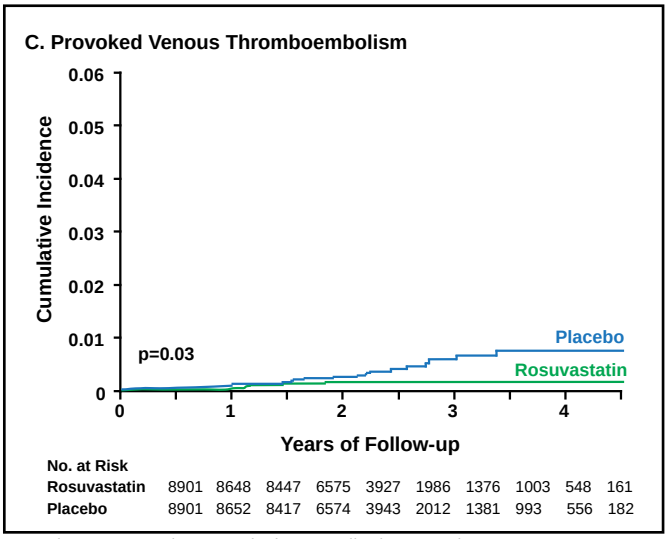

Although lipid levels are significant risk determinants for ischemic stroke and coronary vascular disease (CVD), several studies have shown that individuals with high levels of hsCRP are at increased risk for stroke [Rost NS et al. *Stroke* 2001; Ballantyne CM et al. *Arch Intern Med* 2005; Everett B et al. *JACC* 2006]. The objective of this study was to determine if rosuvastatin would reduce stroke rates among individuals with low levels of cholesterol but elevated levels of hsCRP.

JUPITER enrolled 17,802 apparently healthy men and women at 1315 sites in 26 countries. Patients were required to have LDL levels <130 mg/dL and hsCRP levels >2.0 mL, be aged ≥50 years (men) or ≥60 years (women), and have no CVD or diabetes. The primary endpoint was the first major cardiovascular event (nonfatal myocardial infarction, nonfatal stroke, arterial revascularization, hospitalization for unstable angina, or cardiovascular death).

Median age of the study population was 66 years; 38% was women; 12% was black and 12% was Hispanic; mean blood pressure was 134/80 mm Hg; 16% smoked; and 17% used aspirin. After 12 months, rosuvastatin reduced LDL cholesterol levels by 50% (sustained for the course of the trial), hsCRP by 37% (sustained), triglycerides by 17%, and HDL by 4% compared with placebo.

The trial was stopped after a median follow-up of 1.9 years, because a significant (p<0.00001) change in the HR (0.56; 95% CI, 0.46 to 0.69) of the primary endpoint was reached. Overall, rosuvastatin was associated with a 44% reduction in the composite endpoint. There were 33 stroke events in the rosuvastatin group and 64 in the placebo group, a 48% reduction in HR (0.52; 95% CI, 0.34 to 0.79; p=0.002). For nonfatal stroke, the HR was 0.52 (95% CI, 0.33 to 0.80; p=0.003); ischemic stroke HR was 0.49 (95% CI, 0.30 to 0.81; p=0.004). There was no increase in the risk of hemorrhagic stroke (HR 0.67; 95% CI, 0.24 to 1.88; p=0.44). The secondary endpoint, all-cause mortality, decreased 20% with rosuvastatin (HR 0.80; 95% CI, 0.67 to 0.97; p=0.02).

These results were consistent across all subgroups with patients in high-risk groups (hypertension, smokers, high Framingham risk factors), showing substantial benefits from rosuvastatin treatment. Except for cancer deaths (higher in the placebo group) and the incidence of diabetes (higher in the rosuvastatin group), adverse events were similar between the treatment groups.

Compared with previous trials (WOSCOPS and AFCAPS), the JUPITER trial showed significant positive effects on stroke reduction. Dr. Glynn suggested that these benefits may be due to JUPITER's larger patient population, patient characteristics (more women and lower LDL levels in the JUPITER trial and higher smoking and lipid levels in the WOSCOPS trial), or the treatment (rosuvastatin in JUPITER, pravastatin in WOSCOPS, and lovastatin in AFCAPS).

Whole Genome Association of Intracranial Aneurysm Identifies Susceptibilty Loci

A genome wide genotyping study has identified genetic loci that contribute to intracranial aneurysm (IA) formation and rupture. Single nucleotide polymorphisms (SNPs) on chromosomes 2q, 8q, and 9p showed significant association with IA (p values ranging from 10^{-8} to 10^{-10} and odds ratios 1.24 to 1.36) [Bilguvar et al. *Nat Genet* 2008]. Murat Gunel, MD, Yale University School of Medicine, New Haven, CT, reported that 2 of the loci, 2q and 8q, are novel, while the 9p locus previously has been associated with coronary artery disease and, more recently, with aortic aneurysm and IA.

IA affects 2% to 5% of the population and commonly occurs between the ages of 40 and 60 years, typically with no antecedent event or warning. There is no reliable way to identify at-risk individuals. Genetic identification of these subjects would make it possible to identify individuals before an IA rupture for preventive treatment. The etiology and pathogenesis of intracranial

aneurysms clearly are multifactorial, wherein genetic factors play an increasingly recognized role. First-degree relatives of patients with aneurysmal subarachnoid hemorrhage have a 4-fold increased risk of suffering a ruptured intracranial aneurysm compared with the general population [Schievink WI. *Neurosurgery* 1997].

This Genome Wide Association Study (GWAS) of IA was performed in over 10,000 subjects with Finnish, Dutch, and Japanese cohorts. In the European cohort, a significant association between chromosome 2 and IA was seen from 197.7 Mb to 198.6 Mb, while the association in the Japanese cohort was confined to SNPs in the more telomeric block (198.2 Mb to 198.5 Mb). The locus PLCL1 gene on chromosome 2 association interval is of special interest, because it has significant homology to phospholipase C which lies in a major signaling pathway that is important in CNS angiogenesis downstream of VEGFR2 [Shibuya M. J *Biochem Mol Bio* 2006], which is a marker of endothelial progenitor cells and has been shown to play a role in CNS angiogenesis [Ziegler BL et al. *Science* 1999]. Chromosome 8 association interval is much smaller and includes a single gene, *SOX17,* which is essential for the specification and maintenance of the endoderm in the embryo [Hudson C et al. *Cell* 1997]. Post-natally, it is expressed in the endothelial cells and knock-out models in mice reveal significant vascular abnormalities, including defective endothelial sprouting and vascular remodeling [Matsui TJ. *Cell Sci* 2006].

Based on the results of this study, the authors hypothesize that IA might be due to defective development and/or failure of the repair of the vasculature through the progenitor cell populations. Vascular injury mobilizes bone marrow or potentially vascular wall-derived progenitor/stem cells to localize to sites of damage and that appear to be important in the repair process [Purhonen S et al. *Proc Natl Acad Sci* 2008]. IA genes might be involved in maintenance of these progenitor cells and the vascular repair process, such that the risk alleles identified in IA patients might result in less effective repair which ultimately leads to formation and rupture of aneurysms.

This is the first study to provide a means of identifying at-risk IA individuals preclinically, in which the risk of IA increases more than 3-fold in subjects with all 6 risk alleles compared with those who have none. Because these IA loci accounted for less than 2.3% to 3.8% of the genetic variance, additional common variants are highly likely to play a role in IA. Further studies are underway, using additional cohorts to identify additional loci.

Final Results of the Clear IVH Trial: Clot Lysis, Safety and 180 Day Functional Outcomes

Daniel F. Hanley, MD, Johns Hopkins University, Baltimore, MD, reported 180-day data from the Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage (CLEAR; NCT00784134) study, which showed that the combination of extraventricular drainage (EVD) plus thrombolysis with the thrombolytic rt-PA substantially reduces mortality and poor outcomes in patients with intraventricular hemorrhage (IVH). Severe IVH, as the result of subarachnoid hemorrhage or intracerebral hemorrhage, is difficult to treat and leads to hydrocephalus and frequent poor functional outcomes. A meta-analysis of 7 observational studies reported fatality rates of 9% (RR, 0.13; 95% CI, 0.04 to 0.40) for ICH/IVH patients who were treated with EVD plus fibrinolytic agents compared with 78% for conservative treatment and 58% for EVD alone. The authors concluded that such findings warranted a randomized clinical trial [Nieuwkamp et al. *J Neurol* 2000]. Based on these earlier studies, the CLEAR study (n=52) was designed to assess whether the addition of rt-PA to EVD improves functional outcome compared with EVD alone. Entry subjects included patients with IVH <30 cc and with a hematoma that was stabilized at 6 hours post-IVH. Intracranial catheters were placed in the frontal portion of the least involved lateral ventricle in about 85% of patients. In this dose escalation study, subjects were treated for 4 days or until the third and fourth ventricles opened and lateral shift was reduced. To assess the effect of drug delivery on clot lysis, computer tomography was used to assess the rate of clot lysis in all of the ventricles.

Safety and functional outcomes were measured at 30, 90, and 180 days post-IVH. Functional outcomes were assessed with the modified Rankin Scale (mRS), the Barthel score, NIH Stroke Scale (NIHSS), and Glasgow Outcome Score (GOS). No safety threshold was crossed in CLEAR rates. Mean patient age was 55 (10.3) years; baseline IVH volume was 30 to 40 cc; and ICH volume was 2.5 cc. The majority (19%) of the clots formed in the caudate region.

Mortality, symptomatic bleeding, and bacterial ventriculitis percentages were 17%, 4%, and 2% at 30 days, respectively. Functional outcomes at 180 days