(p<0.001) more subjects in the device group experienced atrial fibrillation (AF; 5.7%) versus subjects in the medical group (0.7%). Sixty percent of the AF in the device group was periprocedural; 70% of AF lasted >24 hours. No significant relationship was identified between the rate of TIA or stroke and the presence of atrial septal aneurysm or the degree of PFO shunting. Recurrence rates did not differ between patients who presented with TIA versus stroke.

An alternative explanation was apparent for 80% of the recurrent strokes in this study, making it difficult to attribute them to paradoxical embolism. Potential alternate explanations for 9 of the 12 strokes in the device group were as follows: 3 were periprocedural, 3 subjects had typical lacunar events, 2 were associated with new AF, and one was related to cardiac catheterization. Alternative explanations were possible for the 13 strokes in the medical group: 8 subjects had multiple comorbidities (migraine, risk factors, etc), 4 were typical lacunar events, and one subject had possible vasculitis.

Results From the LEAPS Trial

Body weight-supported treadmill (BWST) training is an emerging modality to improve walking, but there is limited evidence to support its value. The Locomotor Experience Applied Post-Stroke (LEAPS; NCT00243919) trial was a single-blinded, Phase III, randomized clinical trial that was conducted to provide evidence to guide poststroke walking recovery programs. Pamela W. Duncan, PhD, Duke University, Durham, North Carolina, presented the results.

The objective of the LEAPS trial was to determine if, in addition to usual care, a specialized locomotor training program (LTP) that includes BWST training is superior to a home physical therapy program that is focused on structured, progressive strength and balance exercises (HEP); if the timing of intervention delivery for LTP (Early-LTP at 2 months after stroke vs Late-LTP at 6 months after stroke) affects recovery; and if initial walking impairment severity (moderate vs severe) affects response to the interventions. The primary outcome was the proportion of each group that improved their walking ability by one functional level at 1 year poststroke. The protocol for this study was previously published [Duncan PW et al. *BMC Neurol* 2007].

The LEAPS study was comprised of adults with moderate or severe walking limitations within 30 days of stroke onset who were able to pass an exercise stress test. Study participants (n=408) were stratified by moderate (0.4 to <0.8 m/sec) or severe (≤0.4 m/sec) walking impairment at 2 months poststroke and were randomly assigned to LTP, including BWST training, starting at either 2 months (Early-LTP; n=139) or 6 months poststroke (Late-LTP; n=143) or a home physical therapist-managed exercise program (HEP; n=126) delivered at 2 months poststroke. Each intervention included 36 sessions of 90 minutes each over 12 to 16 weeks.

Subjects had a mean age of 62 years, and 45% were women. The modified Rankin scale score for 99.5% of patients was 2–4. The mean walking speed was 0.38±0.22 m/sec, and the median number of daily steps was 1738; 53.4% of subjects had severe walking impairment.

At 1 year, ~52.0% of all participants had improved their walking ability by one functional level. No differences were found in the proportion that improved with Early-LTP or Late-LTP versus HEP. Six months after stroke, Early-LTP and HEP had similar gains in walking speed (Early-LTP 0.25±0.21m/sec; HEP 0.23±0.20 m/sec), which were sustained at 1 year. The Late-LTP group (which received only usual care from Month 2 to Month 6) improved by 0.13±0.14 m/sec at 6 months. All groups achieved similar and highly clinically relevant improvements in 6-minute walking ability, Stroke Impact Scale (SIS), activities of daily living (ADL) and instrumental activities of daily living (IADL) at 1 year.

Ten related serious adverse events were reported (2.2%, 3.5%, and 1.6 % in Early-LTP, Late-LTP, and HEP groups, respectively). There were more multiple falls in the severe Early-LTP group (p<0.07) and more dizziness/faintness during treatment (p<0.01) in the LTP groups. The HEP group had fewer all-cause rehospitalizations (p<0.09).

"LTP is not superior to HEP. Both physical therapy interventions are effective and have a low risk of adverse events, but HEP is associated with fewer risks and fewer rehospitalizations and is more accessible and feasible in current practice," Dr. Duncan said.

Combination Full-Dose IV-tPA + Argatroban Is Safe and May Result In Higher Rates of Recanalization

The benefit of intravenous recombinant tissue plasminogen activator (tPA) in acute ischemic stroke is related to clot lysis and arterial recanalization. Argatroban is a direct thrombin inhibitor that safely augments the benefit of tPA in animal stroke models; however, human data are limited. The Argatroban tPA Stroke Study (ARTSS; NCT00268762) is a multicenter, Phase II, prospective, open-label, safety and activity study of argatroban and

tPA in patients with ischemic stroke. The final results of ARTSS were presented by Andrew D. Barreto, MD, and James C. Grotta, MD, University of Texas-Houston, Houston, Texas, on behalf of the ARTSS investigators.

The primary (safety) outcome for ARTSS was the incidence of significant (ie, symptomatic or PH-2) intracerebral hemorrhage (ICH). Secondary (signal of efficacy) outcomes included rates of recanalization, measured at 2 and 24 hours by transcranial Doppler (TCD) ultrasonography or CT-angiogram, and modified Rankin Scale score at discharge. There was also a preplanned historical control comparison with the control data (IV-rtPA alone) from the CLOTBUST study [Alexandrov AV et al. *NEJM* 2004].

Eligibility included patients from 18 to 85 years of age who were admitted between 0 and 4.5 hours of stroke onset and met the criteria for intravenous tPA therapy. Subjects were also required to be within the NIH stroke scale (NIHSS) limits of 5–20 on the left hemisphere and 5–15 on the right hemisphere, have a proximal intracranial arterial occlusion that was measured by TCD or CT-angiogram, an INR ≤1.5, and no known hepatic disease. Subjects received full-dose IV-tPA (0.9 mg/kg) plus argatroban, given as a 100-mcg/kg bolus that was started during the tPA infusion and then as a 1-mcg/kg infusion over 48 hours. Argatroban was titrated to a target partial thromboplastin time (PTT)=1.75 by the patient's baseline.

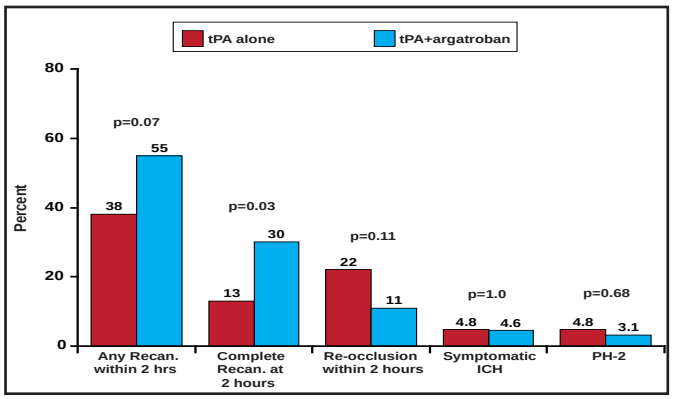
Subjects (n=65) had a mean age of 63 years, and 45% were men. The median subject NIHSS score was 13. Ninety percent of patients had middle cerebral artery occlusions, and the majority of patients were enrolled using TCD (n=47). The median time from the symptom onset to tPA bolus was 128 minutes (interquartile range 94 to 170 minutes). There was a median time of 17 minutes of overlap for the tPA and argatroban.

Target PTT (±10%) was achieved. Significant ICH occurred in 4 subjects (6.2%); three of them were symptomatic hemorrhage (4.6%) and 2 were parenchymal hemorrhage type 2 (PH-2; 3.1%). One patient was symptomatic and had a PH-2. There were 185 adverse events; 28 were considered serious, 3 were likely related to the treatment, and none was considered definitely related to treatment. There were 7 deaths (10.8%) by discharge or Day 7.

Of the 47 subjects who received TCD, 55% recanalized (complete recanalization in 30% and partial recanalization in 26%) at 2 hours. Five subjects (11%) recanalized before 2 hours but reoccluded at 2 hours. Of the 60 subjects with 24-hour data, 60% had complete recanalization and 18% had partial recanalization.

When compared with the controls from the CLOTBUST study, significantly (p=0.03) more patients in ARTSS achieved complete recanalization at 2 hours (Figure 1). There was also a trend toward reduced reocclusion. No difference in symptomatic ICH was found. A randomized, controlled Phase IIb study is planned to confirm and extend these findings.

Figure 1. Comparison to CLOTBUST Controls.



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Results From the SENTIS Trial

The Safety and Efficacy of NeuroFlo™ (CoAxia) Technology in Ischemic Stroke (SENTIS; NCT00119717) study is a multinational, randomized trial that evaluated partial abdominal aortic occlusion using the NeuroFlo™ catheter as a treatment for acute ischemic stroke. Results were presented by Ashfaq Shuaib, MD, University of Alberta, Edmonton, Canada, and William P. Dillon, MD, University of California, San Francisco, California.

Treatment with NeuroFlo™ involves femoral access and placement of the catheter in the descending aorta, followed by sequential inflation of two independently controlled balloons in the infra- and suprarenal positions, each to 70% luminal occlusion, for 45 minutes. Preclinical studies in swine have demonstrated a 35% to 50% increase in cerebral blood flow with this technique [Hammer M et al. *Cerebrovasc Dis* 2009], and studies in small animals have shown a reduction in infarct size [Noor R et al. *J Neuroimaging* 2009]. Safety and indications of clinical benefit have been shown in human feasibility trials in ischemic stroke [Liebeskind D. *Curr Cardiol Rep* 2008]. The hypothesis is that partial occlusion of the abdominal aorta will augment cerebral blood flow via collateral perfusion, thus limiting stroke progression and improving outcomes.

The SENTIS trial included subjects (n=515) with a clinical diagnosis of stroke, a time from symptom onset of 0 to 14 hours, and a baseline NIH Stroke Scale (NIHSS)