Cost-Effectiveness of Rivaroxaban After Total Hip or Total Knee Arthroplasty

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Abstract

Venous thromboembolism (VTE) following joint replacement surgery represents an economic as well as a clinical burden; however, the risk of thromboembolic events is greatly reduced by appropriate anticoagulation. Rivaroxaban, a Factor Xa inhibitor currently in phase III development, was compared with the low molecular weight heparin enoxaparin in 4 clinical trials, collectively called the RECORD program (REgulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism). In a pooled analysis of data from the RECORD trials, rivaroxaban was superior to enoxaparin regimens in reducing the composite end point of symptomatic venous thromboembolism and all-cause mortality in patients following elective primary total hip or total knee arthroplasty (THA or TKA), with a comparable incidence of major bleeding events. In cost-effectiveness analyses, compared with enoxaparin, rivaroxaban showed the potential to reduce costs associated with the prophylaxis and treatment of thromboembolic events in a post-orthopedic surgery/arthroplasty population.

(Am J Manag Care. 2011;17:S22-S26)

For author information and disclosures, see end of text.

This paper reviews the potential cost-effectiveness of the anticoagulant rivaroxaban, a new oral Factor Xa inhibitor, for prophylaxis against VTE after total hip or total knee arthroplasty (THA or TKA). A comprehensive review of rivaroxaban has recently been published,[1] as has a review of its use in patients after THA and TKA.[2] The article by Baser in this supplement[3] describes the clinical burden of VTE after THA/TKA and the associated economic consequences. As outlined in the article by Nutescu in this supplement,[4] the new, more convenient oral anticoagulants have the potential to reduce the incidence of VTE, and are likely to have an important impact on the economic burden associated with this condition.

Rivaroxaban: The RECORD Program

The RECORD program (REgulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism) consisted of 4 phase 3 studies, which compared oral rivaroxaban with subcutaneous enoxaparin regimens for the prevention of VTE after THA (RECORD1 and RECORD2) or TKA (RECORD3 and RECORD4). RECORD1 was a head-to-head comparison of rivaroxaban 10 mg once daily with enoxaparin 40 mg once daily for 31 to 39 days.[5] RECORD2 was a comparison of regimens designed to assess the benefits of extended-duration rivaroxaban 10 mg once daily (31 to 39 days) against short-duration enoxaparin 40 mg once daily (10 to 14 days) followed by placebo.[6] RECORD3 compared rivaroxaban 10 mg once daily with enoxaparin 40 mg once daily for 10 to 14 days.[7] RECORD4 compared rivaroxaban 10 mg once daily with enoxaparin 30 mg every 12 hours for 10 to 14 days.[8]

Rivaroxaban was started 6 to 8 hours after wound closure in all 4 studies. Enoxaparin was started 12 hours before surgery in RECORD1, 2, and 3 and 12 to 24 hours after wound closure in RECORD4. The primary efficacy outcome in each of the studies was the composite of any deep vein thrombosis, non-fatal pulmonary embolism, and all-cause mortality (total VTE). Symptomatic VTE was a secondary efficacy outcome. The main safety outcome in each of the studies was major bleeding occurring after the first dose of study medication and up to 2 days after the last dose (treatment emergent).[5-8]

Table 1. Summary of Results From the Individual RECORD1, 2, 3, and 4 Studies

Study	Indication	Rivaroxaban Regimen	Enoxaparin Regimen	Composite of Any DVT, Non-fatal PE, and All-cause Mortality		Major Bleeding	
				Rivaroxaban, n/N (%)	Enoxaparin, n/N (%)	Rivaroxaban, n/N (%)	Enoxaparin, n/N (%)
RECORD1[5]	THA	10 mg once daily, 31-39 days	40 mg once daily, 31-39 days	18/1595 (1.1)	58/1558 (3.7)	6/2209 (0.3)	2/2224 (0.1)
				P <.001		*P* = .18	
RECORD2[6]	THA	10 mg once daily, 31-39 days	40 mg once daily, 10-14 days followed by placebo	17/864 (2.0)	81/869 (9.3)	1/1228 (<0.1)	1/1229 (<0.1)
				P <.0001		*P* = .980	
RECORD3[7]	TKA	10 mg once daily, 10-14 days	40 mg once daily,10-14 days	79/824 (9.6)	166/878 (18.9)	7/1220 (0.6)	6/1239 (0.5)
				P <.001		*P* = .77	
RECORD4[8]	TKA	10 mg once daily, 10-14 days	30 mg twice daily, 10-14 days	67/965 (6.9)	97/959 (10.1)	10/1526 (0.7)	4/1508 (0.3)
				P = .0118		*P* = .1096	

DVT indicates deep vein thrombosis; PE, pulmonary embolism; RECORD, REgulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism; THA, total hip arthroplasty; TKA, total knee arthroplasty.

RECORD1

Total VTE occurred in 1.1% of patients receiving rivaroxaban compared with 3.7% of patients receiving enoxaparin (*P* <.001; Table 1). Symptomatic VTE occurred in 0.3% versus 0.5% of patients, respectively (*P* = .22). Major bleeding occurred in 0.3% versus 0.1% of patients, respectively (*P* = .18).[5]

RECORD2

Total VTE occurred in 2.0% of patients receiving extended-duration rivaroxaban compared with 9.3% of patients receiving short-duration enoxaparin (*P* <.0001; Table 1). Symptomatic VTE occurred in 0.2% versus 1.2% of patients, respectively (*P* = .004).[6] Rates of major bleeding in both groups were less than 0.1% (*P* = .980).[6,9]

RECORD3

Total VTE occurred in 9.6% of patients receiving rivaroxaban compared with 18.9% of patients receiving enoxaparin (*P* <.001; Table 1). Symptomatic VTE occurred in 0.7% versus 2.0% of patients, respectively (*P* = .005). Major bleeding occurred in 0.6% versus 0.5% of patients, respectively (*P* = .77).[7]

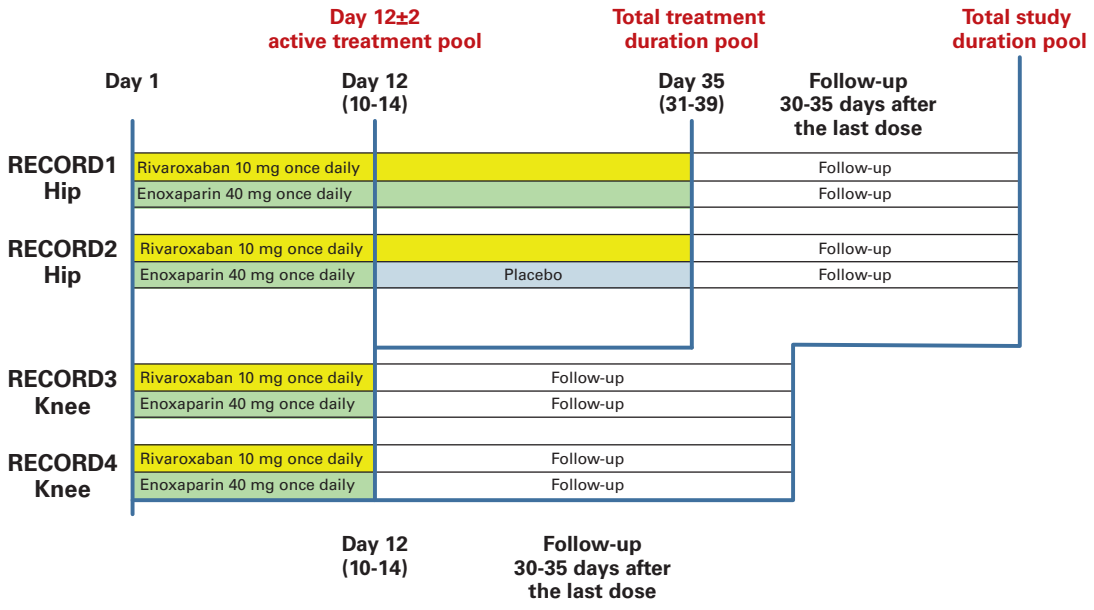
RECORD4

Total VTE occurred in 6.9% of patients receiving rivaroxaban compared with 10.1% of patients receiving enoxaparin (*P* = .0118; Table 1). Symptomatic VTE occurred in 0.7% versus 1.2% of patients, respectively (*P* = .1868). Major bleeding occurred in 0.7% versus 0.3% of patients, respectively (*P* = .1096).[8]

In all 4 studies, the adverse-event profiles for rivaroxaban and enoxaparin were similar. A low incidence of cardiovascular events was seen with both drugs, and there was no indication of compromised liver function attributable to rivaroxaban in any of the studies.[5-8]

In an analysis of pooled data from all 4 RECORD studies, rivaroxaban significantly reduced the incidence of the composite of symptomatic VTE and all-cause mortality compared with enoxaparin regimens in all study pools analyzed (Figure).[10] These benefits were achieved without a significant increase in the risk of major bleeding, although a significant increase in major plus clinically relevant non-major bleeding with rivaroxaban was observed in the total treatment duration pool.[10] In a quantitative benefit-risk analysis based on the pooled data, which used a net clinical benefit approach and a variety of end points defining harms and ben-

■ **Figure.** Study Pools in the RECORD1-4 Pooled Analysis[10]



RECORD indicates REgulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism.
The day 12±2 active treatment pool focused on events occurring in the enoxaparin-controlled period common to all 4 studies. The total treatment duration pool focused on events occurring during the planned treatment period for each study. The total study duration pool focused on events occurring in the planned treatment period plus the follow-up period (30-35 days).
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efits, the benefit-risk profile for rivaroxaban was shown to be consistently improved compared with enoxaparin.[11]

Cost-Effectiveness of Rivaroxaban

RECORD1 and 2

Cost-effectiveness analyses for rivaroxaban have been undertaken, based on data from the RECORD1 and 2 studies.[12,13] The aim of the RECORD1 analysis was to assess the potential economic benefit attributable to the use of oral rivaroxaban (10 mg once daily) relative to subcutaneous enoxaparin (40 mg once daily) after primary THA. The RECORD2 analysis aimed to assess the economic impact of extended-duration thromboprophylaxis with rivaroxaban compared with short-duration enoxaparin after THA. The analyses included only non-drug costs incurred by the healthcare sector and were based on 3 reasonable assumptions, ie: (1) asymptomatic events had no impact on healthcare costs; (2) nurses spent only 3 minutes a day administering enoxaparin and training patients to self-inject; (3) duration of hospital stay was 5 days.

For RECORD1, 2 analyses were performed. One study assumed no difference in the occurrence of symptomatic VTE between treatments, and the other assumed that the observed difference was real but did not reach statistical significance. The cost of symptomatic VTE was taken from published sources in the United States.[14] The results of these analyses, summarized in Table 2, demonstrated a significant cost savings with rivaroxaban after THA compared with enoxaparin. These savings were driven by reduced administration and hospitalization costs associated with fewer venous thromboembolic events with rivaroxaban therapy.

Costs of the post-thrombotic syndrome (PTS) were excluded in these analyses. However, PTS is estimated to affect between 23% and 60% of patients within 2 years of an initial deep vein thrombosis, with a total cost per patient of more than $11,000 in the United States.[15,16] If the incidences of total VTE from RECORD1 and RECORD2 are used to extrapolate the incidence of PTS in these study populations, the potential cost savings with rivaroxaban compared with enoxaparin range from $66 to $165 and $176 to $484 per patient with PTS, respectively.

RECORD3 and 4

The aim of the RECORD3 analysis was to assess the potential economic benefit attributable to the use of oral rivaroxaban (10 mg once daily) relative to subcutaneous enoxaparin (40 mg once daily) after TKA.[17] The analyses included only non-drug costs incurred by the healthcare

Table 2. Cost-Effectiveness Analyses

Study	Total US Healthcare Resources, $ per Patient		Saving, $
	Enoxaparin	Rivaroxaban	
RECORD1[5]	46[a]	42.4	3.5
	57[b]	42.5	14.5
RECORD2[c,6]	192	39	153
RECORD3[7]	290	98	192
RECORD4[8]	469	307	162

[a]Assuming no difference in the incidence of symptomatic venous thromboembolism (VTE).
[b]Assuming the observed difference in the incidence of symptomatic VTE.
[c]Compared extended-duration rivaroxaban with short-duration enoxaparin.
RECORD indicates REgulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism.

sector. As with the other analyses, it was assumed that asymptomatic events had no impact on cost, that nurse time associated with enoxaparin administration would be approximately 3 minutes a day, and that the duration of hospital stay was 5 days. The results of this analysis demonstrated a healthcare utilization cost saving of $192 per patient due to the improved health outcomes with rivaroxaban (Table 2).

The RECORD4 analysis was designed to assess the impact of improved efficacy with oral rivaroxaban 10 mg once daily vs subcutaneous enoxaparin 30 mg twice daily—the enoxaparin regimen approved after TKA in the United States—on US healthcare costs from a payer's perspective.[18] Treatment costs of symptomatic VTE and major bleeding were taken from managed care data in the United States.[14] For costing purposes in this analysis, the duration of hospitalization for TKA (4 days) was obtained from the Global Orthopaedic Registry.[19]

Because nurse time may be underestimated, a sensitivity analysis included incremental costs associated with home nurse visits to administer subcutaneous injections. The duration of prophylaxis was assumed to be 14 days. Because rivaroxaban is not yet approved in the United States, the analysis assumed similar drug acquisition costs to enoxaparin 40 mg, which is less expensive than enoxaparin 30 mg every 12 hours.

The total cost associated with healthcare resource use in the United States for the duration of treatment was $469 per patient with enoxaparin 30 mg twice daily and $307 with rivaroxaban 10 mg once daily, a cost saving of $162 per patient (Table 2). This reduced total cost for rivaroxaban was driven primarily by the reduced drug acquisition cost relative to enoxaparin 30 mg twice daily, and the absence of monitoring costs. Published data suggest home nurse visits during the post-hospital prophylaxis period cost an average of $100 for enoxaparin, suggesting that potential savings with rivaroxaban could rise to $262 per patient.

This analysis excludes any treatment benefits from a reduction in symptomatic events or the impact of PTS. However, if the incidence of total VTE in RECORD3 and RECORD4 is used to extrapolate the incidence of PTS in these study populations, the potential cost savings with rivaroxaban compared with enoxaparin range from $231 to $605 and $77 to $209 per patient with PTS, respectively. Furthermore, pooled data from RECORD1-4 showed a significant reduction in symptomatic VTE and death until day 12±2 for rivaroxaban compared with enoxaparin (0.5% [29/6183] vs 1.0% [60/6200]; $P = .001$).[20] Estimated US costs for the treatment of symptomatic VTE range from $9805 to $14,146 per event.[14] Given the reduced incidence of symptomatic events demonstrated with rivaroxaban in the pooled analysis, this could translate into an additional cost saving of $48.90 to $70.55 per person compared with enoxaparin in the pooled safety population (n = 12,383).

RECORD1-4

This economic model, which followed patients for 1 year post-surgery, was developed based on symptomatic VTE and major bleeding data from the RECORD trials and other published data.[21] Treatment costs for symptomatic VTE and major bleeding were taken from published US sources. The model assumed similar drug acquisition costs to enoxaparin 40 mg once daily.

In THA, 35 days of therapy with rivaroxaban resulted in a cost saving of $5945 per symptomatic event avoided vs 14 days of therapy with enoxaparin and a cost saving of $82 per patient vs 35 days of therapy with enoxaparin. In TKA, 12 days of therapy with rivaroxaban produced a cost saving per patient of $291 and 16 fewer symptomatic events per 1000 patients vs 12 days of therapy with enoxaparin twice daily, and per-patient savings of $284 and 18 fewer symptomatic events per 1000 patients vs enoxaparin 40 mg once daily.

Greater savings with oral rivaroxaban result if costs of home nurse time or training patients to self-administer enoxaparin are included.

Rivaroxaban for 35 days after THA and for 12 days after TKA appears to be cost-effective and, in some instances, a cost-saving alternative to enoxaparin.

Conclusions

Venous thromboembolism after THA and TKA represents a serious economic burden to the US healthcare system. Long-term consequences of VTE, such as PTS, add to this burden. In many cases, VTE is preventable with the use of adequate prophylaxis, and the use of thromboprophylaxis has been shown to be cost-effective compared with no prophylaxis. Compared with enoxaparin, the current standard of care, the new oral anticoagulant rivaroxaban has the potential to reduce healthcare costs associated with drug administration and management of VTE. Furthermore, rivaroxaban reduces the incidence of symptomatic VTE, which could result in further cost savings. Given that over 570,000 total hip replacements and nearly 3.5 million total knee replacements are projected to be performed annually in the United States by 2030,[22] the potential cumulative cost savings with rivaroxaban can be considerable.

Author Affiliation: Department of Orthopaedic Surgery, Harbor-UCLA Medical Center, Torrance, CA.

Funding Source: Financial support for this supplement was provided by Ortho-McNeil Janssen Scientific Affairs, LLC and Johnson & Johnson Worldwide Market Access.

Author Disclosure: Dr Kwong reports an editorial board assignment with the *Journal of Surgical Orthopaedic Advances*. He reports a consultancy/advisory board assignment with Zimmer. Dr Kwong reports receiving honoraria from GlaxoSmithKline, and grants from Astellas, Bayer, GlaxoSmithKline, sanofi-aventis, and Takeda.

Authorship Information: Analysis and interpretation of data; drafting of the manuscript; and critical revision of the manuscript for important intellectual content.

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REFERENCES

1. Perzborn E, Roehrig S, Straub A, Kubitza D, Mueck W, Laux V. Rivaroxaban: a new oral factor Xa inhibitor. *Arterioscler Thromb Vasc Biol*. 2010;30:376-381.

2. Ageno W. Rivaroxaban for the prevention of venous thromboembolism following major orthopedic surgery: the RECORD trials. *Expert Rev Cardiovasc Ther*. 2009;7:569-576.

3. Baser O. Prevalence and economic burden of venous thromboembolism after total hip arthroplasty or total knee arthroplasty. *Am J Manag Care*. 2011;17:S6-S8.

4. Nutescu E. Characteristics of novel anticoagulants and potential economic implications. *Am J Manag Care*. 2011;17:S27-S32.

5. Eriksson BI, Borris LC, Friedman RJ, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N Engl J Med*. 2008;358:2765-2775.

6. Kakkar AK, Brenner B, Dahl OE, et al. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. *Lancet*. 2008;372:31-39.

7. Lassen MR, Ageno W, Borris LC, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med*. 2008;358:2776-2786.

8. Turpie AGG, Lassen MR, Davidson BL, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. *Lancet*. 2009;373:1673-1680.

9. Kakkar AK, Brenner B, Dahl OE, et al. Extended thromboprophylaxis with rivaroxaban compared with short-term thromboprophylaxis with enoxaparin after total hip arthroplasty: the RECORD2 trial. *Blood*. (ASH Annual Meeting Abstracts). 2007;110. Abstract 307.

10. Turpie AG, Lassen MR, Eriksson BI, et al. Rivaroxaban for the prevention of venous thromboembolism after hip or knee arthroplasty. Pooled analysis of four studies. *Thromb Haemost*. 2011;105(3). [In press.]

11. Levitan B, Yuan Z, Turpie AGG, et al. Quantitative benefit–risk assessment of rivaroxaban for the prevention of venous thromboembolism. *Blood*. 2009;114. Abstract 169.

12. Friedman R, Lees M, Sengupta N, Haas S. Rivaroxaban for prevention of venous thromboembolism after total hip replacement: impact on healthcare costs based on the RECORD1 study [abstract]. *J Bone Joint Surg Br*. 2008;92-B(suppl II):288.

13. Kakkar A, Lees M, Sengupta N, Muntz J. Prevention of venous thromboembolism with rivaroxaban after total hip replacement: economic impact of extended thromboprophylaxis [abstract]. *J Bone Joint Surg Br*. 2008;92-B(suppl II):273.

14. Spyropoulos A, Lin J. Direct medical costs of venous thromboembolism and subsequent hospital readmission rates: an administrative claims analysis from 30 managed care organizations. *J Manag Care Pharm*. 2007;13:475-486.

15. MacDougall DA, Feliu AL, Boccuzzi SJ, Lin J. Economic burden of deep-vein thrombosis, pulmonary embolism, and post-thrombotic syndrome. *Am J Health Syst Pharm*. 2006;63:S5-S15.

16. Ashrani AA, Heit JA. Incidence and cost burden of post-thrombotic syndrome. *J Thromb Thrombolysis*. 2009;28:465-476.

17. Kwong LM, Lees M, Sengupta N. Rivaroxaban for prevention of venous thromboembolism after total knee arthroplasty: impact on healthcare costs based on the RECORD3 Study. *Blood*. (ASH Annual Meeting Abstracts.) 2007;110. Abstract 1874.

18. Kwong L, Sengupta N, Lees M. Rivaroxaban for prevention of venous thromboembolism after total knee replacement: impact on healthcare costs based on the RECORD4 study. *Blood* (ASH Annual Meeting Abstracts). 2008;112. Abstract 1289.

19. Friedman RJ, Gallus AS, Cushner FD, Fitzgerald G, Anderson FA Jr; Global Orthopaedic Registry Investigators. Physician compliance with guidelines for deep-vein thrombosis prevention in total hip and knee arthroplasty. *Curr Med Res Opin*. 2008;24:87-97.

20. Turpie AGG, Lassen MR, Kakkar A, et al. A pooled analysis of four pivotal studies of rivaroxaban for the prevention of venous thromboembolism after orthopaedic surgery: effect on symptomatic venous thromboembolism, death, and bleeding. *Blood*. (ASH Annual Meeting Abstracts.) 2008;112. Abstract 36.

21. Kwong LM, Duran A, Diamantopoulos A, Sengupta N, Lees M. Cost-effectiveness of rivaroxaban for prevention of venous thromboembolism (VTE) after total hip or knee replacement (THR, TKR) in the US. *J Thromb Haemost*. 2009;7:787.

22. Iorio R, Robb WJ, Healy WL, et al. Orthopaedic surgeon workforce and volume assessment for total hip and knee replacement in the United States: preparing for an epidemic. *J Bone Joint Surg Am*. 2008;90:1598-1605.