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# Rivaroxaban Versus Enoxaparin for Venous Thromboembolism Prophylaxis after Hip and Knee Arthroplasty

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ABSTRACT

The oral Factor Xa inhibitor rivaroxaban (Xarelto) has been the pharmacologic agent used for venous thromboembolism (VTE) prophylaxis after primary hip and knee arthroplasty (THA/TKA) at our institution since February 2012. The purpose of our study was to compare rates of VTE and major bleeding between rivaroxaban and our previous protocol of enoxaparin after THA/TKA. A retrospective cohort study was performed including 2406 consecutive patients at our institution between 1/1/11 and 9/30/13. Patients who did not have unilateral primary THA/TKA or who received other anticoagulants were excluded. Of the 1762 patients included, 1113 patients (63.2%) received enoxaparin and 649 patients (36.8%) received rivaroxaban. This study found no demonstrable differences between these two anticoagulants in rates of VTE, infection, reoperation, transfusion, or major bleeding. Therapeutic, Retrospective comparative study, Level III.



Venous thromboembolism (VTE) prophylaxis is one of the most controversial topics in hip and knee arthroplasty. The ideal anticoagulant medication would be easy to administer and have low rates of deep venous thrombosis (DVT), pulmonary embolus (PE), bleeding, and wound complications. With the current agents available, however, the challenge is to find the balance of low rates of VTE while minimizing bleeding and wound complications.

Rivaroxaban (Xarelto; Bayer Schering Pharma, Berlin, Germany) is a Factor Xa inhibitor which may have benefits for pharmacologic VTE prophylaxis after primary total hip and knee arthroplasty (THA and TKA, respectively). This oral medication is easy to administer and does not require laboratory monitoring due to its predictable pharmacodynamics and pharmacokinetics [1]. Most of the evidence regarding this new medication consists of the RECORD studies [2–5] and multiple publications that pool data from these same studies [6–12]. Combined, this literature suggests favorable results with decreased VTE rates and no change in bleeding or infectious complications compared to enoxaparin. However, shortly after the introduction of rivaroxaban in Europe, two recent studies raised concerns about wound complications with use of rivaroxaban. A single-institution retrospective study revealed a higher rate of return to the operating room for wound complications [13]. This was followed by a study of all British National Health Service (NHS) hospitals that began using rivaroxaban, which found higher rates of wound complications with rivaroxaban compared to enoxaparin with no difference in reoperation rates [14]. Given the recent independent studies which showed differing results from the industry-sponsored phase III trials, additional independent studies of this medication are necessary.

Prior to February 2012, our institution administered enoxaparin for routine VTE prophylaxis after primary THA and TKA. Enoxaparin is a subcutaneously injected medication which activates antithrombin III. In February 2012, our institution changed the VTE prophylaxis protocol to include the routine use of rivaroxaban. The purpose of our study was to compare rates of VTE and rates of major bleeding between rivaroxaban and enoxaparin after primary THA and TKA.

## Materials and Methods

A retrospective cohort study was conducted according to IRB protocol including 2406 consecutive patients who underwent primary THA or TKA. Patients were included beginning with the calendar year prior to implementation of the rivaroxaban protocol (between 1/1/11 and 9/30/13). Data were collected from 6 fellowship trained surgeons at 2 academically affiliated hospitals. All patients underwent surgery at a large urban tertiary care center or a suburban community hospital in a large metropolitan area.

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Patients were excluded who had a bilateral procedure, complex procedure, unicompartmental knee arthroplasty, hip hemiarthroplasty, resurfacing arthroplasty, or revision surgery. Patients who were concurrently on other anticoagulants were excluded, such as acetylsalicylic acid (Aspirin), clopidogrel, fondaparinux, or warfarin. Patients with a pre-operative creatinine of 1.2 mg/dL or greater were excluded. At our institution, patients with renal insufficiency are routinely placed on enoxaparin, due to the medical team's greater familiarity with this medication in these situations. Both drugs are renally excreted and this exclusion criterion served to minimize the effect of this potential confounder. Patients without at least 6 weeks of follow-up were excluded.

Patients received pharmacologic VTE prophylaxis beginning the morning after surgery with either enoxaparin (40 mg subcutaneous [SQ] daily for 21 days for THA patients, 30 mg SQ twice daily for 14 days for TKA patients) or rivaroxaban (10 mg oral daily for 35 days for THA patients, 10 mg oral daily for 12 days for TKA patients). Patients in both groups wore thromboembolism-deterrent stockings until 2 weeks post-operatively and wore intermittent pneumatic compression devices during their hospital stay. Both groups received 24 h of post-operative antibiotics.

Chart review recorded demographics, comorbidities, surgery performed, length of stay (LOS), symptomatic DVT, symptomatic PE, transfusion, number of units of packed red blood cells transfused, hemorrhagic cerebrovascular event (CVA), superficial infection, deep periprosthetic infection, and reoperation. Patients were not screened for DVT or PE unless they were symptomatic. Superficial infection was defined as infection superficial to the fascia including patients who underwent reoperation for irrigation and debridement superficial to the fascia. Patients were identified as having deep infection if they required reoperation extending deep to the fascia—including deep irrigation and debridement, with or without modular component exchange, or if they required removal of components for infection.

### *Statistical Methods*

T-tests were used to compare continuous variables between treatment groups and Chi-square tests were used, with Cochran corrections as appropriate, to compare categorical variables between treatment groups. For this analysis, the American Society of Anesthesiologists (ASA) score was considered a categorical variable. Alpha = 0.05.

Where results were not statistically significant, a post-hoc power analysis was performed. In addition, a minimum sample size was calculated to achieve power = 0.08 at alpha = 0.05, given the current data's variances and differences between means.

### *Source of Funding*

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

## Results

Of the 2406 patients who had hip or knee arthroplasty at our institution during the study period, 1762 patients met inclusion criteria. The following patients were excluded from the study: 141 patients had a bilateral procedure, complex procedure, unicompartmental knee arthroplasty, hip hemiarthroplasty, resurfacing arthroplasty, or revision surgery; 292 patients required continuation of prior anticoagulant medication post-operatively for medical reasons; and 211 patients had pre-operative creatinine greater than 1.2. Of the 1762 patients ultimately included in the study, 1113 patients (63.2%) received enoxaparin and 649 patients (36.8%) received rivaroxaban for VTE prophylaxis.

There were no differences in gender ($P = 0.989$, post-hoc power = 0.047), body mass index (BMI) ($P = 0.170$, post-hoc power = 0.144), ASA score ($P = 0.965$, post-hoc power = 0.047), or procedure performed ($P = 0.845$, post-hoc power = 0.051) between the 2 groups. The rivaroxaban group was younger, with mean age of 64.7 (± SD 10.4), compared to the mean age of 66.0 (± 10.7) in the enoxaparin group ($P = 0.011$). Pre-operative creatinine was higher in the enoxaparin group with mean creatinine of 0.80 (± 0.19) compared to mean creatinine of 0.73 (± 0.19) in the rivaroxaban group ($P < 0.001$). There was no difference in length of stay (LOS) between the groups ($P = 0.433$, post-hoc power = 0.050). These results are summarized in Table 1.

With the numbers available for study, there were no demonstrable differences in rates of venous thromboembolic disease with similar rates of DVT ($P = 0.208$, post-hoc power = 0.226) and PE ($P = 0.437$, post-hoc power = 0.113). There was no difference in major bleeding with similar rates of transfusion ($P = 0.372$; post-hoc power = 0.135), bleeding requiring transfusion of 2 or more units of packed red blood cells ($P = 0.971$, post-hoc power = 0.047), and hemorrhagic cerebrovascular events (CVA) ($P = 1.00$). The minimum sample size to achieve adequate statistical power ranged from 2798 to 347,691 patients. These results are summarized in Table 2.

There was no difference in rates of superficial infection ($P = 0.748$, post-hoc power = 0.058), deep infection ($P = 0.989$, post-hoc power = 0.047), or reoperation ($P = 0.904$, post-hoc power = 0.049). An analysis of all patients who required reoperation is summarized in Table 3.

## Discussion

This study showed that a pharmacologic VTE prophylaxis protocol with the use of rivaroxaban was as efficacious as enoxaparin at preventing post-operative symptomatic DVT and PE. The DVT rate of the enoxaparin group was 1.8% compared to 0.9% in the rivaroxaban group ($P = 0.208$) and the PE rate of the enoxaparin group was 0.7% compared to 0.3% in the rivaroxaban group ($P = 0.437$). A recent retrospective, industry-sponsored registry study by Beyer-Westendorf et al found a statistical decrease in symptomatic DVT in 54 of 1495 patients (3.6%) who received enoxaparin compared to 20 of 1043 (1.9%) patients who received rivaroxaban, and PE rates of 0.54% and 0.19% in the enoxaparin and rivaroxaban groups, respectively [15]. In contrast, our study found lower overall rates of DVT in both treatment cohorts than were seen in the Beyer-Westendorf study. Moreover, unlike in Beyer-Westendorf et al, we were unable to demonstrate a difference in DVT rates between treatment groups.

The ultimate goal of pharmacologic VTE prophylaxis after arthroplasty surgery is prevention of PE, most importantly fatal PE. In many studies, rates of DVT have been used as a surrogate outcome measure for the efficacy of medications used for pharmacologic VTE prophylaxis, and studies that do not identify statistically significant differences in PE suggest this is because of inadequate power. However, in a large meta-analysis of the available level I studies comparing apixaban and rivaroxaban to enoxaparin in 24,385 patients, Russell et al found no difference in rates of PE (Odds Ratio [OR] 0.6, 95% Confidence Interval [CI] 0.17–2.13, $P = 0.43$) [8]. These results are consistent with our study, which found no statistically demonstrable difference in PE rates between the enoxaparin and rivaroxaban groups.

There is variability in the literature regarding the definition of bleeding complications and the rates of bleeding complications after primary hip and knee arthroplasty. This variability makes it difficult to directly compare our transfusion rates to other studies. In a pooled analysis of 9581 patients from the RECORD 1, 2, and 3 studies, the transfusion rates were 49.8% in the enoxaparin group and 49.7% in the rivaroxaban group [6]. In our study, rivaroxaban was not associated with an increase in bleeding events compared to enoxaparin. The transfusion rate in the enoxaparin group was 13.3% compared to 15.0% in the rivaroxaban group ($P = 0.372$). Major bleeding requiring transfusion of 2 or more units of packed red blood cells occurred in 9.9% of patients receiving enoxaparin compared to 9.7% of patients receiving rivaroxaban ($P = 0.971$). There were no patients with post-operative hemorrhagic stroke in either group. At our institution, we transfuse patients who are symptomatic with hemoglobin less than 8 and asymptomatic with hemoglobin less than 7. During the time period of our study, the clinical

**Table 1**
Demographics and Comorbidities.

| | Enoxaparin ($N = 1113$) | Rivaroxaban ($N = 649$) | Difference Between Groups (Enoxaparin–Rivaroxaban), 95% Confidence Interval | Significance | Post-Hoc Power |
|---|---|---|---|---|---|
| Age | 66.0 (± SD 10.7) | 64.7 (±10.4) | 1.3 (0.2, 2.4) | $P = 0.011$* | |
| Male gender | 355 (31.9%) | 206 (31.7%) | 0.2% (−4.4%, +4.7%) | $P = 0.989$ | power = 0.047 |
| BMI | 31.8 (±7.0) | 32.3 (±7.1) | −0.5 (−1.2, +0.2) | $P = 0.170$ | power = 0.144 |
| Creatinine | 0.80 (±0.19) | 0.73 (±0.19) | 0.07 (0.05, 0.09) | $P < 0.001$* | |
| TKA | 684 (61.5%) | 395 (60.9%) | 0.5% (−4.1%, +5.3%) | $P = 0.845$ | power = 0.051 |
| LOS (days) | 2.8 (±2.0) | 2.8 (±1.2) | 0.0 (−0.2, +0.2) | $P = 0.433$ | power = 0.050 |

* indicates statistical significance with $p < 0.05$.

indications to transfuse packed red blood cells at our institution did not change, nor does it appear that the change in pharmacologic VTE prophylaxis to rivaroxaban changed our transfusion rates.

The rates of superficial and deep infection in the enoxaparin group were 1.7% and 0.9%, respectively, compared to 1.4% and 0.9% in the rivaroxaban group, with no demonstrable difference identified when comparing superficial infection ($P = 0.748$) and deep infection ($P = 0.989$) between the cohorts. This is comparable to the RECORD trials which reported infection rates of 0.2% to 1.7% [2–5]. A recent study by Jensen et al found no difference in deep infection rates in patients who received rivaroxaban (2.5%) compared to patients who received enoxaparin (1.0%) ($P = 0.1$) which is consistent with the results of our study [13].

Recent studies have raised concerns about higher rates of reoperation in patients who receive rivaroxaban. Jensen et al reported a higher rate of reoperation in patients who received rivaroxaban (3.9%) compared to patients who received enoxaparin (1.8%), which was statistically different ($P = 0.046$) [13]. Conversely, Chahal et al found only 2 of 227 patients (0.9%) in the enoxaparin group required reoperation compared to 3 of 160 patients (1.9%) in the rivaroxaban group, with similar rates between the cohorts ($P = 0.70$) [16]. Similarly, we found no difference in reoperation rate, with rates of 0.9% and 1.1% in the enoxaparin and rivaroxaban groups, respectively ($P = 0.904$). 18 out of 19 patients who required reoperation had positive intraoperative cultures, and the indication for reoperation in the patient with negative intraoperative cultures was wound dehiscence (Table 3). There were no patients who had reoperation for hematoma, which differs from the study by Jensen et al, which found 9 of 559 (1.6%) patients receiving rivaroxaban required reoperation for hematoma without infection. The discrepancy in reoperation rates could be due to variability in clinical practice. Another possibility for the higher wound complication rate of rivaroxaban compared to enoxaparin noted in previous studies is patient compliance issues with a subcutaneously administered medication versus an oral medication [13,14].

There is variability in dose scheduling of pharmacologic prophylaxis in the existing literature. At our institution, we initiate pharmacologic venous thromboembolism prophylaxis the morning after surgery. The randomized controlled trials of rivaroxaban differed in when to initiate pharmacologic prophylaxis with enoxaparin, ranging anywhere from 12 h pre-operatively (enoxaparin cohort in RECORD1–3 trials) to up to 24 h post-operatively (enoxaparin cohort in RECORD4 trial) [2–5]. On the other hand, these clinical trials initiated pharmacologic prophylaxis with rivaroxaban consistently 6–8 h after surgery. The duration of prophylaxis is also variable—for example, after hip arthroplasty, the duration of pharmacologic prophylaxis ranged anywhere from 10 to 39 days in the RECORD1 and RECORD2 trials [2,3]. To add to the confusion, a handful of studies combine the data from these clinical trials with different dose scheduling [6–12].

Rivaroxaban is less expensive in our institution than enoxaparin, despite the availability of enoxaparin as a generic medication since July 2010. At our institution, with our VTE prophylaxis protocol, the cost of enoxaparin is $134.29 USD per week compared to $87.87 USD per week for rivaroxaban after THA, and the cost of enoxaparin is $187.14 USD per week compared to $84.45 USD per week for rivaroxaban after TKA. In a study comparing cost-effectiveness of rivaroxaban and enoxaparin, Duran et al found that rivaroxaban was associated with cost savings of $511.93 USD for THA and $465.74 USD for TKA [17]. However, cost estimates in the Duran et al study incorporated the additional savings associated with treatment of fewer VTE into their calculations. Additionally, the rates of VTE in the Duran et al study were based on data from the RECORD 1–4 trials which had a larger difference in VTE rates than we found in our study. Taking into consideration the reduced costs associated with treating fewer VTEs, the overall savings at our institution may not be as dramatic.

There are a number of potential advantages and disadvantages of both enoxaparin and rivaroxaban. An advantage of both medications over alternatives, such as warfarin, is that they have a more predictable pharmacodynamic and pharmacokinetic profile that does not require laboratory monitoring. An advantage of enoxaparin is that there is a better understanding of dosing regimens for this medication in patients with renal impairment compared to rivaroxaban. Taking the oral medication rivaroxaban does not require patient training, whereas patient training is required to administer a subcutaneously injected low molecular weight heparin. Furthermore, there are additional costs associated with subcutaneous injections compared to oral agents. Enoxaparin carries a risk of thrombocytopenia, while rivaroxaban does not. Another disadvantage of rivaroxaban is that there is no reversal agent.

Despite the large sample size, this study has several limitations. Given the low incidence of complications studied, our study may not have been adequately powered to find a difference in rates with a sample size of 1762. However, the rather large minimum sample sizes required to achieve adequately statistical power to formally make a

**Table 2**
Complications.

| | Enoxaparin ($N = 1113$) | Rivaroxaban ($N = 649$) | Significance | Difference Between Groups (Enoxaparin–Rivaroxaban), 95% Confidence Interval | Post-Hoc Power | Min. Sample Size[b] |
|---|---|---|---|---|---|---|
| DVT | 20 (1.8%) | 6 (0.9%) | $P = 0.208$ | 0.9% (−0.3%, +0.02%) | power = 0.226 | 2798 patients |
| PE | 8 (0.7%) | 2 (0.3%) | $P = 0.437$ | 0.4% (−0.3%, +1.1%) | power = 0.113 | 5369 patients |
| Transfusion | 148 (13.3%) | 97 (15.0%) | $P = 0.372$ | −1.6% (−5.0%, +1.7%) | power = 0.135 | 6715 patients |
| Bleeding[a] | 110 (9.9%) | 63 (9.7%) | $P = 0.971$ | 0.2% (−2.7%, +3.1%) | power = 0.047 | 347,903 patients |
| Superficial infection | 19 (1.7%) | 9 (1.4%) | $P = 0.748$ | 0.3% (−0.9%, +1.5%) | power = 0.058 | 27,278 patients |
| Deep infection | 9 (0.9%) | 6 (0.9%) | $P = 0.989$ | −0.1% (−1.0%, +0.8%) | power = 0.047 | 103,691 patients |
| Reoperation | 10 (0.9%) | 7 (1.1%) | $P = 0.904$ | −0.2% (−1.1%, +0.8%) | power = 0.049 | 39,845 patients |
| Hemorrhagic stroke | 0 (0.0%) | 0 (0.0%) | $P = 1.00$ | Not applicable | Not applicable | Not applicable |

[a] Bleeding requiring transfusion of 2 units or more.
[b] Minimum sample size required to detect a statistically significant difference in the post-hoc power analysis, given the variance and differences between groups.

**Table 3**
Patients Requiring Return to Surgery.

| Patient | Surgery Performed | RTS Indication | RTS Surgery Performed | Time to RTS (Days) | Infection | Organism | >1 RTS |
|---|---|---|---|---|---|---|---|
| E1 | THA | Dislocation | DEEP IND | 15 | YES | Coagulase-negative *Staphylococcus* | YES |
| E2 | TKA | Wound drainage | DEEP POLY | 31 | YES | *Staph. aureus* | NO |
| E3 | THA | Wound drainage | DEEP IND | 14 | YES | GBS, Non-hemolytic *Strep* | NO |
| E4 | THA | Wound abscess | DEEP POLY | 31 | YES | Coagulase negative *Staphylococcus* | NO |
| E5 | TKA | Wound drainage | SUP IND | 47 | YES | *E. coli*, alpha hemolytic *Strep* | NO |
| E6 | THA | Dislocation | DEEP IND | 10 | YES | *S. epidermidis* | NO |
| R1 | THA | Wound drainage | DEEP POLY | 20 | YES | MRSA | NO |
| R2 | THA | Wound abscess | DEEP POLY | 74 | YES | *Staph. aureus* | NO |
| R3 | THA | Suture abscess | SUP IND | 40 | YES | MRSA | NO |
| R4 | THA | Fracture, wound drainage | DEEP REV | 21 | YES | MRSA | YES |
| E7 | TKA | Wound drainage | DEEP IND | 22 | YES | *Staph. aureus* | NO |
| R5 | THA | Wound drainage | DEEP POLY | 30 | YES | *Staph. aureus* | NO |
| R6 | THA | Wound SSI | DEEP POLY | 37 | YES | *Staph. aureus* | NO |
| E8 | THA | Hematoma | DEEP IND | 13 | YES | MRSA | NO |
| R7 | TKA | Wound drainage | DEEP POLY | 45 | YES | *Staph. aureus* | YES |
| E9 | TKA | Wound dehiscence | DEEP REV | 28 | YES | *Pseudomonas aeruginosa* | YES |
| E10 | TKA | Wound dehiscence | DEEP IND | 24 | YES | Negative | NO |

SUP IND = Superficial incision and debridement superficial to fascia, DEEP IND = Deep incision and debridement, DEEP POLY = Deep incision and debridement with exchange of modular components, DEEP REV = Removal of prosthesis with antibiotic spacer placement, MRSA = methicillin-resistant *Staphylococcus aureus*, SSI = Surgical Site Infection.

conclusion of "no difference" (with these data, up to 347,903 patients) would argue that, given the variance in the underlying data, differences between these two agents, if present, may be subtle enough to be of limited clinical interest. This study is also limited by its retrospective nature and the completeness of information that was accurately recorded in patient charts during review. Strictly speaking, the study cohorts were not statistically equivalent with a slightly younger age and lower creatinine in the rivaroxaban cohort. Despite this statistical difference, the difference in mean age of 1.3 years may not be clinically significant. Additionally, the average creatinine values in each cohort fell within the normal acceptable range. The fact that data were collected from two academically affiliated hospitals lends itself to potential variation in practice and organization culture. The latter point may also be considered a strength in the sense that the data were collected from a large urban tertiary care center and a suburban community hospital, which makes the cumulative results more broadly generalizable. An additional strength is that this study received no industry funding or support.

## Conclusion

In what we believe to be the largest non-industry-funded study to date evaluating the Factor Xa inhibitor rivaroxaban, there were no statistically demonstrable differences between enoxaparin and rivaroxaban in terms of VTE or major bleeding complications. For standard primary THA and TKA, these medications appear to be equally effective without increased adverse events.

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