

Rivaroxaban: An Ideal Anticoagulant?

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Many patients require continuing anticoagulation therapy due to atrial fibrillation, mechanical valve replacements, and other prothrombotic conditions. Because current options (heparin, low-molecular-weight heparin, warfarin, and fondaparinux) have acknowledged drawbacks¹ research has focused on finding a viable alternative anticoagulant. In 2004, one option seemed promising: the experimental oral direct thrombin inhibitor, ximelagatran, approved in Europe, made it to phase 3 clinical trials in the United States; however, evidence of hepatotoxicity halted further development.

Currently seeking approval in more than 10 countries,² rivaroxaban, an oral factor Xa inhibitor, binds to the active site of factor Xa to competitively inhibit free and clot-bound factor Xa. Well absorbed orally, with an approximate bioavailability of 80%, half of the circulating drug is metabolized hepatically to inactive metabolites. Excretion occurs via two distinct pathways: 2/3 is excreted renally (36% unchanged); 1/3 is excreted via the biliary route (elimination half-life is 5-9 hours). The most promising findings presented, to date, are: aspirin or naproxen adverse interactions are not apparent; the QTc interval is not prolonged; nor is liver toxicity an identified adverse event. However, data on exposure in more patients and for longer durations are needed to confirm safety.^{1,3}

Rivaroxaban has been studied for the prevention of venous thromboembolic events following orthopedic surgery. Four phase III trials, which make up the RECORD studies,^{2,4-6} compared rivaroxaban to a low molecular weight heparin, enoxaparin, for prevention of

venous thromboembolism after hip or knee arthroplasty in more than 12,500 patients. The primary endpoint for all RECORD trials was total venous thromboembolic events, defined as the composite of deep vein thrombosis, nonfatal pulmonary embolism, and all-cause mortality. Secondary endpoints include major and symptomatic venous thromboembolic events, and bleeding. Results are summarized in Table 1. Rivaroxaban appears more effective than enoxaparin for the primary and secondary endpoints.^{2,4-6}

Table 1. RECORD Trials Results^{2,4-6}

Trial	RECORD 1 n=4541	RECORD 2 n=2509	RECORD 3 n=2531	RECORD 4 n=3148
Indication	Hip arthroplasty		Knee arthroplasty	
Enoxaparin	40 mg daily 35 d	40 mg daily 10-14 d	40 mg daily 10-14 d	30 mg bid, 10-14 d
Rivaroxaban	10 mg daily 35 d	10 mg daily 31-39 d	10 mg daily 10-14 d	10 mg daily 10-14 d
DVT/PE/death (%)	3.7 vs 1.1 p<0.001	9.3 vs 2.0 p<0.001	18.9 vs 9.6 p<0.001	10.1 vs 6.9 p=0.012
RRR (%)	70	79	49	31
Symptomatic VTE (%)	0.5 vs 0.3 p=0.22	1.2 vs 0.2 p=0.004	2.0 vs 0.7 p=0.05	1.2 vs 0.7
RRR (%)	--	80	66	--
Major bleeding (%)	0.1 vs 0.3 p=0.178	<0.1 vs <0.1	0.5 vs 0.6 p=0.77	0.3 vs 0.7

RRR=relative risk; bid=twice daily

Given these outcomes, rivaroxaban may seem like a leading candidate for an effective, safe, and convenient agent for thromboprophylaxis. However, RECORD 1, 2, and 3 used approved European dosing (40 mg every 24 hours),^{2,4,5} whereas RECORD 4, published in abstract form only, used approved United States dosing (30 mg every 12 hours).⁶ The American College of Chest Physicians recommends dosing 30 mg every 12 hours following orthopedic procedures.⁷ Disparity between recommended and studied dosages complicates extrapolation to current United States practice because enoxaparin's treatment effect was potentially underestimated compared to standard

practice. Additionally, a trend toward increased bleeding events with rivaroxaban was noted in these trials when compared to enoxaparin. While these results were not statistically significant, the safety of enoxaparin may also have been underestimated since the lower dose was used.

RECORD 1 results support extended thromboprophylaxis after total-hip arthroplasty as more effective than short-term therapy.² Current American College of Chest Physicians guidelines recommend extended therapy although such treatment is currently underused after hospital discharge.⁷ This underutilization is likely due to the subcutaneous administration required for low-molecular-weight heparin and fondaparinux or the constant monitoring required with warfarin. Rivaroxaban could eliminate these barriers to extended, out-of-hospital thromboprophylaxis because 1) monitoring is not required, and 2) administration is oral.

Rivaroxaban use in the United States awaits FDA approval. Barring unforeseen safety issues or prohibitive pricing, rivaroxaban may become a common thromboprophylaxis agent in orthopedic populations, and based on the published data, use in patients undergoing hip or knee replacement appears appropriate. However, the convenient administration route and lack of required monitoring make rivaroxaban a tempting replacement for use in other patient populations that are at higher risk for thromboembolic events. These patient groups include but are not limited to: mechanical valve replacements, atrial fibrillation, acute deep vein thrombosis/pulmonary embolism, stroke, or acute coronary syndromes. Until clinical trial data supporting equivalence or superiority of rivaroxaban compared to current anticoagulation therapy are available, rivaroxaban should not be used in these patient groups.

References

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