Stroke Risk and Efficacy of Apixaban in Atrial Fibrillation Patients with Moderate Chronic Kidney Disease

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Background: Apixaban is superior to aspirin for the prevention of stroke in patients with atrial fibrillation. Apixaban is partially renally excreted and may accumulate in patients with renal impairment. *Methods:* We evaluated the efficacy and safety of apixaban 5 mg twice daily (2.5 mg twice daily in selected patients) compared with aspirin 81 to 324 mg daily in 1697 patients with stage III chronic kidney disease (CKD) enrolled in the Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) trial. Primary outcome was all stroke and non–central nervous system emboli. *Results:* Compared with patients with estimated glomerular filtration rates (eGFRs) ≥60 mL/min per 1.73 m^2, stage III CKD patients (n = 1697; 30% of the cohort; mean eGFR 49 mL/min per 1.73 m^2) were older (mean age 75 *v* 68 years) with more frequent hypertension, diabetes, heart failure, and previous stroke (all $P < .01$). Stage III CKD was an independent predictor of primary events (hazard ratio [HR] 1.6; $P = .01$) and major hemorrhage (HR 2.2; $P = .02$). Apixaban significantly reduced primary events by 68% (5.6% per year on aspirin *v* 1.8% per year on apixaban; HR 0.32; 95% confidence interval [CI] 0.18-0.55; $P < .001$) for stage III CKD participants and by 43% (2.8% per year on aspirin *v* 1.6% per year on apixaban; HR 0.57; 95% CI 0.37-0.87; $P = .009$) for patients with eGFRs ≥60 mL/min per 1.73 m^2 (P for interaction = .10). There was no significant difference in major hemorrhage in stage III CKD patients by treatment: 2.2% per year with aspirin versus 2.5% per year with apixaban (HR 1.2; 95% CI 0.65-2.1). *Conclusions:* Stage III CKD was an independent predictor of stroke in atrial fibrillation patients taking aspirin. Among stage III CKD patients, apixaban significantly reduced stroke relative to aspirin without a significant increase in major hemorrhage. **Key Words:** Anticoagulation—apixaban—atrial fibrillation—chronic kidney disease—stroke.

Chronic kidney disease (CKD) affects about 10% of adults and is associated with increased rates of cardiovascular disease.[1,2] In a large observational study of outpatients with atrial fibrillation (AF), nearly one-third had stage III CKD, and an estimated glomerular filtration rate (eGFR) of <45 mL/min per 1.73 m^2 was an independent predictor of stroke.[3] Independent assessment of the predictive value of stage III CKD for

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stroke in AF patients would potentially influence patient management.

New oral anticoagulants that have been tested in AF patients are partially eliminated by renal excretion.[4,5] Because of the prolongation of half-lives of most novel anticoagulants in CKD patients, the antithrombotic effects may be enhanced for these agents when given to patients with CKD, but this may be counterbalanced by a higher risk of bleeding. Therefore, the efficacy and safety of new oral anticoagulants merit assessment in patients with CKD.

A substantial number of participants with CKD were included in the Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) trial, which compared apixaban, a direct factor Xa inhibitor, with aspirin in AF patients who were deemed unsuitable for warfarin anticoagulation.[5] Here, we assess whether CKD status predicts stroke and major hemorrhage during aspirin therapy and analyze the efficacy and safety of apixaban relative to aspirin in AVERROES participants with stage III CKD.

Methods

The design and main results of the AVERROES trial have been published.[5,6] The trial was terminated at an interim analysis after 1.1 years of mean follow-up because of the clear and substantial efficacy of apixaban. Patients with permanent or paroxysmal AF were eligible if they had ≥1 of the following additional risk factors for stroke: previous stroke or transient ischemic attack (TIA); age ≥75 years; arterial hypertension on treatment; diabetes mellitus; heart failure, left ventricular ejection fraction ≤35%; or documented peripheral arterial disease. In addition, patients were required not to be candidates for oral anticoagulation with a vitamin K antagonist (e.g., warfarin), either because anticoagulant therapy had been demonstrated or was expected to be unsuitable.[5] Serum creatinine >2.5 mg/dL (221 μmol/L) or an estimated creatinine clearance <25 mL/min per 1.73 m^2 by the Cockcroft–Gault equation[7] was an exclusion. Patients were randomized to receive apixaban (5 mg twice daily) or aspirin (81 to 324 mg daily), administered in a double-blinded fashion. A reduced dose of apixaban (2.5 mg twice daily) was assigned to participants who met 2 of the following criteria: (1) age ≥80 years, (2) body weight ≤60 kg, or (3) serum creatinine ≥1.5 mg/dL or 133 μmol/L.

The primary efficacy outcome was stroke (ischemic or hemorrhagic) or systemic embolism. The diagnosis of stroke was clinically suspected by an acute onset of focal neurologic symptoms lasting >24 hours and verified by computed tomographic or magnetic resonance imaging of the brain. The primary safety outcome was major bleeding, defined as clinically overt bleeding accompanied by ≥1 of the following: decrease in hemoglobin of ≥2 g/dL over a 24-hour period, transfusion of ≥2 units of packed red blood cells, bleeding that occurs in a critical site (intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal), or bleeding that was fatal.

Subgroup results for participants with estimated creatinine clearances of <50 mL/min per 1.73 m^2, 50 to <80 mL/min per 1.73 m^2, and ≥80 mL/min per 1.73 m^2 by the Cockcroft–Gault method were included in Figure 2 of the AVERROES main results publication.[5] For the analyses presented here, the eGFR was calculated using the serum creatinine at study entry and the Chronic Kidney Disease Epidemiology Collaboration equation.[8] Serum creatinine measurements at study entry were available for all but 4 of the 5599 AVERROES participants: 4381 had only central laboratory values available, 107 had only local measurements (obtained within 30 days before entry), and 1107 had both. Blood samples were shipped on dry ice to 1 of 7 regional laboratories for central measurement of creatinine levels. Unless otherwise specified, central laboratory values were used to calculate the eGFR when available (i.e., in 98% of participants). Patients designated as CKD stage III had an eGFR of 30 to 59 mL/min per 1.73 m^2, and stage IV patients had an eGFR of 15 to 29 mL/min per 1.73 m^2 at study entry.[9]

We evaluated whether CKD contributed independently to stroke risk prediction using the CHADS2 stroke risk stratification score, which is widely used in AF patients.[10] The CHADS2 scheme uses a point system, with 1 point given for each of *C*ongestive heart failure, *H*ypertension, *A*ge ≥75 years, and *D*iabetes mellitus, and 2 points for previous *S*troke/TIA. In 8 participants, data were missing for calculation of a CHADS2 score. Because only 15 patients in both treatment arms had a CHADS2 score of 0 (qualifying for inclusion based on peripheral vascular disease or reduced left ventricular systolic function), those with a CHADS2 scores of 0 or 1 were grouped for analyses; 99% of this group had a CHADS2 score of 1.

Participants were recruited from 522 clinical sites in 36 countries. The Population Health Research Institute (McMaster University, Hamilton, Canada) was the coordinating center for the trial and was primarily responsible for study management, data collection, and analysis and publications. The study was overseen by a steering committee consisting of representatives from each participating country, the Population Health Research Institute, and study sponsors (Bristol-Myers-Squibb and Pfizer). An independent data safety monitoring board periodically reviewed the data. The protocol was approved by the ethics committees of all participating institutions and relevant regulatory bodies, and all patients provided written informed consent.

Analyses were performed with SAS software (version 9.1; SAS Institute, Cary, NC) on a Unix operating system. Continuous data were summarized as means and categorical data as percentages. Comparison for categorical data used the Chi-square test with *t* tests for continuous