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Major Bleeding in Patients With Atrial Fibrillation Receiving Apixaban or Warfarin

The ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation): Predictors, Characteristics, and Clinical Outcomes

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Objectives This study sought to characterize major bleeding on the basis of the components of the major bleeding definition, to explore major bleeding by location, to define 30-day mortality after a major bleeding event, and to identify factors associated with major bleeding.

Background Apixaban was shown to reduce the risk of major hemorrhage among patients with atrial fibrillation in the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial.

Methods All patients who received at least 1 dose of a study drug were included. Major bleeding was defined according to the criteria of the International Society on Thrombosis and Haemostasis. Factors associated with major hemorrhage were identified using a multivariable Cox model.

Results The on-treatment safety population included 18,140 patients. The rate of major hemorrhage among patients in the apixaban group was 2.13% per year compared with 3.09% per year in the warfarin group (hazard ratio [HR] 0.69, 95% confidence interval [CI]: 0.60 to 0.80; $p < 0.001$). Compared with warfarin, major extracranial hemorrhage associated with apixaban led to reduced hospitalization, medical or surgical intervention, transfusion, or change in antithrombotic therapy. Major hemorrhage followed by mortality within 30 days occurred half as often in apixaban-treated patients than in those receiving warfarin (HR 0.50, 95% CI: 0.33 to 0.74; $p < 0.001$). Older age, prior hemorrhage, prior stroke or transient ischemic attack, diabetes, lower creatinine clearance, decreased hematocrit, aspirin therapy, and nonsteroidal anti-inflammatory drugs were independently associated with an increased risk.

Conclusions Apixaban, compared with warfarin, was associated with fewer intracranial hemorrhages, less adverse consequences following extracranial hemorrhage, and a 50% reduction in fatal consequences at 30 days in cases of major hemorrhage. (J Am Coll Cardiol 2014;63:2141–7) © 2014 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

AF = atrial fibrillation

CI = confidence interval

HR = hazard ratio

INR = international normalized ratio

ISTH = International Society on Thrombosis and Haemostasis

TIA = transient ischemic attack

Atrial fibrillation (AF) is a potent risk factor for stroke. Warfarin is highly efficacious in reducing this risk, but its effectiveness in clinical practice is challenged by its variable dose response, need for frequent monitoring, and associated risk of hemorrhage. Among patients age 65 years or older, warfarin was noted to be the drug most often implicated in medication-related adverse events leading to emergency hospital stay (1). Apixaban, a factor Xa inhibitor, was shown to reduce the risk of major hemorrhage by 31% compared with warfarin among patients with AF in the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial (2). In this report, we sought to: 1) define 30-day mortality after a major bleeding event and determine whether this factor differed between warfarin- and apixaban-treated patients; 2) identify predictors of major bleeding and determine whether predictors of major bleeding varied between warfarin- and apixaban-treated patients; 3) further characterize the reduction in major bleeding based on the components of the major bleeding definition and determine whether these components varied between warfarin- and apixaban-treated patients; and 4) explore major bleeding by location and determine whether bleeding locations varied between warfarin- and apixaban-treated patients.

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Methods

The ARISTOTLE trial design has been reported previously (3). Patients with AF and at least 1 risk factor for stroke were randomized to receive either dose-adjusted warfarin or apixaban, 5 mg twice daily. A reduced dose of apixaban, 2.5 mg twice daily, was designated for participants with 2 or more of the following criteria: age $\geq$80 years, weight $\leq$60 kg, or serum creatinine concentration $\geq$1.5 mg/dl (133 μmol/l). The reduced dose of apixaban was administered to 428 patients (4.7%). To enhance the quality of warfarin management, a dosage algorithm was provided, and a program implemented to provide regular feedback to sites regarding their level of international normalized ratio (INR) control.

The analyses of bleeding events included all patients who received at least 1 dose of a study drug and included all events from the time of the first dose until 2 days after the last dose was received. Major bleeding was defined according to International Society on Thrombosis and Haemostasis (ISTH) criteria as clinically overt bleeding accompanied by a decrease in the hemoglobin level of at least 2 g/dl or transfusion of at least 2 units of packed red cells, occurring at a critical site (intracranial, intraocular, intraspinal, intra-articular, intramuscular with compartment syndrome, pericardial, retroperitoneal), or resulting in death (4). No time restrictions were applied to this definition. Laboratory and transfusion data coupled with clinical event details were used to identify and adjudicate potential bleeding events. Routine collection of hemoglobin occurred every 3 months. Location of bleeding was extracted from the case report form. Additional source documents were collected when necessary. The primary safety outcomes were adjudicated on the basis of pre-specified criteria by a clinical events committee whose members were not aware of study group assignments.

Severity of hemorrhage and 30-day mortality following first ISTH major hemorrhage. Parameters to assess the severity of major hemorrhage, in addition to anatomic location, for apixaban and warfarin were determined and compared. Metrics relevant for major extracranial hemorrhage included decrease of hemoglobin of at least 2 g/dl, hospitalization because of bleeding, transfusion of packed red cells, number of units transfused, medical or surgical consultation or evaluation, medical or surgical intervention to stop the bleeding, hemodynamic compromise, and change in antithrombotic therapy. Thirty-day mortality rates following first ISTH major hemorrhage were evaluated and compared between warfarin- and apixaban-treated patients.

Statistical analyses. Categorical variables were summarized as frequencies and percentages and continuous variables as medians and 25th and 75th percentiles. p Values representing comparisons between patients with and without major bleeding were based on Cox regression models with ISTH criteria first major hemorrhage as a dependent variable. p Values for the interactions between randomized treatment and each covariate were derived using Cox models. Factors associated with the first ISTH major hemorrhage were identified using a multivariable Cox model. Candidate variables included demographics and clinical characteristics, medications, and laboratory values at baseline. Randomized treatment and region of enrollment were also included as candidate variables. Missing values in predictors were imputed using multiple imputations.

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