

ABOUT RECORD STUDIES

FAST FACTS

- RECORD is a global program of four trials in more than 12,500 patients, comparing Xarelto[®] (rivaroxaban) and enoxaparin in the prevention of venous thromboembolism (VTE) after elective (planned) hip or knee replacement surgery
- RECORD1 and RECORD2 evaluated 'Xarelto' in total hip replacement surgery patients. RECORD3 and RECORD4 evaluated 'Xarelto' in total knee replacement surgery patients
- Data from four distinct Phase III trials within the RECORD program showed superior efficacy of 'Xarelto', both in head-to-head comparisons with enoxaparin (RECORD1, 3 and 4) and when comparing extended-duration (5 weeks) 'Xarelto' with short-duration (2 weeks) enoxaparin (RECORD2)
- Results of a pre-specified pooled analysis of RECORD1, 2 and 3 showed that 'Xarelto' significantly reduced the composite of symptomatic VTE and all-cause mortality during the 2-week active controlled period by 56% compared with enoxaparin
- In all four trials, 'Xarelto' and enoxaparin had comparable safety profiles, including low rates of major bleeding
- RECORD1&3 were published in the *New England Journal of Medicine* in June 2008. In the same month, RECORD2 was published in *The Lancet*
- Top-line data from RECORD4 were presented for the first time at the annual meeting of the European Federation of National Associations of Orthopaedics & Traumatology (EFORT) in Nice, France, on 30 May 2008

A major global initiative

RECORD (REGulation of Coagulation in major Orthopedic surgery reducing the Risk of DVT and PE) is a global program of four trials in more than 12,500 patients, comparing Xarelto[®] (rivaroxaban) and enoxaparin in the prevention of venous thromboembolism (VTE) after elective (planned) hip or knee replacement surgery.

'Xarelto' was invented in Bayer's Wuppertal laboratories in Germany, and is being jointly developed by Bayer HealthCare and Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

The four distinct RECORD studies were randomized, double-blind trials:

- In RECORD1, 'Xarelto' demonstrated a 70% relative risk reduction (RRR) in total VTE in patients undergoing total hip replacement (THR) surgery compared with enoxaparin, with a comparable safety profile including low rates of major bleeding. The duration of thromboprophylaxis in both treatments was 35+/-4 days. Results from RECORD1 were recently published in the *New England Journal of Medicine* (2008; 358: 2765–2775)
- In RECORD2, extended-duration 'Xarelto' (35+/-4 days) demonstrated a 79% RRR in total VTE and a comparable safety profile including low rates of major bleeding in patients undergoing THR surgery compared to patients dosed with short-duration therapy with enoxaparin (12+/-2 days). Results from RECORD2 were recently published in *The Lancet* (2008; 372: 29–37)



- In RECORD3, 'Xarelto' demonstrated 49% RRR in total VTE in patients undergoing total knee replacement (TKR) surgery compared to enoxaparin, with a comparable safety profile including low rates of major bleeding. Both treatments were dosed for 12+/-2 days. Results from RECORD3 were recently published in the *New England Journal of Medicine* (2008; 358: 2776–2785)
- In RECORD4, 10 mg once-daily 'Xarelto' was compared to the U.S.-approved regimen for enoxaparin of 30 mg injected twice-daily. 'Xarelto' demonstrated a 31.4% RRR in total VTE in patients undergoing TKR surgery compared with enoxaparin, with a comparable safety profile including low rates of major bleeding. The duration of thromboprophylaxis in both treatments was 12+/-2 days. Top-line data from RECORD4 was recently presented at European Federation of National Associations of Orthopaedics & Traumatology (EFORT), May 30, 2008

Results of a pre-specified pooled analysis of RECORD1, 2 and 3 showed that 'Xarelto' significantly reduced the composite of symptomatic VTE and all-cause mortality during the 2-week active controlled period by 56% compared with enoxaparin (0.4% versus 0.8%, respectively; odds ratio: 0.44; $p < 0.005$) whilst maintaining a comparable safety profile. These results were presented at the 20th International Congress on Thrombosis (ICT) in Athens in June 2008.

Design of studies

RECORD1¹	
<i>Results show that extended prophylaxis with 'Xarelto' had a significantly lower rate of total venous thromboembolism compared to extended enoxaparin in patients following total hip replacement surgery</i>	
Study design	Randomized, double-blind, parallel-group, multicenter, double-dummy
Interventions	Oral, once-daily 'Xarelto' 10 mg started 6 – 8 hours after surgery Subcutaneous, once-daily enoxaparin 40 mg started the evening before surgery Both regimens continued for 35+/-4 days
Number of patients	4,541 patients undergoing total hip replacement surgery
Primary efficacy endpoint	Composite of deep vein thrombosis (DVT), non-fatal pulmonary embolism (PE), all-cause mortality
Secondary efficacy endpoints	- Major VTE: composite of proximal DVT, non-fatal PE and VTE-related death - DVT (any, proximal and distal) - Symptomatic VTE
Safety endpoints	Major bleeding / non-major bleeding
RESULTS	
Primary efficacy endpoint	'Xarelto' reduced relative risk by 70% , $p < 0.001$ 1.1% (18/1595) 'Xarelto' patients versus 3.7% (58/1558) enoxaparin patients
Major VTE	'Xarelto' reduced relative risk by 88% , $p < 0.001$ 0.2% (4/1686) 'Xarelto' patients versus 2.0% (33/1678) enoxaparin patients
Symptomatic VTE	'Xarelto' reduced relative risk by 45% , 0.3% (6/2193) 'Xarelto' patients versus 0.5% (11/2206) enoxaparin patients, $p = 0.200$ (not significant)
Major bleeding	0.3% 'Xarelto' patients 0.1% enoxaparin patients, $p = 0.178$ (not significant)
Non-major bleeding	5.8% 'Xarelto' patients 5.8% enoxaparin patients

RECORD2²	
Results show that extended-duration 'Xarelto' had a significantly lower rate of total venous thromboembolism compared to short-duration enoxaparin in patients following total hip replacement surgery	
Study design	Randomized, double-blind, parallel-group, multicenter, double-dummy
Interventions	Oral, once-daily 'Xarelto' 10 mg started 6 – 8 hours after surgery, continued for 35+/-4 days Subcutaneous, once-daily enoxaparin 40 mg started the evening before surgery, continued for 12+/-2 days, followed by placebo
Number of patients	2,509 patients undergoing total hip replacement surgery
Primary efficacy endpoint	Composite of DVT, non-fatal PE, all-cause mortality
Secondary efficacy endpoints	- Major VTE: composite of proximal DVT, non-fatal PE and VTE-related death - Symptomatic VTE
Safety endpoints	Major bleeding / non-major bleeding
RESULTS*	
Primary efficacy endpoint	'Xarelto' reduced relative risk by 79% , p < 0.001 2.0% (17/864) 'Xarelto' patients versus 9.3% (81/869) enoxaparin patients
Major VTE	'Xarelto' reduced relative risk by 88% , p < 0.001 0.6% (6/961) 'Xarelto' patients versus 5.1% (49/962) enoxaparin patients
Symptomatic VTE	'Xarelto' reduced relative risk by 80% , p = 0.004 0.2% (3/1212) 'Xarelto' patients versus 1.2% (15/1207) enoxaparin patients
Major bleeding	< 0.1% 'Xarelto' patients < 0.1% enoxaparin patients, p = 0.980 (not significant)
Non-major bleeding	6.5% 'Xarelto' patients 5.5% enoxaparin patients

* Comparison of short-duration enoxaparin with extended-duration 'Xarelto'

RECORD3³	
Results show that 'Xarelto' had a significantly lower rate of total venous thromboembolism compared to enoxaparin in patients following total knee replacement surgery	
Study design	Randomized, double-blind, parallel-group, multicenter, double-dummy
Interventions	Oral, once-daily 'Xarelto' 10 mg started 6 – 8 hours after surgery Subcutaneous, once-daily enoxaparin 40 mg started the evening before surgery Both regimens continued for 12+/-2 days
Number of patients	2,531 patients undergoing total knee replacement surgery
Primary efficacy endpoint	Composite of DVT, non-fatal PE, all-cause mortality
Secondary efficacy endpoints	- Major VTE: composite of proximal DVT, non-fatal PE and VTE-related death - Symptomatic VTE
Safety endpoints	Major bleeding / non-major bleeding
RESULTS	
Primary efficacy endpoint	'Xarelto' reduced relative risk by 49% , p < 0.001 9.6% (79/824) 'Xarelto' patients versus 18.9% (166/878) enoxaparin patients
Major VTE	'Xarelto' reduced relative risk by 62% , p = 0.016 1.0% (9/908) 'Xarelto' patients versus 2.6% (24/925) enoxaparin patients
Symptomatic VTE	'Xarelto' reduced relative risk by 66% , p = 0.005 0.7% (8/1201) 'Xarelto' patients versus 2.0% (24/1217) enoxaparin patients
Major bleeding	0.6% 'Xarelto' patients 0.5% enoxaparin patients, p = 0.774 (not significant)
Non-major bleeding	4.3% 'Xarelto' patients 4.4% enoxaparin patients

RECORD4⁴	
Results show that 'Xarelto' had a statistically significant reduction of total venous thromboembolism compared to the U.S.-approved regimen for enoxaparin in patients following total knee replacement surgery	
Study design	Randomized, double-blind, parallel-group, multicenter, double-dummy
Interventions	Oral, once-daily 'Xarelto' 10 mg started 6 – 8 hours after surgery Subcutaneous, twice-daily enoxaparin 30 mg started the evening after surgery Both regimens continued for 12+/-2 days
Number of patients	3,148 patients undergoing total knee replacement surgery
Primary efficacy endpoint	Composite of DVT, non-fatal PE, all-cause mortality
Secondary efficacy endpoints	- Major VTE: composite of proximal DVT, non-fatal PE and VTE-related death - Symptomatic VTE
Safety endpoints	Major bleeding / non-major bleeding
RESULTS	
Primary efficacy endpoint	'Xarelto' reduced relative risk by 31% , p = 0.012 6.9% (67/965) 'Xarelto' patients versus 10.1% (97/959) enoxaparin patients
Major VTE	'Xarelto' reduced relative risk by 41% , p = 0.124 (not significant) 1.2% (13/112) 'Xarelto' patients versus 2.0% (22/1112) enoxaparin patients
Symptomatic VTE	'Xarelto' reduced relative risk by 39% , p = 0.187 (not significant) 1.1% (11/1,526) 'Xarelto' patients versus 1.9% (18/1,508) enoxaparin patients
Major bleeding	0.7% 'Xarelto' patients 0.3% enoxaparin patients, p = 0.110 (not significant)
Non-major bleeding	10.2% 'Xarelto' patients 9.2% enoxaparin patients

To learn more about VTE please visit www.thrombosisadviser.com

To learn more about 'Xarelto' please visit www.xarelto.com

References

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2. Kakkar AK. Lancet 2008; 372: 1-9.
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4. Turpie A, Bauer K, Davidson B, et al. Comparison of 'Xarelto'--an oral, direct factor Xa inhibitor--and subcutaneous enoxaparin for thromboprophylaxis after total knee replacement (RECORD4: a phase 3 study). Abstract F85 presented at European Federation of National Associations of Orthopaedics and Traumatology 2008 Annual Meeting; 29 May – 1 June, 2008; Nice, France.