Rivaroxaban versus high dose nadroparin for thromboprophylaxis after hip or knee arthroplasty

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Keywords
Thrombosis, nadroparin, rivaroxaban

Summary
Deep-vein thrombosis and subsequent pulmonary embolism are major complications in total joint arthroplasty of the lower limbs. New oral anticoagulants are increasingly prescribed as thromboprophylaxis due to their simple administration and encouraging phase III marketing studies. Patients, methods: In this observational study, we compared the efficacy and safety of rivaroxaban with nadroparin in 1302 unselected patients receiving hip or knee arthroplasty. Results: Venous thrombembolism occurred in 3.3% (2.3%; 4.7%, 95% CI, n = 838) of patients receiving rivaroxaban and in 4.3% (2.7%; 6.7%, 95% CI, n = 464) of patients receiving nadroparin resulting in an absolute risk reduction (ARR) of 1.0% (–1.4%; 3.3%, 95% CI). Conclusions: With an odds ratio of 0.6 (0.4; 1.0, 95% CI), rivaroxaban was associated with a decreased perioperative drop in haemoglobin exhibiting an improved thromboprophylactic profile when compared to high dose nadroparin. Furthermore, transfusion rates were 8.8% (~2.7%; 19.9%, 95% CI) lower in patients receiving rivaroxaban. However, as previous studies have shown, low preoperative haemoglobin remains the most predictive factor for postoperative transfusions (OR: 2.4 [1.3; 4.4, 95% CI]).

Schlüsselwörter
Venenthrombose, Nadroparin, Rivaroxaban

Zusammenfassung
Tiefe Venenthrombose und in der Folge Lungenembolien sind gefürchtete Komplikationen der endoprothetischen Versorgung der unteren Extremität. Aufgrund der guten Studienlage ihrer Phase III Studien, werden zur Prophylaxe immer mehr auch neue orale Antikoagulanzien verschrieben. Patienten, Methoden: In dieser Beobachtungsstudie verglichen wir die Effektivität und Sicherheit von Rivaroxaban mit Nadroparin anhand 1302 nicht ausgewählter Patienten, die eine Knie- oder Hüft-TEP erhalten hatten. Ergebnisse: Ein thrombembolisches Ereignis wurde bei 3.3% (2.3%; 4.7%, 95%-KI, n = 838) der Patienten unter Rivaroxaban und bei 4.3% (2.7%, 6.7%, 95%-CI, n = 464) der Patienten unter Nadroparin festgestellt, was eine absolute Risikoreduktion (ARR) von 1.0% (~1.4%; 3.3%, 95%-KI) ergab. Patienten unter Rivaroxaban hatten weiter mit einer Odds-Ratio von 0.6 (0.4; 1.0, 95% KI) einen geringeren perioperativen Hämaglobinabfall. Schlussfolgerung: Rivaroxaban zeigte im Vergleich zu hoch dosierten Nadroparin ein besseres thromboprophylaktisches Profil. Weiter waren 8,8% (~2.7%; 19.9%, 95%-KI) weniger Bluttransfusionen unter Rivaroxaban zu verzeichnen. Der stärkste prädiktive Faktor für eine postoperative Transfusion blieb, wie in anderen Studien, ein niedriger präoperativer Hämaglobinwert (OR: 2.4 [1.3; 4.4, 95%-CI]).

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Despite great advances in thromboprophylaxis, venous thrombembolism (VTE) still remains a common and life threatening complication after hip or knee arthroplasty. Historic data suggests the incidence of thrombosis following major orthopaedic surgery ranges between 40% and 60% in patients not receiving thromboprophylaxis (7). Keeping this in mind, it seems quite surprising that antithrombotic agents are generally still underused (10). Although some ethnicities seem to be more susceptible to VTE than others, sufficient thromboprophylaxis following major orthopaedic surgery is still generally recommended (3, 6).

While every thrombosis might lead to pulmonary embolism (PE), proximal deep vein thrombosis (DVT) are more likely to cause VTE than distal DVT or calf muscle vein thrombosis (MVT) (20). However, since distal DVT and MVT are far more common than proximal DVT, pulmonary embolism is most frequently associated with distal DVT and MVT stressing the importance of adequate detection and treatment of these often underestimated complications (13, 26).

Following arthroplasty, clinical manifestations of DVT and MVT characterized by pain, leg swelling, and discoloration may be masked by the pain and swelling associated with surgery (1, 16). Furthermore, D-dimers are always elevated after surgery and therefore lose their diagnostic power.

Thus, if no postoperative screening is performed, MVT and DVT might first manifest as dyspnoea accompanying PE.

Screening for DVTs comprises a combination of clinical findings and imaging. Gold standard imaging modalities for DVT

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or MVT include contrast venography, whole-leg compression ultrasonography, and colour Doppler ultrasonography with venography representing the reference standard (16, 19). Due to possible complications and its invasive nature, venography has been replaced by non-invasive whole-leg compression sonography in clinical routine diagnostics. Relatively high sensitivity rates (90–100%) using whole-leg compression ultrasound build the basis for reasonable and safe clinical decision (11, 19).

Thromboprophylaxis comprising both mechanical and pharmacological approaches has tremendously reduced the risk of VTE following major orthopaedic surgery. Although there is only little evidence that compression stockings provide an additional benefit in anti-coagulated patients, the use of compression stockings combined with low molecular weight Heparins (LMWH) have dominated clinical guidelines constituting the gold standard in thromboprophylaxis (4, 8). The increased thromboprophylactic potential of new oral anticoagulants (NOAC) compared to LMWH lead to the marketing approval of rivaroxaban in the EU (EMA doc. ref.: EMEA/543519/2008) and the US (FDA ref. ID: 3353958) for thromboprophylaxis after total hip or knee arthroplasty and to the inclusion of rivaroxaban in clinical guidelines (5, 7, 8, 14, 18).

Published data on the use of rivaroxaban is quite convincing. Its use was associated with a decreased incidence of VTEs, shorter hospitalisations, and less transfusions (2, 15, 16, 23, 24). Nonetheless, independent prospective trials on its use in unselected patients in a normal clinical setting are rare. The aim of this study was to evaluate the efficacy of rivaroxaban versus high dose nadroparin for thromboprophylaxis in patients receiving either total hip or total knee arthroplasty in our clinic. Patients were either administered nadroparin body-weight adapted 5700 to 7600 IU subcutaneously, beginning during surgery, or oral rivaroxaban 10 mg daily, starting 8 h after surgery depending on the surgeon’s preference resulting in a gradual change in our treatment protocol. Thromboprophylaxis was continued for 35 days. Apart from body-weight adapted dosing in the nadroparin group, thromboprophylactic therapy was not adjusted to other risk factors such as prior VTE or known thrombophilia. Previous oral anticoagulation was continued 3 days after surgery.

patients screened

<table>
<thead>
<tr>
<th>type of surgery: TEP</th>
<th>n = 1412</th>
</tr>
</thead>
<tbody>
<tr>
<td>joint: hips or knees</td>
<td>n = 1381</td>
</tr>
<tr>
<td>prophylaxis: nadroparin or rivaroxaban</td>
<td>n = 1302</td>
</tr>
<tr>
<td>type of surgery: other</td>
<td>n = 73</td>
</tr>
<tr>
<td>joint: ankle or both hip and knee</td>
<td>n = 31</td>
</tr>
<tr>
<td>prophylaxis: other</td>
<td>n = 79</td>
</tr>
</tbody>
</table>

Fig. 1
Inclusion criteria: Patients screened for venous thromboembolism were filtered by type of surgery, affected joint, and prophylaxis including only patients receiving total knee or hip arthroplasty that were administered either rivaroxaban or nadroparin for thromboprophylaxis.

Tab. 1
Study population

<table>
<thead>
<tr>
<th>patients</th>
<th>rivaroxaban</th>
<th>nadroparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>total</td>
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<td>64</td>
</tr>
<tr>
<td>gender</td>
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<td>53</td>
</tr>
<tr>
<td>female</td>
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<td>47</td>
</tr>
<tr>
<td>age (years)</td>
<td>65.7 ± 9.6*</td>
<td>66.1 ± 9.4*</td>
</tr>
<tr>
<td>joint</td>
<td></td>
<td></td>
</tr>
<tr>
<td>knees</td>
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<td>h.o. VTE</td>
<td>30</td>
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<td>known thrombophilia</td>
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<tr>
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<td>0</td>
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<tr>
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<td>4</td>
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<tr>
<td>pDVT</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>dDVT, cMVT</td>
<td>24</td>
<td>85</td>
</tr>
</tbody>
</table>

* ± standard deviation; VTE: venous thromboembolism; PE: pulmonary embolism; pDVT: proximal deep vein thrombosis; dDVT: distal deep vein thrombosis; cMVT: calf muscle vein thrombosis

Patients, methods

In an non-interventional study, patients receiving total hip or knee replacement in our clinic were either administered nadroparin or rivaroxaban. Previous oral anticoagulation was preferred to our department. Physical therapy was administered for 30 minutes a day during hospitalization and continued during rehabilitation.

Clinical endpoints were assessed by both sonography screening and 7-week follow-up visits. All patients were screened for DVT or MVT using bilateral whole-leg combined compression colour-Doppler sonography between day 5 and 9 after surgery. A follow-up visit of the patient with the surgeon was performed 7 weeks after surgery. In case of a suspected VTE, patients were directly referred to our department.
Routine laboratory tests were performed according to the standard operating procedure of each surgeon including a complete blood count (CBC), electrolytes, and C-reactive protein (CRP).

Data concerning thrombosis prophylaxis and VTE comprising age, gender, affected joint, type of prosthesis, surgeon, thromboprophylaxis, and VTE was collected prospectively as part of our routine quality control. Although post-operative blood loss and bleeding attributed to thromboprophylaxis were monitored in each patient, our study analysis was performed retrospectively by randomly selecting 1 out of 5 patients screened negative for DVT or MVT as well as all patients with diagnosed VTE. Maximal drop in haemoglobin (Hb) measured before surgery, the first day after surgery, and between day 3 and 5 and transfusion of packed red blood cells (PRBC) was used as main indicators for perioperative blood loss.

Results

A total of 1485 Patients were screened for VTE, of which 1302 met the criteria mentioned above (Fig. 1). The study populations consisted of 55% (n = 715) men and 45% (n = 587) women. 4.0% (n = 52) had a history of prior VTE, 1.5% (n = 19) had been diagnosed with thrombophilia, and 0.8% (n = 11) had an indication for oral anticoagulation. The mean age was 66 ± 10 years (mean ± standard deviation (SD)) with women being 2.8 years older [1.7; 3.9, 95% CI] than men.

No deaths occurred in our study. PE occurred in one patient (0.08%), pDVT in 3 (0.23%) patients, and dDVT or cMVT in 44 (3.38%) patients (see Table 1 for further details). VTE occurred in 3.3% (2.3%; 4.7%, 95% CI, n = 838) of patients receiving rivaroxaban and in 4.3% (2.7%; 6.7%, 95% CI, n = 464) of patients receiving nadroparin resulting in an absolute risk reduction (ARR) of 1.0% (~1.4%; 3.3%, 95% CI, Fig. 2). One patient initially screened negative using combined Doppler-coded compression ultrasound screening eventually developed a distal venous thrombosis resulting in a sensitivity of 97.9% (87.5%, 99.9%, 95%CI, n = 48) and negative predictive value of 99.9% (99.5%, 100.0%, 95% CI, n = 1254).

Only patients undergoing unilateral total joint arthroplasty of the hip or knee receiving either nadroparin or rivaroxaban for thromboprophylaxis were included for data analysis (Fig. 1). For data concerning the incidence of VTE, statistical testing was performed by Pearson's Chi squared analyses applying the Yate's continuity correction. Perioperative drop in Hb was evaluated using a Welch two sample t test following testing for normal distribution applying the Shapiro-Wilk normality test. Multivariate logistic regression models were established for the incidence of VTE and postoperative transfusion of PRBC. A multivariate linear regression model was created analysing the risk for perioperative blood loss. All error bars represent 95% confidence intervals (CI). Statistics were performed using R (21, 25).

Fig. 1. The study population consisted of patients undergoing unilateral total joint arthroplasty of the hip or knee receiving either nadroparin or rivaroxaban for thromboprophylaxis. The incidence of VTE was collected prospectively as part of our routine quality control. Although post-operative blood loss and bleeding attributed to thromboprophylaxis were monitored in each patient, our study analysis was performed retrospectively by randomly selecting 1 out of 5 patients screened negative for DVT or MVT as well as all patients with diagnosed VTE. Maximal drop in haemoglobin (Hb) measured before surgery, the first day after surgery, and between day 3 and 5 and transfusion of packed red blood cells (PRBC) was used as main indicators for perioperative blood loss.

Fig. 2. The incidence of venous thromboembolism (VTE) by joint and prophylaxis (a) displayed a notable tendency towards a higher efficacy of rivaroxaban regardless of the affected joint. However, this tendency did not reach significance (b). 

Fig. 3. Multivariate logistic regression model for VTE: Odds ratio for venous thromboembolism (VTE) displayed by odds ratio (OR) and 95% confidence interval. Higher incidences of VTE were significantly associated with patients receiving arthroplasty of the knee and younger age. Patients receiving nadroparin also exhibited a similar tendency while gender and the number of total joint arthroplasties (TJA) implanted by the surgeon per year did not correlate with VTE.
A multivariate logistic regression model taking into account the number of total joint arthroplasties (TJA) performed by the surgeon per year, gender, age, the affected joint, and the prophylaxis yielded a significant association of VTE with patients aged 65 and less (odds ratio (OR): 2.3 [1.3; 4.5, 95% CI]) and with knee arthroplasty (OR: 4.3 [2.0; 10.7, 95% CI]). The association of young age with VTE was more pronounced in patients receiving rivaroxaban. Gender and the number of TJA performed by the surgeon per year did not seem to influence the incidence of VTE. Patients receiving rivaroxaban were less frequently affected by VTE (OR: 1.6 [0.8; 2.9, 95% CI]). Both treatment groups did not differ in age and a decreased incidence of VTE was observed regardless of the affected joint (Fig. 2).

Blood loss estimated by postoperative decrease in Hb and transfusion requirements were retrospectively analysed from 267 patients, of which 166 received rivaroxaban and 101 nadroparin (Tab. 2). Perioperative decrease in Hb levels was significantly lower in patients receiving rivaroxaban (p < 0.03). Transfusion rates exhibited a similar tendency displaying an ARR of 8.8% (~2.7%; 19.9%, 95% CI).

Multivariate regression analyses of the perioperative decrease in Hb with regard to age, initial Hb levels, the number of TJAs performed by the surgeon per year, the affected joint, and the thromboprophylaxis used showed a significant association of rivaroxaban with a decreased perioperative blood loss (OR: 0.6 [0.4; 1.0, 95% CI]). Patients receiving arthroplasty of the knee also exhibited a tendency towards a decreased perioperative blood loss (OR 0.7 [0.5;1.1, 95% CI]), while the patient’s age and the number of TJAs performed by the surgeon per year did not seem to correlate with perioperative blood loss (Fig. 4a).

In addition to the established variables, preoperative Hb was added as a variable for the transfusion model as a low preoperative Hb had been the main risk factor for postoperative transfusion in previous studies (9). The established model also yielded a significant association of low preoperative Hb levels with postoperative transfusion (OR: 2.4 [1.3; 4.4, 95% CI]) while the prophylaxis used, age, and the surgeon’s experience was not (Fig. 4b).

**Discussion**

Symptomatic VTE following arthroplasty of the knee and hip shows a sharp increase between day 1 and 7 followed by steady increase until day 35 (28). The incidence of asymptomatic DVTs peak are high until day 4 and decrease subsequently (29). This discrepancy is due to two distinct phenomena: (1) most asymptomatic DVT dissolve spontaneously and (2) clinical manifestations of DVT and MVT are masked by prior surgery leading to undiagnosed symptomatic DVTs in the postoperative setting (1, 16, 29). Combined Doppler-coded compression ultrasound screening between day 5 and 9, thus, enabled us to screen for DVTs with an increased likeli-

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**Fig. 4** Odds ratios for perioperative blood loss analyzed in a multivariate linear regression model (a): Low perioperative blood loss was significantly associated with rivaroxaban while the number of total endoprostheses (TEP) implanted by the surgeon per year and the patient’s age did not play a notable role. Regarding transfusion rates, a low preoperatively measured hemoglobin level was the most powerful predictor for postoperative transfusion (b).

(a) postoperative drop in hemoglobin levels; (b) transfusion of packed red blood cells

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**Tab. 2** Bleeding: safety analysis performed on randomly selected patients from this study.

<table>
<thead>
<tr>
<th>patients, parameter</th>
<th>rivaroxaban</th>
<th>nadroparin</th>
</tr>
</thead>
<tbody>
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<td>total</td>
<td>166</td>
<td>101</td>
</tr>
<tr>
<td>gender</td>
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<td>male</td>
<td>99</td>
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<tr>
<td>female</td>
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<td>43</td>
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<tr>
<td>age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 65</td>
<td>66.6 ± 9.4*</td>
<td>66.6 ± 9.4*</td>
</tr>
<tr>
<td>joint</td>
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<td></td>
</tr>
<tr>
<td>knees</td>
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<td>48</td>
</tr>
<tr>
<td>hips</td>
<td>51</td>
<td>53</td>
</tr>
<tr>
<td>hemoglobin (g/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>preoperative drop</td>
<td>12.4 (1.5)</td>
<td>12.7 (1.5)</td>
</tr>
<tr>
<td>transfusions required</td>
<td>33</td>
<td>29</td>
</tr>
<tr>
<td>PRBCs transfused</td>
<td>74</td>
<td>67</td>
</tr>
<tr>
<td>per case</td>
<td>0.45</td>
<td>0.66</td>
</tr>
</tbody>
</table>

* ± standard deviation; *(standard deviation); Hb: hemoglobin; PRBC: packed red blood cells.
hood of becoming symptomatic. With a negative predictive value reaching almost 100%, our study also shows its importance for safe clinical decision-making.

Some meta-analyses have attributed the decreased incidence of VTE under rivaroxaban to a wrong reference dose of enoxaparin (9). Within the limitations of a non-interventional study, our findings suggest otherwise. In our study nadroparin was administered at half the therapeutic dose. Before the emergence of NOACs, several studies noted the increased thromboprophylactic efficacy of fondaparinux when compared to LMWHs (22). These findings prompted us to change our recommendation from certoparin to fondaparinux. Monitoring our treatment regimens, we were able to reproduce these findings in our clinic (unpublished data). However, similar to the findings published in a recent Japanese trial, surgeons in our clinic noticed an increase in perioperative bleeding in patients receiving fondaparinux as thromboprophylaxis (unpublished data) (17). As both prophylactic treatments were unsatisfactory either for the surgeon or the physician, nadroparin administered at half the therapeutic dose was established as a compromise. Even when compared to an increased reference dose, rivaroxaban did not prove inferior to nadroparin, but exhibited a markedly stronger thromboprophylactic effect while showing a decreased perioperative drop in Hb and transfusion rates of PRBCs. Rivaroxaban displayed an improved thromboprophylactic profile when compared to nadroparin.

An interesting finding was the association of younger age with VTE, which is contrary to what has been reported in the literature (27). As this effect was more pronounced in patients receiving rivaroxaban, it might be seen as a distinct feature of this anticoagulant or NOAC in general. However, as previous meta-analyses on age and VTE have stressed, further research comprising a complete analysis on each patient’s co-morbidities and larger cohorts are required to tackle this pending issue (12).

Although differences in DVT incidence between the two groups were not significant, perioperative decrease in Hb favoured the use of rivaroxaban over high dose nadroparin. With a decrease in perioperative drop in Hb, rivaroxaban also showed lower transfusion rates of PRBCs. However, the pre-operative Hb level was determined to be the most predictive factor for postoperative need for PRBC. Thus, in the setting of major elective surgery, adequate treatment of anaemia takes precedence over choosing the right thromboprophylaxis when it comes to reducing the need for postoperative transfusions (9).

Conclusion

This study has shown that

- rivaroxaban 10 mg applied once daily is associated with a lower perioperative drop in hemoglobin and exhibits similar thromboprophylactic properties even when compared to nadroparin administered at higher dosages and
- a low pre-operative hemoglobin level is the most predictive factor for postoperative transfusions of PRBCs.

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Conflict of interest

E. Heckmann received travel grants from Bayer Healthcare and is a consultant for Daiichi Sankyo. The other authors have no conflict of interest to declare.

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