

# Ximelagatran was not inferior to warfarin for preventing stroke and systemic embolism in nonvalvular atrial fibrillation

Executive Steering Committee for the SPORTIF V Investigators. Ximelagatran vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: a randomized trial. *JAMA*. 2005;293:690-8.

**Clinical impact ratings:** GIM/FP/GP ★★★★★☆ Hospitalists ★★★★★☆ Cardiology ★★★★★☆ Hematol/Thrombo ★★★★★★

## QUESTION

In patients with nonvalvular atrial fibrillation requiring long-term oral anticoagulant therapy, is fixed-dose oral ximelagatran noninferior to adjusted-dose warfarin for preventing stroke and systemic embolism?

## METHODS

**Design:** Randomized controlled trial (Stroke Prevention using an Oral Thrombin Inhibitor in Atrial Fibrillation [SPORTIF V]).

**Allocation:** Concealed.\*

**Blinding:** Blinded (clinicians, patients, and outcome assessors).\*

**Follow-up period:** Mean 20 months.

**Setting:** 409 sites in the United States and Canada.

**Patients:** 3922 patients (mean age 72 y, 69% men) who had persistent or paroxysmal nonvalvular atrial fibrillation and  $\geq 1$  risk factor for stroke (e.g., previous stroke, transient ischemic attack, or systemic embolism; hypertension; left ventricular dysfunction; and age  $\geq 75$  y or  $\geq 65$  y with coronary disease or diabetes mellitus).

**Intervention:** Fixed-dose oral ximelagatran, 36 mg twice daily ( $n = 1960$ ), or adjusted-dose warfarin (target international normalized ratio 2.0 to 3.0) ( $n = 1962$ ).

**Outcomes:** Composite endpoint of stroke (ischemic and hemorrhagic) or systemic embolism. Secondary outcomes included

major bleeding, major and minor bleeding combined, myocardial infarction, and elevated liver enzymes (serum alanine aminotransferase level  $> 3$  times the upper limit of normal).

**Patient follow-up:** 100% (intention-to-treat analysis).

## MAIN RESULTS

Ximelagatran was noninferior to warfarin for preventing the composite endpoint of stroke or systemic embolism (Table). The groups did not differ for rates of myocardial infarction and major bleeding (Table). However, the rate of major and minor bleeding combined was lower in the ximelagatran group

than in the warfarin group (Table), and more patients in the ximelagatran group had elevated liver enzymes (6.0% vs 0.8%,  $P < 0.001$ ).

## CONCLUSION

In patients with nonvalvular atrial fibrillation requiring long-term oral anticoagulant therapy, fixed-dose oral ximelagatran was noninferior to adjusted-dose warfarin for preventing stroke and systemic embolism.

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\*See Glossary.

## Fixed-dose oral ximelagatran vs adjusted-dose warfarin in nonvalvular atrial fibrillation requiring long-term anticoagulation therapy at mean 20 months†

Outcomes	Event rate per patient-y		Difference (95% CI)
	Ximelagatran	Warfarin	
Any stroke (ischemic or hemorrhagic) or systemic embolism	1.6%	1.2%	0.45% (−0.13 to 1.0)‡
Myocardial infarction	1.0%	1.4%	−0.4% {−0.9 to 0.2}§
Major bleeding (excluding extracerebral)	2.4%	3.1%	−0.66% (−1.6 to 0.23)
Major and minor bleeding combined	37%	47%	−10% (−14 to −6.0)  ¶

†CI defined in Glossary.

‡Intention-to-treat analysis; criterion for noninferiority was met because the upper limit of the 95% CI was  $< 2\%/y$ .

§CI provided by author.

||On-treatment analysis that discounted events after treatment cessation.

¶Significant difference favors ximelagatran.

## COMMENTARY

The SPORTIF V trial showed that ximelagatran was noninferior to warfarin for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation and, compared with warfarin, was associated with a somewhat lower incidence of bleeding. These findings are similar to those from the SPORTIF III trial, which also compared ximelagatran with warfarin therapy in the same patient population (1). Taken together, these studies suggest that ximelagatran is an alternative to warfarin in patients with atrial fibrillation.

Unlike warfarin, ximelagatran is not known to interact with other drugs or foods and has a predictable anticoagulant effect, thereby obviating the need for laboratory monitoring or dose-adjustments. It may be speculated that the stable anticoagulation associated with ximelagatran accounts for the lower incidence of bleeding complications compared with warfarin treatment.

Based on these trials, the potential for ximelagatran to replace warfarin for atrial fibrillation is promising, but several issues need to be addressed. First, ximelagatran is excreted by the kidneys and patients with a creatinine clearance  $< 30$  mL/min were not studied. Elderly

patients with atrial fibrillation may have unrecognized renal insufficiency, because the serum creatinine level remains in the normal range for a long time after the onset of impaired renal function. Second, the availability of an antidote in case of life-threatening bleeding would be desirable, and the options appear limited for ximelagatran (2). Finally, 6% of ximelagatran-treated patients developed increased liver enzymes between the 2nd and 6th month of treatment, which has been a consistent finding in all clinical trials so far. It is not clear whether the increase in liver enzymes is associated with a clinically important impairment in liver function, although in virtually all patients the liver enzymes normalized spontaneously or after cessation of ximelagatran. This last issue, especially, requires further study and resolution before ximelagatran will be considered by licensing agencies for clinical use.

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## References

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