Note: This is a two-article spread with a shared commentary. Please scroll down for the second article.

Ximelagatran reduced venous thromboembolism more than warfarin after total knee replacement

Francis CW, Berkowitz SD, Comp PC, et al. **Comparison of ximelagatran with warfarin for the prevention of venous thromboembolism after total knee replacement.** N Engl J Med. 2003;349:1703-12.

QUESTION

In patients having total knee replacement, is ximelagatran better than warfarin in preventing venous thromboembolism (VTE)?

DESIGN

Randomized (allocation concealed*),blinded (clinicians, patients, {data collectors, outcome assessors, and data analysts}†),* controlled trial with 4- to 6-week follow-up (Exanta Used to Lessen Thrombosis A [EXULT A]).

SETTING

116 centers in the United States, Canada, Israel, Mexico, and Brazil.

PATIENTS

2301 patients who were having primary total knee replacement and weighed between 40 and 136 kg. Exclusion criteria included pneumatic leg compression; immobilization ≥ 3 days; major surgery, stroke, myocardial infarction, or receipt of study drug ≤ 30 days before surgery; increased risk for bleeding ≤ 90 days before surgery; uncontrolled hypertension; thrombocytopenia; drug or alcohol abuse in the past 6 months; and potential for pregnancy. 2285 patients (99%) (mean age 68 y, 62% women) were included in the safety analysis and 1851 (80.4%) in the efficacy analysis.

INTERVENTION

Patients were allocated to twice-daily tablets of ximelagatran (Exanta, AstraZeneca), 36 mg (n = 775); 24 mg (n = 762); or once-daily warfarin (Coumadin, Bristol-Myers Squibb) (n = 764). Placebos were given for each study drug. Ximelagatran was started ≥ 12 hours after surgery when hemostasis had been achieved, and warfarin was started the evening of the day of surgery and adjusted to achieve an international normalized ratio (INR) of 2.5.

MAIN OUTCOME MEASURES

Composite primary endpoint of total deep venous thrombosis (DVT), pulmonary embolism (PE), and all-cause mortality during treatment (7 to 12 d); composite of proximal DVT, PE, and all-cause mortality; and bleeding.

MAIN RESULTS

Fewer patients who received ximelagatran, 36 mg, had an occurrence of the composite primary endpoint than did patients who received warfarin (Table). The ximelagatran 24-mg group did not differ from the warfarin group (Table). Neither ximelagatran group differed from warfarin for the secondary composite endpoint of proximal DVT, PE, and all-cause mortality (P values > 0.10). Groups did not differ for bleeding (Table).

CONCLUSION

In patients having total knee replacement, ximelagatran, 36 mg twice-daily, was more effective than warfarin in preventing venous thromboembolism.

Source of funding: AstraZeneca.

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*See Glossary.

†Information provided by author.

Ximelagatran (xim), 36 mg twice-daily and 24 mg twice-daily, vs warfarin (warf) after total knee replacement at 7 to 12 days‡

Outcomes	Comparisons	Event rates	RRR (95% CI)	NNT (CI)
Composite primary endpoint	Xim 36 mg vs warf	20.3% vs 27.6%	26% (9.9 to 40)	14 (9 to 40)
	Xim 24 mg vs warf	24.9% vs 27.6%	9.8% (–8.8 to 25)	Not significant
			RRI (CI)	**NNH**
Major bleeding	Xim 36 mg vs warf	0.8% vs 0.7%	18% (–61 to 264)	Not significant
	Xim 24 mg vs warf	0.8% vs 0.7%	20% (–61 to 270)	Not significant

‡Composite primary endpoint = venous thromboembolism, pulmonary embolism, and all-cause mortality. Abbreviations defined in Glossary; NNT, NNH, and CI calculated from data in article.

COMMENTARY

The trial by Francis and colleagues shows the superiority of a 36-mg, twice-daily dose of ximelagatran over warfarin, both started after surgery, for prevention of VTE after total knee replacement surgery. However, as the greater efficacy came entirely from a decreased incidence of isolated (largely asymptomatic) calf-vein thrombosis, the interpretation of these results deserves comment.

In most studies, comparing low-molecular-weight heparins (LMWHs), which have a rapid onset of action, and oral anticoagulants, which require 2 to 4 days to render an anticoagulant effect, the latter category of drugs has been less effective. Because both the study and the comparator drugs were started at the same time after surgery, I wonder whether the superiority of ximelagatran simply reflects the different onset of action of the 2 drugs. All that oral anticoagulants can do in this setting is prevent thrombus from growing. Indeed, both in this trial and in virtually all those assessing LMWHs, the incidence of proximal-vein thrombosis and that of PE, when taken together, did not differ between patients receiving oral anticoagulants and those receiving heparin.

Despite this consideration, warfarin is problematic for VTE prophylaxis because of the need for laboratory monitoring and potential drug interactions, and LMWHs are the standard of care for prevention of VTE after orthopedic surgery. Although ximelagatran was shown to be more effective than enoxaparin in the EXPRESS study (1), it has not been compared with fondaparinux, a synthetic anti-Xa inhibitor that is more effective than enoxaparin for VTE prophylaxis after orthopedic surgery. The ultimate comparison of efficacy in the prevention of VTE after orthopedic surgery may be a head-to-head comparison between ximelagatran and fondaparinux.

The optimal long-term treatment of patients who present with unprovoked (or idiopathic) VTE is controversial. 15% to 30% of patients with idiopathic VTE will have recurrent VTE in the first year after 3 to 6 months of anticoagulation. Prolonging the duration of anticoagulation beyond 3 to 6 months may delay recurrences while exposing patients to the hemorrhagic risk associated with extended anticoagulation. The possibility that a lower-intensity warfarin regimen

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Ximelagatran prevented secondary venous thromboembolism

Schulman S, Wåhlander K, Lundström T, Clason SB, Eriksson H. **Secondary prevention of venous thromboembolism with the oral direct thrombin inhibitor ximelagatran.** N Engl J Med. 2003;349:1713-21.

QUESTION

What is the long-term efficacy and safety of ximelagatran after 6 months of standard anticoagulant therapy for secondary prevention of venous thromboembolism (VTE)?

DESIGN

Randomized (allocation concealed*), blinded (clinicians, patients, {data collectors, outcome assessors, and data analysts}†),* placebo-controlled trial with 18-month follow-up (Thrombin Inhibitor in Venous Thromboembolism [THRIVE III]).

SETTING

142 centers in 18 countries.

PATIENTS

1233 patients who were ≥ 18 years of age with symptomatic, objectively confirmed deep venous thrombosis (DVT) or pulmonary embolism (PE) and had received anticoagulant therapy for 6 months with no recurrent VTE event. Exclusion criteria were indication for continuous anticoagulant therapy, hemoglobin level < 9.0 g/dL, platelet count < 90 000/mm^3, pregnancy, lactation, expected survival < 18 months, renal impairment, clinically important liver disease, or persistent elevation of the aminotransferase level > 3 times the upper limit of normal. 1223 patients (99%) (mean age 57 y, 53% men) were included in the intention-to-treat analysis.

INTERVENTION

Patients were allocated to twice-daily ximelagatran, 24 mg (n = 612), or placebo (n = 611) for 18 months. All patients discontinued anticoagulant therapy but did not begin study treatment until the international normalized ratio (INR) was < 1.5.

MAIN OUTCOME MEASURES

VTE (recurrent DVT and PE), major and minor bleeding, and all-cause mortality.

MAIN RESULTS

Analysis was by intention to treat. Fewer patients who received ximelagatran had recurrent VTE events than did patients who received placebo (Table). Groups did not differ for major or minor bleeding or for all-cause mortality (Table).

CONCLUSION

In patients with deep venous thrombosis or pulmonary embolism receiving standard anticoagulant therapy for 6 months, ximelagatran reduced recurrent venous thromboembolism and did not increase bleeding.

Source of funding: AstraZeneca Research and Development.

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*See Glossary.

†Information provided by author.

Ximelagatran vs placebo for secondary prevention of venous thromboembolism (VTE) at 18 months‡

Outcomes	Ximelagatran	Placebo	RRR (95% CI)	NNT (CI)
VTE	2.8%	12.6%	83% (69 to 90)	10 (9 to 12)
All-cause mortality	1.1%	1.4%	17% (–143 to 72)	Not significant
Major bleeding	1.1%	1.3%	16% (–65 to 273)	Not significant
			RRI (CI)	NNH
Major and minor bleeding	23.9%	21.0%	16% (–6 to 44)	Not significant

‡Abbreviations defined in Glossary; RRR, RRI, NNT, NNH, and CI calculated from data in article using estimates from hazards ratios in article.

COMMENTARY *(continued from page 8)*

(INR 1.5 to 1.9) would allow safer anticoagulation without compromising efficacy (2) was trumped by the results of another study that showed that conventional-intensity anticoagulation (INR 2.0 to 3.0) has better efficacy than a lower-intensity regimen (3). The results of the trial by Schulman and colleagues show that long-term ximelagatran therapy, administered orally in a fixed dose and without laboratory monitoring, is effective for preventing recurrent VTE in patients who received 6 months of conventional anticoagulant therapy and is not associated with an increased hemorrhagic risk.

However, the extent to which ximelagatran prevented recurrent VTE was not different from that of oral anticoagulants in the many trials that addressed their benefit. Furthermore, the apparent lack of hemorrhagic potential may have been because of the unusually high rate of bleeding in patients who received placebo. Finally, in about 6% of patients, aminotransferase levels increased to > 3 times the upper limit of normal. Additional research is required to identify the optimal strategy of long-term anticoagulation in patients with idiopathic VTE. There is the potential that disease recurrence can be predicted on an individual basis after 3 to 6 months of conventional therapy if venous ultrasonography shows persistent abnormalities or D-dimer levels are elevated (4, 5).

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