

# Potential Impact of Rivaroxaban on Surgical Safety Outcomes after Total Hip or Knee Replacement Surgery

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## Introduction

- ◆ Patients undergoing total hip and knee replacement (THR and TKR) surgery are at risk of developing surgical complications such as hemorrhagic events and postoperative wound infections
- ◆ The use of anticoagulants, which are recommended for the prevention of postoperative venous thromboembolism (VTE) after THR and TKR, may affect the development and severity of surgical complications
- ◆ The efficacy and safety of rivaroxaban – an oral, direct Factor Xa inhibitor – was investigated for the prevention of VTE after THR and TKR in the RECORD program, which comprised four phase III trials
- ◆ In each individual trial, rivaroxaban regimens demonstrated superior efficacy for the prevention of VTE compared with enoxaparin regimens, with no statistically significant difference in any or major bleeding with and without surgical-site bleeding<sup>1–4</sup>
- ◆ A prespecified pooled analysis of the RECORD data showed that rivaroxaban significantly reduced the composite of symptomatic VTE and death compared with enoxaparin, with no statistically significant difference in the risk of major bleeding<sup>5</sup>

## Objective

- ◆ To evaluate the potential impact of rivaroxaban on surgical safety outcomes compared with enoxaparin after THR and TKR, from the RECORD1–4 pooled data

## Methods

- ◆ A total of 12,729 patients scheduled to undergo elective THR or TKR were randomized to receive oral rivaroxaban 10 mg once daily or subcutaneous enoxaparin 40 mg once daily (RECORD1–3) or enoxaparin 30 mg twice daily (RECORD4) (Figure 1)
  - Patients received prophylaxis for 31–39 days in RECORD1 (THR), and for 10–14 days in RECORD3 and 4 (TKR). In RECORD2 (THR), patients received rivaroxaban for 31–39 days or enoxaparin for 10–14 days followed by placebo
- ◆ Adverse events (AEs) were reported by the individual investigators
- ◆ Treatment-emergent bleeding events were assessed by the same central, independent, blinded adjudication committees in all four studies

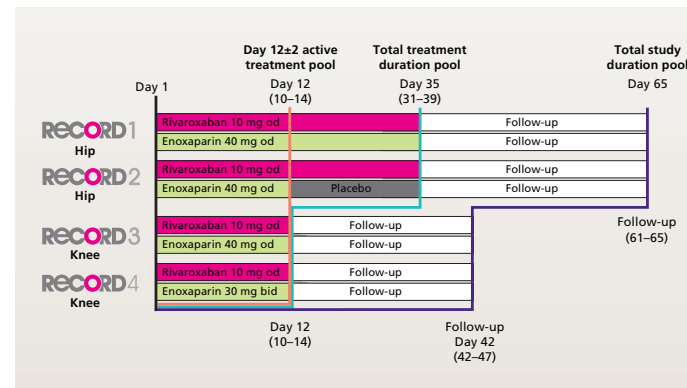


Figure 1. RECORD1–4 study design. bid, twice daily; od, once daily.

- ◆ Patients who were randomized, but did not take any study medication, were excluded from the safety population (safety population n=12,383: 6,183 in the rivaroxaban group and 6,200 in the enoxaparin group)

### Investigator-reported adverse events

- ◆ All investigator-reported AEs were analyzed descriptively, and classified according to the Medical Dictionary for Regulatory Activities (MedDRA) version 10.0
- ◆ Of the AEs reported in the RECORD1–4 studies, those of interest in this analysis were the surgical AEs: post-procedural infection, postoperative wound infection, incision-site hemorrhage, operative hemorrhage, wound dehiscence, and hemarthrosis
- ◆ These were recorded over the total study duration, which comprised the treatment and follow-up period of each study (Figure 1)
- ◆ Serious AEs (including serious surgical AEs) were defined as those that resulted in death or persistent/significant disability/incapacity; were life-threatening; required in-patient hospitalization or prolongation of existing hospitalization; congenital anomalies or birth defects; or important medical events requiring intervention

### Adjudicated bleeding endpoints

- ◆ The main bleeding endpoints analyzed were treatment-emergent major bleeding, clinically relevant non-major bleeding, and any bleeding
- ◆ Other bleeding endpoints assessed were bleeding leading to re-operation, clinically overt extra-surgical-site bleeding leading to the transfusion of  $\geq 2$  units of whole blood or packed cells, excessive wound hematoma and surgical-site bleeding
- ◆ Treatment-emergent events were defined as events occurring after the first dose of double-blind study medication and up to 2 days after the last dose of double-blind study medication
- ◆ Other non-adjudicated safety outcomes were also assessed

## Results

- ◆ Over the total study duration, the incidence of any AE was similar between the rivaroxaban and enoxaparin groups (70.6% and 72.5%, respectively; Table 1)
- ◆ The overall incidence of surgical AEs was similar between groups: 1.83% with rivaroxaban versus 2.11% with enoxaparin (Table 1 and Figure 2)
- ◆ The incidence of serious surgical AEs was also similar between groups, occurring in 0.49% of patients in the rivaroxaban group and in 0.56% in the enoxaparin group (Table 1 and Figure 2)
- ◆ The incidences of treatment-emergent major bleeding were increased but not statistically different between the rivaroxaban and enoxaparin study groups (Table 2)
- ◆ Major bleeding leading to re-operation occurred in 0.19% of patients receiving rivaroxaban and in 0.11% of patients receiving enoxaparin (treatment emergent; Table 2), and in 0.24% and 0.15%, respectively, over the total study duration pool
- ◆ ‘Any bleeding’ was not significantly different between the study groups (Table 2)

Table 2. Safety outcomes (safety population, n=12,383)

	Rivaroxaban (n=6,183) n (%)	Enoxaparin (n=6,200) n (%)	Hazard ratio (95% confidence interval)	p-value
<b>Total treatment duration pool</b>				
Adjudicated bleeding events				
Major	24 (0.4)	13 (0.2)	1.84 (0.94–3.62)	0.08
Bleeding leading to re-operation	12 (0.2)	7 (0.1)	–	–
Clinically overt extra-surgical-site bleeding leading to transfusion of $\geq 2$ units of whole blood or packed cells	8 (0.1)	1 (<0.1)	–	–
Clinically relevant non-major bleeding	177 (2.9)	145 (2.3)	1.22 (0.98–1.52)	0.08
Excessive wound hematoma	53 (0.9)	58 (0.9)	–	–
Surgical-site bleeding	47 (0.8)	49 (0.8)	–	–
Any	434 (7.0)	401 (6.5)	1.08 (0.94–1.24)	0.26
Other safety outcomes				
Hemorrhagic wound complications*	100 (1.6)	107 (1.7)	–	–
Hemorrhagic wound complications* + hemoglobin drop $\geq 2$ g/dL or transfusion of $\geq 2$ units of packed blood cells	53 (0.9)	54 (0.9)	–	–
Postoperative wound drainage	6 (0.1)	3 (<0.1)	–	–
Postoperative wound infection	27 (0.4)	28 (0.5)	–	–
Requirement for blood transfusion	2,942 (47.6)	2,935 (47.3)	–	–
Adverse bleeding events (adjudicated) leading to permanent discontinuation of study medication	47 (0.8)	36 (0.6)	–	–
<b>Day 12±2 active treatment pool</b>				
Adjudicated bleeding events				
Major	21 (0.3)	13 (0.2)	1.61 (0.81–3.22)	0.18
Any	409 (6.6)	384 (6.2)	1.06 (0.93–1.22)	0.38

\*Composite of excessive wound and surgical-site bleeding.

Table 1. Incidence of adverse events in the safety population\*

	Rivaroxaban (n=6,183) n (%)	Enoxaparin (n=6,200) n (%)
<b>Adverse events</b>		
Any adverse event	4,365 (70.6)	4,497 (72.5)
Any surgical adverse event	113 (1.8)	131 (2.1)
Post-procedural infection	4 (0.1)	15 (0.2)
Postoperative wound infection	30 (0.5)	33 (0.5)
Incision-site hemorrhage	14 (0.2)	10 (0.2)
Operative hemorrhage	35 (0.6)	39 (0.6)
Wound dehiscence	14 (0.2)	14 (0.2)
Hemarthrosis	21 (0.3)	22 (0.4)
<b>Serious adverse events<sup>†</sup></b>		
Any serious adverse event	511 (8.3)	622 (10.0)
Any serious surgical adverse event	30 (0.5)	35 (0.6)
Post-procedural infection	0	7 (0.1)
Postoperative wound infection	10 (0.2)	10 (0.2)
Incision-site hemorrhage	2 (<0.1)	0
Operative hemorrhage	11 (0.2)	7 (0.1)
Wound dehiscence	5 (0.1)	5 (0.1)
Hemarthrosis	2 (<0.1)	6 (0.1)

\*Total study duration pool.

<sup>†</sup>Serious adverse events were defined as those that resulted in death or persistent/significant disability/incapacity; were life-threatening; required in-patient hospitalization or prolongation of existing hospitalization; congenital anomalies or birth defects; or important medical events requiring intervention.

## Conclusions

- ◆ The incidence of surgical complications, including serious adverse events, was low and similar between rivaroxaban and enoxaparin groups
- ◆ Rivaroxaban significantly reduced the incidence of symptomatic events,<sup>5</sup> while demonstrating similar safety to enoxaparin after total hip replacement and total knee replacement, showing an improved benefit–risk profile

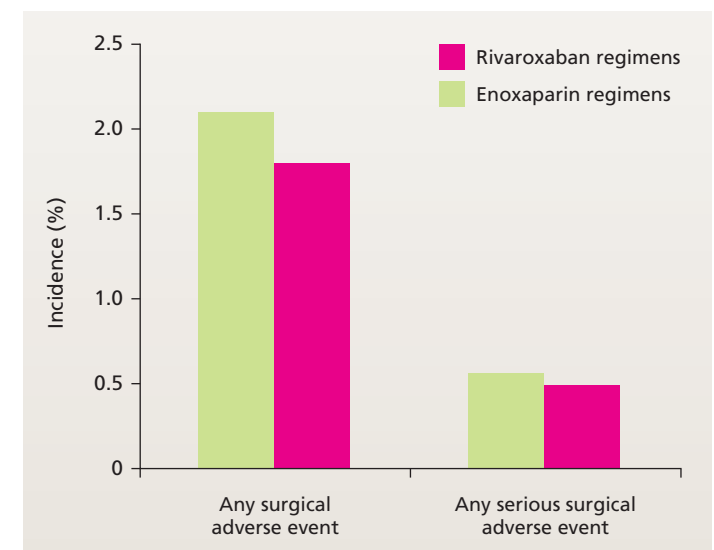


Figure 2. Incidence of surgical adverse events and serious surgical adverse events over the total study duration with rivaroxaban and enoxaparin regimens (safety population).

## References

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### Disclosure of conflict of interest

This study was supported by Bayer Schering Pharma AG and Johnson & Johnson Pharmaceutical Research & Development, L.L.C. The data contained within this poster do not support or recommend the use of rivaroxaban in indications or countries in which it is not licensed.

Presented at the International Society on Thrombosis and Haemostasis (ISTH) XXII Congress, Boston, MA, USA; July 11–16, 2009