

Wound Complications Following Rivaroxaban Administration

A Multicenter Comparison with Low-Molecular-Weight Heparins for Thromboprophylaxis in Lower Limb Arthroplasty

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Background: The oral anticoagulant rivaroxaban is recommended for venous thromboembolic prophylaxis following lower limb arthroplasty. Concerns regarding high rates of wound complications following its use have prompted this multicenter comparison with low-molecular-weight heparins.

Methods: English hospital trusts that replaced a low-molecular-weight heparin with rivaroxaban for thromboprophylaxis in lower limb arthroplasty during 2009 were identified. Prospectively collected national data for these units were analyzed to determine the thirty-day rates of wound complications and major bleeding (cerebrovascular event or gastrointestinal hemorrhage) and the ninety-day rates of symptomatic deep venous thrombosis (proximal or distal), symptomatic pulmonary embolism, and all-cause inpatient mortality before and after the change to rivaroxaban. A total of 2762 patients prescribed rivaroxaban following knee or hip arthroplasty were compared with 10,361 patients prescribed a low-molecular-weight heparin. Data were analyzed with use of odds ratios (ORs).

Results: There were significantly fewer wound complications in the low-molecular-weight heparin group (2.81% compared with 3.85%; OR = 0.72, 95% confidence interval [CI] = 0.58 to 0.90; $p = 0.005$). There were no significant differences between the low-molecular-weight heparin and rivaroxaban groups in the rates of pulmonary embolism (0.55% compared with 0.36%; OR = 1.52, 95% CI = 0.78 to 2.98), major bleeding (OR = 0.73, 95% CI = 0.48 to 1.12), or all-cause mortality (OR = 0.93, 95% CI = 0.46 to 1.89). There were significantly more symptomatic deep venous thromboses in the low-molecular-weight heparin group (0.91% compared with 0.36%; OR = 2.51, 95% CI = 1.31 to 4.84; $p = 0.004$).

Conclusions: The rivaroxaban group had a higher wound complication rate and a lower deep venous thrombosis rate; there were no differences in symptomatic pulmonary embolism or all-cause mortality. Longer follow-up is needed to assess any potential relationship between wound complications and joint stiffness, latent infection, and limb consequences of deep venous thrombosis.

Level of Evidence: Therapeutic Level III. See Instructions for Authors for a complete description of levels of evidence.

Rivaroxaban (Xarelto; Bayer Schering Pharma, Berlin, Germany), an orally active direct factor-Xa inhibitor, is currently recommended for the prevention of venous

thromboembolism (VTE) in adults undergoing total hip or knee replacement surgery in the United Kingdom^{1,2} and Canada³, and has recently been approved for use in the United States by the

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Food and Drug Administration (FDA). Each of the RECORD (Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism) trials has demonstrated rivaroxaban's superiority over enoxaparin, a low-molecular-weight heparin (LMWH), in terms of the primary efficacy outcome: a composite of any deep venous thrombosis (DVT), nonfatal pulmonary embolism (PE), and death from all causes⁴⁻⁷. However, symptomatic VTE is rare, and a significant benefit in patients receiving rivaroxaban was seen in only two of the four trials (RECORD2 and RECORD3)⁸. Importantly, there was no significant difference in mortality between the two groups in any of the trials.

The National Institute for Health and Clinical Excellence (NICE) produces recommendations, based on the best available evidence, for the optimal treatment of patients within the National Health Service (NHS) in England and Wales⁹. In 2010, NICE published guidelines recommending rivaroxaban for thromboprophylaxis following lower limb arthroplasty² after it was concluded that rivaroxaban was at least as effective as an LMWH at preventing VTE. As a result, many arthroplasty units in the United Kingdom have changed to rivaroxaban as a patient-friendly and resource-friendly alternative to LMWH.

Orthopaedic surgeons have not universally adopted the use of pharmacological thromboprophylaxis because of the risk of surgical site hemorrhage¹, which can compromise functional outcome and increase the rates of transfusion, reoperation, and revision surgery¹⁰. One of the orthopaedic surgeons on the steering committee for the RECORD4 trial specifically stated in a

Letter to the Editor of the *New England Journal of Medicine* that he would "not recommend rivaroxaban" for his patients, despite its superior efficacy to enoxaparin, because the trials did "not measure the surgical outcomes, such as wound healing, drainage, [and] infection."¹¹ More recently, a retrospective study at one hospital in the United Kingdom demonstrated that return to surgery for wound-related complications following arthroplasty increased significantly ($p = 0.046$) after routine thromboprophylaxis changed from an LMWH to rivaroxaban¹².

The aim of the present multicenter study, based on prospectively collected national data, was to evaluate the surgically relevant complications of using either rivaroxaban or an LMWH as thromboprophylaxis. These complications included wound complications, readmission, and return to surgery for deep infection as well the incidence of major bleeding and VTE. We believe this to be the first study to describe the impact of using rivaroxaban for patients undergoing hip or knee arthroplasty across the English NHS.

Materials and Methods

Hospital trusts that replaced an LMWH (of any type) with rivaroxaban for routine thromboprophylaxis in lower limb arthroplasty during 2009 were identified through the British Orthopaedic Directors Society (an orthopaedic clinical directors organization representing over 170 hospitals in the United Kingdom). Information regarding the thromboprophylaxis policies of the individual trusts, including the duration of treatment and the date of the policy change, were obtained by direct communication with the clinical director. Units were included if they had changed from using an LMWH to rivaroxaban at least six months prior to our analysis and were using rivaroxaban in accordance with

TABLE I Patient Demographics*

	LMWH Group (N = 10,361)	Rivaroxaban Group (N = 2762)	P Value†
Age‡ (yr)	68.5 (10.7)	67.8 (10.8)	0.004
Charlson score§			
0	7539 (72.8)	1981 (71.7)	0.287
1	2162 (20.9)	586 (21.2)	0.708
2	458 (4.4)	126 (4.6)	0.788
>2	202 (1.9)	69 (2.5)	
Sex§			
Female	6086 (58.7)	1500 (54.3)	<0.001
Male	4275 (41.3)	1262 (45.7)	<0.001
Procedure§			
Total knee replacement	4996 (48.2)	1257 (45.5)	0.012
Total hip replacement	4780 (46.1)	1194 (43.2)	0.007
Hip resurfacing	585 (5.6)	311 (11.3)	<0.001
Comorbidity§			
Non-insulin-dependent diabetes mellitus	962 (9.3)	284 (10.3)	0.121
Insulin-dependent diabetes mellitus	53 (0.5)	16 (0.6)	0.772
Rheumatoid arthritis	273 (2.6)	65 (2.4)	0.445

*LMWH = low-molecular-weight heparin. †Calculated with use of the chi-square test except in the case of age, which was calculated with use of the two-sample t test. ‡Values are given as the mean, with the standard deviation in parentheses. §Values are given as the number of patients, with the percentage in parentheses.

TABLE II Complications Following Lower Limb Arthroplasty*

Complication	LMWH Group (N = 10,361)†	Rivaroxaban Group (N = 2762)†	OR (95% CI)	P Value
Total wound complications	291 (2.81)	106 (3.84)	0.72 (0.58, 0.90)	0.005
Managed nonoperatively	243 (2.35)	97 (3.51)	0.66 (0.52, 0.84)	<0.001
Return to surgery for infection	55 (0.53)	17 (0.62)	0.86 (0.50, 1.49)	0.586
Major bleeding	80 (0.77)	29 (1.05)	0.73 (0.48, 1.12)	0.148
30-day readmission	214 (2.07)	47 (1.70)	1.21 (0.88, 1.67)	0.224
90-day symptomatic VTE	147 (1.42)	20 (0.72)	1.97 (1.23, 3.15)	0.004
Symptomatic DVT (proximal or distal)	94 (0.91)	10 (0.36)	2.52 (1.31, 4.84)	0.004
Symptomatic PE	57 (0.55)	10 (0.36)	1.52 (0.78, 2.98)	0.223
All-cause inpatient mortality	35 (0.34)	10 (0.36)	0.93 (0.46, 1.89)	0.848

*LMWH = low-molecular-weight heparin, OR = odds ratio, CI = confidence interval, major bleeding = major cerebrovascular event or gastrointestinal hemorrhage, VTE = venous thromboembolism, DVT = deep venous thrombosis, and PE = pulmonary embolism. †Values are given as the number of patients, with the percentage in parentheses.

the 2010 NICE guidelines (beginning six to ten hours after surgery and continuing for fourteen days following total knee replacement and twenty-eight to thirty-five days following total hip replacement)¹. Twelve NHS units in England met the inclusion criteria. Data from one unit had already been published and were therefore excluded¹², leaving eleven units. Bayer Schering Pharma AG declined to provide names of other hospitals in England at which rivaroxaban was being used.

Data for patients undergoing planned primary total hip replacement, total knee replacement, or hip resurfacing at these units from January 1, 2008, to February 28, 2010, were extracted from the administrative Hospital Episode Statistics (HES) database. Patients who underwent surgery prior to the date of the policy change were analyzed in the LMWH group, and those who underwent surgery following the change were analyzed in the rivaroxaban group. The HES database covers all admissions to English hospitals that provide care for NHS patients, and it includes fifteen diagnosis fields (coded with use of the International Statistical Classification of Diseases and Related Health Problems, 10th revision [ICD-10]) and fifteen surgical procedure fields (coded with use of the Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures, 4th revision [OPCS-4]). Records belonging to the same patient (determined with use of a combination of NHS number, date of birth, sex, and postal code) were linked, and the number of days between the index operation and any subsequent orthopaedic readmission (to any NHS hospital) was extracted. Patients for whom the date of the operation was not recorded were excluded. Complication rates were established by employing the appropriate ICD-10 or OPCS codes. Data linkage was carried out anonymously at the NHS Information Centre.

The primary outcome measure was wound complications (including hematoma, superficial wound infection, and deep infection requiring return to surgery) within thirty days of the procedure. Any evidence of wound drainage, erythema, or surrounding cellulitis identified by the medical staff and recorded in the patient's medical notes is coded in the HES database as a wound complication. It was not possible to discriminate between repeat surgical wound irrigation for infection and surgery for hematoma. However, as there is substantial

overlap in the treatment and immediate health care requirements of these conditions, it was felt that the combined data were adequate for the needs of this study.

Secondary outcomes were the thirty-day rate of readmission to the hospital orthopaedic service, the thirty-day rate of major bleeding (cerebrovascular event or gastrointestinal hemorrhage), the ninety-day rate of symptomatic VTE (proximal or distal DVT or PE), and the ninety-day rate of all-cause inpatient mortality. The relevant ICD-10 and OPCS-4 codes are summarized in the Appendix. Age, sex, and Charlson Comorbidity Index¹³ were recorded for each patient. The Charlson Comorbidity Index predicts the one-year mortality for a patient (see Appendix).

Statistical Methods

A two-sample t test (two-tailed) was used to compare the patient ages in the two groups¹⁴. The chi-square test with continuity correction was used to compare all other demographic data, as described by Fleiss et al.¹⁵. A p value of <0.05 was considered significant. Odds ratios (ORs) and 95% confidence intervals (CIs)¹⁶ were calculated for the outcome measures. The null hypothesis of no difference between agents (OR = 1) was tested with use of the chi-square test for a 2 × 2 contingency table¹⁴. The Smith-Welch-Satterthwaite test (or unequal-variance t test) was used to compare the mean length of stay during the primary admission^{14,17,18}.

Source of Funding

There were no external sources of funding associated with this study.

Results

During the study period, 2762 patients received rivaroxaban and 10,361 received an LMWH (Table I). As shown in Table II, there were significantly fewer wound complications in the LMWH group (2.81% compared with 3.84%; OR = 0.72, 95% CI = 0.58 to 0.90; p = 0.005). However, the rate of return to

TABLE III Effect of Wound Complications on Length of Stay Following Lower Limb Arthroplasty

	Wound Complications, Including Return to Surgery (N = 397)*	No Recorded Wound Complications (N = 12,726)*	P Value
Length of primary hospitalization (d)	14.2 (18.5)	6.6 (5.2)	<0.001

*Values are given as the mean, with the standard deviation in parentheses.

surgery for wound complications did not differ significantly. There was a trend toward fewer major bleeding events in the LMWH group (0.77% compared with 1.05%; OR = 0.73, 95% CI = 0.48 to 1.12; $p = 0.15$), although the difference did not reach significance. There were no significant differences in the rates of hospital readmission (OR = 1.21, 95% CI = 0.88 to 1.67), symptomatic PE (OR = 1.52, 95% CI = 0.78 to 2.98), or all-cause mortality (OR = 0.93, 95% CI = 0.46 to 1.89). There were significantly more symptomatic DVTs in the LMWH group (0.91% compared with 0.36%; OR = 2.51, 95% CI = 1.31 to 4.84; $p = 0.004$).

Post hoc calculations showed the statistical power to be 77.3% for total wound complications, 89.9% for DVT, 9.2% for return to surgery, 20.1% for PE, and 5.7% for death. The mean length of hospital stay during the primary admission was significantly longer for patients who developed a wound infection (14.2 compared with 6.6 days, $p < 0.001$) (Table III).

Discussion

Rivaroxaban acts by interrupting the blood coagulation cascade through the inhibition of factor Xa to prevent thrombin formation^{1,19}. Although it has several benefits, including the convenience of an oral preparation and the absence of risk of thrombocytopenia^{8,20}, the risk of surgically relevant complications has not been adequately evaluated. The impact of hematoma and infection on wound-healing can substantially hinder recovery, leading to restricted joint movement, reoperation, and revision arthroplasty^{21,22}. The data presented in this study show a significantly higher wound complication rate, without a reduction in symptomatic PE or mortality, in patients receiving rivaroxaban compared with an LMWH.

Wound hematoma, even when sufficient to warrant blood transfusion, was excluded from the RECORD studies²³. Although this strategy was agreed on by the manufacturer and an external steering committee²³, the resulting difference in definition limits direct comparison with other trials of anticoagulants. In the pooled FDA analysis of all four RECORD trials, surgical site bleeding meeting hemoglobin level or transfusion criteria was included as a “major event,” and this increased the absolute risk difference in the trials from 0.18% to 0.64% in favor of enoxaparin. The incidence of each type of bleeding event was higher in the rivaroxaban group, and the difference reached significance for the composite of major and non-major, clinically relevant bleeding ($p = 0.039$)⁸. A meta-analysis of these trials led to the conclusion that two to three patients would be harmed for each patient who would benefit from avoiding symptomatic VTE with rivaroxaban¹⁰. In addition, a recently published study demonstrated a significant increase in return to surgery due to wound complications (1.8% to 3.94%, $p = 0.046$) following change from an LMWH to rivaroxaban¹².

The cost-benefit ratio of rivaroxaban has been estimated to be £67 (\$108) per patient, representing a potential saving of £937,000 (\$1.53 million) if 20% of patients treated annually in the English NHS receiving an LMWH after arthroplasty were to receive rivaroxaban instead⁸. However, the higher cost burden of prolonged wound drainage would offset the apparent savings¹². If an additional 1% of patients prescribed rivaroxaban stayed in the hospital for an average of eight days longer (at £285 [\$467] per

day)²⁴ because of wound complications (as observed in the present study), the annual cost for the extended length of stay alone would amount to over £500,000 (\$820,000) even before additional treatment costs such as revision for infection are considered.

The DVT rates in the RECORD studies (0.66% and 1.77%²³) were higher than those observed in the present study (0.36% and 0.91%). This difference can be explained by the inclusion of asymptomatic DVT (a surrogate clinical end point) in the RECORD trials and by possible underreporting of symptomatic DVTs in the HES data used in the present study. The prevention of asymptomatic DVT, diagnosed on the basis of venography alone, has not been clearly demonstrated to reduce the sequelae of postphlebotic syndrome, and several studies suggest the risk of postphlebotic syndrome in patients with asymptomatic DVT may be no higher than in patients with no DVT²⁵⁻²⁷. However, the reduction in symptomatic DVTs observed in the present study, together with the perceived benefits of oral anticoagulants—improved compliance and avoidance of needles and of the requirement for monitoring—may entice surgeons to switch to oral anticoagulants.

In developing their clinical guideline on rivaroxaban, the members of the NICE Committee were persuaded that “there was a ‘trade off’ to be made between increasing anticoagulant efficacy and the risk of adverse effects, including major bleeding.”²¹ The FDA has similarly concluded that rivaroxaban carries a higher risk of bleeding complications²³. There is a need to balance the risk of rare fatal PE with the much more common risk of major and clinically important bleeding in patients taking anticoagulants after total knee replacement. It must also be stressed that the thromboembolic agent (LMWH) used to evaluate the efficacy of rivaroxaban has never been proven to reduce fatal PE, and the benefits of chemical thromboprophylaxis are not universally accepted. As the professional bodies representing surgeons provide conflicting advice, many surgeons feel obliged to use chemical prophylaxis.

We acknowledge that the methodology employed in this study is not comparable with prospective randomized controlled trials, but the results provide evidence of the effect of rivaroxaban across a number of centers. We do not have data on the type of thromboprophylaxis received by individual patients. Instead, we made the assumption that all patients would receive one drug or the other depending on the policy of the trust at that time. We were also unable to determine the number of patients who were compliant with self-medication following discharge, and our study therefore represents an intention-to-treat analysis. Coding inaccuracies should theoretically affect both groups equally, thereby allowing adequate comparison. Long-term problems associated with using VTE prophylaxis, such as joint stiffness, chronic infections, and limb consequences of previous DVT, could not be determined.

The proper method of VTE prophylaxis following lower limb arthroplasty is a contentious issue, and there is currently no perfect solution. To our knowledge, this study is the first to describe the impact of the use of rivaroxaban, in accordance with national guidelines, across the English NHS system. When compared with an LMWH, rivaroxaban use was associated with a lower DVT rate at the expense of a higher rate of wound

complications. Longer follow-up is required to assess the actual consequences of these adverse outcomes. Within the constraints of the study design, there were no differences in symptomatic PE or all-cause mortality. Randomized studies with higher power are necessary to establish the true differences (if any) in PE and mortality between chemical thromboprophylaxis agents.

Appendix

eA Tables showing the ICD-10 and OPCS-4 codes used in the analysis and the Charlson Comorbidity Index are available with the online version of this article as a data supplement at jbjs.org. ■

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