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Rivaroxaban versus nadroparin for preventing deep venous thrombosis after total hip arthroplasty following femoral neck fractures: A retrospective comparative study

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Abstract

Objective: This study was performed to evaluate the efficacy of rivaroxaban versus nadroparin for preventing deep venous thrombosis (DVT) in elderly patients with osteoporosis undergoing initial total hip arthroplasty (THA) for femoral neck fractures.

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Methods: Prospectively maintained databases were reviewed to retrospectively compare elderly patients with osteoporosis who underwent initial THA for femoral neck fractures from 2007 to 2015. The patients received peroral rivaroxaban at 10 mg/day for 2 weeks or subcutaneous injections of nadroparin at 0.3 mL/day for 2 weeks until the primary analysis cut-off date. The time to first on-study DVT was the primary endpoint.
Results: In total, 399 patients were included (rivaroxaban group: n=200; mean age, 70.20 ± 9.16 years and nadroparin group: n = 199; mean age, 69.90 ± 8.87 years), with a mean 3-year follow-up. The time to first on-study DVT was significantly longer in the rivaroxaban than nadroparin group (12 and 5 days, respectively). The incidence of DVT within the 2-week follow-up was significantly higher in the nadroparin than rivaroxaban group (6.8% and 19.7%, respectively), but this difference was no longer present at the final follow-up.
Conclusion: Rivaroxaban was associated with a significant reduction in the occurrence of first on-study DVT compared with nadroparin.

Keywords
Rivaroxaban, nadroparin, deep venous thrombosis, total hip arthroplasty, femoral neck fracture, osteoporosis

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Introduction

In recent years, the incidence of femoral neck fractures has significantly increased given the growth of the aging population.[1,2] Total hip arthroplasty (THA) remains one of the most efficacious reconstructive orthopaedic procedures for most elderly patients with osteoporosis who sustain femoral neck fractures.[1] Neither anticoagulant therapy nor routine anticoagulation laboratory monitoring obviate the need to prevent the occurrence of lower extremity venous thrombosis. Furthermore, the demand for THA has increased by 18% annually during the past few years, and the incidence of this procedure is approximately 750,000 cases per year in China. The incidence of acute symptomatic deep venous thrombosis (DVT), pulmonary embolism (PE), or both conditions following THA is also increasing.[3] Traditional anticoagulation therapy for patients presenting with DVT and/or PE consists of warfarin.[4] Nevertheless, warfarin requires a long time to achieve therapeutic anticoagulation.[5] Consequently, it is rarely used to prevent DVT after initial THA.

Prior studies have shown that rivaroxaban or nadroparin can be successfully used to prevent DVT after initial THA following femoral neck fractures.[6–8] However, the differences between the two treatment strategies remain unclear.[9,10] Moreover, few studies have compared rivaroxaban and nadroparin for preventing DVT after initial THA following femoral neck fractures in elderly patients with osteoporosis. No clear conclusion regarding the superiority of one approach over the other has yet been established. In the EINSTEIN DVT study, the results of a pooled analysis involving more than 8000 patients indicated that rivaroxaban, which had a peak anticoagulant effect within 2 to 4 hours and no need for routine anticoagulation

monitoring, was associated with a substantial reduction in the occurrence or recurrence of DVT.[11] In addition, rivaroxaban is associated with dose-dependent inhibition of factor Xa activity, and maximum inhibition of this activity failed to vary significantly between initial and steady-state administration.[12,13] Elderly patients with osteoporosis undergoing initial THA following femoral neck fractures have reported very low rates of complications (DVT and/or PE) while on rivaroxaban therapy.[14,15] However, nadroparin was not evaluated in these studies.

To our knowledge, a direct comparison between rivaroxaban and nadroparin for the prevention of DVT after initial THA following femoral neck fractures has rarely been reported in the published literature.[4,6] The purpose of this retrospective cohort study was to evaluate the efficacy of rivaroxaban and nadroparin for the prevention of DVT after initial THA using the time to first on-study DVT throughout the follow-up period as an endpoint in elderly patients with osteoporosis.

Materials and methods

Study population and end points

Institutional review board approval was obtained from The First Affiliated Hospital of Sun Yat-sen University and Jinshan Hospital of Fudan University and included an exemption from informed consent. We conducted a retrospective review of consecutive patients who underwent initial THA following femoral neck fractures from June 2007 to December 2015 in two medical centres. The primary objective of this study was to evaluate the efficacy of rivaroxaban or nadroparin in elderly patients with osteoporosis undergoing initial THA following femoral neck fractures. The primary endpoint was the time to first on-study DVT as confirmed by vascular ultrasound throughout the follow-up period. The inclusion criteria for both groups of patients were as follows: age of $\geq$60 years, bone mineral density T score of ≤ -2.5 standard deviations at the lumbar spine or femoral neck, and performance of initial THA (Smith & Nephew, Memphis, TN, USA) following femoral neck fractures from June 2007 to December 2015. Patients who met any of the following main criteria were excluded: previous anticoagulant drug use (rivaroxaban, nadroparin, etc.) during the 6 months before treatment; image-proven vein thrombosis on compression ultrasonography of an extremity or computed tomographic pulmonary angiography of the chest during the 3 months before treatment; bleeding events (>1.0 L); chronic or acute hepatic disease associated with coagulopathy leading to a relevant bleeding risk; creatinine clearance rate of <30 mL/min; primary tumours or advanced malignancy; modification, discontinuation, or interruption of rivaroxaban or nadroparin treatment during the follow-up period; drug abuse; hematologic disease; laboratory signs of bleeding disorders; diseases of erythrocyte injury; consumption of nonsteroidal anti-inflammatory drugs; organ failure; infectious diseases (e.g., acquired immune deficiency syndrome); diabetes; hypertension; mental illness; or an American Society of Anesthesiologists physical status of IV or V.

Definitions of descriptive variables

A major bleeding event (primary bleeding) was defined as fatal bleeding (bleeding into a critical organ or bleeding leading to reoperation), a $\geq$20-g/L reduction in haemoglobin, or transfusion of $\geq$2 U of blood. The definition of DVT was based on objective evidence observed from compression ultrasonography or computed tomography.

Study design and treatment

This was a retrospective, multicentre study in which eligible patients underwent either peroral administration of 10 mg/day of rivaroxaban (20 mg; Bayer, Leverkusen, Germany) for 2 weeks or subcutaneous injection of 0.3 mL/day of nadroparin (Fraxiparine; 7500 AXa ICU; Sanofi, Paris, France) for 2 weeks within 3 to 6 hours after the initial THA.

Statistical analysis

Categorical variables are expressed as count and percentage, and Pearson's chi-square test or the Mann–Whitney U test was used to assess the difference in distributions between the two groups. Continuous numeric variables are expressed as mean ± standard deviation. The Wilcoxon test was used to compare population location parameters between the two groups. The time to first on-study DVT was assessed using Kaplan–Meyer analysis and the log-rank test. The risk of first on-study DVT was managed using a Cox regression model. Statistical analyses were conducted using IBM SPSS Statistics, Version 23.0 (IBM Corp., Armonk, NY, USA). A P-value of <0.05 was considered statistically significant for all tests.

Results

In total, 881 patients were assessed for study eligibility. Of these, 399 patients (rivaroxaban group: $n = 200$; mean age, 70.20 ± 9.16 years and nadroparin group: $n = 199$; mean age, 69.90 ± 8.87 years) met the inclusion criteria. A study flow chart is presented in Figure 1, and the patients' demographics are shown in Table 1.

The mean duration of the retrospective cohort study at the primary analysis cut-off date was 36 months [interquartile range (IQR), 32.4–38.3 months] for patients on rivaroxaban and 38 days (IQR, 35.7–40.9 days) for those on nadroparin. Table 2 compares treatment-related factors, Table 3 compares 1- to 3-day preoperative platelet and blood coagulation function, and Table 4 compares 7-day postoperative platelet and blood coagulation function between the two groups. The mean time to first on-study DVT was 12 days in the rivaroxaban group and 5 days in the nadroparin group [hazard ratio (HR), 0.33; 95% confidence interval (CI), 0.19–2.15; P 0.0001]. No significant differences were detected in major bleeding events. Compared with the nadroparin group, rivaroxaban-treated patients had a significantly delayed time to first on-study DVT (HR, 0.46; 95% CI, 0.24–2.64; $P < 0.0001$). An increased incidence of DVT was observed within the 2-week follow-up, with rates of 6.4% and 18.3% in the rivaroxaban and nadroparin groups, respectively ($P=0.01$). This significant difference was no longer present at the final follow-up.

Discussion

In this analysis of elderly patients with osteoporosis from prospectively maintained databases who underwent initial THA following femoral neck fractures, we evaluated the efficacy of rivaroxaban versus nadroparin using the time to first on-study DVT as the primary endpoint. We found that the rivaroxaban-treated patients had a lower incidence of first on-study DVT than did nadroparin-treated patients.

THA is an effective and technically mature treatment for elderly patients with osteoporosis who sustain femoral neck fractures.[1,16] However, DVT is one of the most common and serious complications after THA.[1] Although patients undergoing THA in major hospitals are currently administered anticoagulant therapy, differences exist in the medication principles among hospitals, and the effect of DVT prevention is unsatisfactory. Certain

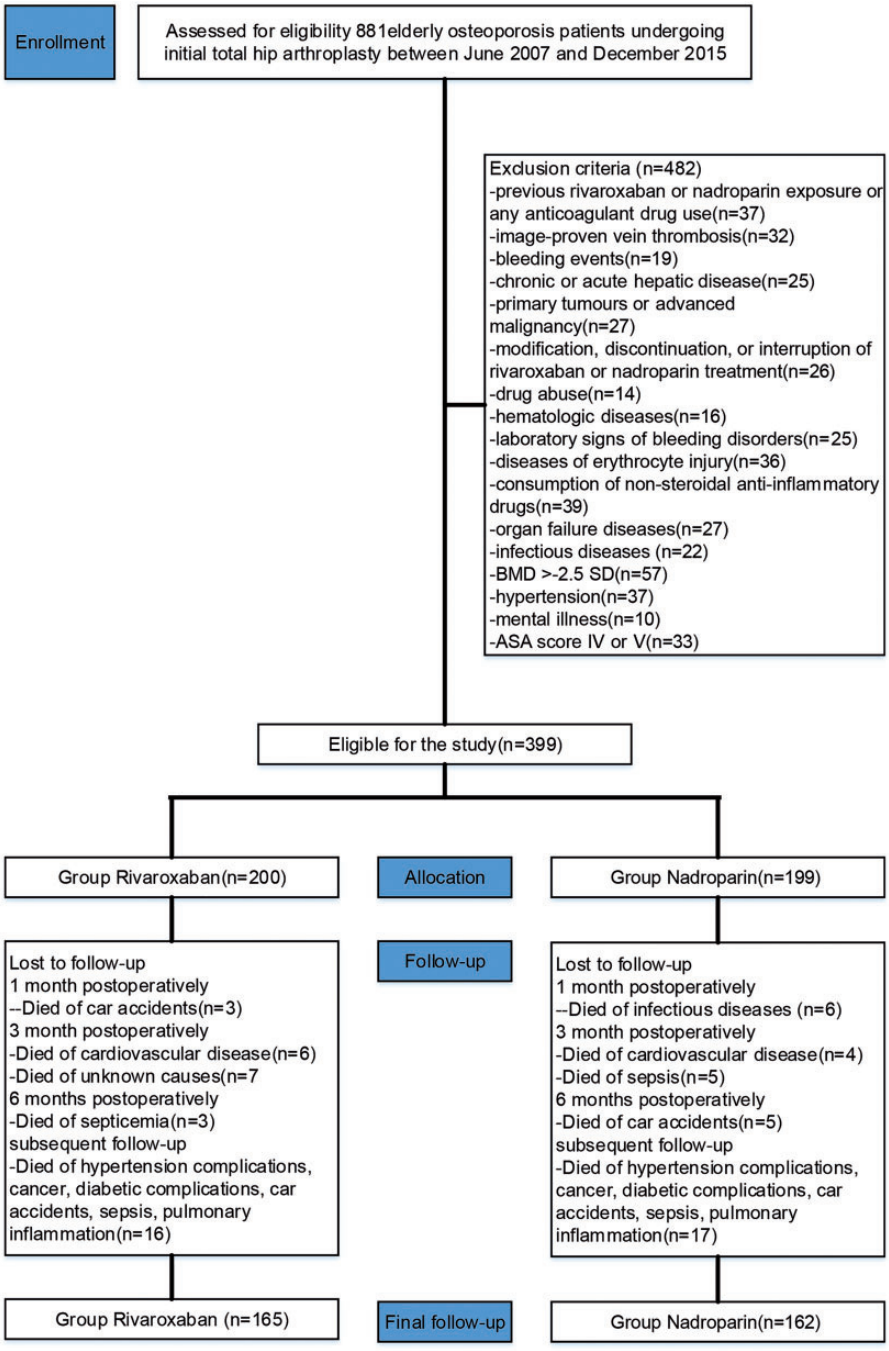

Figure 1. Flow diagram demonstrating method of patient identification to evaluate the efficacy of rivaroxaban or nadroparin using the time to first on-study deep venous thrombosis as the primary endpoint in elderly patients with osteoporosis undergoing initial total hip arthroplasty following femoral neck fractures. BMD, bone mineral density; ASA, American Society of Anesthesiologists.

Table 1. Patient demographics between groups

Variable	Rivaroxaban (n=200)	Nadroparin (n=199)	P-value
Age (years)	70.20 ± 9.16	69.90 ± 8.87	0.22*[a]
Sex (M:F)	113:87	110:89	0.81*[b]
ASA physical status			0.99*[c]
I	71	68	
II	73	78	
III	56	53	
IV	0	0	
V	0	0	
Laterality (L/R)	94/106	97/102	0.73*[b]
BMI (kg/m^2)	23.5 ± 3.27	24.3 ± 2.86	0.37*[a]
BMD	−2.3 ± 0.14	−2.3 ± 0.17	0.16*[a]
Garden classification			0.80*[c]
I	43	46	
II	65	61	
III	75	78	
IV	17	14	
TC (mmol/L)	4.69 ± 0.65	4.71 ± 0.34	0.61*[a]
TG (mmol/L)	1.56 ± 0.49	1.57 ± 0.73	0.16*[a]
HDL-C (mmol/L)	2.76 ± 0.41	2.77 ± 0.18	0.11*[a]
LDL-C (mmol/L)	3.34 ± 0.60	3.37 ± 0.71	0.67*[a]
Apo-A1 (mg/dL)	94.03 ± 4.25	93.91 ± 3.73	0.38*[a]
Apo-B (mg/dL)	50.48 ± 7.58	50.51 ± 8.51	0.42*[a]

Data are presented as n or mean ± standard deviation. *No statistical significance. [a]Analysed using an independent-samples t-test; [b]Analysed using the chi-square test; [c]Analysed using the Mann–Whitney test. M: male; F: female; ASA: American Society of Anesthesiologists; L: left; R: right; BMI: body mass index; BMD: bone mineral density; TC: total cholesterol; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; Apo-A1: apolipoprotein A1; Apo-B: apolipoprotein B.

Table 2. Comparison of treatment-related factors in patients with osteoporosis undergoing initial THA between the two groups

Variable	Rivaroxaban (n=200)	Nadroparin (n=199)	P-value
Harris hip score	78.90±5.84	78.60±7.22	0.42*[a]
Injury–operation interval			0.79*[b]
<1 d	35	33	
1–2 d	67	65	
2–3 d	74	78	
>3 d	24	23	
Weight-bearing activity time (<2 mo/≥2 mo)	93/107	95/104	0.80*[c]
Mechanical failure	20 (10.0)	23 (11.6)	0.62*[c]

Data are presented as n, n (%), or mean ± standard deviation. *No statistical significance. [a]Analysed using an independent-samples t-test; [b]Analysed using the Mann–Whitney test; [c]Analysed using the chi-square test.

Table 3. Comparison of platelet and blood coagulation function 1 to 3 days before surgery in the two groups

Variable	Rivaroxaban (n=200)	Nadroparin (n=199)	P-value
PLT ($\times 10^9$ /L)	221.80 ± 36.73	220.20 ± 39.27	0.19*[a]
APTT (s)	24.70 ± 3.36	23.90 ± 3.92	0.26*[a]
PT (s)	9.80 ± 2.48	9.70 ± 2.95	0.34*[a]

*No statistical significance. [a]Analysed using an independent-samples t-test. PLT: blood platelets; APTT: activated partial thromboplastin time; PT: prothrombin time.

Table 4. Comparison of platelet and blood coagulation function 7 days after surgery in the two groups

Variable	Rivaroxaban (n=90)	Nadroparin (n=86)	P-value
PLT ($\times 10^9$ /L)	207.10 ± 49.24	217.60 ± 50.06	0.00*[a]
APTT (s)	25.90 ± 5.33	28.20 ± 4.68	0.00*[a]
PT (s)	11.70 ± 0.46	12.90 ± 1.31	0.00*[a]

*Statistically significant. [a]Analysed using an independent-samples t-test. PLT: blood platelets; APTT: activated partial thromboplastin time; PT: prothrombin time.

limitations in nadroparin use have been reported in the published literature.[17,18] When nadroparin is used, the platelet count should be monitored; the activated partial thromboplastin time (APTT) does not need to be monitored, and if in doubt, activated factor X can be measured. The dosage of nadroparin should be adjusted according to the patient's weight. Furthermore, prolonged nadroparin application may further aggravate osteoporosis.[19] However, rivaroxaban has the following advantages: convenient use, simple treatment scheme, no need to adjust the dosage, no requirement for bridging therapy and coagulation monitoring, rapid onset, and no influence of drugs or food.[4–6] Notably, the curative effect of rivaroxaban for preventing DVT has been well documented.[3,12]

In China, more than 5 million new cases of DVT are diagnosed annually, and the total number of deaths caused by DVT approaches 700,000.[3,19] DVT is a common complication of THA, and its incidence following THA treatment ranges from 20% to 34% without preventive anticoagulant therapy.[7,10,17,20–22] Smythe et al.[6] performed a multicentre study in Europe in which they analysed 230 patients undergoing elective THA. They found that obese patients (body mass index of $\geq 32\,kg/m^2$) were at risk of DVT.

In patients undergoing THA, routine thrombosis prophylaxis is discontinued at the time of discharge. A meta-analysis of THA revealed that patients with symptomatic venous thromboembolism who had been treated with nadroparin during hospitalisation and those with symptomatic venous thromboembolism who received nadroparin after discharge accounted for 5.5% and 2.9% of all patients, respectively (absolute risk reduction, 2.6%; 95% CI, 0.4–3.3).[23] Ricket et al.[24] compared the treatment effect of rivaroxaban and nadroparin in elderly patients undergoing THA and found that the incidence of DVT was 3.75% (6/160) in the rivaroxaban group and 10.63% (17/160) in the nadroparin

group. The difference was statistically significant ($P<0.02$). The factor Xa activity levels, fibrinogen content, and D-dimer concentrations in the rivaroxaban group were significantly lower than those in the nadroparin group, and the APTT exhibited obvious differences between the two groups. Rivaroxaban is a highly selective and direct inhibitor of coagulation factor Xa.[25] Through inhibition of coagulation factor Xa, the endogenous and exogenous pathways of coagulation are disrupted and production of thrombin and thrombosis are inhibited.[26] Factor Xa is a common intersection of the inner and outer pathways of thrombin formation.[27] Via selective inhibition of factor Xa, which is expected to block the explosive amplification effect of thrombin, rivaroxaban may more efficiently and safely inhibit thrombosis.[25,27,28] The bioavailability of rivaroxaban is >80%, and the drug takes effect quickly.[28] The peak serum concentration is observed 2 to 4 hours after administration. The terminal half-life is 4 to 9 hours. The drug exhibits minimal interaction with other drugs, double channel excretion, and no accumulation after repeated administration. In addition, rivaroxaban is not affected by food, and no coagulation function test results have been reported.[11,27] Lazo-Langner et al.[4] studied the curative effects in 1471 elderly patients with osteoporosis undergoing initial THA administered oral rivaroxaban (2.5–30 mg twice daily) with subcutaneous nadroparin (40 mg once daily, both preoperatively and postoperatively). The postoperative bleeding rates in patients treated with rivaroxaban were 0.7%, 1.9%, 2.0%, 3.7%, and 4.1%. The postoperative bleeding rates in the nadroparin group were 1.2%, 2.7%, 4.6%, 5.8%, and 6.4%. Statistically significant differences were noted between the two groups.

Lower extremity venous thrombosis is a common vascular disease in the clinical setting. The condition refers to the coagulation of venous blood in the deep veins of the lower extremities.[4,26] In 1856, Rudolf Virchow postulated that three major factors are involved in thrombus formation: abnormalities in blood flow, blood hypercoagulability, and injury to the vessel wall. In recent years, through a large number of clinical and experimental observations, these three major factors were proven reliable.[12,28,29] The risk of lower extremity venous thrombosis increases significantly after initial THA.[3,11,30] The following factors contribute to this result.[12,30,31] First, the lower limb needs to be braced within a certain period of time, whereas joint flexion, limb compression, and prolonged bed rest after surgery reduce the venous blood flow velocity. Second, activation of endogenous coagulation factors induced by surgery results in hypercoagulability. Therefore, it is generally believed that routine anticoagulant therapy should be performed after initial THA to avoid the occurrence of lower extremity DVT or PE.[11,26] In the literature, the incidence of DVT after initial THA is as high as 11.0% and the incidence of fatal PE is approximately 1.3%.[12,22,27] Beyer-Westendorf et al.[32] explored the clinical efficacy of rivaroxaban and nadroparin in anticoagulation after initial THA. They enrolled 148 patients, including 73 patients taking rivaroxaban and 75 patients taking nadroparin, and the incidence of DVT, bleeding tendency, and postoperative drainage were obviously different between the two groups of patients after treatment. The efficacy of rivaroxaban and nadroparin to prevent the risk of venous thrombosis after initial THA was comparable and relatively safe. Kaeberich et al.[33] analysed 152 of 351 patients who underwent initial THA surgeries and developed postoperative DVT and noted that the following clinical risk factors influenced DVT after initial THA: female sex, obesity, and use of bone cement. Rheumatoid arthritis was a

protective factor in the reduction of DVT after surgery. Given the large number of asymptomatic patients with DVT after initial THA, postoperative double lower limb angiography or colour Doppler imaging examination should routinely be performed.[4,6] Once DVT occurs, preventing the occurrence of fatal PE is critical. Although fatal PE is rare after initial THA, and although some studies[21–23] have shown that potent pharmacologic prophylaxis for venous thromboembolism does not decrease the rate of fatal PE after hip or knee arthroplasty, early detection and timely treatment are important in the management of this life-threatening complication and could offer a good prognosis.[4,34]

In the current study, rivaroxaban was associated with a low incidence of major bleeding events, which were similar to those detected in patients receiving nadroparin. Rivaroxaban was also associated with a numerically low incidence of other adverse events. Nadroparin is thought to be less likely to cause haemorrhage with a reduced risk of bleeding, especially during the perioperative period. The RECORD trials[17,20,34] demonstrated superior efficacy of rivaroxaban over nadroparin without an increased bleeding risk, as seen in our population.

Our study has some limitations. First, we performed a retrospective analysis of a series of patients. The retrospective nature of the study limits the level of evidence of our conclusion. Second, potential selection bias may exist, possibly reducing the strength of our findings. However, this influence is possibly limited because a very high participation rate of 82% (327/399 patients) was achieved in the present study. Finally, although every attempt was made to adjust for all potential confounders, it is possible that other relevant unmeasured factors exist.

The results of this study indicate that rivaroxaban can significantly reduce the risk of DVT after initial THA and that there is a significant difference between rivaroxaban and nadroparin. However, only a small number of patients were enrolled, the follow-up time was relatively short, and a long-term curative effect was not observed. Therefore, follow-up studies should have larger sample sizes with a longer follow-up time and should further analyse the efficacy and safety of rivaroxaban and nadroparin in the prevention of DVT after initial THA following femoral neck fractures.

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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