Ximelagatran was non-inferior 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.

This article contains extra text on the EBM website

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Q In patients with atrial fibrillation (AF) at risk for ischaemic stroke, is ximelagatran non-inferior to warfarin in preventing stroke and systemic embolism?

METHODS

Design: randomised controlled trial (Stroke Prevention using an ORal Thrombin Inhibitor in atrial Fibrillation [SPORTIF]).

Allocation: concealed.*

Blinding: blinded (outcome assessors).*

Follow up: mean 17.4 months.

Setting: 259 hospitals, doctor's offices, and clinics in 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 ischaemic 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 of bleeding, and need for cardiac intervention or major surgery.

Intervention: ximelagatran, 36 mg twice daily (n = 1704), or warfarin dose adjusted to maintain the international normalised ratio (INR) between 2.0 and 3.0 (n = 1703).

Outcomes: All stroke (ischaemic and hemorrhagic) and systemic embolic events. Secondary outcomes included composite endpoints of major and minor bleeding; ischaemic stroke, TIA, and systemic embolism; and death, stroke, systemic embolism, and myocardial infarction.

Patient follow up: 3407 patients (99.9%) were included in the analysis.

*See glossary.

MAIN RESULTS

Analysis was by intention to treat. Ximelagatran was not inferior to warfarin for stroke and systemic embolism (table), or for the composite secondary endpoints. 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 increased (>3 times the upper limit of normal) more with ximelagatran than warfarin (6% *v* 1%, p<0.001).

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CONCLUSION

In patients with atrial fibrillation at risk of ischaemic stroke, ximelagatran was non-inferior to warfarin in preventing stroke and systemic embolism.

Abstract and commentary also appear in ACP Journal Club.

Ximelagatran *v* warfarin in patients with atrial fibrillation at risk of ischaemic 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 of 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 EBM notebook (http://ebm.bmjjournals.com/cgi/content/9/2/38). 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 (see table on web site).[3 4 5] Most studies of long term ximelagatran showed almost all patients were asymptomatic and about half had complete resolution of transaminitis despite continuing the drug. With few exceptions, transaminases 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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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, *et al. N Engl J Med* 2003;**349**:1762–4.

Table W1 Hepatotoxicity of ximelagatran*

Studies	Patients	Ximelagatran	Control	Duration of treatment	Definition of hepatotoxicity	Event rates	
						Ximelagatran	Control
SPORTIF II[1]	NVAF	20/40/60 mg twice daily	Warfarin INR 2.5	3 mo	ALT >3 × n	4.3%	0%
ESTEEM[2]	Post MI	24-60 mg twice daily + aspirin	Aspirin, 160 mg once daily	6 mo	ALT >5 × n	7.0%	1.0%
THRIVE III[3]	DVT	24 mg twice daily	Placebo	16.8 mo	ALT >3 × n	6.4%	1.2%
SPORTIF III	NVAF	36 mg twice daily	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.

1 Petersen P, Grind M, Adler J**.** Ximelagatran versus warfarin for stroke prevention in patients with nonvalvular atrial fibrillation. SPORTIF II: a dose-guiding, tolerability, and safety study. *J Am Coll Cardiol* 2003;**41**:1445–51.
2 Wallentin L, Wilcox RG, Weaver WD, *et al***.** Oral ximelagatran for secondary prophylaxis after myocardial infarction: the ESTEEM randomized controlled trial. *Lancet* 2003;**362**:789–97.
3 Schulman S, Wahlander K, Lundstrom T**,** *et al.* Secondary prevention of venous thromboembolism with the oral direct thrombin inhibitor ximelagatran. *N Engl J Med* 2003;**349**:1762–4.