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ANTICOAGULATION THERAPY

Direct factor Xa inhibition improves stroke prevention in patients with AF

The oral direct factor Xa inhibitor rivaroxaban is noninferior to warfarin for the prevention of stroke or systemic embolism in patients with atrial fibrillation (AF), according to the results of the randomized, controlled Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF), which have now been published in the *New England Journal of Medicine*.

According to Dr Manesh Patel, lead author of the report, "AF is a worldwide disease that accounts for up to 25% of all strokes." Patients with AF are, therefore, commonly prescribed an anticoagulant drug, such as the vitamin K antagonist warfarin (which inhibits factors II, VII, IX, and X), to reduce this risk. However, "many patients have difficulty with warfarin control because of food, medication, and other interactions that lead to under-treatment and over-treatment," says Professor Keith Fox from the University of Edinburgh, UK, who is co-chair of ROCKET AF. "There are concerns about major and intracranial bleeding with warfarin (because of factor VII antagonism, a bleed into the brain might have worse consequences than with a [direct factor] Xa inhibitor)."

The ROCKET AF investigators recruited 14,264 patients with nonvalvular AF who were at moderate-to-high risk of stroke (indicated by a history of stroke, transient ischemic attack, or systemic embolism, or at least two of the following factors: heart failure or a left ventricular ejection fraction ≤35%, hypertension, age ≥75 years, or the presence of diabetes mellitus). Patients from 1,178 participating sites in 45 countries were then randomly allocated to receive either fixed-dose rivaroxaban (20 mg daily, or 15 mg daily in patients with a creatinine clearance of 30–49 ml/min) or adjusted-dose warfarin (target international normalized ratio 2–3). The median durations of treatment exposure and follow-up were 590 and 707 days, respectively.

The rate of stroke or systemic embolism was significantly lower in the rivaroxaban group compared with warfarin therapy (1.7% vs 2.2% per year, HR 0.79, 95% CI 0.66–0.96, $P<0.001$). Importantly, the rate of major and nonmajor clinically relevant bleeding was not different between the groups (14.9% vs 14.5% per year, HR 1.03, 95% CI 0.96–1.11, $P=0.44$). Rivaroxaban was associated with significantly lower rates of intracranial hemorrhage and fatal bleeding, but a higher incidence of major bleeding from a gastrointestinal site, than warfarin. "These findings were striking," says Dr Patel, "in that this group of patients, with a median age of 73 years and several risk factors for stroke, tolerated the therapy well and were protected from stroke."

"For the first time," remarks Professor Fox, "we have a factor Xa inhibitor at least as good as warfarin and with less fatal bleeding. Rivaroxaban (and dabigitran) now provide alternatives [to warfarin] for patients with AF and [increased] stroke risk." Rivaroxaban is already approved for prophylaxis and treatment of deep vein thrombosis, and research will be performed to investigate whether the drug can improve therapy in other populations, such as patients with artificial heart valves.

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