

# A Comparison of Complications Requiring Return to Theatre in Hip and Knee Arthroplasty Patients Taking Enoxaparin versus Rivaroxaban for Thromboprophylaxis

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## SUMMARY

**Background.** There is no consensus on the optimal form of venous thromboembolic prophylaxis treatment in hip and knee arthroplasty patients, or on the safety and complication profile of the available chemical prophylaxis modalities. In this study we aimed to measure the return to theatre rate for any cause related to wound complications in patients undergoing total hip replacement and total knee replacement, and compare these rates between patients on oral Rivaroxaban 10 mg OD and subcutaneous Enoxaparin 40 mg OD in our department.

**Material and methods.** There were a total of 387 patients included in the study; 227 patients in group 1, who received Enoxaparin 40 mg OD, and 160 patients in group 2, who received Rivaroxaban 10 mg OD.

**Results.** The primary outcome measure was re-operation rate due to wound complications. Secondary outcome measures were infection rate, incidence of deep vein thrombosis, pulmonary emboli, duration of hospital stay, change in haemoglobin and haematocrit and blood transfusion rate. In this retrospective cohort study we found that patients who received Rivaroxaban were more than twice as likely to return to theatre for wound complications compared to patients receiving Enoxaparin. Although not statistically significant, this increase is in line with previous studies. Infection rates increased from 0.9% to 1.9% after the introduction of Rivaroxaban and microbiologically confirmed superficial infections rose from 1.3% to 3.1% after Rivaroxaban was introduced in our unit. These rises were not statistically significant.

**Conclusion.** Our study highlights the need for large randomised controlled trials to assess post-operative complications following the introduction of Rivaroxaban for post-arthroplasty thromboprophylaxis.

**Key words:** complications, arthroplasty, enoxaparin, rivaroxaban, venous thromboembolism, thromboprophylaxis

## BACKGROUND

Rivaroxaban (Xarelto; Bayer Schering Pharma AG, Wuppertal, Germany) is a factor Xa inhibitor. Following approval by the National Institute for Health and Clinical Excellence (NICE), it has recently been introduced to many orthopaedic units in the UK for thromboprophylaxis after total knee and hip replacement [1]. The evidence considered by NICE consisted of 4 large multicentre randomized controlled trials conducted by the RECORD group (The Regulation of Coagulation in Orthopaedic Surgery to Prevent deep Vein Thrombosis and Pulmonary Embolism) and concluded that Rivaroxaban was at least as efficient in preventing venous thromboembolism (VTE) as Enoxaparin (Clexane/Lovenox; Sanofi-Aventis, Frankfurt, Germany). NICE also concluded that the use of Rivaroxaban resulted in a small increase in major bleeding when compared to Enoxaparin [2-6].

However, despite the comprehensive and extensive nature of the work from the RECORD group it has come under some criticism for inconsistent and suboptimal dosing and duration of treatment in the enoxaparin groups, being underpowered to detect a difference in major bleeding rates and concerns regarding safety evaluations and in particular the definitions used for bleeding events [7]. Furthermore, concerns have also been raised by other authors regarding the use of Rivaroxaban for post-operative thromboprophylaxis, including by an author of the RECORD 4 group who stated that he would not use it in his own patients because the study did not measure key surgical outcomes, such as wound healing, drainage, prolonged hospital stay, infection, range of motion, and chronic pain [8-12].

Jensen et al. 2011 discontinued the use of Rivaroxaban in their unit after auditing wound complications in arthroplasty patients. They discovered a significantly increased rate of return to theatre for patients taking Rivaroxaban when compared to Tinzaparin (Innohep; LEO Pharma A/S, Ballerup, Denmark) following total hip replacement (THR) or total knee replacement (TKR) for wound complications including haematoma and persistent ooze [13]. Based on their study Jensen et al recommended a randomised controlled trial to determine the safety and efficacy of rivaroxaban for thromboprophylaxis in arthroplasty patients [13]. However, in the absence of randomised controlled trials powered to investigate these specific parameters, additional case series lend weight to the literature. We therefore felt that it was appropriate to audit and report our own experience with Rivaroxaban. This study therefore aimed to measure the return to theatre rate for any cause related to wound

complications in patients undergoing THR and TKR and compare these rates between patients on oral Rivaroxaban 10 mg OD and subcutaneous Enoxaparin 40 mg OD in our department.

## MATERIAL AND METHODS

Rivaroxaban was introduced as the default thromboprophylaxis agent in our unit on 1<sup>st</sup> April 2010 for hip and knee arthroplasty. We undertook a retrospective review of all the elective arthroplasty patients undergoing surgery for ten weeks prior and eight weeks following the introduction of Rivaroxaban i.e. from the 21<sup>st</sup> January 2010 to the 26<sup>th</sup> of May 2010. The Clinical Results Reporting System (CRRS) was utilised to obtain patients results, clinical letters and operation reports for a minimum of 12 months follow up.

Group 1 comprised of patients who received Enoxaparin 40 mg OD (Once Daily) starting 10 hours after surgery. Patients subsequently either received Enoxaparin for 6 weeks or stopped it on discharge from hospital and continued with Aspirin 150mg OD for 6 weeks.

Group 2 comprised patients who received Rivaroxaban in accordance with NICE Technology Appraisal Guidance 170, i.e. 10mg OD, starting 6-10h after surgery and continuing for 10 days following total knee replacement or 30 days following total hip replacement. Although the policy came into force on 1<sup>st</sup> April a small number of patients (n=24) continued to receive non-Rivaroxaban prophylaxis for a short period after this date due to unfamiliarity of the change by some of the medical team. These patients have been included in Group 1. A consort flowchart showing patient selection is shown in Figure 1.

Intermittent pneumatic compression devices and early mobilisation were used as the standard post-operative protocol for hip and knee arthroplasty. All patients received the standard dose and frequency of intra operative intravenous antibiotics, (Flucloxacillin and Gentamicin, Teicoplanin replaced Flucloxacillin if penicillin allergy was present).

The medical records of all patients undergoing elective hip or knee arthroplasty during the study period were reviewed. Exclusion criteria for the study were patients who were already anticoagulated (e.g. warfarin), those who underwent revision TKR/THR or unicompartmental knee arthroplasty and those who returned to theatre for a non-wound related indication. The decision to return to theatre for a wound complication was taken by the operating consultant in each case taking into account inflammatory markers and clinical findings. There were no predeter-

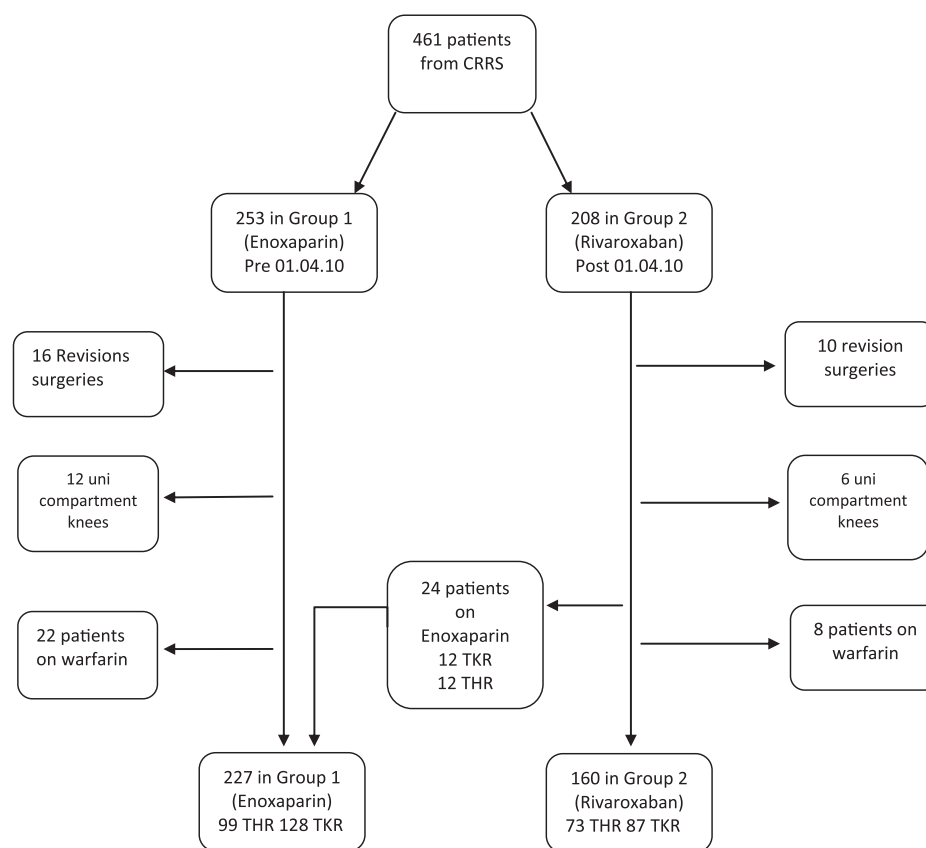


Fig. 1. A consort flowchart showing patient selection

mined criteria for indications to return to theatre post operatively. In cases where infection was suspected microbiological sampling was standardised with a minimum of five samples being sent for analysis.

Statistical analyses were performed using SPSS version 14.0 (SPSS Inc., Chicago, Illinois). Categorical data were analysed using a  $2 \times 2$  contingency table with Chi squared and Fisher's exact tests as dictated by sample size. Continuous data were analysed using Student's *t*-test. The null hypothesis was that there would be no difference in the return to theatre rates between Group 1 and Group 2.

The primary outcome measure was re-operation rate due to wound complications. Secondary outcome measures were infection rate, incidence of DVT/PE, duration of hospital stay, change in haemoglobin and haematocrit and blood transfusion rate.

## RESULTS

461 patients underwent knee and hip arthroplasty surgery during the study period. 74 were excluded after application of the eligibility criteria (Fig. 1). A total of 387 were included. 227 patients received Enoxaparin 40mg OD (Group 1) and 160 patients

received Rivaroxaban 10mg OD (Group 2). The proportions of hip and knee arthroplasties in both groups were similar. Group 1 had 44% THR and 56% TKR whilst group 2 had 46% THR and 54% TKR.

Tables 1 and 2 show details of patients who returned to theatre for wound complications. All patients (regardless of group) who returned to theatre had positive microbiology from deep samples. In Group 1 (Enoxaparin), 2 of 227 patients, 0.9% (95% C.I. 0.15 to 3.50) returned to theatre for wound complications. Patient A was a 50 year old male who underwent primary THR. Time between surgery and return to theatre for washout of an infected haematoma was 19 days. He subsequently underwent successful single stage revision for infection (Coagulase Negative Staphylococcus). Patient B was a 75 year old male who underwent primary THR for failed fixation (lag screw cut out) of a hip fracture. At 26 days postoperatively he underwent conversion of THR to Girdlestone's for dislocation associated with infection (Pseudomonas).

In Group 2 (Rivaroxaban), 3 of 160 patients, 1.9% (95% C.I. 0.50 to 5.80) returned to theatre for wound complications, ( $p=0.70$ ). Patient C was a 74 year old male who underwent successful washout and ex-

Tab. 1. Analysis of all patients who returned to theatre Group 1 (E1 and E2) Group 2 (R1-R3)

Patient	Operation	Indication	Organism	Surgery	Revision
E1	THR	Dislocated infected hip	P. aeruginosa	Open reduction and washout	No
E2	THR	Wound sinus	Coag Neg Staph	Washout & 1 stage revision	Yes 1 stage
R1	THR	Wound cellulitis	Coag Neg Staph	Aspiration of THR	Yes 1 stage
R2	THR	Pain	Enterococcus sp.	Aspiration of THR	Yes 1 stage
R3	TKR	Haematoma & dehiscence	Staph aureus	Washout & change of polyethylene tray	No

Tab. 2. Number of patients returned to theatre for infection by type of arthroplasty

n(%)	Enoxaparin		Rivaroxaban	
	THR n = 99	TKR n= 128	THR n = 73	TKR = 87
	2 (2%)	0	2 (2.7%)	1 (1.1%)

change of polyethylene at 6 weeks following primary TKR for infection (Staphylococcus). Patient D was a 79 year old female who was diagnosed with deep infection at 7 months following THR (Enterococcus). She was successfully managed with single stage revision. Patient E was a 61 year old female who underwent THR. She also had a deep infection (Coagulase Negative Staphylococcus) requiring 2-stage revision 6 months after THR.

Three of 227 patients in Group 1 had microbiologically confirmed superficial wound infection (1.3%, (95% C.I. 0.34 to 4.13)) compared to five of 160 in Group 2 (3.1%, (95% C.I. 1.16 to 7.52)). This showed a trend towards increased superficial wound infections in patients anticoagulated with Rivaroxaban (p=0.39). All superficial wound infections were successfully treated with oral/IV antibiotic and did not return to theatre.

The incidence of VTE in Group 1 was two of 227, 0.9% (95% C.I. 0.15 to 3.49): one deep vein thrombosis and one pulmonary embolus confirmed by ultrasound scan and CT pulmonary angiogram respectively. In Group 2 the incidence was two of 160, 1.3% (95% C.I. 0.22 to 4.91): both had radiologically confirmed deep vein thrombosis. In both groups all confirmed VTEs occurred only in the TKR subgroup of patients. There was no significant difference between Group 1 and Group 2 in the incidence of VTE.

The median duration of hospital inpatient stay for both groups 1 and 2 was identical at five days (range 2-30 for both groups). The change in haemoglobin pre- and post-operatively was also similar in both groups: a drop of 3.3g/dL (1-7.6) for Group 1 and a drop of 3.2g/dL (1-6.2) for Group 2. Change in haematocrit was the same for both groups at 0.1L/L range (0.02-1.5) Group 1 and (0-1.6) in Group 2. Red cell transfusion rates for group 1 were 0.19 units per patient (with 9.4% of patients being transfused). In group 2 the rate was not significantly different at 0.2 units per patient (10% of patients being transfused).

## DISCUSSION

Patients who received Rivaroxaban were more than twice as likely to return to theatre for wound complications compared to patients receiving Enoxaparin (0.9% vs. 1.9%). Although not statistically significant, this increase is in line with the work published by Jensen et al [13].

When separated out the THR patients that received Rivaroxaban had an increased rate of return to theatre from 2% (95% C.I. 0.35 to 7.81) to 2.7% (95% C.I. 0.48 to 10.40) (p = 0.84) and TKR patients that received Rivaroxaban increased from 0% (95% C.I. 0.00 to 3.63) to 1.1% (95% C.I. 0.06 to 7.13) (p = 0.85). All patients who returned to theatre were also found to have deep infection. Our deep infection rates increased from 0.9% to 1.9% after the introduction of Rivaroxaban and microbiologically confirmed superficial infections rose from 1.3% to 3.1%. These rises were not statistically significant. Deep infection can have devastating consequences and so any trend towards an increased infection rate is a cause for concern. However, no firm conclusions regarding incidence of infection can be drawn from a modest retrospective series such as this.

Changes in haemoglobin were similar in both groups as were transfusion rates (3.3g/dL in group 1 vs 3.2g/dL in group 2) indicating no difference in significant post-operative bleeding. The incidence of deep vein thrombosis and pulmonary embolus was also similar in both groups (0.9% in group 1 vs. 1.3% in group 2).

Length of hospital stay was equal in both groups with a median stay of 5 days for both Group 1 and Group 2. Although patients who had to return to theatre had longer stays, there was no overall difference between the two groups in total number of hospital days as inpatients.

Although the results from our study are not statistically significant, the trend towards higher re-operation rates for wound complications and the trend towards increased incidence of infection is a cause

for concern and concurs with the work of other authors. In the absence of randomised controlled trials providing definitive evidence we consider the potential risk to outweigh the benefits of an oral agent. On this basis

the use of Rivaroxaban has been discontinued and Enoxaparin reintroduced as routine chemical thromboprophylaxis.

The limitations of this study include the modest number of patients included. Numbers were limited specifically due to the cessation of the use of Rivaroxaban earlier than expected. Additional limitations were inherent to the retrospective design of the study and included lack of accurate documentation of wound ooze and records of quantity of dressing changes post operatively. The primary outcome measure was therefore set as return to theatre for wound complications. The decision to return to theatre was ultimately made by the operating consultant surgeon. There may be differing threshold of acceptable wound ooze within individual units as well as between different centres.

There is a paucity of data regarding the association between thromboprophylaxis with Rivaroxaban

and rates of key surgical key outcomes such as wound healing, persistent ooze, prolonged hospital stay, infection, and range of motion. This study showed no difference between Rivaroxaban and Enoxaparin with respect to post-operative transfusion rates or length of hospital stay. However, a trend towards increased rates of deep and superficial infection with Rivaroxaban was noted. Although we did not demonstrate a statistically significant difference, our work concurs with that of Jensen et al., who also showed increased rates of return to theatre [13]. We therefore no longer use Rivaroxaban in our department. However, we appreciate that our study is limited by modest numbers and recognise the need for further study.

## CONCLUSION

Our study highlights the need for large randomised controlled trials to assess post-operative complications following the introduction of Rivaroxaban for post-arthroplasty thromboprophylaxis.

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