

# Indirect comparison of rivaroxaban regimens vs standard prophylaxis for the prevention of venous thromboembolism in patients undergoing total hip or total knee replacement

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## 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, respectively)<sup>1,2</sup>
- ◆ Rivaroxaban is an oral, direct Factor Xa inhibitor in advanced clinical development for the prevention and treatment of VTE. Three multinational phase III studies have consistently shown superiority for rivaroxaban regimens compared with enoxaparin regimens<sup>3–5</sup>
- ◆ Extended prophylaxis (35±4 days) with rivaroxaban had superior efficacy to 12±2 days or 35±4 days with enoxaparin following THR.<sup>3,4</sup> Similar results were seen with 12±2 days' prophylaxis for rivaroxaban vs enoxaparin following TKR<sup>5</sup>

## Objective

- ◆ To estimate the differences in efficacy and safety of rivaroxaban regimens vs thromboprophylactic regimens utilizing dabigatran, fondaparinux or warfarin in the prevention of VTE after THR or TKR. This is an indirect comparison of rivaroxaban regimens with these alternatives using enoxaparin as a common comparator

## Methods

- ◆ A literature search was conducted to identify relevant randomized controlled trials of dabigatran, fondaparinux and warfarin following THR or TKR
- ◆ Data were extracted from these trials as well as for the rivaroxaban studies for key efficacy and safety endpoints (VTE, total deep vein thrombosis [DVT], symptomatic VTE, fatal pulmonary embolism and major bleeding)
- ◆ Indirect comparisons were conducted using the indirect comparison methodology described by Bucher *et al.*<sup>6</sup> A meta-analysis of each treatment was run against the common comparator, enoxaparin, to obtain a pooled RR and associated variance. Analysis was performed using the Mantel–Haenszel test<sup>7</sup> and, if appropriate, DerSimonian and Laird random-effect model.<sup>8</sup> Indirect comparisons were then conducted based on the summary statistics obtained in each meta-analysis
- ◆ When enough data were available, meta-regressions were also run following the methodology described by Thompson *et al.*<sup>9</sup> The methodology extends a random-effects meta-analysis to estimate the degree to which one or more covariates account for differences between treatment (prophylaxis) effects
  - In this analysis, the type of prophylaxis was the only covariate considered
- ◆ The analyses compare drug regimens irrespective of duration of prophylaxis (Tables 1 and 2) or enoxaparin protocol (40 mg once daily or 30 mg twice daily). This approach is consistent with that taken in the major meta-analysis of the fondaparinux phase III trials<sup>10</sup>
- ◆ Outcomes are expressed as RR or relative risk reductions (RRRs) for both methods of analysis (RRR = 1 – RR)

**Table 1.** Summary of trial characteristics used in the total hip replacement comparisons

Study design	Drug treatment	Comparator	Prophylaxis duration <sup>a</sup>
Eriksson <i>et al.</i> 2007 RECORD1	Rivaroxaban 10 mg od post-operative	Enoxaparin 40 mg od pre-operative	35 days
Kakkar <i>et al.</i> 2007 RECORD2	Rivaroxaban 10 mg od post-operative	Enoxaparin 40 mg od pre-operative	35 days' rivaroxaban or 10–14 days' enoxaparin
Lassen <i>et al.</i> 2002	Fondaparinux 2.5 mg od post-operative	Enoxaparin 40 mg od pre-operative	5–9 days
Turpie <i>et al.</i> 2002	Fondaparinux 2.5 mg od post-operative	Enoxaparin 30 mg bid post-operative	5–9 days
Colwell <i>et al.</i> 1999	Warfarin 7.5 mg initially then dose adjusted to INR of 2–3 post- or pre-operative	Enoxaparin 30 mg bid post-operative	7 days
Eriksson <i>et al.</i> 2007 RENOVATE	Dabigatran 220 mg od post-operative	Enoxaparin 40 mg od pre-operative	28–35 days

bid, twice daily; INR, international normalized ratio; od, once daily. <sup>a</sup>Prophylaxis duration was the same for both study arms, except in RECORD2. Prophylaxis duration and enoxaparin dose regimen (40 mg od or 30 mg bid) were not included as covariates in the analysis.

**Table 2.** Summary of trial characteristics used in the total knee replacement comparisons

Study design	Drug treatment	Comparator	Prophylaxis duration <sup>a</sup>
Lassen <i>et al.</i> 2007 RECORD3	Rivaroxaban 10 mg od post-operative	Enoxaparin 40 mg od pre-operative	10–14 days
Bauer <i>et al.</i> 2001	Fondaparinux 2.5 mg od post-operative	Enoxaparin 30 mg bid post-operative	5–9 days
Fitzgerald <i>et al.</i> 2001	Warfarin dose adjusted to INR 2–3 post-operative	Enoxaparin 30 mg bid post-operative	4–14 days
Leclerc <i>et al.</i> 1996	Warfarin dose adjusted to INR 2–3 post-operative	Enoxaparin 30 mg bid post-operative	Up to discharge or up to 14 days
Eriksson <i>et al.</i> 2007 REMODEL	Dabigatran 220 mg od post-operative	Enoxaparin 40 mg od pre-operative	6–10 days

bid, twice daily; INR, international normalized ratio; od, once daily. <sup>a</sup>Prophylaxis duration shows duration for both study arms. Prophylaxis duration and enoxaparin dose regimen (40 mg od or 30 mg bid) were not included as covariates in the analysis.

## Results

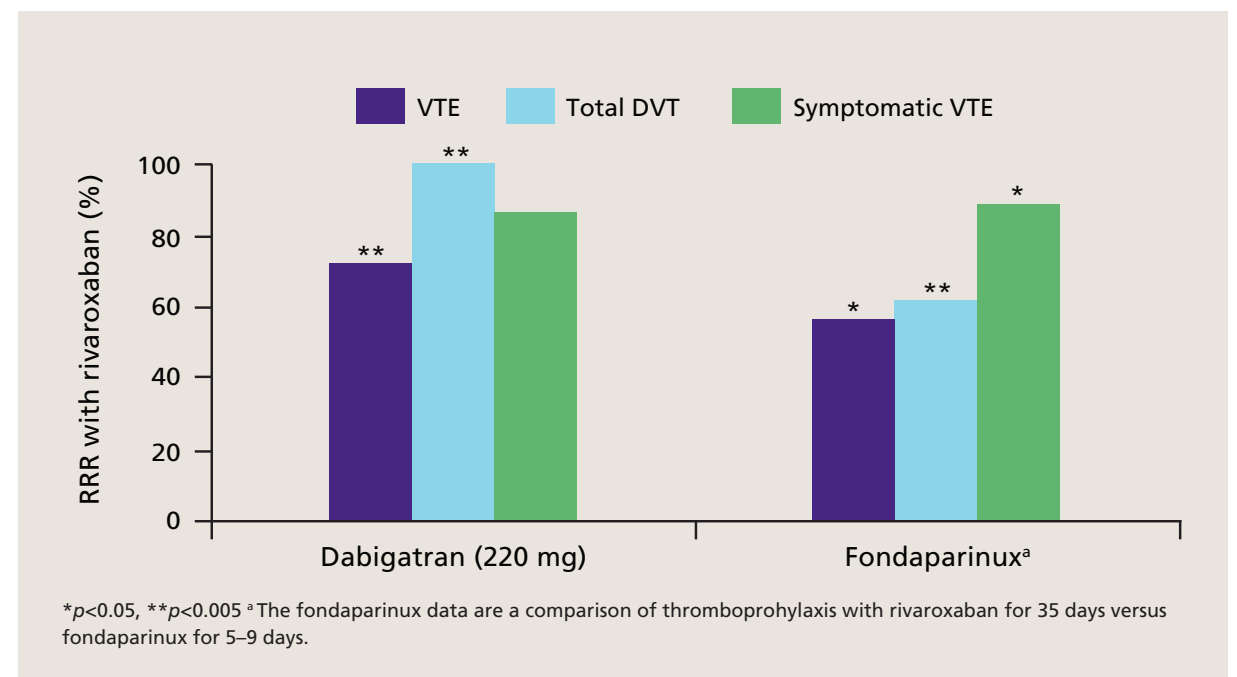
### Rivaroxaban compared with alternative prophylaxes after THR

- ◆ When rivaroxaban was compared with the standard dabigatran dose of 220 mg daily, meta-regression analysis results indicated statistically significant reductions in total VTE and symptomatic VTE of 72% and 87%, respectively (Table 3)
- ◆ Meta-regression analysis for rivaroxaban compared with fondaparinux suggested an RRR of 56% in total VTE ( $p=0.015$ ) and 89% in symptomatic VTE ( $p=0.015$ ) (Table 3)
- ◆ A summary of the efficacy results for rivaroxaban compared with dabigatran and fondaparinux regimens is provided in Figure 1

**Table 3.** Rivaroxaban compared with dabigatran, fondaparinux and warfarin in the hip replacement population. Results derived from the meta-regression analysis, showing relative risk (RR) for venous thromboembolism (VTE) and deep vein thrombosis (DVT)

	RR	RR 95% CI	RR $p$ -value
Endpoint dabigatran 220 mg			
VTE	0.28	0.17, 0.47	<0.001
Total DVT	0.03	0.004, 0.30	0.002
Symptomatic VTE	0.13	0.02, 0.72	0.02
Endpoint fondaparinux <sup>a</sup>			
VTE	0.44	0.23, 0.86	0.015
Total DVT	0.38	0.21, 0.69	0.002
Symptomatic VTE	0.11	0.02, 0.65	0.015
Endpoint warfarin			
Symptomatic VTE 35 days <sup>b</sup>	0.31	0.13, 0.75	0.009

CI, confidence interval. <sup>a</sup>The fondaparinux data are a comparison of thromboprophylaxis with rivaroxaban for 35 days vs fondaparinux for 5–9 days. <sup>b</sup>Symptomatic VTE was evaluated for up to 35 days after a mean treatment period of 7.3 days.



**Figure 1.** Relative risk reduction (RRR) of total and symptomatic venous thromboembolism (VTE) and total deep vein thrombosis (DVT) with rivaroxaban compared with dabigatran and fondaparinux in the total hip replacement population. Results derived from meta-regression analyses.

- ◆ Meta-regression analysis indicates that 35 days' rivaroxaban reduces symptomatic VTE by 69% vs warfarin prophylaxis (followed up for 35 days) ( $p=0.009$ ) after THR (Table 3); however, analyses for THR are limited because of a lack of published data for warfarin in THR
  - Results for major bleeding associated with warfarin are not shown, because the definition of this endpoint used in the warfarin study is substantially different from that used in contemporary trials

### Rivaroxaban compared with alternative prophylaxes after TKR

- ◆ There were not enough data available to perform a meta-regression analysis for rivaroxaban compared with dabigatran; therefore, results represent analysis using the indirect comparison method
  - The occurrence of VTE and total DVT were reduced by 47% for rivaroxaban compared with the standard dabigatran dose of 220 mg (Table 4)
  - Because the 95% confidence interval includes 1, observed risk reductions of symptomatic DVT and major bleeding are not shown
- ◆ Indirect comparison results showed no statistically significant differences in total or symptomatic VTE for rivaroxaban compared with fondaparinux (data not shown)
- ◆ Meta-regression analysis for rivaroxaban compared with warfarin suggested significant reductions of 67% and 66% ( $p<0.001$ ) in VTE and total DVT, respectively (Table 4)

**Table 4.** Rivaroxaban compared with dabigatran and warfarin in the knee replacement population. Results show relative risk (RR) for venous thromboembolism (VTE) and deep vein thrombosis (DVT)

	RR	RR 95% CI	RR $p$ -value
Endpoint dabigatran 220 mg (Results derived from indirect comparison analysis)			
VTE	0.53	0.39, 0.71	
Total DVT	0.53	0.39, 0.71	
Endpoint warfarin (Results derived from meta-regression analysis)			
VTE	0.33	0.23, 0.47	<0.001
Total DVT	0.34	0.24, 0.50	<0.001

CI, confidence interval.

Other meta-regression results were not statistically significant, either because of a lack of statistical power in less frequent events or a real lack of difference in events.

A limitation of these analyses is that the RECORD1 and RECORD2 data were pooled for the THR comparisons. Additional analyses are being performed.

Importantly for a new anticoagulant, there were no significant increases in major bleeding. This is consistent with the results of the RECORD studies, where there were no statistically significant differences in major bleeding between rivaroxaban and enoxaparin.

## Conclusions

- ◆ In these indirect comparisons, rivaroxaban regimens showed statistically significant reductions in overall or symptomatic VTE events relative to alternative prophylaxis regimens
- ◆ There was no increase in major bleeding with rivaroxaban relative to alternative prophylaxes, reflecting a better clinical profile

## References and disclosures

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