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

Olsson SB. **Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomised controlled trial.** Lancet. 2003;362:1691-8.

QUESTION

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 previous valvular heart surgery, transient AF, stroke in the past 30 days or TIA in the past 3 days, risk for bleeding, and need for cardiac intervention or major surgery. 3407 patients (99.9%) were included in the analysis.

INTERVENTION

Ximelagatran, 36 mg twice daily (n = 1704), or warfarin dose-adjusted to maintain the INR between 2.0 and 3.0 (n = 1703).

MAIN OUTCOME MEASURES

All stroke and systemic embolic events. Secondary outcomes included composite endpoints of major and minor bleeding; ischemic stroke, TIA, and systemic embolism; and death, stroke, systemic embolism, and myocardial infarction.

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).

CONCLUSION

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

Source of funding: AstraZeneca.

For correspondence: Professor S.B. Olsson, University Hospital, Lund, Sweden. E-mail bertil.olsson@kard.lu.se.

*See Glossary.

Ximelagatran vs warfarin in patients with atrial fibrillation at risk for ischemic stroke at mean 17.4 months†

Outcomes	Event rates per year		Difference (95% CI)
	Ximelagatran	Warfarin	
All stroke and systemic embolism‡	1.6%	2.3%	–0.7% (–0.1 to 1.4)‖
Major or minor bleeding§	25.8%	29.8%	–4.0% (–6.9 to –1.1)
Major bleeding§	1.3%	1.8%	–0.5% (–1.2 to 0.2)‖

†CI defined in Glossary; ‡Intention-to-treat analysis; §On-treatment analysis; ‖Not significant.

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 (1). 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.

Carl van Walraven, MD
Ottawa Health Research Institute
Ottawa, Ontario, Canada

Hepatotoxicity of ximelagatran* (xim) twice daily

Studies	Patients	Xim	Control	Duration of treatment	Definition of hepatotoxicity	Event rates	
						Xim	Control
SPORTIF II (3)	NVAF	20/40/60 mg	Warfarin INR 2.5	3 mo	ALT > 3 × n	4.3%	0%
ESTEEM (4)	Post MI	24–60 mg + aspirin	Aspirin, 160 mg once daily	6 mo	ALT > 5 × n	7.0%	1.0%
THRIVE III (5)	DVT	24 mg	Placebo	16.8 mo	ALT > 3 × n	6.4%	1.2%
SPORTIF III	NVAF	36 mg	Warfarin INR 2.5	17.4 mo	ALT > 3 × n	6.0%	1.0%

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

References

1. **Wilson SJ, Wells PS, Kovacs MJ, et al.** CMAJ. 2003;169:293-8.
2. **Verheugt FW.** Lancet. 2003;362:1686-7.
3. **Petersen P, Grind M, Adler J.** J Am Coll Cardiol. 2003;41:1445-51.
4. **Wallentin L, Wilcox RG, Weaver WD, et al.** Lancet. 2003;362:789-97.
5. **Schulman S, Wahlander K, Lundstrom T, Clason SB, Eriksson H.** N Engl J Med. 2003;349:1762-4.