Comparison of Bleeding in Patients With Nonvalvular Atrial Fibrillation Treated With Ximelagatran or Warfarin

Assessment of Incidence, Case-Fatality Rate, Time Course and Sites of Bleeding, and Risk Factors for Bleeding

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Background Ximelagatran is a novel direct thrombin inhibitor that can be administered as a fixed oral dose, without the need for anticoagulant monitoring.

Methods We undertook a pooled analysis of 7329 patients with nonvalvular atrial fibrillation from the Stroke Prevention Using Oral Thrombin Inhibitor in Atrial Fibrillation III and V trials to compare bleeding outcomes in patients who received ximelagatran, 36 mg twice daily, or warfarin sodium (target international normalized ratio, 2.0-3.0). We determined annual risk of bleeding (any, major), case-fatality rate, time course and anatomic sites of major bleeding, and risk factors for major bleeding with ximelagatran and warfarin treatment.

Results Annual incidence of any bleeding was 31.75% with ximelagatran and 38.82% with warfarin (relative risk reduction, 18.2%; 95% confidence interval [CI], 13.0-23.1; \( P < .001 \)). Annual incidence of major bleeding was 2.01% with ximelagatran and 2.68% with warfarin (relative risk reduction, 25.1%; 95% CI, 3.2-42.1; \( P = .03 \)). Case-fatality rate of bleeding was comparable in ximelagatran- and warfarin-treated patients (8.16% vs 8.09%; \( P = .98 \)). Cumulative incidence of major bleeding was higher with warfarin than ximelagatran after 24 months of treatment (4.7% vs 3.7%; \( P = .04 \)). Anatomic sites of bleeding were comparable with both treatments. Risk factors for bleeding with ximelagatran were as follows (hazard ratios and 95% CIs in parentheses): diabetes mellitus (1.81; 1.19-2.77; \( P = .006 \)), previous stroke or transient ischemic attack (1.78; 1.16-2.73; \( P = .008 \)), age 75 years or greater (1.70; 1.33-2.18; \( P < .001 \)), and aspirin use (1.68; 1.08-2.59; \( P = .02 \)). Risk factors for bleeding in warfarin-treated patients were previous liver disease (4.88; 1.55-15.39; \( P = .007 \)); aspirin use (2.41; 1.69-3.43; \( P < .001 \)); and age 75 years or greater (1.26; 1.03-1.52; \( P = .02 \)).

Conclusions Treatment with ximelagatran, 36 mg twice daily, is associated with a lower risk of bleeding than warfarin in patients with nonvalvular atrial fibrillation. Aspirin use and increasing age were associated with an increased risk of bleeding in ximelagatran- and warfarin-treated patients.