Definitions include those from The National Institute of Neurological Disorders and Stroke-tPA study (NINDS) [The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. *N Engl J Med* 1995], the second European-Australasian Acute Stroke Study (ECASS-II) [Larrue V et al. *Stroke* 2001], ECASS-III [Hacke W. et al. *N Engl J Med* 2008], and The Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) [Wahlgren N. et al. *Lancet* 2007]. Outcomes differ according to clinical, radiological, and relational criteria.

Neal M. Rao, MD, University of Colorado School of Medicine, Denver, Colorado, USA, presented results from a study on the most accurate definition of clinically relevant hemorrhagic transformation (HT) after thrombolytic therapy for stroke with IV tissue plasminogen activator (tPA).

The specific aim of this study was to determine which definition of sICH best identifies hemorrhages that alter final patient outcomes after administration of intravenous tPA in acute stroke. Analysis was based on the NINDS database, which defines sICH as any hemorrhagic transformation that is temporally related to any worsening.

Methods included an analysis of candidate definitions—ie, radiological (any radiological hemorrhage or parenchymal hematoma [PH])—and clinical-radiological criteria (NINDS-tPA Study, ECASS-II, and modified SITS-MOST: PH and ≥4 National Institutes of Health Stroke Scale [NIHSS] worsening).

Clinically relevant hemorrhages were defined as those that altered final outcome. A predictive model from the placebo group was derived, and outcomes with tPA were compared with predicted outcomes without tPA using a modified Rankin Scale (mRS).

The data of 312 patients who were treated with IV tPA were analyzed; 48 patients (15.4%) experienced any radiological intracranial hemorrhage (ICH). Hemorrhage frequency varied by definition (6.4%, any [PH]; 6.4%, NINDS-tPA; 5.1%, ECASS-II; and 1.9%, modified SITS-MOST). ECASS-II sICH patients had worse actual (with tPA) versus predicted (without tPA) outcomes. The mean final mRS was 5.6 (observed) versus 3.5 (predicted); death occurred in 75% (observed) versus 25.4% (predicted) of patients.

Radiological hemorrhage patients who did not meet ECASS sICH criteria showed no difference between actual and predicted outcomes. Mean final mRS was 4.2 (observed) versus 4.0 (predicted); death occurred in 35% (observed) versus 35.1% (predicted) of patients. Table 1 shows actual and predicted mean mRS and mortality with and without the five definitions (any radiographic, PH, NINDS, ECASS-II, and SITS-MOST).

Table 1. Outcomes With and Without Definitions.

	With Definition		Without Definition	
	Mean mRS Actual/ predicted	Mortality Actual/ predicted	Mean mRS Actual/ predicted	Mortality Actual/ predicted
Any Radiographic	4.94/4.22	56.0%/ 37.8%		
PH	4.50/3.53	50.0%/ 26.9%	4.25/4.22	38.0%/ 38.7%
NINDS	4.96/3.82	60.0%/ 32.3%	4.27/3.92	36.0%/ 31.6%
ECASS II	5.56/3.53	75.0%/ 25.4%	4.16/4.02	35.0%/ 35.1%
SITS-MOST	5.67/2.52	36.0%/ 33.6%	4.00/3.92	36.0%/ 33.6%

Study limitations were: only a subset of the proposed definitions of sICH was analyzed, data from the NINDS trials may not fully reflect contemporary practice, and there were a small number of patients in the NINDS dataset.

The authors concluded that the ICH classification that best identifies clinically relevant hemorrhages that alter final global disability and fatal outcome is any radiological HT that is associated with ≥4 early NIHSS worsening. They also determined that asymptomatic hemorrhages under this definition have no adverse impact on final outcomes.

Solitaire™ FR Device Achieves Successful Recanalization Almost Free of Symptomatic Hemorrhage Transformation

Written by Rita Buckley

According to the Primary Results of the Solitaire™ FR With the Intention for Thrombectomy Multicenter, Randomized Clinical Trial [SWIFT; NCT01054560], the Solitaire flow restoration (FR) device is superior to the Merci Retrieval System® in achieving successful recanalization that is almost free of symptomatic hemorrhagic transformation. Jeffrey L. Saver, MD, FAHA, FAAN, UCLA Stroke Center, Los Angeles, California, USA, reported outcomes from the study.

SWIFT was a 21-site, blinded endpoint observer, international, active comparator, noninferiority trial that tested the Solitaire™ FR as the initial device against the Merci Retriever® as the initial device. The purpose of the study was to demonstrate substantial equivalence of the Solitaire FR revascularization device with the legally marketed Merci retrieval system.

The primary efficacy endpoint was successful recanalization—TIMI 2 or 3 flow in all treatable vessels—with no symptomatic intracranial hemorrhage, assessed at completion of the first device strategy prior to rescue therapy. Secondary efficacy endpoints were time to recanalization, good neurological outcome at 90 days, and global disability at 90 days. Key inclusion criteria included ability to be treated within 8 hours of onset, National Institute of Health Stroke Scale (NIHSS) 8 to 29, and proximal intracranial occlusion.

Enrollment totaled 144 patients at 18 sites; 113 were randomized 1:1 to receive treatment with the Solitaire FR (n=58) or Merci device (n=55). All baseline demographic features were similar, with no significant differences. Higher rates of atrial fibrillation (p=0.02) was the only significant difference in medical and neurological history (44.8% in the Solitaire group vs 67.3% in the Merci group).

Of the 58 patients who were randomized to Solitaire FR, 60.7% (34/56) achieved the primary trial endpoint versus 24.1% (13/54) with the Merci device (noninferiority p<0.0001; superiority p=0.0001). Rescue therapy was used in 20.7% (12/58) of Solitaire patients versus 43.6% (24/55) of Merci patients (noninferiority p<0.0001; superiority p=0.015).

Good neurological outcomes at 90 days (defined as modified Rankin Scale [mRS] score ≤2 or equal to the prestroke mRS if >2, or NIHSS score improvement ≥10) were achieved by 58.2% (32/55) of Solitaire patients versus 33.3% (16/48) of Merci patients (noninferiority p=0.0001; superiority p=0.017). Mortality at 90 days occurred in 17.2% (10/58) of the Solitaire patients versus 38.2% (21/55) of the Merci patients (noninferiority p=0.0001; superiority p=0.020).

sICH occurred in 1.7% (1/58) of the Solitaire FR patients versus 10.9% (6/55) of the Merci patients (noninferiority p<0.0001; superiority p=0.057). Total intracranial hemorrhage percentages were 17.2% in the Solitaire FR group versus 38.2% in the Merci group (noninferiority p=0.0001; superiority p=0.020). In the Solitaire group, 8.6% of patients suffered study device-related serious adverse events (SAEs) versus 16.4% in the Merci group (p=0.26). The percentages for all procedure-related SAEs were 13.8% in the former versus 16.4% in the latter (p=0.80).

The first patient was enrolled in February 2010. At the end of July 2011, the trial met the interim efficacy stopping rule and was halted by the Data Safety Monitoring Board, Steering Committee, and sponsor for overwhelming efficacy.

FIA II Seeks Genetic Underpinnings of Familial Intracranial Aneurysm

Written by Rita Buckley

Prior studies indicate that genetic factors are important in the formation and rupture of intracranial aneurysms (IAs) [Broderick JP et al. *BMC Med Genet* 2005]. Joseph P. Broderick, MD, University of Cincinnati, Cincinnati, Ohio, USA, presented initial results from the Familial Intracranial Aneurysm Study II [FIA II; NCT00071565].

Most deaths from subarachnoid hemorrhage (SAH) are due to rapid and massive brain injury from the initial bleeding; therefore, prevention of aneurysm formation is of paramount importance. Scientific evidence suggests that a genetic component plays an important role in the development of IAs, but the specific genes that are involved have not been identified.

The purposes of FIA II were to identify genes that may increase the risk of aneurysm development in the brain and to determine the effect of environmental factors, such as cigarette smoking and high blood pressure, on the expression of those genes.

According to Dr. Broderick, approaches to dissect the genetic contribution to IAs have had mixed results. Linkage has been largely unsuccessful and, to this point, has not identified genetic variants that are associated with a risk of IA. Genomewide association studies (GWAS) have been somewhat successful, identifying several replicated genes with modest effect size (OR approximately 1.2 to 1.3), but again have yet to identify specific variants within these genes that are causally related to IA.

Whole exome sequencing (WES) is a promising new approach that focuses on the coding region of the genome (the exome). This method is designed to find variants that affect protein structure or function, which are relatively common in Mendelian disorders. WES complements GWAS but is best suited to the identification of rare (r)