

About the RECORD Clinical Trial Program



Fast facts

- ◆ RECORD was 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 *Journal of Bone and Joint Surgery*. RECORD1 and 3 were published in the *New England Journal of Medicine* in June 2008. RECORD2 and 4 were published in *The Lancet*

*Compared with enoxaparin (0.4% versus 0.8%, respectively; odds ratio: 0.44; p<0.005)

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 composite of any deep vein thrombosis (DVT), nonfatal 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 previously published in the *New England Journal of Medicine*¹

- ◆ 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 previously published in *The Lancet*²
- ◆ 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 previously published in the *New England Journal of Medicine*³
- ◆ 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



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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. Results from RECORD4 were published in *The Lancet*⁴

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 previously published in the *Journal of Bone and Joint Surgery*.⁵

Design of studies

RECORD1¹

Results show that prophylaxis with 'Xarelto' had a significantly lower rate of total venous thromboembolism compared to enoxaparin in patients following total hip replacement surgery

Study design	<ul style="list-style-type: none"> ◆ Randomized, double-blind, parallel-group, multicenter, 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 after 12–24 hours ◆ 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 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
Safety endpoints	<ul style="list-style-type: none"> ◆ Major bleeding/non-major bleeding
RESULTS	
Primary efficacy endpoint	<ul style="list-style-type: none"> ◆ 'Xarelto' reduced relative risk by 70%, p<0.001 ◆ 1.1% (18/1,595) 'Xarelto' patients versus 3.7% (58/1,558) enoxaparin patients
Major VTE	<ul style="list-style-type: none"> ◆ 'Xarelto' reduced relative risk by 88%, p<0.001 ◆ 0.2% (4/1,686) 'Xarelto' patients versus 2.0% (33/1,678) enoxaparin patients
Symptomatic VTE	<ul style="list-style-type: none"> ◆ 'Xarelto' reduced relative risk by 45%, ◆ 0.3% (6/2,193) 'Xarelto' patients versus 0.5% (11/2,206) enoxaparin patients, p=0.22 (not significant)
Major bleeding	<ul style="list-style-type: none"> ◆ 0.3% 'Xarelto' patients versus 0.1% enoxaparin patients, p=0.178 (not significant)
Non-major bleeding	<ul style="list-style-type: none"> ◆ 5.8% 'Xarelto' patients versus 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 after 12–24 hours, 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
RESULTS²	
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% (3/1,212) 'Xarelto' patients versus 1.2% (15/1,207) enoxaparin patients
Major bleeding	◆ <0.1% 'Xarelto' patients versus <0.1% enoxaparin patients, p=0.980 (not significant)
Non-major bleeding	◆ 6.5% 'Xarelto' patients versus 5.5% enoxaparin patients



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 after 12–24 hours ◆ 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% , $p = 0.008$ ◆ 0.7% (8/1,201) 'Xarelto' patients versus 2.0% (24/1,217) enoxaparin patients
Major bleeding	◆ 0.6% 'Xarelto' patients versus 0.5% enoxaparin patients, $p = 0.774$ (not significant)
Non-major bleeding	◆ 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

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 after 12–24 hours ◆ 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=0.016 ◆ 6.9% (67/965) 'Xarelto' patients versus 10.1% (97/959) enoxaparin patients
Major VTE	◆ 'Xarelto' reduced relative risk by 41% , p=0.0165 (not significant) ◆ 1.2% (13/112) 'Xarelto' patients versus 2.0% (22/1,112) enoxaparin patients
Symptomatic VTE	◆ 'Xarelto' reduced relative risk by 39% , p=0.187 (not significant) ◆ 0.7% (11/1,526) 'Xarelto' patients versus 1.2% (18/1,508) enoxaparin patients
Major bleeding	◆ 0.7% 'Xarelto' patients versus 0.3% enoxaparin patients, p=0.110 (not significant)
Non-major bleeding	◆ 10.2% 'Xarelto' patients versus 9.2% enoxaparin patients



References

- 1 Eriksson BI, Borris LC, Friedman RJ et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N Eng J Med* 2008;358:2765-75
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- 3 Lassen MR, Angeno W, Borris LC et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med*. 2008;358:2776-86
- 4 Turpie AG, Lassen MR, Davidson BL et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomized trial. *Lancet*. 2009;373:1673-80
- 5 Eriksson B, Kakkar AK, Turpie AGG, et al. Oral rivaroxaban for the prevention of symptomatic venous thromboembolism after elective hip and knee arthroplasty. *J Bone Joint Surg*. 2009;91-B:636-644

About Rivaroxaban

Rivaroxaban is a novel oral anticoagulant that was invented in Bayer Schering Pharma's Wuppertal laboratories in Germany, and is being jointly developed by Bayer HealthCare and Johnson & Johnson Pharmaceutical Research & Development, L.L.C. In clinical studies, rivaroxaban has been shown to be effective in preventing VTE in adult patients following elective hip or knee replacement surgery. It has a rapid onset of action with a predictable dose response and high bioavailability, no requirement for coagulation monitoring, as well as 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 new oral anticoagulant that has consistently demonstrated superior efficacy over enoxaparin for this indication. Xarelto® is approved in more than 100 countries worldwide and has been successfully launched in more than 75 countries by Bayer Schering Pharma achieving the market leader position among the new oral anticoagulants.

The extensive clinical trial program supporting rivaroxaban makes it the most studied oral, direct Factor Xa inhibitor in the world today. More than 65,000 patients are expected to be enrolled into the rivaroxaban clinical development program, which will evaluate the product in the prevention and treatment of a broad range of acute and chronic blood-clotting disorders, including stroke prevention in patients with atrial fibrillation, secondary prevention of acute coronary syndrome, and VTE prevention in hospitalized, medically ill patients.

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



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