No Significant Improvement in Vasospasm-Related Morbidity or All-Cause Mortality with Clazosentan After aSAH

Results from the Clazosentan in Reducing Vasospam-Related Morbidity and Mortality in Adult Patients with Aneurysmal Subarachnoid Hemorrhage Treated By Surgical Clipping (CONSCIOUS-2; NCT00558311) study, presented by Robert Loch Macdonald, MD, PhD, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada, indicate that the use of the endothelin receptor antagonist clazosentan does not significantly improve vasospasm-related morbidity or all-cause mortality after aneurysmal subarachnoid hemorrhage (aSAH).

Cerebral vasospasm is a frequent complication of aSAH that leads to significant morbidity and mortality. In a previous study [R. Loch Macdonald et al. *Stroke* 2008], clazosentan significantly and dose-dependently reduced angiographic vasospasm after aSAH, with a trend toward a reduction in morbidity and mortality. CONSCIOUS-2 was designed to assess whether clazosentan reduces cerebral vasospasm-related morbidity and all-cause mortality within 6 weeks post-aSAH.

This was a randomized, double-blind, placebo-controlled study of men and women aged 18 to 75 years with a ruptured saccular aneurysm, confirmed by angiography and successfully secured by surgical clipping, for which the time of rupture was known or estimated with a reasonable degree of certainty. Subjects were required to have a World Federation of Neurological Surgeons (WFNS) grade I–IV prior to the clipping procedure that did not worsen to grade V postprocedure (based on regular Glasgow Coma Scale) and a diffuse subarachnoid clot on the baseline computed tomography (CT) scan.

Eligible subjects were randomly assigned 2:1 to receive intravenous clazosentan (5 mg/hour; n=764) or placebo (n=383), starting within 56 hours of clipping and continuing for up to 2 weeks. The primary composite endpoint was vasospasm-related morbidity and all-cause mortality within 6 weeks of aSAH (ie, death, new cerebral infarcts due to vasospasm, delayed ischemic neurological deficit [DIND] due to vasospasm, and/or the use of rescue therapy). The main secondary endpoints were functional clinical outcome, as measured by extended Glasgow Outcome Scale (GOSE), dichotomized into good (score >4) and poor (score ≤4), at Week 12; total volume of new cerebral infarcts of all etiologies at Week 6; and the individual components of the primary endpoint. Safety was assessed by adverse events.

Subjects had a mean age of 52 years, and about 70% were women. Most (~77%) were WFNS class I–II. Approximately 50% of the subjects had diffuse thick hemorrhages. There was a nonsignificant 17% reduction in the primary endpoint in the treated group (Figure 1). There was a trend toward poor outcomes (GOSE score ≤4) in the clazosentan-treated group (29.3%) versus placebo-treated patients (24.8%; RRR, -18%; 95% CI, -45% to 4%; p=0.1048, logistic regression adjusted for WFNS). When the individual endpoint components were analyzed separately, clazosentan had no effect on mortality; however, drug treatment did reduce the formation of new vasospasm-related cerebral infarcts, the occurrence of vasospasm-related DIND, and the use of rescue therapy, although none of these effects was significant (Figure 2).

Figure 1. Vasospasm-Related Morbidity/All-Cause Mortality Within 6 Weeks

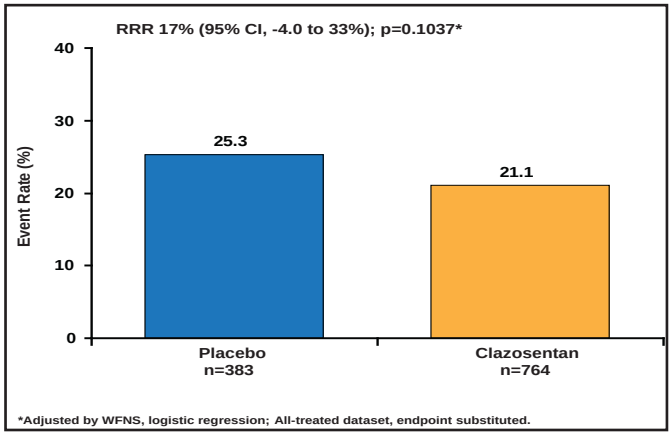

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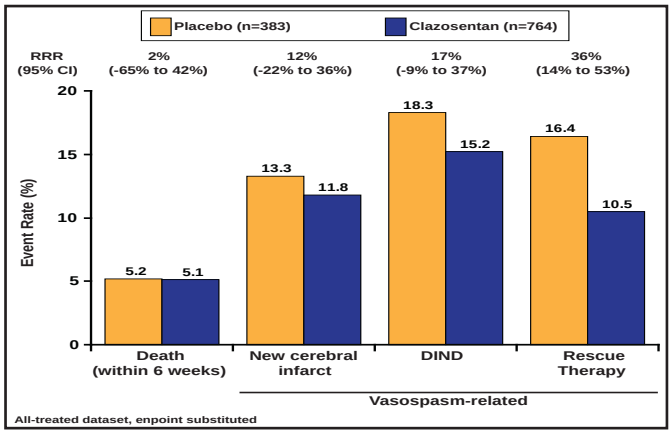
Figure 2. Individual Components of the Composite Endpoint.



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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