Abstract Body:

Background: LDL cholesterol is not a major risk factor for stroke, yet statin therapy reduces stroke risk. As increased levels of the inflammatory biomarker high sensitivity C-reactive protein (hsCRP) predict stroke, we sought evidence that statin therapy might reduce stroke rates among individuals with low levels of cholesterol but elevated levels of hsCRP.

Methods: 17,802 apparently healthy men and women with low-density lipoprotein cholesterol levels (LDLC) <130mg/dl and hsCRP levels >2.0mg/L were randomly allocated to rosuvastatin 20mg daily or placebo and then followed for occurrence of a first major cardiovascular event (nonfatal myocardial infarction, nonfatal stroke, arterial revascularization, hospitalization for unstable angina, or cardiovascular death). All endpoints, including stroke, were adjudicated by an independent committee of physicians unaware of treatment status.

Results: The trial was stopped after a median follow-up of 1.9 years (maximum 5.0 years) because, compared to placebo, rosuvastatin resulted in a 44 percent reduction in the hazard of the primary trial endpoint (cumulative incidence 3.0 vs 6.2 percent at 4 years, hazard ratio [HR] 0.56, 95% confidence interval 0.46-0.69, P<0.00001). With regard to stroke events, there were 33 among those allocated to rosuvastatin and 64 among those allocated to placebo, a 48 percent reduction in hazard (HR 0.52, 95%CI 0.34-0.79, P=0.002) almost all of which were thromboembolic. In contrast to a prior study of high-dose statin therapy, there was no increase in risk of hemorrhagic stroke (6 vs 9 events in the rosuvastatin and placebo groups, respectively, P=0.44). Details of the stroke data according to gender, ethnicity, and baseline risk factor status will be presented for the first time.

Conclusions: Rosuvastatin reduces by almost half the incidence of thromboembolic stroke among men and women with elevated levels of hsCRP.
Abstract Body:

Intracranial aneurysm (IA) affects 2-5% of the population and results in hemorrhagic strokes commonly in mid-life, most often resulting in death or severe neurological impairment. Even though the pathogenesis of IA is unknown, both environmental and genetic factors are known to play a role. In order to identify genetic loci that contribute to IA formation and rupture, we performed a large multistage genome-wide association study (GWAS) of European and Japanese cohorts with over 10,000 subjects including ~2,200 IA cases and more than 8,000 controls. Genome-wide genotyping of the European cohorts and replication studies in the Japanese cohort identified common SNPs on chromosomes 2q, 8q and 9p that show significant association with IA with p values ranging from $10^{-8}$ to $10^{-10}$ and odds ratios 1.24 to 1.36. The loci on 2q and 8q are novel, whereas the 9p locus was previously associated with coronary artery disease and, more recently, with aortic and intracranial aneurysms. Even though the risk alleles in these loci significantly increase the risk of having an aneurysm (greater than 3 fold for all 6 risk alleles), they account for less than 4% of the genetic variance. This suggests the presence of other IA susceptibility loci. In order to identify these loci, we recruited additional case-control cohorts and performed association tests. Importantly, all the IA susceptibility loci identified to date contain genes required for formation and maintenance of endothelial cells, suggesting a role in development and repair of the vasculature. These findings have implications for the pathophysiology, diagnosis and therapy of IA.
K. Bilguvar, None; K. Yasuno, None; M. Niemelä, None; Y.M. Ruigrok, Netherlands Heart foundation, M,B; M. von und zu Fraunberg, None; E. Gaál, None; N. Nayak, None; A. Slowik, None; B. Krischek, None; Z. Arlier, None; M. Simon, None; D. Krex, None; G. Auburger, None; A. Ozturk, None; C. Wijmenga, None; C.M. van Duijn, None; M.W. State, NIH, S,B; G.J.E. Rinkel, None; J. Hernesniemi, None; J.E. Jääskeläinen, None; A. Palotie, None; I. Inoue, Japan Science and Technology Corporation, S,B; R.P. Lifton, HHMI, S,B; M. Gunel, NIH, S,B.
Intraventricular hemorrhage (IVH) is a major intracerebral hemorrhage (ICH) severity factor and appears to be an important treatment target (STICH, fVIIa trials). While substantial reduction in predicted mortality appears achievable with catheter-based clot lysis treatment, only limited multi-site, international, prospective assessments of this treatment have been performed. A safety trial has demonstrated daily rt-PA enhanced clot lysis, but the dose-response relationship(s) between rt-PA and overall clot lysis rate ($C_T$) have not been tested. Similarly, the safety of various lower doses (0.6mg, 2.0 mg and 3.0mg/day) has not been explored. CLEAR IVH A (n=16) tested dose-response for rt-PA mediated clearance of blood from the ventricular system. Clear B (n=36) tested for benefit of more frequent dosing with shorter dose intervals (Q8 vs. Q12). Subjects were treated 4 days or until 3rd and 4th ventricles opened and lateral shift was reduced. In August 2008, CLEAR A & B completed follow up of all 52 patients (I/E criteria ICH <30 cc, large IVH, EVD, 6-hr stability CT). Data has now been monitored and reviewed an by independent DSMB. Median clinical severity will be determined for important domains (admit BP, GCS, age, ICH volume, IVH volume). ICH location, hypertension, drug use, and ETOH will be assessed and compared to the prior safety study (n=48). Primary outcome is $C_T$ and safety; secondary outcomes are mRS and GOS at days 30, 90, and 180. To assess the effect of drug delivery site on clot lysis, we will compare $C_T$ to rate of clot lysis in the 3rd and 4th ventricular regions ($C_r$) closest to the extra ventricular drainage (EVD). Safety limits for DSMB review were constant for CLEAR A & B studies: mortality (55%), rebleeding (35%) and ventriculitis (30%). No safety threshold was crossed in CLEAR IVH rates: 30 day mortality (17%), rebleeding (6%) and bacterial ventriculitis (2%). Detailed 180-day modified Rankin Scale and Stroke Impact Scale results of CLEAR IVH will be presented. The low mortality compared to expected mortality in the 60% to 80% range strongly suggests that removal of blood form the ventricles will be beneficial to individuals with IVH. A pivotal trial to test this potentially life saving therapy will begin in the spring of 2008.
Abstract Body:

Objective: Migraine, particularly with aura, has been associated with ischemic stroke and with silent infarct-like lesions in one cross-sectional population-based MRI study (Kruit et al). In a large population-based cohort, we consider whether symptoms of migraine in middle age predict late-life infarct-like lesions measured in late life.

Methods: Study participants are from the Age Gene/Environment Susceptibility [AGES]-Reykjavik Study (n=4,689, 57% women). Participants were initially examined in the Reykjavik Study at an average age of 51 years(range 33-65). Subjects reporting headaches once or more per month were asked about migraine symptoms including: nausea, unilateral location, photophobia, visual disturbance during or just before headache (defined as “visual aura”), and numbness on one side during or just before headache (defined as “sensory aura”). Brain imaging was performed as part of the AGES-Reykjavik study in 2002-2006, an average of 25 years after the migraine assessment. The presence of infarct-like lesions (cortical, sub-cortical, cerebellar, and total) was measured by trained readers blinded to migraine status. A comprehensive cardiovascular risk assessment was performed at both examinations.

Results: After adjusting for age, sex, and duration of follow-up, mid-life headache with visual aura was associated with any infarct-like lesion (OR=1.5 [1.2-2.0], p<0.002). This reflected a specific association with cerebellar lesions (OR= 1.8 [1.3-2.4], and not cortical (OR=1.3 [0.9-1.9], p<0.0.17) or sub-cortical (OR=1.0 [0.7-1.5], p<0.93) lesions. Sensory aura alone and other migraine symptoms were not associated with infarcts. Results were similar after adjustment for cardiovascular risk factors. In secondary analyses, the relationship between headache with visual aura and cerebellar infarcts was similar by mid-life age strata and presence or absence of a history of coronary artery disease or TIA/stroke but was stronger for women than men (OR=2.2 [1.5-3.1] vs. OR=1.1 [0.6-2.0]).

Conclusions: In this large population-based prospective study, headache with visual disturbances - particularly in women - predicts MRI-evident cerebellar infarct-like lesions assessed an average of 25 years after headache diagnosis.

Author Disclosure Block:

A.I. Scher, None; A. Ghabaryan, None; S. Sigurdsson, None; L. Gudmundsson, None; G. Eiriksdottir, None; T. Aspelund, None; M.A. van Buchem, None; V. Gudnason, None; L.J. Launer, None.
Abstract Body:

Introduction: Acute ischemic stroke affects 700,000 patients annually. Although acute revascularization is associated with improved outcomes, it is unclear which method of intervention, if any, is ideal. PROACT II and MERCI trials achieved recanalization rates ranging from approximately 60 to 70% percent. Numerous case series, as well as cardiac literature parallels, suggest that acute stenting may achieve high levels of revascularization with low associated morbidity. We have therefore conducted an FDA-approved, multicenter, prospective pilot trial to evaluate the safety of intracranial stenting for acute thromboembolic stroke using the Wingspan self-expanding stent.

Methods: Eligibility criteria included presentation within 8 hours of stroke onset, age \( \geq 18 \) years, NIHSS \( \geq 8 \), angiographic demonstration of focal intracerebral artery occlusion not \( >14 \text{mm} \), and either contraindication to IV tPA or failure to improve 1 hour after tPA administration. Exclusion criteria included inability to obtain informed consent, known hemorrhagic diathesis or coagulopathy, platelet count <100,000, ICH, a blood glucose level of less than 51mg/100ml, or CT perfusion imaging demonstrating >1/3 at-risk territory with non-salvageable brain (low CBV). Data is presented as mean+/-SD. Statistical analysis was performed using paired Students t test for normally distributed continuous data and Wilcoxon match-pairs signed-rank test for ordinal or non-parametric data.

Results: Mean patient age was 63+/-18 years. There were 14 women. Mean presenting NIHSS score was 14+/-3.8(median 13). Presenting TIMI score was 0(85 percent) or 1(15 percent). All patients achieved recanalization to TIMI 3(60 percent) or 2(40 percent) (p<0.0001). Improvement in NIHSS was documented in 85 percent of patients, with 65 percent improving by \( \geq 4 \) NIHSS points. Median NIHSS improvement from intervention to discharge was 9(-6 to 14) (p<0.001).

Conclusion: This FDA-approved prospective study suggests intracranial stenting for acute stroke may be a valuable addition to the stroke treatment armamentarium.

Author Disclosure Block:

J. Mocco, Brain Aneurysm Foundation, M,B; K.V. Snyder, None; A.M. Crumlish, None; D.J. Fiorella, Micrus, S,G; A.H. Siddiqui, University at Buffalo (local), M,B; Genetech, M,E; American Association of Neurological Surgeons, M,E; Emergency Medicine Conference, M,E; L.N. Hopkins, Boston Scientific, S,B; Cordis, S,B; Micrus, S,B; Bard, M,E; Boston Scientific, M,E; Cordis, M,E; Access Closure, S,F; Boston Scientific, S,F; Micrus, S,F; Square One, Inc., S,F; Abbott, M,G; Bard, M,G; Boston Scientific, M,G; Cordis, M,G; Micrus, M,G; E.L. Levy, Boston Scientific, S,B; ev3, S,B; Boston Scientific (devices-Wingspan stents), S,C; Boston Scientific, S,E; Micrus (shares), S,F; Cordis, S,G; Micrus, S,G; Abbott (carotid stent training fees), S,H; ev3 (carotid stent training fees), S,H.
Abstract Body:

**Background & Purpose:** Microspheres (µS) reach intracranial occlusions and transmit energy momentum from an ultrasound wave to residual flow to promote recanalization. We report a randomized multi-center phase II trial of µS dose escalation with systemic thrombolysis.

**Subjects & Methods:** Stroke patients receiving 0.9 mg/kg tPA with pre-treatment proximal intracranial occlusions on TCD were randomized (2:1 ratio) to µS (MRX-801) infusion over 90 min (Cohort1 1.4 mL, Cohort2 2.8 mL) with continuous TCD-insonation while Controls received tPA and brief TCD-assessments. Primary safety endpoint was symptomatic intracerebral hemorrhage (sICH) within 36 hours post-tPA. Favorable outcome (modified Rankin Scale 0-1) was assessed at three months.

**Results:** Among 35 patients (Cohort1=12, Cohort2=11, Controls=12) no sICH occurred in Cohort 1 and Controls while 3 (27%, with 2 fatal) sICH's occurred in Cohort2. Patients with sICH had higher blood pressures during and after treatment (p<0.04). Sustained complete recanalization rates at the end of TCD-monitoring were 67% Cohort1, 46% Cohort2, and 33% Controls (p=0.255). The median-time-to-any-recanalization tended to be shorter in Cohort 1 (30min, IQR 6) and Cohort 2 (30min, IQR 69) compared to controls (60min, IQR 5; p=0.054). At 3 months, 75% in Cohort1, 50% - Cohort2, and 36% Controls (p=0.167) achieved favorable outcome.

**Conclusions:** Perflutren-lipid µS can be safely combined with systemic tPA and ultrasound at a dose of 1.4mL. Safety concerns in the second dose tier may necessitate extended enrollment and further experiments to determine the mechanisms how microspheres interact with tissues. In both dose tiers, sonothrombolysis with µS and tPA shows a trend towards higher early recanalization and clinical recovery rates compared to standard iv tPA therapy.