CHEST

Original Research

ANTITHROMBOTIC THERAPY

Bleeding Risk in Patients With Atrial Fibrillation

The AMADEUS Study

Deirdre A. Lane, PhD; Pieter W. Kamphuisen, MD; Pascal Minini, PhD; Harry R. Büller, MD; and Gregory Y. H. Lip, MD

Objective: **This study aimed to assess the impact of combination antithrombotic therapy on stroke and bleeding risk compared with anticoagulation therapy only in patients with atrial fibrillation (AF).**

Methods: **Post hoc analysis of 4,576 patients with AF (mean ± SD age, 70.1 ± 9.1 years; men, 66.5%) enrolled in the Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients With Atrial Fibrillation (AMADEUS) trial were randomized to receive either subcutaneous idraparinux (2.5 mg weekly) (n = 2,283) or dose-adjusted vitamin K antagonists (VKAs) (international normalized ratio, 2.0-3.0) (n = 2,293). Of these patients, 848 (18.5%) received antiplatelet therapy (aspirin, clopidogrel, ticlopidine, etc) in addition to anticoagulation treatment (combination antithrombotic therapy).**

Results: **A total of 572 (15.3% per year) clinically relevant bleeding and 103 (2.6% per year) major bleeding events occurred. Patients receiving combination antithrombotic therapy had a 2.3- to 2.5-fold increased risk of clinically relevant bleeding events and major bleeding events, respectively, compared with those receiving anticoagulation therapy only. Multivariate analyses (hazard ratio, 95% CI) revealed that the risk of clinically relevant bleeding was significantly increased by age 65 to 74 years (1.44, 1.14-1.82) and ≥ 75 years (1.59, 1.24-2.04, *P* = .001) and by combination antithrombotic therapy (2.47, 2.07-2.96, *P* < .0001). The same held true for major bleeding events, with analogous figures for age 65 to 74 years (2.26, 1.08-4.71) and ≥ 75 years (4.19, 1.98-8.87, *P* = .0004) and for combination antithrombotic therapy (2.23, 1.49-3.34, *P* < .0001). Combination antithrombotic therapy was not associated with a decrease in ischemic stroke risk compared with anticoagulation therapy only (11 [1.4% per year] vs 22 [0.7% per year]; adjusted hazard ratio, 2.01; 95% CI, 0.94-4.30; *P* = .07).**

Conclusions: **Combination antithrombotic therapy increases the risk of clinically relevant bleeding and major bleeding in patients with AF and does not appear to reduce the risk of stroke.**

CHEST 2011; 140(1):146–155

Abbreviations: ACS = acute coronary syndrome; AF = atrial fibrillation; AMADEUS = Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients With Atrial Fibrillation; CAD = coronary artery disease; $CHADS_2$ = congestive heart failure, hypertension, age ≥ 75 years, diabetes, and prior stroke or transient ischemic stroke; CIAC = Central Independent Adjudication Committee; INR = international normalized ratio; TIA = transient ischemic attack; VKA = vitamin K agonist

Prescription of antithrombotic therapy for atrial fibrillation (AF) must consider both the patient's stroke risk and his or her risk of bleeding while on anticoagulant therapy; that is, there must be a net clinical benefit to initiate anticoagulant therapy. Given that AF commonly coexists with associated atherosclerotic vascular disease, a significant proportion of patients with AF receiving anticoagulation therapy also receive concomitant antiplatelet therapy.[1,2] The benefit of combination antithrombotic therapy (anticoagulant plus antiplatelets) in patients with AF has yet to be elucidated from clinical trials, but combination antithrombotic therapy in this population has been shown to be associated with an increased risk of bleeding[1,3-7] with no significant reduction in thromboembolic events.[6]

The present study is a post hoc analysis of predictors of major bleeding and clinically relevant bleeding