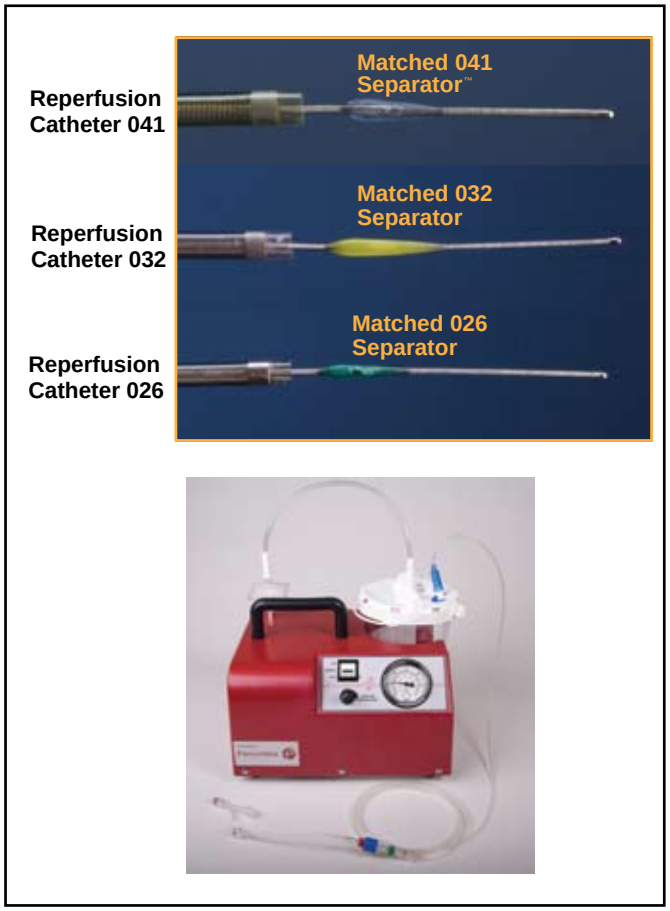
TLT is apparently safe and well tolerated, with no important effect of time from onset to treatment within the 24-hour time window. Although there was no difference in efficacy in the overall population, results from a prespecified subset of 434 patients with mRS 7 to 15 showed a significant (p=0.044) treatment effect in 51.6% of TLT patients versus 41.9% of patients in the sham group. "In light of the demonstrated safety of TLT, the results of this post hoc analysis are promising," said Justin Zivin, MD, San Diego VA Medical Center, San Diego, CA, "as they may indicate a benefit for patients who suffer moderate to moderately severe stroke." A multinational phase III study is planned (NEST-3).

Initial Post-Market Experience of the Penumbra System: Revascularization of Large Vessel Occlusion in Acute Ischemic Stroke in the United States and Europe

The Penumbra System is a mechanical clot removal device that is indicated for the revascularization of occluded large vessels in acute ischemic stroke (AIS). It has been approved for commercial use in the United States and Europe. In a postmarket study to assess its safety and effectiveness in a "real world" setting, the performance of the device was deemed to be comparable with the results of the pivotal Penumbra trial with regard to revascularization rate, incidence of adverse events, intracerebral hemorrhage (ICH), all-cause mortality, and 90-day good functional outcome.

The Penumbra System consists of a reperfusion catheter that is optimized for navigation and aspiration and a separator that cleans and clears clots from the occluded vessel (Figure 1). This was a retrospective case review study of 139 patients who were treated with the device at 7 centers. The primary endpoints were the rate of revascularization of the target vessel (TIMI 2 or 3) and procedural serious adverse events (SAEs). Secondary endpoints included percentage of patients with modified Rankin Score (mRS) ≤2 at 90 days, symptomatic ICH (sICH), and all-cause mortality. Eligible patients had an NIHSS score >8, symptom onset within 8 hours, and TIMI score of 0 or 1 at presentation.

Figure 1. Penumbra Aspiration System.



Mean age of the patient population (72 men and 67 women) was 64±15 years. Mean NIHSS score was 16±6. Target vessels included 26% internal carotid artery (ICA), 51% middle cerebral artery (MCA), and 24% vertebrobasilar artery. This compared with 18% ICA, 70% MCA, and 8% vertebrobasilar artery in the pivotal trial. Arterial puncture was initiated within 4.5 hours from symptom onset, and mean time for revascularization was 48 minutes, similar to that in the pivotal trial.

After use of the Penumbra System, 84% of the treated vessels were revascularized to TIMI 2 or 3. ICH rates at 24 hours were 5.8% and 7.2% for asymptomatic ICH and symptomatic ICH, respectively, which were lower, but not significantly, compared with those in the pivotal trial. There were a total of 8 SAEs and 2 device malfunctions (none of which resulted in patient injury). All-cause mortality was 22% (31/139). At discharge, 34% of the patients had a ≥10 point NIHSS improvement or NIHSS score 0-1. Of the patients who had reached the 90-day follow-up, 40% had a mRS ≤2.

Overall patients in the postmarket study had slightly higher revascularization rates (84% vs 82%), procedural SAEs (5.8% vs 3%), and mRS ≤2 scores (40% vs 25%), while patients in the pivotal study had higher rates of sICH (11% vs 7.2%) and all-cause mortality (33% vs 22%). These results suggest that the postmarket experience of the Penumbra System is consistent with that from the preapproval pivotal trial. Follow-up for some patients is ongoing.

Eligibility for rt-PA Within a Population: The Effect of the ECASS-3 Trial

According to standard emergency department (ED) guidelines, ischemic stroke patients must present to an ED within <3 hours of symptom onset to be eligible for rt-PA therapy. The European Cooperative Acute Stroke Study-3 (ECASS-3) expanded this eligibility window to 4.5 hours but with additional exclusion criteria. Dawn Kleindorfer, MD, University of Cincinnati Hospital Neuroscience Institute, Cincinnati, OH, presented data in a poster that showed that even with this expanded time window, eligibility for rt-PA remains low—about 9% versus 8% for the older time window.

This retrospective, observational study reviewed the primary/secondary hospital ICD-9-CM codes 430 to 436 from the year 1999 at 17 acute care hospitals in the greater Cincinnati/Northern Kentucky region. Of the 2441 ischemic stroke patients who were identified, 1968 presented to an ED. Fifty-four percent (54%) of these patients were female, 19% were black, and 80% were white. The mean age of the patients was 72 years.

In addition to the standard medical, time, and severity exclusions for rt-PA, the ECASS-3 excludes patients who are aged >80 years, those with an NIHSS score >25, those who have both diabetes mellitus and prior stroke history, and patients who have been given previous anticoagulant therapy. The purpose of the study was to compare the number of patients that is eligible for rt-PA therapy using the standard and revised ECASS-3 time frames and exclusion criteria.

Of the 2441 adult inpatient and out-of-hospital ascertained ischemic strokes, 1968 presented to an emergency department (81%) in 1999, 519 (22%) arrived in the ED in <3 hours from symptom onset and 87 (3.6%) arrived in 3 to 4.5 hours. Of the patients who arrived at the ED in <3 hours, 225 (11.4%) were eligible for standard regimen rt-PA, which is 9.2% of all ischemic stroke patients. Of the 87 patients who arrived between 3 and 4.5 hours, 23 (0.94%) were eligible using standard rt-PA exclusions, and only 24 (1.2%) would have been eligible using the additional exclusion criteria from the ECASS-3. Prevalence of the exclusion criteria for the 3 to 4.5 hour patients are listed in Table 1.

Table 1. Eligibility for rt-PA within a Population of Ischemic Stroke Patients Arriving 3 to 4.5 Hours After Symptom Onset.*

Standard Criteria†	n(%)
Partial thromboplastin time >40 sec	2 (3.5)
Platelet count <100,000	0
Mild Stroke (NIHSS <5)	21 (24.1)
INR <1.5	4.(4.6)
Glucose <50	0
Glucose >400	2 (2.3)
Seizure at onset	0
History of aneurysm or arteriovenous malformation	0
History of recent stroke, ICH/SAH	0
History of recent CEA or CABG	0
Systolic BP>185 or distolic BP>110	21(24.1)
ECASS-3 Exclusion Criteria†	
Age >80 years	27 (31.0)
NIHSS >25	1 (1.5)
Diabetes + prior stroke	12 (13.8)
Any anticoagulant use	7 (8.1)

*Categories are not mutually exclusive

†Does not agree with text since the same patient could be excluded for multi-reasons

NIHSS=National Institute of Health Stroke Scale; INR=international normalized ratio; ICH=intracranial hemorrhage; SAH=subarachnoid hemorrhage; CEA=carotid endarterectomy; CABG=coronary artery bypass grafting.

Dr. Kleindorfer concluded that the ECASS-3 expanded time window does not increase stroke patient eligibility for rt-PA very much since the majority of hyperacute patients arrives at the ED in <2 hours. She estimated that only an additional 0.94% of all stroke patients would have been eligible using the expanded ECASS-3 criteria. The ECASS-3 criteria excludes a significant portion of stroke patients, especially those aged >80 years (31%). However, the increased time window may still have an impact on rt-PA treatment rates and should not be ignored.