

About the RECORD Clinical Trial Programme

What is the RECORD Clinical Trial Programme?

- ◆ RECORD (**RE**gulation of **Co**agulation in major **O**rthopedic surgery reducing the **R**isk of **DVT** and **PE**) is a global programme 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

RECORD Results: Summary

- ◆ Data from four distinct Phase III trials within the RECORD programme 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)
- ◆ 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 were randomised, double blind trials:

- ◆ In RECORD1, '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 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 published in the New England Journal of Medicine (NEJM)¹
- ◆ In RECORD2, extended-duration 'Xarelto' (35+/-4 days) demonstrated a 7.1% ARR 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 published in The Lancet²
- ◆ In RECORD3, 'Xarelto' demonstrated 9.2% ARR 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 published in the NEJM³

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RIVAROXABAN

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- ◆ 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. Results from RECORD4 were published in The Lancet⁴
 - ◆ 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. 'Xarelto' was also more effective at the end of the planned medication period (0.5% vs 1.3%, respectively). Results of this pooled analysis were published in the Journal of Bone and Joint Surgery⁵
 - ◆ Results of a pre-specified pooled analysis of RECORD 1-4 showed that 'Xarelto' demonstrated a statistically significant risk reduction of more than 50% in those treated with 'Xarelto' by comparison to enoxaparin. 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





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	◆ 4,541 patients undergoing total hip replacement surgery
Primary efficacy endpoint	◆ Total VTE: composite of 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 proximal DVT, non-fatal PE and VTE-related death ◆ Symptomatic VTE
Primary safety endpoint	◆ Major bleeding
Other safety endpoint	◆ 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	◆ 0.3% 'Xarelto' patients versus 0.1% enoxaparin patients, p=0.178 (not significant)
Non-major clinically relevant bleeding	◆ 2.9% 'Xarelto' patients versus 2.4% 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
Number of patients	<ul style="list-style-type: none"> ◆ 2,509 patients undergoing total hip replacement surgery
Primary efficacy end	<ul style="list-style-type: none"> ◆ Total VTE: Composite of DVT, non-fatal PE, all-cause mortality
Secondary efficacy endpoints	<ul style="list-style-type: none"> ◆ Major VTE: composite of proximal DVT, non-fatal PE and VTE-related death ◆ Symptomatic VTE
Primary safety endpoint	<ul style="list-style-type: none"> ◆ Major bleeding
Other safety endpoint	<ul style="list-style-type: none"> ◆ Non-major clinically relevant bleeding
RESULTS²	
Total VTE	<ul style="list-style-type: none"> ◆ 'Xarelto' reduced absolute risk by 7.3%, p<0.001 ◆ 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<0.001 ◆ 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"> ◆ <0.1% 'Xarelto' patients versus <0.1% enoxaparin patients, p=0.980 (not significant)
Non-major clinically relevant bleeding	<ul style="list-style-type: none"> ◆ 6.5% 'Xarelto' patients versus 5.5% 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 DVT, non-fatal PE, all-cause mortality
Secondary efficacy endpoints	<ul style="list-style-type: none"> ◆ Major VTE: composite of proximal DVT, non-fatal PE and VTE-related death ◆ Symptomatic VTE
Primary safety endpoint	<ul style="list-style-type: none"> ◆ Major bleeding
Other 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=0.016 ◆ 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=0.008 ◆ 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"> ◆ 0.6% 'Xarelto' patients versus 0.5% enoxaparin patients, p=0.774 (not significant)
Non-major clinically relevant bleeding	<ul style="list-style-type: none"> ◆ 4.3% 'Xarelto' patients versus 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. 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 DVT, non-fatal PE, all-cause mortality
Secondary efficacy endpoints	<ul style="list-style-type: none"> ◆ Major VTE: composite of proximal DVT, non-fatal PE and VTE-related death ◆ Symptomatic VTE
Primary safety endpoint	<ul style="list-style-type: none"> ◆ Major bleeding
Other 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=0.0016 ◆ 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=0.0165 (not significant) ◆ 1.2% (13 of 112) 'Xarelto' patients versus 2.0% (22 of 1,112) enoxaparin patients
Symptomatic VTE	<ul style="list-style-type: none"> ◆ 'Xarelto' reduced absolute risk by 0.5%, 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"> ◆ 0.7% 'Xarelto' patients versus 0.3% enoxaparin patients, p=0.110 (not significant)
Non-major clinically relevant bleeding	<ul style="list-style-type: none"> ◆ 10.2% 'Xarelto' patients versus 9.2% 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
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- 6) Gomez-Outes A, Suarez-Gea ML, Blazquez-Perez A, et al. Will oral rivaroxaban improve clinically relevant outcomes and thromboprophylaxis management in the orthopedic patient? *J Thromb Haemost.* 2009; 7: 2149-51

About Rivaroxaban (Xarelto®)

Rivaroxaban is an oral anticoagulant that was discovered in Bayer HealthCare's Wuppertal laboratories in Germany, and is being jointly developed by Bayer HealthCare and Johnson & Johnson Pharmaceutical Research & Development, L.L.C. It has a rapid onset of action with a predictable dose response and high bioavailability, no requirement for routine coagulation monitoring, and a limited potential for food and drug interactions.

Rivaroxaban is marketed under the brand name Xarelto® for VTE prevention in adult patients following elective hip or knee replacement surgery, and it is the only oral anticoagulant that has consistently demonstrated superior efficacy over enoxaparin in this indication. Rivaroxaban is approved in more than 110 countries worldwide and marketed outside the U.S. by Bayer HealthCare in this indication.

In the U.S., where rivaroxaban has been available since July 2011 for VTE prevention in adult patients following elective hip or knee replacement surgery, Janssen Pharmaceuticals, Inc. (a Johnson & Johnson Company) holds marketing rights. The Bayer HealthCare sales force is supporting Janssen Pharmaceuticals, Inc. in designated hospital accounts. On November 4, Xarelto® received further marketing approval in the U.S. for the prevention of stroke in patients with Atrial Fibrillation.

The extensive clinical trial programme supporting rivaroxaban makes it the most studied and widely published oral, direct Factor Xa inhibitor. The studies, reported and ongoing, involve over 75,000 patients for the prevention and treatment of venous and arterial thromboembolic (VAT) disorders across a broad range of acute and chronic conditions, including stroke prevention in patients with Atrial Fibrillation, DVT treatment and the prevention of recurrent DVT or PE, and the secondary prevention of Acute Coronary Syndrome.

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

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