ARRHYTHMIAS

Apixaban triumphs over aspirin for stroke prevention in patients with atrial fibrillation

The investigational factor Xa inhibitor apixaban is superior to aspirin for the prevention of stroke in patients with atrial fibrillation (AF), and does not increase the risk of bleeding. These findings from the AVERROES trial, which were first presented at the European Society of Cardiology Congress in August 2010, have now been published in the *New England Journal of Medicine*.

AF is the most common arrhythmia encountered in clinical practice, particularly among elderly patients. The prevalence of AF has increased over the past two decades and, with aging of the population, will continue to rise. The management of this condition will, therefore, be an ongoing challenge for health-care professionals.

Stroke is perhaps the most devastating and feared complication of AF. The risk of stroke in patients with this disease is approximately fivefold higher than that in the general population. Vitamin K antagonists, such as warfarin, are the cornerstone of stroke prevention in patients with AF. However, patients receiving warfarin therapy require continuous monitoring, and maintaining the international normalized ratio (INR) within the therapeutic range is challenging. Consequently, some investigators have estimated that one-third of patients with AF and an indication for warfarin therapy do not receive this drug. An urgent need exists for new anticoagulant medications to replace warfarin.

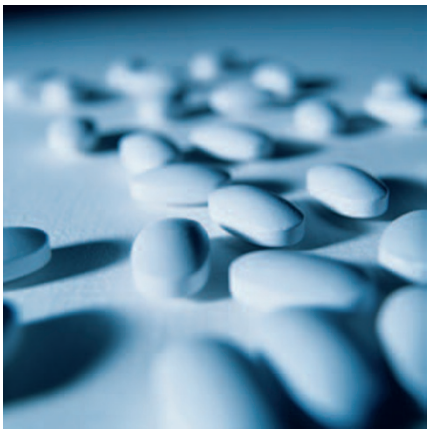
Apixaban, which is being developed by Bristol-Myers Squibb and Pfizer, is undergoing phase III testing in the ongoing EXPANSE program—a series of clinical trials that includes the AVERROES trial. Apixaban has already been shown to be safe and effective for the prevention of venous thromboembolism in patients undergoing orthopedic surgery. The AVERROES study saw the investigation of this agent in patients with AF for whom warfarin therapy was unsuitable.

Enrollment for the AVERROES trial commenced in September 2007 and continued until December 2009. A total of 5,599 patients from 36 countries were recruited. All participants were at least 50 years of age, had been diagnosed as having AF during the 6 months before enrollment, and had a least one additional risk factor for stroke. In addition, warfarin therapy was either documented to be, or expected to be, inappropriate for these patients.

Participants were randomly assigned to receive apixaban 5 mg twice daily or aspirin 81–324 mg daily. The primary outcome measure for efficacy was the incidence of stroke (ischemic or hemorrhagic) or systemic embolism. The rate of major bleeding was assessed as the primary safety end point. In addition, all-cause mortality and a composite of major vascular events —including myocardial infarction and death from vascular causes—were assessed.

Among the 2,216 patients who had received warfarin therapy before study enrollment, 42% had discontinued this treatment because the INR could not be maintained within the therapeutic range, whereas 37% of patients had refused to continue taking the drug.

The AVERROES trial was terminated early at the first interim analysis in February 2010, owing to a clear evidence of benefit for apixaban. Follow-up continued until August 2010 (mean duration 1.1 years). The incidence of the primary end point was reduced by more than 50% in the apixaban group as compared with the aspirin group (1.6% per year versus 3.7% per year; hazard ratio [HR] 0.45, 95% CI 0.32–0.62, $P<0.001$). When the two types of stroke were assessed independently, although apixaban was associated with a reduced rate of ischemic stroke (1.1% per year versus 3.0% per year for aspirin; HR 0.37, 95% CI 0.25–0.55, $P<0.001$), no difference was found in the rate of hemorrhagic stroke between the two groups. The rate of hospitalization for



cardiovascular causes was also reduced with the use of apixaban. No significant treatment effect was observed on the rate of major bleeding (apixaban: 1.4% per year; aspirin: 1.2% per year).

Professor Stanley Nattel from the University of Montreal, Canada who was not involved in the study, highlights that the findings from the AVERROES trial represent a new and important contribution to the literature. He suggests that "there could be concerns about the judgment that warfarin therapy was not appropriate, exposing patients at increased risk of stroke to the possibility of treatment with an inadequate therapy (aspirin). One has to be comfortable with the reasonable assumption that physicians did not withhold warfarin therapy in order to include patients in the trial." Looking to the future, Professor Nattel indicates that, if granted regulatory approval, apixaban could become a useful therapy for patients with AF who are at low-to-medium risk of stroke and who might not presently receive warfarin because of the risks.

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