Apixaban for reduction in stroke and other ThromboemboLic events in atrial fibrillation (ARISTOTLE) trial: design and rationale.

Abstract:
Atrial fibrillation (AF) is associated with increased risk of stroke that can be attenuated with vitamin K antagonists (VKAs). Vitamin K antagonist use is limited, in part, by the high incidence of complications when patients' international normalized ratios (INRs) deviate from the target range. The primary objective of ARISTOTLE is to determine if the factor Xa inhibitor, apixaban, is noninferior to warfarin at reducing the combined endpoint of stroke (ischemic or hemorrhagic) and systemic embolism in patients with AF and at least 1 additional risk factor for stroke. We have randomized 18,206 patients from over 1,000 centers in 40 countries. Patients were randomly assigned in a 1:1 ratio to receive apixaban or warfarin using a double-blind, double-dummy design. International normalized ratios are monitored and warfarin (or placebo) is adjusted aiming for a target INR range of 2 to 3 using a blinded, encrypted point-of-care device. Minimum treatment is 12 months, and maximum expected exposure is 4 years. Time to accrual of at least 448 primary efficacy events will determine treatment duration. The key secondary objectives are to determine if apixaban is superior to warfarin for the combined endpoint of stroke (ischemic or hemorrhagic) and systemic embolism, and for all-cause death.
These will be tested after the primary objective using a closed test procedure. The noninferiority boundary is 1.38; apixaban will be declared noninferior if the 95% CI excludes the possibility that the primary outcome rate with apixaban is >1.38 times higher than with warfarin. ARISTOTLE will determine whether apixaban is noninferior or superior to warfarin in preventing stroke and systemic embolism; whether apixaban has particular benefits in the warfarin-naïve population; whether it reduces the combined rate of stroke, systemic embolism, and death; and whether it impacts bleeding.