In subgroup analyses, clazosentan reduced mortality/vasospasm-related morbidity in patients with poor WFNS grade (≥III) (RRR, 33%; 95% CI, 8% to 51%) and diffuse thick SAH (diffuse thick clot on baseline [CT] scan; RRR, 25%; 95% CI, 5% to 41%); however, no effect was observed on GOSE. Rescue therapy, a primary endpoint component, was used in 11% of clazosentan-treated and 16% of placebo-treated patients.

Treatment-emergent lung complications, anemia, and hypotension occurred in 34%, 22%, and 12% of clazosentan-treated patients versus 18%, 15%, and 4% of placebo-treated patients, respectively. Mortality was similar between the two groups (6%).

Severity of Deficit Strongly Predicts Long-Term Survival Among Stroke Survivors

Results of a long-term follow-up study in patients with atrial fibrillation (AF), presented by Margaret C. Fang, MD, PhD, University of California, San Francisco, California, demonstrated that deficit severity is a strong predictor of long-term poststroke survival.

AF increases the risk for ischemic stroke approximately 5-fold and causes an estimated 15% of all strokes in the United States [Wolf PA et al. *Stroke* 1991]. Studies of AF-related stroke typically describe only short-term (ie, 30-day) mortality. The goal of this long-term follow-up was to estimate the impact of ischemic stroke on the survival of patients with AF beyond the initial 30-day period.

The Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study is a cohort of 13,559 patients with diagnosed nonvalvular AF who were enrolled in an integrated health care delivery system for a median of 6 years. Incident ischemic strokes were identified using computerized databases and validated by medical record review. Functional status at discharge was obtained through chart review and was measured using a modified Rankin severity scale. Warfarin status at stroke presentation was obtained though chart review. Mortality was obtained from health plan databases and the State Death Index. The survival of patients with and without ischemic stroke was compared using multivariable Cox regression models, adjusted for clinical factors.

A total of 1025 incident ischemic strokes, occurring over 66,717 person-years of follow-up, were identified. A comparison of baseline characteristics of the 1025 cohort members who developed stroke with 12,534 cohort members who did not develop stroke showed several significant ($p<0.01$) differences. At 5 years, >70% of subjects without stroke were still alive compared with fewer than 40% of those who had a stroke. Subjects who were taking warfarin at the time of their stroke had less severe strokes (44% vs 47%), lower 30-day mortality rates (19.6% vs 27.7%; $p<0.01$), and lower rates of ischemic stroke (1.2% per year vs 2%).

Compared with cohort members without stroke, subjects who experienced a stroke had worse long-term survival (adjusted HR, 3.4; 95% CI, 3.1 to 3.7). Stroke severity at the time of discharge was a strong predictor of worse survival.

"The effects of stroke on mortality in patients with AF persist far beyond the initial event," Dr. Fang said, noting the results of this study highlight the importance of preventing strokes and reducing the severity of strokes when they do occur.

Apixaban Associated With Reduction in Stroke and SE in Patients Unsuitable for VKA Therapy

Hans-Christoph Diener, MD, University Hospital, Essen, Germany, presented the results of the Apixaban Versus Acetylsalicylic Acid to Prevent Strokes (AVERROES; NCT00496769) Study on behalf of the steering committee and the investigators. The study revealed clear evidence of a clinically important reduction in stroke and systemic embolism (SE) with apixaban over aspirin in patients with atrial fibrillation (AF) who were intolerant or otherwise considered unsuitable for vitamin K antagonist (VKA) therapy.

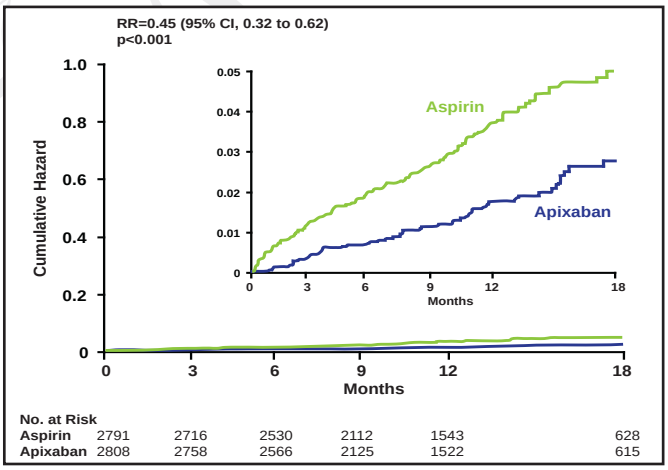
Patients with AF have an increased risk of stroke, and although VKA therapy is effective in reducing stroke, it is complex to manage and is associated with an increased risk of hemorrhage. For patients who are unsuitable for VKA therapy, the only alternative treatment is aspirin, which provides insufficient protection from stroke in high-risk patients (RR, 22%). Apixaban is an investigational oral anticoagulant that selectively inhibits factor Xa. It is efficacious as prophylaxis for venous thromboembolism and has a favorable risk-benefit ratio compared with low-molecular-weight heparin.

The purpose of the AVERROES Study was to evaluate apixaban for the prevention of stroke or SE patients

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.



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