10:30am – 12:00 noon

LATE-BREAKING SCIENCE abstracts/studies presented at the INTERNATIONAL STROKE CONFERENCE 2016:

For late-breaking science being presented at ISC 2016, the embargo lifts when the first presentation begins in the scientific session in which the abstract is being presented: either 11:20 am PST on Wednesday, Feb. 17; 3:30 pm PST on Wednesday, Feb. 17; 6:15 pm PST on Wednesday, Feb. 17; 11:00 am PST on Thursday, Feb. 18; 1:30 pm PST on Thursday, Feb. 18; or 11:53 am PST on Friday, Feb. 19. News media activities promoting late-breaking science are under embargo until the times noted above.

Presentation Number: LB10

Publishing Title: Carotid Endarterectomy versus Stenting for Treatment of Carotid Artery Stenosis: Long-term Results of the Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST)

Author Block: Thomas G Brott, Mayo Clinic Jacksonville, Jacksonville, FL; George Howard, Univ of Alabama at Birmingham, Birmingham, AL; Gary S Roubin, Cardiovascular Associates of the Southeast, Birmingham, AL; Ariane Mackey, Hôpital de l'Enfant-Jésus, Quebec, QC, Canada; William Brooks, Baptist Health Lexington, Lexington, KY; Michael D Hill, Univ of Calgary, Cumming Sch of Med Foothills Hosp, Calgary, AB, Canada; Vito A Mantese, St. John's Mercy, St Louis, MO; Wayne M Clark, Oregon Health & Science Univ, Portland, OR; Carlos Timaran, Univ of Texas Southwestern, Dallas, TX; Donald Heck, Novant Health Clinical Res, Winston-Salem, NC; Pierre P Leimgruber, Providence Sacred Heart Medical Ctr and Children's Hosp, Spokane, WA; Alice J Sheffet, New Jersey Medical Sch, Newark, NJ; Virgnia Howard, Univ of Alabama at Birmingham, Birmingham, AL; Wesley S Moore, Univ of California at Los Angeles, Los Angeles, CA; Seemant Chaturvedi, Univ of Miami, Maimi, FL; James F Meschia, Mayo Clinic Jacksonville, Jacksonville, FL; Brajesh K Lal, Univ of Maryland Sch of Med, Baltimore, MD; Jenifer H Voeks, Medical Univ of South Carolina, Charleston, SC; Robert W Hobson II, Gagnon Heart Hosp, Morristown, NJ

Abstract Body: PURPOSE: Because of increases in patient life-expectancy, the long-term results and clinical durability of carotid endarterectomy (CEA) and carotid stenting (CAS) were compared in CREST after up to 10 years of follow-up.

METHODS AND MATERIALS: Patients with symptomatic or asymptomatic carotid stenosis who were randomized to CEA or CAS were evaluated every 6-months at 117 centers in the U.S. and Canada. The primary endpoint was stroke, myocardial infarction, or death from any cause during the periprocedural period, or any ipsilateral stroke thereafter. Endpoint stroke included all periprocedural strokes and subsequent ipsilateral strokes.

RESULTS: For 2502 patients over a median follow-up period of 7.2 years, there was/was not a significant difference in the 10-year rates of the primary endpoint between the CEA group and the CAS group (XX% and XX%, respectively; hazard ratio with CEA, XX; 95% confidence interval, XX to XX; P = XXX). The 10-year rate of endpoint stroke was XX% with CEA and XX% with CAS (hazard ratio, XX; P = XXX); the rates among symptomatic patients were XX% and XX% (hazard ratio, XXX; P =XXX), and the rates among asymptomatic patients were XX% and XX% (hazard ratio, XXX; P = XXX), respectively. After the periprocedural period, the incidences of ipsilateral stroke with CEA and CAS were/were not similarly low for symptomatic (XX% and XX%, respectively; P = 0.XX) and asymptomatic patients (XX% and XX%, respectively; P =XXX)

CONCLUSIONS: In this report of longest follow-up of CEA and CAS to date, the risk of stroke, myocardial infarction, or death did/did not differ significantly in the group undergoing CEA and the group undergoing CAS. For symptomatic and asymptomatic patients, clinical durability was/was not superior for CEA/CAS.

Author Disclosure Block: T.G. Brott: None. **G. Howard:** None. **G.S. Roubin:** None. **A. Mackey:** None. **W. Brooks:** None. **M.D. Hill:** None. **V.A. Mantese:** None. **W.M. Clark:** None. **C. Timaran:** None. **D. Heck:** None. **P.P. Leimgruber:**

None. **A.J. Sheffet:** None. **V. Howard:** None. **W.S. Moore:** None. **S. Chaturvedi:** None. **J.F. Meschia:** None. **B.K. Lal:** None. **J.H. Voeks:** None. **R.W. Hobson:** None.

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Presentation Number: LB11

Publishing Title: A Randomized Trial of Unruptured Brain Arteriovenous Malformations (ARUBA): 5-year Results

Author Block: Christian Stapf, Univ de Montréal - CRCHUM, Montreal, QC, Canada; Jessica R Overbey, InCHOIR - Icahn Sch of Med at Mount Sinai, New York, NY; J P Mohr, Columbia Univ, New York, NY; Alan J Moskowitz, InCHOIR - Icahn Sch of Med at Mount Sinai, New York, NY; Eric Vicaut, URC - APHP Hôpital Lariboisière, Paris, France; Michael K Parides, InCHOIR - Icahn Sch of Med at Mount Sinai, New York, NY; The International ARUBA Investigators

Abstract Body: Background: ARUBA is a prospective, multicenter, parallel design, open, randomised controlled clinical trial comparing medical management with interventional therapy in patients diagnosed with an unruptured brain arteriovenous malformation (AVM). In 2013, patient recruitment had been halted by the NIH/NINDS-appointed DSMB after a planned interim analysis showed a significantly lower risk of death or stroke in patients followed without intervention (HR=0.27, 95% CI 0.14-0.54). The DSMB recommended pursuing the planned 5-year follow-up in order to determine if these differences persist over time.

Methods: The primary aim of the trial is to determine whether medical management alone is superior to invasive therapy in averting death (any cause) or stroke (symptomatic hemorrhage or infarction). The secondary aim is to determine whether treatment of unruptured brain AVMs by medical management alone offers a lower risk of death or clinical impairment (modified Rankin Score (mRS) >/= 2) at 5 years post-randomization compared to invasive therapy.

Results: Overall, 226 patients (aged ≥18 years, diagnosed with an unruptured brain AVM suitable for curative intervention) have been randomly assigned (1:1) to best possible invasive therapy (medical management plus endovascular, surgical, and/or radiation therapy) versus medical management alone. The 5-year results of the primary (symptomatic stroke or death) and secondary (mRS) endpoints will be presented.

Conclusion: The final results of the trial offer important data on the eventual long-term benefit of non-interventional management of patients diagnosed with an unruptured brain AVM.

Funding: NIH/NINDS cooperative agreements U01NS051483 and U01 NS051566.

Trial registration: ClinicalTrials.gov NCT00389181**.**

Author Disclosure Block: C. Stapf: None. **J.R. Overbey:** None. **J.P. Mohr:** None. **A.J. Moskowitz:** None. **E. Vicaut:** None. **M.K. Parides:** None.

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Presentation Number: LB12

Publishing Title: Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage (CLEAR III) Results

Author Block: Daniel F Hanley, Johns Hopkins Univ, Baltimore, MD; CLEAR III Investigators

Abstract Body: Severe IVH with small ICH is a subtype of ICH where specific therapy to control ICP and remove IVH may be efficacious. Historical data show these subjects have 50% mortality and 80% poor outcome. CLEAR III, a randomized double-blinded, placebo controlled trial tested if pragmatically inserted EVD plus rt-PA improved outcome by controlling ICP and removing 80% of IVH clot. We enrolled 500 subjects from 73 sites between 2009-2014. Consented subjects were randomized to receive up to 12 rt-PA or saline doses Q8hr via the EVD. Administration occurred until at least 3rd & 4th ventricles opened. Blinded assessment of mRS occurred at 30, 180 and 365 days. Follow up was 98%.

Subjects received an EVD at 11hr (10,12 CI) post ictus; clot was determined stable by 52hr (51,54) and 1st dose at 58hr (57,59). Clot location was thalamus 57% and 44% other. Presenting ICH (9ml [8,10]), IVH (30ml [28,32]), GCS (10 [9.6,10.4]), NIHSS (21 [20,22]), MAP (137 [135,139]), ICP (10 [2,27]) were similar by group. Most subjects (73%) experienced at least one ICP>20mmHg. Median 5 rt-PA or 12 saline doses were given. End of treatment IVH volume was independently associated with % of ICP events >20 and >30mmHg. Measures of care, including ICU time (14 v 15) days, time to return home (53 v 59), number of EVDs employed (36 v 53) trended towards rt-PA (NS). Safety favored rt-PA: infection (7% v 12%, p=0.05), symptomatic bleeding (2.4% v 2.0%, NS), and number of subjects with SAEs (49% v 62%, p=0.003). Proportion of low CPP readings (<70mmHg; 2% v 5%, p=0.01) and time to open 3rd/4th ventricles favored rt-PA (2 v 6 days, p<0.001). mRS 0-3 did not differ between groups (47% v 45%, NS); adjusted difference was 3.3% (NS). Kaplan Meier mortality was improved throughout the 365-day follow-up (p=0.007). Importantly, the extent of IVH removal correlated with good outcome (p=0.0001) and mortality (p=0.04). CLEAR III provides historical comparisons and controlled evidence about a policy of treatment for IVH. Historically that a policy of EVD use with rt-PA or saline produces better outcome (46% mRS 0-3). Controlled use of rt-PA produces 10% lower mortality (NNT=10) with more efficient and safer care. Further investigation of EVD use, rt-PA treatment goals, and ICP control measures are imperative.

Author Disclosure Block: **D.F. Hanley:** Research Grant; Significant; NIH/NINDS. Other Research Support; Significant; Genentech, Inc..

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Presentation Number: LB13

Publishing Title: Efficiency of Intraventricular Hemorrhage Removal Determines Modified Rankin Scale Score (CLEAR III)

Author Block: Issam A Awad, Univ of Chicago, Chicago, IL; CLEAR III Investigators

Abstract Body: Severe IVH with small ICH is a subgroup of hemorrhagic stroke where specific ICP therapy and IVH removal produced lower mortality and fewer ventricular infections and adverse events. CLEAR III, a randomized, double-blinded, placebo controlled trial, demonstrated benefits of rt-PA over current "best care" in mortality and other clinical parameters. Clinically pragmatic selection of subjects for EVD and AHA ICH Guidelines (levels 2 & 3) dictated the protocol for care. Consented subjects received saline(A) or rt-PA (B) Q8hr via the EVD. Early end of treatment (EOT) was considered when at least the 3rd & 4th ventricles cleared; sites were encouraged to attempt >80% clot removal with the protocolized options for multiple catheters and further dosing up to 12 doses. Our secondary hypothesis tested mediation of mRS benefits at 180 days via IVH clot reduction—the main goal of the CLEAR III intervention.

Treatment groups were balanced with respect to epidemiologic, medical presentation, severity factors, IVH size, ICH size, and clot location. Presenting factors were ICH (8ml), IVH (28ml), GCS (8), NIHSS (21), MAP (165), and ICP (10). Use of rt-PA led to greater EOT clot removal (62% vs 44%, p<0.001). Utilization of guidelines and study protocol achieved >80% clot removal in only 21.2% of subjects. When efficiency of IVH removal was substituted for A/B assignment, mRS 0-3 correlated directly with extent of clot removal (AOR=0.96/ml time-averaged IVH, p < 0.001). AORs were consistent within IVH size (<20 vs ≥20, p=0.019 and <0.001) and ICH location (thalamic vs non-thalamic, p=0.002 and <0.001) subgroups. Treatment fidelity analysis of IVH volume reduction showed the absence of A/B removal differences for IVH <20 ml (n=215, AOR=0.62, NS); conversely, for IVH >20 ml (n=274), rt-PA treatment demonstrated a benefit in mRS 0-3 (AOR=1.84, p=0.046; p-interaction=0.02). Where rt-PA achieved ≥ 90% removal, odds of mRS 0-3 were greater (AOR=2.02, p=0.05). Among patients receiving rt-PA, multiple EVD catheters (diff. dual vs single of 8.4%, p=0.08) and greater number of doses (1.82% per dose, p=0.01) achieved greater IVH removal. Complete IVH removal must be pursued, if good mRS status is to be optimized for all patients with IVH.

Author Disclosure Block: I.A. Awad: Research Grant; Significant; NIH/NINDS. Other Research Support; Significant; Genentech, Inc..

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Presentation Number: LB14

Publishing Title: Randomized Trial on Normalization of International Normalized Ratio Using Prothrombin Complex or Fresh Frozen Plasma in Vitamin-k Related Intracranial Bleeding

Author Block: Thorsten Steiner, Klinikum Frankfurt Höchst, Frankfurt, Germany; Sven Poli, Dept of Neurology & Stroke, Hertie Inst for Clinical Brain Res, Tuebingen, Germany; Martin Griebe, Dept of Neurology, Mannheim UMM, Heidelberg Univ, Germany, Mannheim, Germany; Johannes Huesing, Janek Hajda, Coordination center for clinical trials, Heidelberg Univ Hosp, Germany, Heidelberg, Germany; Martin Bendszus, Dept of Neuroradiology, Heidelberg Univ Hosp, Germany, Heidelberg, Germany; Hanne Christensen, Dept of Neurology, Bispebjerg and Frederiksberg Hosp, Univ of Copenhagen, Copenhagen, Denmark; Christian Dohmen, Dept of Neurology, Koeln Univ Hospita, Köln, Germany; Anja Freiberger, Coordination center for clinical trials, Heidelberg Univ Hosp,, Heidelberg, Germany; Michael Hennerici, Dept of Neurology, Mannheim UMM, Heidelberg Univ, Mannheim, Germany; J Kollmer, Dept of Neuroradiology, Heidelberg Univ Hosp, Heidelberg, Germany; H Stetefeld, Dept of Neurology, Koeln Univ Hosp, Cologne, Germany; Katja E Wartenberg, Dept of Neurology, Halle Univ Hospita, Hallo, Germany; Christian Weimar, Dept of Neurology, Essen Univ Hosp, Essen, Germany; Roland Veltkamp, Dept of Stroke Med, Imperial Coll London, United Kingdom and Dept of Neurology, Heidelberg Univ Hosp, London, Germany

Abstract Body: Background: Hematoma expansion (HE) predicts mortality in vitamin K antagonist related intracranial hemorrhage (VKA-ICH). Normalizing the international normalized ratio (INR) is recommended but optimal hemostatic management is controversial. We compared the effect of fresh frozen plasma (FFP) and prothrombin complex concentrate (PCC) on early coagulation and HE.

Methods: This investigator-initiated trial had a multicenter, prospective, randomized, controlled, open, blinded endpoint (PROBE) design. Patients with VKA-ICH presenting within 12 hours after symptom-onset with an INR ≥ 2.0 received FFP or 4-factor PCC within 1 hour after initial cerebral computed tomography. The primary endpoint was the proportion of patients with INR ≤1.2 within 3 hours. Secondary endpoints included HE, early mortality and thromboembolic events.

Results: The trial was terminated after inclusion of 50 patients after a safety analysis due to safety constraints. Mean age was 75.6 years, 19 (38%) being women. The primary endpoint was reached by 2/23 patients receiving FFP versus 18/27 receiving 4-factor PCC (adjusted odds ratio 30.6, 95%-CI: [4.7; 197.9], p=0.001). Adjusted difference in hematoma expansion was significantly smaller in the PCC-group: 16.9 ml (95%-CI: [2.5; 31.3], p=0.026) at 3 hours and 16.4 ml (95%-CI: [2.9; 29.9], p=0.018) at 24 hours. There were 13 deaths, 8 in the FFP-group and 5 in the PCC-group. Five of the 8 deaths in the FFP-group were due to HE and occurred within 48 hours. All deaths in the PCC-group occurred after day 5, one was classified due to HE. One early thromboembolic event occurred in each group.

Discussion: In patients with VKA-ICH, 4-factor PCC was significantly more effective in normalizing the INR compared to FFP, reduced the risk of HE, and the associated early mortality.

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