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Experimental Agent Better Than Aspirin at Preventing Stroke, Study Suggests

A new anti-clotting agent is vastly superior to aspirin at reducing stroke risk (1.6 percent per year versus 3.6 percent per year) in Atrial Fibrillation (AF) patients unable to take stronger drugs, according to final data reported February 10 at the American Stroke Association's International Stroke Conference 2011. Researchers found the drug also works better in people with a history of stroke or a warning stroke.

Atrial fibrillation is a heartbeat abnormality that can cause blood clots which raise the risk of stroke, particularly in the elderly.

The AVERROES: Apixaban Versus Acetylsalicylic Acid (ASA) to Prevent Strokes trial is a randomized trial of 5,600 AF patients at moderate to high risk of stroke who were not willing or able to take oral vitamin-K antagonists like warfarin, a drug commonly prescribed to prevent blood clots in people with AF. They were treated at 520 medical centers worldwide. A May 2010 interim analysis found evidence that the investigational oral drug apixaban was so much more superior to aspirin that the researchers were advised to end the trial early, said Hans-Christoph Diener, M.D., professor and chairman, Department of Neurology and Stroke Center, University Hospital Essen, Essen, Germany.

In releasing the study's final results, he reported that apixaban was far superior to aspirin at preventing stroke or systemic embolism (blood clot) and was also very safe. The drug blocks factor Xa, a crucial step in blood clot formation, said Diener, co-chair of the study's adjudication committee.

"Apixaban was highly superior to aspirin. We had not anticipated that apixaban would show such a big difference compared with aspirin while showing no significant increase in major bleeds," he said. "Everyone had expected that a more powerful drug like apixaban would be associated with more severe bleeding complications compared to aspirin, but it wasn't."

The study's primary endpoint was the reduction of ischemic stroke (stroke caused by blockages in the brain's circulation), hemorrhagic stroke (stroke due to bleeding in the brain) and systemic embolism (blockages due to blood clots elsewhere in the body), he said. The primary safety endpoint was major bleeding incidents.

Up to 50 percent of all AF patients with moderate or high stroke risk are unsuitable for the most effective class of anti-clotting treatment known as vitamin K antagonists (VKA). That class includes the well-known drug warfarin.

All of the AVERROES patients were unsuitable for VKA therapy, which carries an increased risk of hemorrhage and requires frequent blood testing to monitor its effectiveness. For such patients the only alternate treatment is aspirin, which is just modestly effective, Diener said.

The patients in this study, all over age 50, were at moderate to high risk because they had at least one stroke risk factor in addition to AF, such as being age 75 or older, having high blood pressure, heart failure, diabetes or having a history of stroke or transient ischemic attack (a possible precursor of stroke), he explained.

Patients were randomized to receive either apixaban at 5 milligrams (mg) twice a day (2.5 mg twice a day in selected patients) or between 81 mg and 324 mg of aspirin per day. The study's double-dummy design mandated that patients randomized to receive apixaban took an aspirin-placebo and those randomized to receive aspirin got an apixaban-placebo, he explained.

During an average of 1.1 years of follow up, the researchers found 51 strokes or systemic embolism events

in the 2,808 patients taking apixaban compared to 113 strokes and systemic embolic events in the 2,791 patients taking aspirin. That represents an annual rate of 1.6 percent for apixaban vs. 3.6 percent for aspirin, meaning apixaban carries about half the relative risk of stroke or systemic embolism compared to aspirin. Although bleeding events were slightly higher with apixaban, the difference fell short of statistical significance.

The researchers will also report on a subgroup of patients with a history of stroke or transient ischemic attack often a precursor to stroke.

"If validated by future studies I think this is the end of aspirin as a drug to prevent stroke in patients with AF," he added.

Diener said the study's major limitation is the limited time period of observation, shortened further by the study's early conclusion. "AF patients need anticoagulation for the rest of their lives and we would have liked to see a much longer duration of the trial," he said.

"By evaluating the use of apixaban as a replacement for aspirin in AF patients who are unsuitable for VKA therapy, the AVERROES study is addressing an important unmet clinical need."

Co-authors are Salim Yusuf M.D., Ph.D.; John Eikelboom, M.D.; Martin O. O'Donnell, M.D.; and Stuart J. Connolly, M.D. Disclosures are on the abstract. Bristol-Myers Squibb and Pfizer funded the study.

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