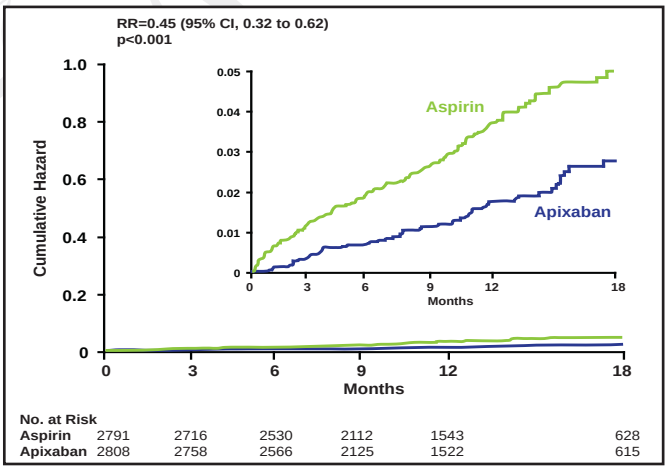
with AF who are at risk for stroke and unsuitable for VKA therapy. AVERROES was a double-blind, randomized, active comparator trial that compared apixaban with aspirin. Patients with documented AF and at least one risk factor for stroke who were also unsuitable for VKA therapy were randomly assigned to receive either apixaban 5 mg bid (n=2808) or aspirin 81–324 mg per day (n=2791). The primary study outcome was stroke or a systemic embolic event (SEE).

Subjects had a mean age of 70 years, and 59% were men. Approximately 75% of subjects were on aspirin therapy at baseline, and 40% had been on VKA therapy previously but had discontinued its use; 60% were considered unsuitable for VKA therapy. AVERROES was stopped early, based on overwhelming evidence of efficacy against stroke or SE, together with an excellent safety profile. The relative risk reduction in favor of apixaban was 0.45 (95% CI, 0.32 to 0.62; p<0.001; Figure 1).

Figure 1. Stroke or SEE.



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When the primary outcome events were assessed separately, there were 49 strokes with apixaban versus 105 with aspirin (RR, 0.46; 95% CI, 0.33 to 0.65; p<0.001) and 2 SEEs with apixaban versus 13 with aspirin (RR, 0.15; 95% CI, 0.03 to 0.68; p=0.01). There was no difference in the secondary outcomes of myocardial infarction, vascular death, or mortality. Hospitalizations for cardiovascular events were significantly lower with apixaban (367 vs 455; p<0.001).

Apixaban was well tolerated, with no evidence of liver toxicity. There was a small increase in bleeding with apixaban compared with aspirin, but the difference was not significant (RR, 1.13; 95% CI, 0.74 to 1.75; p=0.57). Adverse events were similar in both groups, with the exception of nervous system disorders, which were significantly more common in the aspirin group (6.6%) compared with the apixaban group (3% of patients; p<0.001) [Connolly SJ et al. *N Engl J Med* 2011].

No Advantage for Percutaneous Closure of PFO Versus Medical Therapy in Reducing Recurrent Neurological Events

Lawrence Wechsler, MD, University of Pittsburgh, Pittsburgh, Pennsylvania, presented the results of the CLOSURE I trial (NCT00201461). This trial was conducted to determine if percutaneous patent foramen ovale (PFO) closure using the STARFlex® Septal Closure System in combination with medical therapy, is superior to medical therapy alone to prevent recurrent ischemic neurological symptoms in patients with transient ischemic attack (TIA) or ischemic stroke.

CLOSURE I was a prospective, randomized, open-label, two-arm superiority trial. The study population included patients ≤60 years of age with a cryptogenic TIA or stroke and PFO, with or without atrial septal aneurysm, within 6 months of randomization. The primary endpoint was the 2-year incidence of stroke or TIA, all-cause mortality for the first 30 days, and neurological mortality from ≥31 days of follow-up, as adjudicated by a panel of physicians who were unaware of treatment allocation.

At 87 sites in the United States and Canada, subjects were randomized to either best medical therapy (n=462; aspirin 325 mg daily or warfarin [target INR 2.0-3.0] or a combination of the two) or percutaneous PFO closure with the STARFlex® system within 30 days of randomization followed by clopidogrel 75 mg for 6 months and aspirin 325 mg for 24 months (n=447). The mean age of study participants was ~46 years. Most (~90%) were white, and approximately 50% were men. Large shunts were significantly (p=0.04) more common in the device group, and atrial septal aneurysms were present in about one-third of each group. About 70% of both groups had stroke as the entry event.

There was no significant difference between the two groups in the primary composite endpoint (5.9% in the device group and 7.7% in the medical group; p=0.30) or in either of the individual components: a 3.1% rate of stroke for the device group versus 3.4% for medical therapy (p=0.77); and a 3.3% rate of TIA for the device group versus 4.6% for medical therapy (p=0.39). No significant differences between the groups were noted when subjects with only subcortical or lacunar infarcts were excluded.

There were significantly more major vascular complications (eg, perforation; hematoma >5 cm at access site; retroperitoneal bleed) in the device group (3.2% vs 0.0% in the medical group; p<0.001). Significantly

(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