Ximelagatran was noninferior to warfarin in preventing stroke and systemic embolism in atrial fibrillation


In patients with atrial fibrillation (AF) at risk for ischemic stroke, is ximelagatran noninferior to warfarin in preventing stroke and systemic embolism?

**Design**
Randomized (allocation concealed*), blinded (outcome assessors),† controlled trial with mean 17.4-month follow-up [SPORTIF].

**Setting**
23 countries.

**Patients**
3410 patients ≥ 18 years of age who had nonvalvular AF and ≥ 1 additional risk factor for stroke: treatment for hypertension but blood pressure < 180/100 mm Hg; age ≥ 75 years; previous stroke, transient ischemic attack (TIA), or systemic embolism; left ventricular dysfunction; or age ≥ 65 years and coronary artery disease or diabetes mellitus. Exclusion criteria included mitral stenosis or coronary artery disease or diabetes mellitus.

**Main results**
Analysis was by intention to treat. Ximelagatran was not inferior to warfarin for stroke and systemic embolism (Table), or for the secondary outcomes. An on-treatment analysis showed that ximelagatran had less combined major and minor bleeding events than warfarin and was not inferior to warfarin for major bleeding only (Table). Serum alanine aminotransferase levels (ALT) increased (>3 times the upper limit of normal) more with ximelagatran than warfarin (6% vs 1%, *P < 0.001*).

**Conclusions**
In patients with atrial fibrillation at risk for ischemic stroke, ximelagatran was noninferior to warfarin in preventing stroke and systemic embolism.

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**Commentary**
SPORTIF III compared ximelagatran, 36 mg twice daily, with therapeutic warfarin in patients with AF at moderate to high risk for thromboembolic outcomes. INR control in the warfarin group was similar to that in the community (*P < 0.001*). The results, along with the recently reported SPORTIF V (2), showed that ximelagatran is at least as efficacious as warfarin and at least as safe for bleeding complications (see Editorial). From a practical standpoint, ximelagatran is an easier drug to use than warfarin because it can be administered in a fixed-dose regimen, without the need for laboratory monitoring of its anticoagulant effect to make dose adjustments, and does not appear to have drug- and food-related interactions that occur with warfarin. These advantages have the potential to greatly simplify the anticoagulant management of patients with AF. However, ximelagatran is potentially hepatotoxic (Table). Most studies of long-term ximelagatran showed almost all patients were asymptomatic, and about half had complete resolution of increased ALT levels despite continuing the drug. With few exceptions, increased ALT levels resolved in the remaining patients after the drug was stopped. Although patients treated with ximelagatran will require hepatic monitoring in the initial 3 months of therapy, the intensity of such monitoring will probably not match that required for long-term warfarin therapy.

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**Hepatotoxicity of ximelagatran**

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*ALT = alanine aminotransferase; DVT = deep venous thrombosis; MI = myocardial infarction; NVAF = nonvalvular atrial fibrillation; 3 × n = 3 times the upper limit of normal.

**References**