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# Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty

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**Abstract**
**Background: Introduction:** Total hip arthroplasty (THA) is a successful surgical procedure for reducing pain and improving physical function in osteoarthritis. It is one of the most effective orthopaedic procedures.
**Material and methods:** Patients were eligible for the study if they were aged 18 years or older and were scheduled for total hip arthroplasty. Patients were ineligible if they were scheduled to undergo staged, bilateral hip arthroplasty were pregnant or breastfeeding, had active bleeding or a high risk of bleeding, or any disorder contraindicating the use of Rivaroxaban/enoxaparin that might necessitate enoxaparin dose adjustment.
**Results:** Of the 52 patients enrolled in study, 52 patients were randomized to receive either Rivaroxaban **(**n=26) or enoxaparin (n=26). The baseline demographic characteristics of the two randomized treatment groups are well balanced as described in Table 1. The surgical characteristics are described in Table 2.
**Conclusion:** Rivaroxaban, given as a once-daily 10 mg fixed dose 6–8 h postoperatively, is the first new oral anticoagulant to significantly reduce the incidence of venous thromboembolism after total knee arthroplasty, compared with enoxaparin 30 mg twice daily, starting 12–24 h postoperatively, without a significant difference in the risk of major or clinically relevant bleeding.

**Keywords:** Rivaroxaban versus enoxaparin Total hip arthroplasty successful surgical patients

## Introduction
Total hip arthroplasty (THA) is a successful surgical procedure for reducing pain and improving physical function in osteoarthritis [1]. Severe osteoarthritis and hip fragility fractures due to osteoporosis are the chief conditions needful of THA. In India, osteoarthritis, secondary to avascular necrosis and/or trauma to the hip joint as well as arthritis are the commonest signs for THA. It is one of the most effective orthopaedic procedures. The requirement for THA is probable to continually rise [2].
Venous thromboembolism (VTE) is a main, possibly fatal problem after major orthopaedic procedure such as total knee arthroplasty. [3] Subsequently total hip arthroplasty, extensive prophylaxis for 5 weeks after surgery decreases the frequency of characteristic and asymptomatic venous thromboembolism more efficiently than short-term prophylaxis [2]. Deep-vein thromboses (DVT) have been exposed to form after the cessation of short-term prophylaxis [4]. Numerous meta-analyses recommend that extended thromboprophylaxis after total hip arthroplasty results to a decrease in symptomatic venous thromboembolic events, without increasing the risk of major bleeding [5].
The present possibilities for prolonged thromboprophylaxis are inadequate. Low-molecular-weight heparin (LMWH) preparations decreases thromboembolic incidence but essential to be managed subcutaneously, and their cost-effectiveness has been shown only if patients or relative can be taught to inject the medicine at home [6]. Vitamin K antagonists, alike warfarin, have variable pharmacologic properties and several food and drug interactions, need continuous supervision, and hence difficult to manage [7]. Moreover, there is sign to recommend that the frequency of major bleeding is more with vitamin K antagonists than with low-molecular-weight heparin preparations given after total hip arthroplasty [8].
Rivaroxaban is an oral, direct factor Xa inhibitor that is approved globally for the prevention of venous thromboembolism after elective hip and knee arthroplasty, in some countries, it has

a broader label to include use after lower-limb orthopaedic surgery [9]. Despite widespread approval, there are still outstanding questions from clinicians relating to the everyday use of rivaroxaban. These questions relate to the optimal duration of thromboprophylaxis after surgery; its use with other medications; the risk of adverse events, such as bleeding or wound-related complications; the optimal timing of the first thromboprophylactic dose; periprocedural care of the anticoagulated patient; use with general and regional anaesthesia; and use in fracture-related cases [10].

Enoxaparin dose adjustment is commonly recommended for thromboprophylaxis in patients with severe renal insufficiency (CrCl of <30 mL/minute); however, the exact dose reduction varies among different countries and practice guidelines [11]. The American College of Chest Physicians (ACCP) guidelines and enoxaparin US labelling recommend 30 mg subcutaneously (SC) daily for deep vein thrombosis prophylaxis in hip or knee replacement, and in medical patients during acute illness when the CrCl rate is <30 mL/minute [12]. Moreover, different medical associations and countries may adopt different enoxaparin dosing protocols in patients with renal failure, and prescribers tend to reflect the practices predominant in the institutions where they completed their medical specialty training [13]. In practice, medical centers in Europe and the Middle East use a further reduced dose of enoxaparin (20 mg) for prophylaxis in patients with a CrCl rate of 20 to 30 mL/minute and then switch to UFH at 5000 units SC twice daily for patients with a CrCl rate of <20 mL/minute [14].

To date, the safety and efficacy of reduced-dose enoxaparin (20 mg) have not been completely assessed for the prevention of VTE in THA patients. In fact, large dose-finding studies have not been conducted, and contemporary studies either omitted patients with renal failure or did not stipulate whether such patients were recruited [15]. To our knowledge, no randomized study has been done to compare the standard prophylactic enoxaparin dose (30 mg) with a reduced dose (20 mg) in THA patients. Consequently, inadequate data exist on the preference of one dose over the other in THA patients [16]. This pilot study reports the initial findings of the efficacy and safety of enoxaparin at 20 mg daily for DVT prophylaxis in hospitalized THA patients was good. The study was completed in accordance with the hospital's ethics code and approved by the hospital's institutional review board. Because this was a retrospective cohort study with a comprehensive chart review, patient consent was not necessary per the institutional review board.

## Material and methods

Patients were eligible for the study if they were aged 18 years or older and were scheduled for total hip arthroplasty. Patients were ineligible if they were scheduled to undergo staged, bilateral hip arthroplasty were pregnant or breastfeeding, had active bleeding or a high risk of bleeding, or any disorder contraindicating the use of Rivaroxaban/enoxaparin that might necessitate enoxaparin dose adjustment. Other exclusion criteria included clinically history of liver disease, severe renal impairment (creatinine clearance <30 mL per min), concomitant use of drugs that strongly inhibit cytochrome P450, such as protease inhibitors or ketoconazole, pregnancy or breastfeeding, planned intermittent pneumatic compression, or the requirement for ongoing anticoagulant therapy.

### Study design and drugs

Before surgery, participants were randomly assigned to study drug group with permuted blocks and stratification according to centre by means of a central telephone system with generated randomization list. Patients received either once daily oral rivaroxaban 10 mg tablets or subcutaneous injections of 40 mg enoxaparin sodium. Drug was dispensed by nurses in the hospital and by nurse, relative, or patient after discharge. Rivaroxaban was started 6–8 h after wound closure or after adequate haemostasis had been achieved. Enoxaparin was started 12–24 h after wound closure. Thereafter, study drugs were administered every 24 hours (range, 22 to 26) in the evening through day 35 (range, 31 to 39) after surgery (with the day of surgery defined as day 1).

Patients underwent mandatory bilateral venography the day after the last dose of the study drug, at 36 days (range, 30 to 42). No further study medication was given after venography, although further thromboprophylaxis was continued at the investigator's discretion. Patients had a follow-up visit 30 to 35 days after the last dose of the study drug.

The study was done in accordance with the Declaration of Helsinki and local regulations. Independent ethics committees or institutional review boards for each study centre approved the protocol.

### Outcome measures

All outcome was assessing by central independent adjudication committees masked to allocation assessed all outcomes. The primary efficacy outcome was the composite of any deep-vein thrombosis, non-fatal pulmonary embolism, or death from any cause up to 36 days after surgery. The main secondary efficacy outcome was major venous thromboembolism (ie, proximal deep-vein thrombosis, non-fatal pulmonary embolism, or death related to venous thromboembolism). Other efficacy outcomes included the incidence of asymptomatic deep-vein thrombosis (any, any proximal, and distal only), symptomatic venous thromboembolism in the treatment and follow-up (30 to 35 days) periods, and death during the follow-up period.

Deep-vein thrombosis was assessed at 36 days between days 30 and 45 by systematic, ascending, bilateral venography with a standardised technique. Suspected symptomatic deep vein thrombosis was assessed by ultrasound and, if positive, was to be confirmed with venography. Suspected pulmonary embolism was confirmed by pulmonary angiography, by ventilation-perfusion lung scintigraphy with chest radiography, or by contrast-enhanced spiral CT.

The main safety outcome was the incidence of major bleeding between intake of the first dose of study drug and 2 days after the last dose (on-treatment). Major bleeding was defined as clinically overt bleeding that was fatal, occurred in a critical organ (eg, retroperitoneal, intracranial, intraocular, or intraspinal), necessitated operation, was outside of the surgical site and associated with a fall in haemoglobin of 2 g/dL or more (calculated from the postoperative haemoglobin baseline value before the event), or required an infusion of two or more units of blood. One of the secondary safety outcomes was clinically relevant non-major bleeding, defined as multiple-source bleeding, unexpected haematoma (>25 cm.), excessive wound haematoma, nose bleeding (>5 min), gingival bleeding (>5 min), macroscopic haematuria, rectal bleeding, coughing or vomiting blood, vaginal bleeding, blood in semen, intra-articular bleeding with trauma, or surgical-site bleeding. Other safety outcomes included any on-treatment bleeding, any non-major bleeding, haemorrhagic wound complications (the composite of excessive wound haematoma and reported surgical site bleeding), adverse events, and death. Laboratory variables and cardiovascular

events were monitored during treatment and follow-up periods.

## Results

Of the 52 patients enrolled in study, 52 patients were randomized to receive either Rivaroxaban **(**n=26) or enoxaparin (n=26). The baseline demographic characteristics of the two randomized treatment groups are well balanced as described in Table 1. The surgical characteristics are described in Table 2.

**Table 1:** Demographic and Clinical Characteristics of the Patients (Safety Population).

| Characteristic | Rivaroxaban (n=26) | Enoxaparin (n=26) |
|---|---|---|
| **Age - yrs** | | |
| Mean | 53.2 | 52.4 |
| Range | 18-80 | 18-80 |
| **Weight - kg** | | |
| Mean | 73.2 | 71.8 |
| Range | 40-96 | 42-98 |
| **Body-mass index - kg/m$^2$** | | |
| Mean | 26.3 | 25.8 |
| Range | 15.6-49.3 | 15.1-48.6 |
| History of venous thromboembolism - no. (%) | 2 | 1 |
| | | |
| Previous orthopedic surgery— no. (%) | 8 | 9 |
| **Type of surgery — no. (%)** | | |
| Primary | 23 | 22 |
| Revision | 3 | 4 |
| **Type of anesthesia — no. (%)** | | |
| General only | 9 | 7 |
| General and regional | 3 | 4 |
| Regional only | 14 | 15 |
| **Duration of surgery — min** | | |
| Mean | 90.3 | 93.7 |
| Range | 31-432 | 32-413 |

**Table 2:** Incidence of Efficacy Events (Modified Intention-to-Treat Population)

| Outcome | Rivaroxaban | Enoxaparin | P Value |
|---|---|---|---|
| | **no. with events/ total no.** | **no. with events/ total no.** | |
| Primary efficacy outcome: | 3/23 | 4/23 | |
| Major venous thromboembolism | 2/25 | 3/25 | |
| Nonfatal pulmonary embolism | 3/23 | 3/23 | |
| Deep-vein thrombosis | 6/23 | 11/23 | |
| Proximal | 1/23 | 5/23 | |
| Distal only | 3/23 | 4/23 | |
| Symptomatic venous thromboembolism | | | |
| During treatment | 3/24 | 4/24 | |
| During follow-up | 1/24 | 1/24 | |

**Table 3:** Adverse Events (Safety Population)

| Event | Rivaroxaban (n=26) | Enoxaparin (n=26) | P Value |
|---|---|---|---|
| Any on-treatment bleeding — no. (%) | 3 | 3 | |
| **Major bleeding** | | | |
| No. of patients (%) | 2 | 1 | |
| Fatal bleeding — no. (%) | 1 | 0 | |
| Bleeding into a critical organ — no. (%) | 1 | 0 | |
| Bleeding leading to reoperation — no. (%) | 2 | 1 | |
| **Clinically overt extra surgical-site bleeding — no. (%)** | | | |
| Leading to a fall in hemoglobin | 2 | 1 | |
| Leading to transfusion of >2 units of blood | 2 | 1 | |
| Non-major bleeding — no. (%) | 7 | 6 | |
| Clinically relevant | 3 | 2 | |
| Hemorrhagic wound complication | 3 | 2 | |
| Postoperative wound infection — no. (%) | 2 | 2 | |
| Patients receiving blood transfusions — no. (%) | 8 | 7 | |
| **Volume of blood transfusion— ml** | | | |
| Median | 576 | 586 | |
| Range | 50-3494 | 52-3684 | |
| Patients with postoperative drain — no. (%) | 17 | 16 | |
| **Volume in drain in — ml** | | | |
| Median | 554 | 537 | |
| Range | 14-3246 | 15-3017 | |
| Any on-treatment adverse event — no. (%) | 7 | 6 | |
| Drug-related adverse event — no. (%) | 5 | 4 | |

**Discussion**

Deep vein thrombosis and pulmonary embolism are considered two of the most important complications after THA, warranting thromboprophylaxis. The peak incidence of clinical DVT seems to occur 5-10 days after hip arthroplasty and continues to be diagnosed up to 6 weeks or 8 weeks after hospital discharge [17]. The American College of Chest Physicians recommend extended period of thromboprophylaxis for 28-35 days post-surgery. With LMWH, extended thromboprophylaxis is notably more efficient in preventing venous thromboembolism in orthopaedic surgery patients than the recommended practice of 10 days [18]. Extended thromboprophylaxis with enoxaparin for 4 weeks after THA has shown to considerably decrease the frequency of VTE significantly (0.5% vs. 3.27%) compared with short-term thromboprophylaxis (7-11 days) in Indian patients [19].

In our study, the mean age of the patients were 53.2 years in Rivaroxaban group and 52.4 years in enoxaparin group, whereas patients of both the sex equally participated in the study. Similar study conducted by Turpie AG *et al.* shows that mean age was 67.6 years in foreign country [20]. The mean body mass index of the patients was (26.3 vs 25.8 kg/m$^2$) Rivaroxaban and enoxaparin respectively compared with that of the global population (27.8±4.8 kg/m2). In our study, surgical procedures were performed by mostly use of regional anaesthesia in both the groups. According to Malhotra *et al.*, performed by regional anaesthesia [21].

In the study, the primary efficacy outcome (total VTE and all-cause mortality) occurred in 13.0% of patients in the Rivaroxaban group and 17.3% of patients in the enoxaparin group. Rivaroxaban was found to be roughly inferior to enoxaparin in the study. In another study conducted by alexander *et al.*, primary outcome occurred in 7.7% patients in the dabigatran group and 8.8% patients in the enoxaparin group with an absolute risk difference of 1.1% (95% CI, -3.8% to 1.6%) [22]. Furthermore, meta-analysis by Gomez-Outes *et al.*, reported risk of symptomatic VTE with dabigatran (relative risk 0.71, CI 0.23 to 2.12) is similar and comparable to enoxaparin [23]. In our study, Rivaroxaban is non-inferior to enoxaparin for the prevention of recurrent and non-fatal pulmonary embolism (3/23 vs 3/23). A systematic review by Xing J *et al.* reported an overall 30-day mortality rate of 0.3% across all type of arthroplasties in 28 out of 80 studies [24].

In our study fewer patients were diagnosed with proximal and distal DVT in the Rivaroxaban group (4.3% and 13% patients) compared with the enoxaparin group (21.7% and 17.3%). However, in the Indian patients, distal DVTs were more often reported in the dabigatran group (10.7%) compared with the enoxaparin group (2.7%); whereas in the global population 5.4% and 4.5% of the patients had distal DVTs in the dabigatran and enoxaparin groups respectively. Distal DVTs (associated with calf veins) are less serious than the proximal DVTs as thrombi in calf veins are generally small and have little chance of embolization. Distal DVTs are therefore not usually associated with clinical disability or other complications. Distal DVTs may be at risk of embolization if they extend proximally [25]. PE occurs frequently in Indian patients with symptomatic DVT [26]. In a prospective study conducted in New Delhi, the overall incidence of VTE was reported to be 6.12% and that of PE was 0.6% among patients undergoing major orthopaedic surgeries (THA, TKA, and proximal femur fracture fixation) [27].

Rivaroxaban and enoxaparin had similar safety profiles. There were no clinically significant differences in the incidence of bleeding or other safety outcomes between the two groups. These rates are in line with the rates found in similar trials. [28] This design resulted in a conservative estimate of the incidence of bleeding with rivaroxaban [29]. Anticoagulants are drugs prevent Venous thromboembolism and pulmonary embolism after THA but risk of bleeding associated with their use can be fatal. Rivaroxaban and enoxaparin pose a similar risk of clinically significant bleeding, major bleeding, and clinically relevant non-major bleeding. Assessed using the same bleeding criteria, the incidence of major bleeding events for enoxaparin was comparatively lower than Rivaroxaban group. Bleeding was defined in this trial as bleeding occurring after the intake of the first blinded dose of study medication. In the rivaroxaban group, bleeding that occurred during or shortly after surgery was included (6 major bleeding event and 7 non-major bleeding events), even though rivaroxaban had not been administered.

In our study, only few patients had a major bleeding event prior to the administration of Rivaroxaban and enoxaparin as evidenced by a fall in haemoglobin level leading to blood transfusion. The occurrence of all Adverse Events in the enoxaparin group was slightly lower 23% than Rivaroxaban group and 26.9%. Occurrence of drug related adverse events was more in the Rivaroxaban (19.2%) group compared with enoxaparin (15.3%) group patients. Whereas, negligible risk of hepatic dysfunction with dabigatran was observed in previously reported study of hip and knee arthroplasty studies, as well as other studies in which Rivaroxaban was administered for up to 18 months [30].

The superior efficacy of rivaroxaban was not associated with any significant increases in the incidence of major bleeding or any other bleeding events. The number of major bleeding events in this study was lower than that reported in several other studies [31], which may be due, in part, to the difference in definitions of bleeding that were used in the various studies. Almost half the patients who undergo this type of surgical procedure require a transfusion of 2 or more units of blood [32]. In our study, the inclusion of a secondary bleeding outcome, haemorrhagic wound complication (which encompassed surgical-site bleeding and excessive wound hematoma), allowed such events to be reported, and there was no significant difference in bleeding outcomes between the two groups.

The analyses supported the main finding of the study that there was a significant reduction in the incidence of the primary outcome in patients receiving rivaroxaban, as compared with those receiving enoxaparin. When all adjudicated events — positive results on venography, symptomatic events - and all venograms that were adjudicated to show minor deep-vein thrombosis were considered (regardless of whether they occurred outside the predefined time windows), the weighted absolute risk reduction for the primary outcome in the rivaroxaban group, as compared with the enoxaparin group was good.

Thus, our study showed that extended thromboprophylaxis with 10 mg of rivaroxaban once daily for 5 weeks resulted in a very low incidence of thrombosis, with a safety profile similar to that of enoxaparin.

The limitation of the study was sample size for the Indian population was not sufficiently powered to compare the two drugs. Descriptive statistics used in this study, however, helped us to understand the general trends seen in the Indian population compared with the global population.

## Conclusion

Rivaroxaban, given as a once-daily 10 mg fixed dose 6–8 h postoperatively, is the first new oral anticoagulant to significantly reduce the incidence of venous thromboembolism after total knee arthroplasty, compared with enoxaparin 30 mg twice daily, starting 12–24 h postoperatively, without a significant difference in the risk of major or clinically relevant bleeding.

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