



The RECORD Clinical Trial Programme

What is the RECORD Clinical Trial Programme?

- ◆ RECORD (**RE**gulation of **Co**agulation in major **Orth**opedic surgery reducing the **R**isk of **DVT** and **PE**) is a global programme of four randomised, double blind, Phase III studies in 12,729 patients, comparing Xarelto® (rivaroxaban) and enoxaparin in the prevention of venous thromboembolism (VTE) after elective (planned) hip or knee replacement surgery
- ◆ RECORD is the most wide-ranging clinical trial programme assessing novel oral anticoagulation in people requiring hip or knee replacement
- ◆ RECORD1 and RECORD2 evaluated 'Xarelto' in total hip replacement surgery patients
- ◆ RECORD3 and RECORD4 evaluated 'Xarelto' in total knee replacement surgery patients

RECORD Results: Summary

- ◆ Data from four distinct Phase III trials within the RECORD programme showed superior efficacy of oral, once-daily '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)
- ◆ In all four trials, 'Xarelto' and enoxaparin had comparable safety profiles, including low rates of major bleeding

RECORD Results: Detail

The four distinct RECORD studies proved once-daily 'Xarelto' provides clot prevention:

- ◆ In RECORD1, 10 mg once-daily 'Xarelto' demonstrated a 2.6% absolute risk reduction (ARR) in total VTE, a composite of any deep vein thrombosis (DVT), non-fatal pulmonary embolism (PE) and all cause mortality, in patients undergoing total hip replacement (THR) surgery compared with once daily injections of enoxaparin 40 mg, with a comparable safety profile including low rates of major bleeding. The duration of thromboprophylaxis in both treatment arms was 35+/-4 days. Results from RECORD1 were published in the New England Journal of Medicine (NEJM)¹ in June 2008
- ◆ In RECORD2, extended-duration 10 mg once-daily 'Xarelto' (35+/-4 days) demonstrated a 7.3% ARR in total VTE and a comparable safety profile, including low rates of major bleeding, in patients undergoing THR surgery compared to patients receiving short-duration therapy with once daily injections of enoxaparin 40 mg (12+/-2 days) followed by placebo. Results from RECORD2 were published in The Lancet² in June 2008

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- ◆ In RECORD3, 10 mg once-daily 'Xarelto' demonstrated 9.2% ARR in total VTE in patients undergoing total knee replacement (TKR) surgery compared to once daily injections of enoxaparin 40 mg, with a comparable safety profile including low rates of major bleeding. Both treatments were dosed for 12+/-2 days. Results from RECORD3 were published in the NEJM³ in June 2008
- ◆ In RECORD4, 10 mg once-daily 'Xarelto' was compared to the North American dosing regimen for enoxaparin of 30 mg injected twice daily. 'Xarelto' demonstrated a 3.2% ARR in total VTE with a comparable safety profile including low rates of major bleeding. Results from RECORD4 were published in The Lancet⁴ in August 2009
- ◆ 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% vs 0.8%, p=0.005). 'Xarelto' was also more effective at the end of the planned medication period (0.5% vs 1.3%, respectively). The rates of major bleeding were similar at both timepoints. Results of this pooled analysis were published in the Journal of Bone and Joint Surgery⁵ in August 2009
- ◆ Results of a pre-specified pooled analysis of RECORD1-4 showed that 'Xarelto' demonstrated a statistically significant risk reduction in the composite of symptomatic VTE and all-cause mortality of more than 50% in those treated with 'Xarelto' by comparison to enoxaparin. At two weeks, major bleeding occurred in 0.3% patients receiving 'Xarelto' versus 0.2% patients receiving enoxaparin regimens. The composite of major and non-major clinically relevant bleeding occurred in 2.8% versus 2.5% patients, respectively. These findings confirmed the results of the four individual RECORD studies. Results of this pooled analysis were published in the Journal of Thrombosis and Haemostasis⁶ in December 2009

'Xarelto' Experience

- ◆ Since the first approval of 'Xarelto' in 2008 in the orthopaedic setting, more than two and a half million patients worldwide have received 'Xarelto' in daily clinical practice in this indication alone

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RECORD 1¹	
Results show that prophylaxis with 'Xarelto' led to a significantly lower rate of total venous thromboembolism compared with enoxaparin in patients following total hip replacement surgery. Major bleeding was low and comparable between groups.	
Study design	<ul style="list-style-type: none"> ◆ Randomised, double-blind, parallel-group, multicentre, double-dummy
Interventions	<ul style="list-style-type: none"> ◆ Oral, once-daily 'Xarelto' 10 mg started 6–8 hours after surgery ◆ Subcutaneous, once-daily enoxaparin 40 mg started 12 hours before surgery and restarted 6 to 8 hours after wound closure ◆ Both regimens continued for 35+/-4 days
Number of patients	<ul style="list-style-type: none"> ◆ 4,541 patients undergoing total hip replacement surgery
Primary efficacy endpoint	<ul style="list-style-type: none"> ◆ Total VTE: composite of any deep vein thrombosis (DVT), non-fatal pulmonary embolism (PE), all-cause mortality
Secondary efficacy endpoints	<ul style="list-style-type: none"> ◆ Major VTE: composite of any proximal DVT, non-fatal PE and VTE-related death ◆ Symptomatic VTE
Primary safety endpoint	<ul style="list-style-type: none"> ◆ Major bleeding
Other bleeding-related safety endpoint	<ul style="list-style-type: none"> ◆ Non-major clinically relevant bleeding
RESULTS	
Total VTE	<ul style="list-style-type: none"> ◆ 'Xarelto' reduced absolute risk by 2.6%, p<0.001 ◆ 1.1% (18 of 1,595) 'Xarelto' patients versus 3.7% (58 of 1,558) enoxaparin patients
Major VTE	<ul style="list-style-type: none"> ◆ 'Xarelto' reduced absolute risk by 1.7%, p<0.001 ◆ 0.2% (4 of 1,686) 'Xarelto' patients versus 2.0% (33 of 1,678) enoxaparin patients
Symptomatic VTE	<ul style="list-style-type: none"> ◆ 'Xarelto' reduced absolute risk by 0.2% p=0.22 (not significant) ◆ 0.3% (6 of 2,193) 'Xarelto' patients versus 0.5% (11 of 2,206) enoxaparin patients
Major bleeding	<ul style="list-style-type: none"> ◆ Comparable and low rates of major bleeding ◆ 0.3% (6 of 2,209) 'Xarelto' patients versus 0.1% (2 of 2,224) enoxaparin patients, p=0.18 (not significant)
Non-major clinically relevant bleeding	<ul style="list-style-type: none"> ◆ 2.9% (65 of 2,209) 'Xarelto' patients versus 2.4% (54 of 2,224) enoxaparin patients





RECORD2²	
Results show that with extended-duration 'Xarelto', patients had a significantly lower rate of total venous thromboembolism compared to short-duration enoxaparin in patients following total hip replacement surgery. Major bleeding was low and comparable between groups.	
Study design	<ul style="list-style-type: none"> ◆ Randomised, double-blind, parallel-group, multicentre, double-dummy
Interventions	<ul style="list-style-type: none"> ◆ Oral, once-daily 'Xarelto' 10 mg started 6–8 hours after surgery, continued for 35+/-4 days ◆ Subcutaneous, once-daily enoxaparin 40 mg started 12 hours before surgery and restarted 6 to 8 hours after wound closure, continued for 12+/-2 days, followed by oral placebo ◆ Both arms received matching placebo, oral placebo was continued until 35+/-4 days in the enoxaparin arm
Number of patients	<ul style="list-style-type: none"> ◆ 2,509 patients undergoing total hip replacement surgery
Primary efficacy endpoint	<ul style="list-style-type: none"> ◆ Total VTE: composite of any DVT, non-fatal PE, all-cause mortality
Secondary efficacy endpoints	<ul style="list-style-type: none"> ◆ Major VTE: composite of any proximal DVT, non-fatal PE and VTE-related death ◆ Symptomatic VTE
Primary safety endpoint	<ul style="list-style-type: none"> ◆ Major bleeding
Other bleeding-related safety endpoint	<ul style="list-style-type: none"> ◆ Non-major clinically relevant bleeding
RESULTS	
Total VTE	<ul style="list-style-type: none"> ◆ 'Xarelto' reduced absolute risk by 7.3%, p<0.0001 ◆ 2.0% (17 of 864) 'Xarelto' patients versus 9.3% (81 of 869) enoxaparin patients
Major VTE	<ul style="list-style-type: none"> ◆ 'Xarelto' reduced absolute risk by 4.5%, p<0.0001 ◆ 0.6% (6 of 961) 'Xarelto' patients versus 5.1% (49 of 962) enoxaparin patients
Symptomatic VTE	<ul style="list-style-type: none"> ◆ 'Xarelto' reduced absolute risk by 1.0%, p=0.004 ◆ 0.2% (3 of 1,212) 'Xarelto' patients versus 1.2% (15 of 1,207) enoxaparin patients
Major bleeding	<ul style="list-style-type: none"> ◆ Comparable and low rates of major bleeding ◆ <0.1% (1 of 1,228) 'Xarelto' patients versus <0.1% (1 of 1,129) enoxaparin patients, p=0.980 (not significant)
Non-major clinically relevant bleeding	<ul style="list-style-type: none"> ◆ 3.3% (40 of 1,128) 'Xarelto' patients versus 2.7% (33 of 1,129) enoxaparin patients





RECORD3³	
Results show that with 'Xarelto', patients had a significantly lower rate of total venous thromboembolism compared to enoxaparin in patients following total knee replacement surgery. Major bleeding was low and comparable between groups.	
Study design	<ul style="list-style-type: none"> ◆ Randomised, double-blind, parallel-group, multicentre, double-dummy
Interventions	<ul style="list-style-type: none"> ◆ Oral, once-daily 'Xarelto' 10 mg started 6–8 hours after surgery ◆ Subcutaneous, once-daily enoxaparin 40 mg started 12 hours before surgery and restarted 6 to 8 hours after wound closure ◆ Both regimens continued for 12+/-2 days
Number of patients	<ul style="list-style-type: none"> ◆ 2,531 patients undergoing total knee replacement surgery
Primary efficacy endpoint	<ul style="list-style-type: none"> ◆ Total VTE: composite of any DVT, non-fatal PE, all-cause mortality
Secondary efficacy endpoints	<ul style="list-style-type: none"> ◆ Major VTE: composite of any proximal DVT, non-fatal PE and VTE-related death ◆ Symptomatic VTE
Primary safety endpoint	<ul style="list-style-type: none"> ◆ Major bleeding
Other bleeding-related safety endpoint	<ul style="list-style-type: none"> ◆ Non-major clinically relevant bleeding
RESULTS	
Total VTE	<ul style="list-style-type: none"> ◆ 'Xarelto' reduced absolute risk by 9.2%, p<0.001 ◆ 9.6% (79 of 824) 'Xarelto' patients versus 18.9% (166 of 878) enoxaparin patients
Major VTE	<ul style="list-style-type: none"> ◆ 'Xarelto' reduced absolute risk by 1.6%, p=0.01 ◆ 1.0% (9 of 908) 'Xarelto' patients versus 2.6% (24 of 925) enoxaparin patients
Symptomatic VTE	<ul style="list-style-type: none"> ◆ 'Xarelto' reduced absolute risk by 1.3%, p=0.005 ◆ 0.7% (8 of 1,201) 'Xarelto' patients versus 2.0% (24 of 1,217) enoxaparin patients
Major bleeding	<ul style="list-style-type: none"> ◆ Comparable and low rates of major bleeding ◆ 0.6% (7 of 1,120) 'Xarelto' patients versus 0.5% (6 of 1,239) enoxaparin patients, p=0.77 (not significant)
Non-major clinically relevant bleeding	<ul style="list-style-type: none"> ◆ 2.7% (33 of 1,120) 'Xarelto' patients versus 2.3% (28 of 1,239) enoxaparin patients





RECORD4⁴	
Results show that 'Xarelto' demonstrated a statistically significant reduction of total venous thromboembolism compared to the U.S.-approved regimen for enoxaparin in patients following total knee replacement surgery. Major bleeding was low and comparable between groups.	
Study design	<ul style="list-style-type: none"> ◆ Randomised, double-blind, parallel-group, multicentre, double-dummy
Interventions	<ul style="list-style-type: none"> ◆ Oral, once-daily 'Xarelto' 10 mg started 6–8 hours after surgery ◆ Subcutaneous, twice-daily enoxaparin 30 mg started 12–24 hours after surgery ◆ Both regimens continued for 12+/-2 days
Number of patients	<ul style="list-style-type: none"> ◆ 3,148 patients undergoing total knee replacement surgery
Primary efficacy endpoint	<ul style="list-style-type: none"> ◆ Total VTE: composite of any DVT, non-fatal PE, all-cause mortality
Secondary efficacy endpoints	<ul style="list-style-type: none"> ◆ Major VTE: composite of any proximal DVT, non-fatal PE and VTE-related death ◆ Symptomatic VTE
Primary safety endpoint	<ul style="list-style-type: none"> ◆ Major bleeding
Other bleeding-related safety endpoint	<ul style="list-style-type: none"> ◆ Non-major clinically relevant bleeding
RESULTS	
Total VTE	<ul style="list-style-type: none"> ◆ 'Xarelto' reduced absolute risk by 3.2%, p=0.0118 ◆ 6.9% (67 of 965) 'Xarelto' patients versus 10.1% (97 of 959) enoxaparin patients
Major VTE	<ul style="list-style-type: none"> ◆ 'Xarelto' reduced absolute risk by 0.8%, p=0.1237 (not significant) ◆ 1.2% (13 of 1,122) 'Xarelto' patients versus 2.0% (22 of 1,112) enoxaparin patients
Symptomatic VTE	<ul style="list-style-type: none"> ◆ 'Xarelto' reduced absolute risk by 0.47%, p=0.187 (not significant) ◆ 0.7% (11 of 1,526) 'Xarelto' patients versus 1.2% (18 of 1,508) enoxaparin patients
Major bleeding	<ul style="list-style-type: none"> ◆ Comparable and low rates of major bleeding ◆ 0.7% (10 of 1,526) 'Xarelto' patients versus 0.3% (4 of 1,508) enoxaparin patients, p=0.11 (not significant)
Non-major clinically relevant bleeding	<ul style="list-style-type: none"> ◆ 2.6% (39 of 1,526) 'Xarelto' patients versus 2.0% (30 of 1,508) enoxaparin patients





References

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- 3) Lassen MR, Ageno W, Borris LC, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N.Engl.J.Med.* 2008;358,(26)2776-2786
- 4) Turpie AG, Lassen MR, Davidson BL, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. *Lancet.* 2009;373,(9676)1673-1680
- 5) Eriksson BI, Kakkar AK, Turpie AG, et al. Oral rivaroxaban for the prevention of symptomatic venous thromboembolism after elective hip and knee replacement. *J Bone Joint Surg [Br].* 2009;91-B:636-44
- 6) Turpie AGG, 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: 444-453

About Xarelto® (Rivaroxaban)

Rivaroxaban is the most broadly indicated novel oral anticoagulant and is marketed under the brand name Xarelto®. To date, Xarelto has been approved for use in the following venous arterial thromboembolic (VAT) indications:

- The prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (AF) with one or more risk factors in more than 70 countries worldwide
- The treatment of deep vein thrombosis (DVT) and prevention of recurrent DVT and pulmonary embolism (PE) in adults in more than 70 countries worldwide
- The prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery in more than 120 countries worldwide

Rivaroxaban was discovered by Bayer HealthCare, and is being jointly developed with Janssen Research & Development, LLC. Xarelto is marketed outside the U.S. by Bayer HealthCare and in the U.S. by Janssen Pharmaceuticals, Inc. (a Johnson & Johnson Company).

Anticoagulant medicines are potent therapies used to prevent or treat serious illnesses and potentially life threatening conditions. Before initiating therapy with anticoagulant medicines, physicians should carefully assess the benefit and risk for the individual patient.

Responsible use of Xarelto is a high priority for Bayer, and the company has developed a [Prescribers Guide](#) for physicians and a [Xarelto Patient Card](#) for patients to support best practices. To learn more, please visit: <https://prescribe.xarelto.com>.

To learn more about thrombosis, please visit www.thrombosisadviser.com
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