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

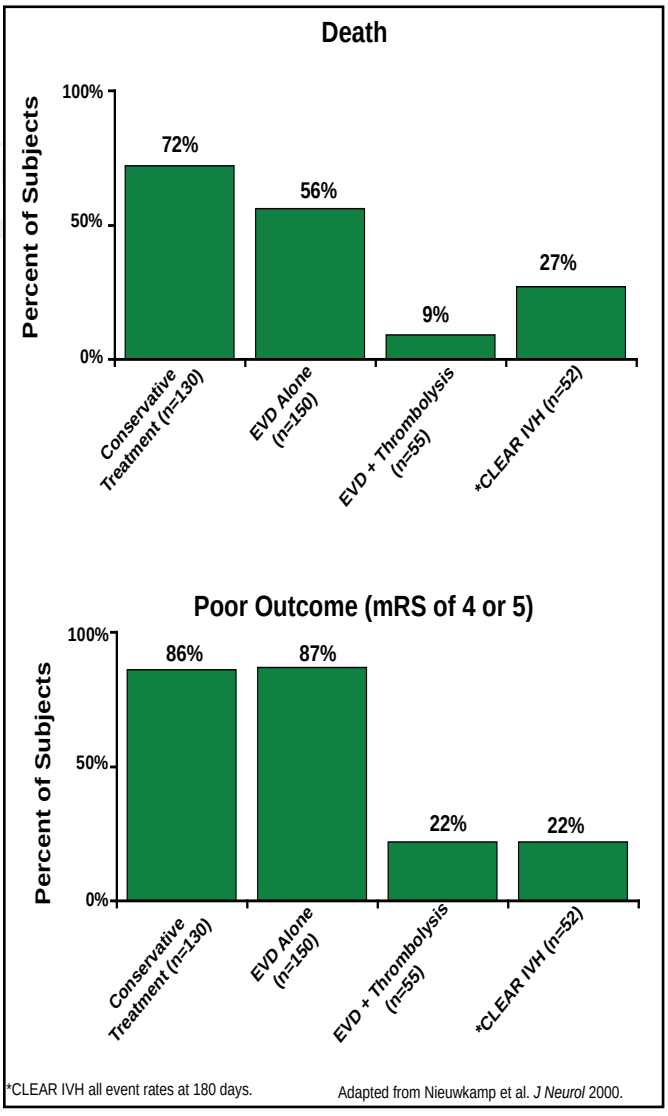
Daniel F. Hanley, MD, Johns Hopkins University, Baltimore, MD, reported 180-day data from the Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage (CLEAR; NCT00784134) study, which showed that the combination of extraventricular drainage (EVD) plus thrombolysis with the thrombolytic 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

were as follows: 17 patients had mRS scores between 0-3 (0=no disability; 3=moderate disability); average Barthel score=93.8; average NIHSS=1.17 (0 indicates normal); and GOS=1.17 (1 indicated good recovery). Overall, these patients were highly functional as indicated by these scales. Those patients (n=13) who scored 0 to 3 on the mRS also demonstrated good daily functionality as measured by the Stroke Impact Scale (SIS-16), validating the mRS measurements. Five patients were totally normal. By 180 days, 27% (14/52) of the patients had died and 22% (11/15) were rated as having poor outcomes (mRS of 4 or 5). The effect of rt-PA on good clinical outcome at 30 days (mRS 0-4) had an OR of 0.24 (Figure 1).

Figure 1. CLEAR IVH All Event Rates at 180 Days.



*CLEAR IVH all event rates at 180 days.

Adapted from Nieuwkamp et al. *J Neurol* 2000.

The positive findings from this study will allow the authors to proceed to a CLEAR Phase III trial, which has a projected enrollment of 500 patients at 50 to 70 worldwide sites that have neurosurgical and stroke expertise. The hypothesis that is to be tested in this placebo-controlled, blinded, randomized trial is whether EVD plus rt-PA treatment of IVH obstruction in the third and fourth ventricles will increase the percentage of patients in the mRS 0 to 3 group compared with EVD alone.

Final Results of an FDA-approved Prospective, Multicenter, Single-arm Trial of Stent-Assisted Recanalization for Acute Ischemic Stroke

Results from an FDA-approved, prospective pilot trial that were presented by J. Duffy Mocco, MD, University of Buffalo Neurosurgery, Buffalo, NY, suggest that the use of a self-expanding, intracranial stent for acute stroke may achieve high levels of revascularization. This follows on the heels of the Mechanical Embolus Removal in Cerebral Ischemia (MERCI; NCT00318071) trials that reported recanalization rates that ranged from approximately 60% to 70% percent with low associated morbidity.

Stroke is a leading cause of long-term disability and the third-leading cause of death. It is estimated that 795,000 strokes occur each year in the United States. This number is projected to increase 40% by the year 2025 (Figure 1). The MERCI 1 [Gobin YP et al. *Stroke* 2004] and Multi MERCI [Flint AC et al. *Stroke* 2007] trials, which used the MERCI Retrieval System, compared outcomes in patients who received mechanical embolectomy (recanalization) with outcomes in patients who were not recanalized. Significantly improved clinical outcomes and reduced mortality were reported for the recanalized patient group.

Although mechanical recanalization appears to work, there are patients for whom the MERCI device fails. Based on the results of this pilot study, Dr. Mocco said he believes that the use of intracranial stenting for acute ischemic stroke after failed thrombolysis with other means is now possible.

Based on preliminary results [Levy EI et al. *Neurosurgery* 2006; Zaideat OO et al. *Stroke* 2008] that have demonstrated