

Indirect Comparisons of Rivaroxaban versus Alternative Prophylaxes for the Prevention of VTE in Patients Undergoing Total Knee Replacement

Alex Diamantopoulos¹, Corinne LeReun², Farhat Rasul¹, Michael Lees³, Maria Kubin⁴, Phil Wells⁵

¹IMS Health, London, UK; ²Independent statistician, Carrigaline, Ireland; ³Bayer HealthCare, Uxbridge, UK; ⁴Bayer HealthCare AG, Wuppertal, Germany; ⁵Ottawa Health Research Institute/University of Ottawa, Ottawa, Canada

Introduction

- ◆ Venous thromboembolism (VTE) is an important, and potentially fatal, complication of major orthopaedic surgery, particularly after total hip or total knee replacement (THR and TKR)^{1,2}
- ◆ Rivaroxaban is a novel, oral, direct Factor Xa inhibitor approved in the European Union and Canada for the prevention of VTE after elective THR/TKR
- ◆ Two large, randomized controlled trials (RCTs) compared 10 mg rivaroxaban once daily (od) with enoxaparin 40 mg od (RECORD3)³ and enoxaparin 30 mg twice daily (bid) (RECORD4)⁴ for 12±2 days in patients undergoing TKR
- ◆ In RECORD3, rivaroxaban was associated with a relative risk reduction of 49% in total VTE (composite of any deep vein thrombosis [DVT], non-fatal pulmonary embolism, and all-cause mortality) and 66% in symptomatic VTE versus enoxaparin ($p=0.005$)
- ◆ In RECORD4, rivaroxaban reduced total VTE by 32% versus enoxaparin ($p=0.012$)
- ◆ There were similar rates of major bleeding between rivaroxaban and enoxaparin in each study
- ◆ There are no existing head-to-head comparisons between rivaroxaban and alternative prophylaxes such as warfarin, fondaparinux, and dabigatran

Objective

- ◆ This analysis was designed to assess the relative efficacy and safety of rivaroxaban versus warfarin, fondaparinux, and dabigatran. This is important for clinical decision makers, and provides important inputs for cost-effectiveness analyses of rivaroxaban versus these comparators

Methods

- ◆ A systematic review identified RCTs comparing enoxaparin with warfarin, fondaparinux, or dabigatran in TKR (Table 1)

Table 1. Summary of trial characteristics used in the TKR comparisons*

	Lassen <i>et al.</i> 2008 RECORD3	Turpie <i>et al.</i> 2008 RECORD4	Bauer <i>et al.</i> 2001	Fitzgerald <i>et al.</i> 2001	Leclerc <i>et al.</i> 1996	Eriksson <i>et al.</i> 2007 RE-MODEL	Ginsberg <i>et al.</i> 2008 RE-MOBILIZE
Drug treatment	Rivaroxaban 10 mg od post-surgery	Rivaroxaban 10 mg od post-surgery	Fondaparinux 2.5 mg od post-surgery	Warfarin dose adjusted to INR 2–3 post-surgery	Warfarin dose adjusted to INR 2–3 post-surgery	Dabigatran 220 mg or 150 mg od post-surgery	Dabigatran 220 mg or 150 mg od post-surgery
Comparator	Enoxaparin 40 mg od pre-surgery	Enoxaparin 30 mg bid pre-surgery	Enoxaparin 30 mg od post-surgery	Enoxaparin 30 mg od post-surgery	Enoxaparin 30 mg bid post-surgery	Enoxaparin 40 mg od pre-surgery	Enoxaparin 30 mg bid post-surgery
Prophylaxis duration[†]	12±2 days	12±2 days	5–9 days	4–14 days	Up to discharge or up to 14 days	6–10 days	12–15 days

*Each of these publications was reviewed by independent analysts. [†]The duration for both study arms is shown. Prophylaxis duration and enoxaparin dose regimen (40 mg od or 30 mg bid) were not included as covariates in the analysis. bid, twice daily; INR, international normalized ratio; od, once daily; TKR, total knee replacement.

- ◆ The efficacy of rivaroxaban relative to fondaparinux and dabigatran was assessed by comparing the occurrence of total VTE and total DVT (proximal and distal). Because total VTE and total DVT were not measured in all warfarin trials, the efficacy of rivaroxaban versus warfarin was assessed by comparing the occurrence of symptomatic VTE and symptomatic DVT
- ◆ Comparisons were conducted using an adjusted indirect comparison method⁹ and a meta-regression where more than three studies provided data for a particular endpoint
- ◆ Enoxaparin was used as the common comparator between rivaroxaban and the other comparators in order to facilitate the indirect comparison
- ◆ Given the potential for the different enoxaparin doses to generate bias, separate analyses were performed for data from trials using an enoxaparin regimen of 30 mg bid^{4–7,10} and from trials using an enoxaparin regimen of 40 mg od^{3,8}
- ◆ The results from such analyses do not represent the same level of evidence as comparative trials, but provide a guide to potential relative efficacy and safety in the absence of a comparative trial, and could be used by authorities to aid decision making¹¹
- ◆ Relative safety was assessed using rates of major bleeding. However, differences in the definition of major bleeding between the rivaroxaban and warfarin, fondaparinux, and dabigatran studies do not allow for an indirect comparison of major bleeding between rivaroxaban and these comparators
- ◆ In individual trials, no difference in major bleeding was shown between enoxaparin and rivaroxaban, and warfarin and dabigatran.^{3–8} However, given that bleeding is an important consideration in the selection of an anticoagulant, more research is needed to compare major bleeding between these different anticoagulants
- ◆ Data for relevant efficacy and safety outcomes were extracted from these studies, and from RECORD3 and 4 for rivaroxaban versus enoxaparin
- ◆ If more than one RCT was available for a comparator, a meta-analysis was undertaken to obtain pooled results for efficacy and safety

Results

- ◆ When data from trials using enoxaparin 30 mg bid were included, rivaroxaban reduced total VTE by 46% versus dabigatran ($p<0.05$) and reduced symptomatic VTE by 56% versus warfarin ($p<0.001$) (Table 2)
- ◆ There was no statistical difference in total VTE or total DVT between rivaroxaban and fondaparinux based on the analysis using trials with enoxaparin 30 mg bid included

Table 2. RR of VTE and DVT: rivaroxaban versus dabigatran, warfarin, and fondaparinux after TKR (enoxaparin 30 mg bid common comparator)

	RR	RR 95% CI	RR p -value
Endpoint dabigatran 220 mg			
Results derived from adjusted indirect comparison analysis			
Total VTE	0.56	0.39, 0.81	<0.05
Endpoint warfarin			
Results derived from meta-regression analysis			
Symptomatic VTE	0.44	0.29, 0.67	<0.001
Symptomatic DVT	0.46	0.30, 0.71	<0.001
Endpoint fondaparinux			
Results derived from adjusted indirect comparison analysis			
Total VTE	1.53	0.99, 2.37	>0.05
Total DVT	1.54	0.98, 2.41	>0.05

bid, twice daily; CI, confidence interval; DVT, deep vein thrombosis; RR, relative risk; TKR, total knee replacement; VTE, venous thromboembolism.

- ◆ When data from trials using enoxaparin 40 mg od were included, rivaroxaban reduced total VTE by 47% versus dabigatran ($p<0.05$) (Table 3)

Table 3. RR of VTE and DVT: rivaroxaban versus dabigatran after TKR (enoxaparin 40 mg od common comparator)

	RR	RR 95% CI	RR p -value
Endpoint dabigatran 220 mg			
Results derived from adjusted indirect comparison analysis			
Total VTE	0.53	0.39, 0.71	<0.05
Total DVT	0.53	0.39, 0.71	<0.05

CI, confidence interval; DVT, deep vein thrombosis; od, once daily; RR, relative risk; TKR, total knee replacement; VTE, venous thromboembolism.

- ◆ In each analysis, similar reductions were shown in total DVT as in total VTE. No other statistically significant differences were found, likely due to the small number of events in other endpoints
- ◆ A sensitivity analysis where all data were included supported the results of the individual analyses (Table 4)

Table 4. RR of VTE and DVT: rivaroxaban versus dabigatran, fondaparinux, and warfarin after TKR (all data)

	RR	RR 95% CI	RR p -value
Endpoint dabigatran 220 mg			
Results derived from meta-regression analysis			
Total VTE	0.54	0.37, 0.78	0.001
Total DVT	0.60	0.41, 0.87	0.007
Endpoint warfarin			
Results derived from meta-regression analysis			
Symptomatic VTE	0.37	0.26, 0.54	<0.001
Symptomatic DVT	0.39	0.27, 0.55	<0.001
Endpoint fondaparinux			
Results derived from meta-regression analysis			
Total VTE	1.30	0.75, 2.25	0.345
Total DVT	1.31	0.77, 2.21	0.319

CI, confidence interval; DVT, deep vein thrombosis; RR, relative risk; TKR, total knee replacement; VTE, venous thromboembolism.

Conclusions

- ◆ An indirect statistical comparison showed that rivaroxaban is likely to reduce the incidence of VTE events relative to warfarin and dabigatran
- ◆ In the absence of direct comparisons, this approach should provide the best evidence regarding the relative efficacy and safety of these options¹¹
- ◆ These results can also be used in economic models to assess the cost-effectiveness of rivaroxaban versus warfarin, fondaparinux, and dabigatran

References and Disclosures

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