A Systematic Review and Adjusted Indirect Comparison of Oral Anticoagulants

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**Educational Objectives**

As a result of reading this article, physicians should be able to:

1. Recognize the high risk of postoperative venous thromboembolism (VTE) in patients undergoing major orthopedic surgery.

2. Distinguish the different pharmacological mechanisms of VTE prophylaxis drugs.

3. Delineate the advantages and disadvantages of each VTE prophylaxis drug.

4. Recognize that rivaroxaban is as efficacious as apixaban but can increase the risk of hemorrhage.

**Abstract**

Patients undergoing major orthopedic surgery are at high risk for developing postoperative venous thromboembolism (VTE). The authors analyzed the available evidence on the efficacy and safety of dabigatran, apixaban, and rivaroxaban vs low-molecular-weight heparins (LMWHs) as VTE prophylaxis in major orthopedic surgery. Outcomes evaluated included total VTE, deep venous thrombosis (DVT), pulmonary embolism (PE), death, and major bleeding. Rivaroxaban and apixaban are more efficacious than...
Rivaroxaban is as efficacious as apixaban but can increase the risk of hemorrhage. [Orthopedics. 2014; 37(11):763-771.]

Patients undergoing major orthopedic surgery, including total hip arthroplasty (THA), total knee arthroplasty (TKA), and hip fracture surgery, are at high risk of developing venous thromboembolism (VTE), which is a common cause of significant postoperative morbidity. Prophylaxis for VTE has been established for 20 years and supported by many guidelines. Traditionally, low-molecular-weight heparins (LMWHs) have been used as VTE prophylaxis after major orthopedic surgery. With the development of innovative treatments, new oral anticoagulants are available to decrease the occurrence of VTE, including the direct thrombin inhibitor dabigatran and direct factor Xa inhibitors apixaban and rivaroxaban. Compared with traditional therapy, the new agents have been proposed to be more advantageous. Several randomized, controlled trials (RCTs) have been performed to compare the efficacy and safety of the new oral anticoagulants with those of traditional therapy; however, a head-to-head comparison of the new agents is lacking. Therefore, the current authors explored the comparative efficacy and safety of the new oral anticoagulants (dabigatran, apixaban, and rivaroxaban) through indirect comparisons.

**Materials and Methods**

**Data Sources and Literature Searches**

The authors conducted a systematic literature search using PubMed (up to May 2012) and Embase (up to May 2012) for relevant RCTs. The search strategy combined the keywords low-molecular-weight heparins, oral anticoagulant, and oral anticoagulation combined with major orthopedic surgery. Studies were restricted to RCTs published in English. Furthermore, a manual search was conducted of reference lists of eligible studies or review articles to identify additional relevant studies. Authors of articles not available online were contacted.

**Data Collection**

Data were extracted from the included studies by 2 investigators independently using a standardized data abstraction tool. In cases of disagreement regarding data extraction, a consensus was reached through discussion. The following data were sought from each trial when applicable: author, year of publication, study design characteristics, study population, surgical type, thromboprophylaxis regimen, duration of follow-up, and clinical outcomes. Primary efficacy outcomes included VTE (defined as proximal or distal deep venous thrombosis [DVT] or nonfatal pulmonary embolism [PE]) and all-cause mortality during treatment. Pri-
primary safety outcome was a hemorrhagic adverse event, divided into 2 categories: major bleeding events and clinically relevant non-major bleeding events. Only data from the intention-to-treat analysis of each study were included in this analysis.

Quality Assessment
The authors assessed study quality following the Jadad scoring system. Both reviewers assessed the quality of each study by answering 3 questions: (1) Was the study described as randomized? (2) Was the study described as double-blind? (3) Was there a description of withdrawals and dropouts? One point was respectively awarded for the presence of randomization, blinding, and data on study withdrawals and dropouts. If any of these 3 procedures was not deemed appropriate, 1 point was deducted for each. The maximum score for an RCT was 5. An RCT with a score higher than 2 was considered to be an RCT of adequately high quality.

Data Analysis and Statistical Methods
Review Manager version 5.1 (Cochrane Collaboration, Oxford, United Kingdom) was used to conduct random-effects meta-analysis for the pooled relative risks (RRs), with 95% confidence intervals (CIs) for dichotomous outcomes. Analyses were conducted for each pairwise comparison separately. The main analysis was on an intention-to-treat basis, and all reported $P$ values were 2-sided, with a $P$ value less than .05 being significant. Statistical heterogeneity was assessed using the $I^2$ statistic, with $I^2$ values of 30% to 60% representing a moderate level of heterogeneity. In the absence of a clear explanation for heterogeneity, a random-effects model for the RRs was planned. Publication bias and related biases were examined by funnel plot. Heterogeneity was assessed through subgroup analyses. Due to the small number of included trials for each anticoagulant, the authors were limited in detecting publication bias. The authors also performed predefined sensitivity analyses using the fixed-effects model in the meta-analysis with the use of per-protocol and safety populations rather than the intention-to-treat data set. Because the manufacturer recommends 2 different doses of dabigatran (150 or 220 mg depending on patient population), the authors chose to perform a meta-analysis on both doses together and then to assess each dose separately.

Adjusted indirect comparison using Bucher’s method was conducted with the help of ITC software (Canadian Agency for Drugs and Technologies in Health, Ottawa, Ontario, Canada). From the traditional separate rivaroxaban, apixaban, and dabigatran meta-analyses, RRs were indirectly compared with enoxaparin as the common control. The validity of the adjusted indirect comparison was assessed by checking the degree of similarity between the rivaroxaban, apixaban, and dabigatran trials.

RESULTS
Study Selection Process
The authors searched PubMed and Embase. A total of 82 studies evaluating the VTE prophylactic effect of new oral anticoagulants in orthopedic surgery were screened. Seventy of them were excluded, leaving 12 studies included for detailed evaluation.

Study Characteristics
Table 1 lists the characteristics of the 12 included trials. The total population of the included trials was 35,738 patients. All patients in the included RCTs were adults. Seven trials performed TKA and 5 trials performed THA. All RCTs followed correct methodology (double-blind and double-dummy protocols), and their high Jadad scores were in accordance with high methodological quality.

Comparability
Mean patient age, average body weight, and proportion of females were similar and comparable across 3 sets of trials.

The timing and doses of the experimental anticoagulants were comparable. In the rivaroxaban group, patients received rivaroxaban 10 mg once daily 6 to 8 hours postoperatively. In the apixaban group, patients received apixaban 2.5 mg twice daily 12 to 24 hours after wound closure. In the dabigatran group, patients received dabigatran 220 or 150 mg once daily, and the first dose in this group was halved. Among them, 3 trials gave dabigatran 1 to 4 hours postoperatively and 1 trial gave dabigatran 6 to 12 hours postoperatively.

The control group anticoagulant in all RCTs was enoxaparin; there were 2 approved regimens. The first was in Europe, where patients in 8 trials received 40 mg once daily, with the first dose received 12 hours preoperatively and the second received 6 to 8 hours postoperatively. The other regimen was in the United States, where patients in 3 trials received 30 mg every 12 hours, with the first dose received subcutaneously 12 to 24 hours postoperatively.

Independent adjudication committees masked to allocation assessed both efficacy and safety outcomes. Although differences existed in the intensity of monitoring and detecting and variation occurred in the events rate, it would affect both intervention arms equally in the same trial, so it was not thought to result in dramatic changes in the estimates of relative treatment effect in the adjusted indirect comparison.

Primary Outcome: Venous Thromboembolism
Eleven included RCTs provided data to assess the prespecified composite VTE (defined as proximal or distal DVT or nonfatal PE). The primary outcomes are shown in Figure 2.

Results of the comparison of rivaroxaban vs enoxaparin are shown in Figure 2A. The pooled data from 4 trials involving 8512 patients indicates that rivaroxaban significantly reduced the risk of VTE compared with enoxaparin (RR=0.40 [95%
Table 1

Characteristics of the Included Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Study Design</th>
<th>Surgery Type</th>
<th>Time of First Drug Administration</th>
<th>Treatment Duration, d</th>
<th>Diagnosis of DVT After Treatment</th>
<th>Follow-up</th>
<th>Jadad Score</th>
</tr>
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<tbody>
<tr>
<td>Turpie et al</td>
<td>Rivaroxaban 10 mg once daily (n=1584)</td>
<td>Randomized, double-blind</td>
<td>TKA</td>
<td>6-8 h postop</td>
<td>11.7±2.5</td>
<td>Bilateral venography</td>
<td>30-35 d after last dose</td>
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<tr>
<td></td>
<td>Enoxaparin 30 mg every 12 h (n=564)</td>
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<td>Kakkar et al</td>
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<td>Randomized, double-blind</td>
<td>Elective THA</td>
<td>6-8 h postop</td>
<td>31-39</td>
<td>Bilateral venography</td>
<td>30-35 d after last dose</td>
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<td>12 h postop</td>
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<tr>
<td>Lassen et al</td>
<td>Rivaroxaban 10 mg once daily (n=1254)</td>
<td>Randomized, double-blind</td>
<td>TKA</td>
<td>6-8 h postop</td>
<td>10-14</td>
<td>Bilateral venography</td>
<td>30-35 d after last dose</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Enoxaparin 40 mg once daily (n=1277)</td>
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<td>12 h preop</td>
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<td>Eriksson et al</td>
<td>Rivaroxaban 10 mg once daily (n=2266)</td>
<td>Randomized, double-blind</td>
<td>THA</td>
<td>6-8 h postop</td>
<td>Mean, 35 (range, 31-39) postop</td>
<td>Bilateral venography</td>
<td>30-35 d after last dose</td>
<td>7</td>
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<td>Enoxaparin 40 mg once daily (n=2275)</td>
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<td>12 h preop</td>
<td>Mean, 35 (range, 31-39) postop</td>
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<td>Lassen et al</td>
<td>Apixaban 2.5 mg twice daily (n=2708)</td>
<td>Double-blind, double-dummy</td>
<td>THA</td>
<td>12-24 h postop</td>
<td>34.0±7.7</td>
<td>Bilateral venography</td>
<td>60 d</td>
<td>7</td>
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<td>Enoxaparin 40 mg every 24 h (n=2699)</td>
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<td>12 h preop</td>
<td>33.9±7.8</td>
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<td>Randomized, double-blind</td>
<td>TKA</td>
<td>12–24 h postop</td>
<td>10-14 d</td>
<td>Bilateral ascending venography</td>
<td>30 and 60 d after last dose</td>
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<td>Enoxaparin 40 mg once daily (n=1529)</td>
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<td>12 h preop</td>
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<tr>
<td>Lassen et al</td>
<td>Apixaban 5, 10, or 20 mg once daily or 2.5, 5, or 10 mg twice daily (n=N/R)</td>
<td>Randomized</td>
<td>TKA</td>
<td>12-24 h postop</td>
<td>12±2</td>
<td>Bilateral venography</td>
<td>N/A</td>
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<td></td>
<td>Enoxaparin 30 mg every 12 h/ warfarin 5 mg once daily (n=N/R)</td>
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<td></td>
<td>Enoxaparin=12-24 h postop/warfarin-evening of day of surgery</td>
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<tr>
<td>Lassen et al</td>
<td>Apixaban 2.5 mg twice daily (n=1599)</td>
<td>Double-blind, double-dummy</td>
<td>TKA</td>
<td>12-24 h postop</td>
<td>10-14</td>
<td>Bilateral venography</td>
<td>60 d</td>
<td>7</td>
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<tr>
<td></td>
<td>Enoxaparin 30 mg every 12 h (n=1596)</td>
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<td></td>
<td>12-24 h postop</td>
<td>10-14</td>
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CI, 0.25-0.64; \( P=0.03 \)), with high heterogeneity (\( I^2=84\% \)). Results of the comparison of apixaban vs enoxaparin are shown in Figure 2B. The pooled data from 3 trials involving 8126 patients showed that apixaban reduced the risk of VTE compared with enoxaparin (RR=0.63 [95% CI, 0.39-1.01]; \( P=0.06 \)), with high heterogeneity (\( I^2=89\% \)). Results of the comparison of dabigatran vs enoxaparin are shown in Figure 2C. The pooled data from 4 trials involving 7665 patients showed that rivaroxaban did not significantly reduce the risk of VTE compared with enoxaparin (RR=1.09 [95% CI, 0.93-1.27]; \( P=0.03 \)), with moderate heterogeneity (\( I^2=55\% \)).

Safety Outcome: Overall Hemorrhage Risk

Data on safety outcomes were available to count hemorrhage adverse events. The results of new agents vs enoxaparin are shown in Figure 3. Results of the comparison of rivaroxaban vs enoxaparin are shown in Figure 3A. The pooled data from 4 trials involving 12,383 patients showed that no significant differences were seen for the risk of hemorrhage compared with enoxaparin (RR=1.28 [95% CI, 1.04-1.57]; \( P=0.02 \)), with no heterogeneity (\( I^2=0\% \)). Results of the comparison of apixaban vs enoxaparin are shown in Figure 3B. The pooled data from 3 trials involving 11,525 patients showed that the risk of hemorrhage was slightly reduced compared with enoxaparin (RR=0.80 [95% CI, 0.65-1.00]; \( P=0.05 \)), with mild heterogeneity (\( I^2=34\% \)). Results of the comparison of dabigatran vs enoxaparin are shown in Figure 3C. The pooled data from 4 trials involving 10,148 patients showed no significant differences in the risk of hemorrhage compared with enoxaparin (RR=1.02 [95% CI, 0.82-1.27]; \( P=0.88 \)), with mild heterogeneity (\( I^2=31\% \)).

Adjusted Indirect Comparison

Table 1 (cont’d)
The pooled data showed that, in preventing total VTE events, rivaroxaban and apixaban were superior to dabigatran (RR=0.37 [95% CI, 0.23-0.60] and RR=0.58 [95% CI, 0.35-0.96], respectively). There was no significant difference between rivaroxaban and apixaban (RR=0.64 [95% CI, 0.33-1.25]). Rivaroxaban was also superior to dabigatran at 2 dosages: dabigatran 220 mg (RR=0.39 [95% CI, 0.24-0.64]) and dabigatran 150 mg (RR=0.33 [95% CI, 0.20-0.55]). Regarding surgery site, RR was 0.51 (95% CI, 0.35-0.74) for the knee and 0.25 (95% CI, 0.16-0.39) for the hip. Regarding the use of the US dose of enoxaparin, RR was 0.54 (95% CI, 0.39-0.75) for 30 mg twice daily as the common control in TKA. Apixaban was also superior to dabigatran in 2 outcomes: dabigatran 150 mg (RR=0.66 [95% CI, 0.51-0.87]) and hip surgery site (RR=0.36 [95% CI, 0.22-0.60]).

Rivaroxaban increased the overall risk of hemorrhage compared with apixaban (RR=1.57 [95% CI, 1.20-2.07]) and with dabigatran (RR=1.25 [95% CI, 0.93-1.70]). There was no significant difference in the comparison of apixaban vs dabigatran (RR=0.78 [95% CI, 0.58-1.07]). Rivaroxaban caused a higher risk of hemorrhage compared with apixaban in 2 outcomes: knee surgery site (RR=1.86 [95% CI, 1.25-2.77]) and use of the US dose of enoxaparin 30 mg twice daily as the common control in TKA (RR=2.14 [95% CI, 1.21-3.79]). Rivaroxaban also increased risk compared with dabigatran in the outcome of knee surgery site (RR=1.56 [95% CI, 1.04-2.33]). However, results were inconclusive because CIs were wide.

The major outcomes (symptomatic DVT and PE and major hemorrhage) basically reflected the directions of effects described above of total VTE and overall hemorrhage. In the comparison of rivaroxaban with apixaban, rivaroxaban seemed more effective but more likely to induce major hemorrhage. However, because of the low incidence of these outcomes and wide CIs, these results were not confirmed.

**Sensitivity Analysis**

**Sorted by Dose.** The authors conducted the meta-analysis on different doses of dabigatran and found that dabigatran 150 mg daily was less efficacious than enoxaparin (RR=1.20 [95% CI, 1.03-1.41]; P=0.02) in preventing total VTE, whereas dabigatran 220 mg had a similar efficacy outcome (RR=1.02 [95% CI, 0.86-1.20]; P=0.84) compared with enoxaparin.

**Sorted by Model.** When analyzing RCTs that set enoxaparin 40 mg once daily as the control, in both the random or fixed model, the authors found that there were no differences between rivaroxaban and dabigatran in preventing total VTE. However, the outcome for apixaban changed (RR=0.49 [95% CI, 0.29-0.83]; P=0.008) in the random model compared with the outcome (RR=0.80 [95% CI, 0.65-1.00]; P=0.05) in the fixed model.

**Sorted by Statistical Model: Random vs Fixed.** Two outcomes for apixaban and dabigatran in preventing total VTE were significantly affected. The fixed meta-analysis of VTE showed that apixaban was more efficacious than enoxaparin (RR=0.67 [95% CI, 0.58-0.77]; P<0.0001). Dabigatran was less efficacious.
cious than enoxaparin (RR=1.10 [95% CI, 1.01-1.21]; P=.04). The other outcomes were not significantly affected.

**Discussion**

The objective of this analysis was to evaluate the benefit-to-harm ratio among new oral anticoagulants. Because direct evidence from head-to-head comparisons of the new oral anticoagulants is lacking, this meta-analysis allows an indirect comparison across common control arms and provides valuable information for physicians choosing between these newly launched anticoagulants in knee or hip surgeries.

This meta-analysis of 35,738 patients from 12 clinical trials found that, compared with dabigatran, rivaroxaban is significantly more efficacious in preventing total VTE and increased the risk of hemorrhage, and apixaban is more efficacious in preventing total VTE and has a similar bleeding profile. Compared with apixaban, rivaroxaban has no difference in preventing total VTE but has a higher risk of hemorrhage. This suggests that apixaban has a better safety-to-efficacy ratio than other drugs. Dabigatran may not be a good option compared with rivaroxaban and apixaban. The different effects of rivaroxaban, apixaban, and dabigatran may partly originate from their mechanisms and targets. Bauer reported that factor Xa inhibitor may be a more effective and safer anticoagulant than direct thrombin inhibitor because it allowed traces of thrombin to escape neutralization and thereby facilitate hemostasis. In another trial, the direct factor Xa inhibitors were found to have a significantly greater therapeutic index compared with enoxaparin. Furthermore, the direct factor Xa inhibitors were found to have an advantage over any other anticoagulants analyzed, including the direct thrombin inhibitors such as dabigatran. This indicates that this mechanism may provide the best safety-to-efficacy margin. The wider safety limits of direct factor Xa inhibitors vs thrombin inhibitors is consistent with the findings of the current meta-analysis.

The dose relationship for both efficacy and safety demonstrated that dabigatran (220 or 150 mg daily) is no better than enoxaparin. The optimal dose needs to be defined. The explanation for the disparity of P values in the comparison of apixaban vs enoxaparin in different models may be that apixaban at a dosage of 2.5 mg twice daily was more efficacious than enoxaparin at a dose of 40 mg daily and has a similar bleeding outcome, whereas compared with a more intensive enoxaparin dose (30 mg twice daily), apixaban has a similar efficacy and a lower risk of hemorrhage. The safety of dabigatran (220 or 150 mg daily) appears similar to that of enoxaparin; however, dabigatran at a dosage of 220 mg daily is not inferior to enoxaparin. On the contrary, dabigatran at a dosage of 150 mg daily is inferior to enoxaparin. That could explain why dabigatran at all doses is inferior to enoxaparin in the fixed model.

Strengths of this meta-analysis are that it included RCTs with large numbers of patients (12,729 for rivaroxaban, 11,623 for apixaban, and 10,265 for dabigatran); the RCTs were randomized, double-blind, and double-dummy; the administration route and doses of drugs were comparable; and independent adjudication committees masked to allocation assessed efficacy and safety outcomes.

![Figure 3: Forest plots comparing rivaroxaban vs enoxaparin (A), apixaban vs enoxaparin (B), and dabigatran vs enoxaparin (C) for preventing hemorrhage.](image-url)
Limitations of the meta-analysis are as follows: (1) The authors pooled data from RCTs without sufficient direct evidence, which may cause bias in the assessment of outcomes, but adjusted indirect comparisons are presently the most commonly accepted method and use links through one or more common comparators. All indirect analyses are based on the same underlying assumption as meta-analyses, namely that the study populations in the trials being compared are similar.26 (2) Two RCTs included patients weighing at least 40 kg, and there are several minor differences in exclusion criteria (eg, studies did not share the same renal insufficiency standard; all RCTs ruling out patients at high risk of hemorrhage may not reflect the real-world incidence of events).27 (3) Heterogeneity varies in the direct meta-analysis, including type of surgery, treatment duration, dose of enoxaparin, and efficacy and safety assessments; however, individual patients were assessed by a reasonably unbiased committee in the comparison of new anticoagulants, so in the adjusted indirect comparison subgroups sorted by doses and surgery site, trials of new anticoagulants become more similar and comparable, and the authors got consistent results.28 (4) The authors did not conduct the analysis for clinically important events such as death and PE due to a low incidence, which may result in wide CIs. The vague estimates of treatment effect may be underpowered to determine treatment differences.29

**Conclusion**

Despite the limitations of this meta-analysis, the authors provide valuable information on the choice of new oral anticoagulants for physicians and pharmacists. Their findings are relevant to current clinical practice. Other published meta-analyses have only looked at one specific agent or one type of surgery in isolation and not statistically compared the new oral anticoagulant drugs’ relative effects. The current authors demonstrate that, in preventing VTE after orthopedic surgery, rivaroxaban and apixaban are more efficacious than dabigatran, rivaroxaban and apixaban are as safe as dabigatran, rivaroxaban is as efficacious as apixaban, and rivaroxaban increases the risk of hemorrhage compared with apixaban. Current evidence suggests that, given in a fixed, unmonitored oral dose for preventing VTE after knee and hip surgery, rivaroxaban and apixaban are better than apixaban as alternatives to enoxaparin.

**References**


2. Eikelboom JW, Karthikeyan G, Fagel N,
Adjusted Indirect Comparison Between Rivaroxaban and Dabigatran

<table>
<thead>
<tr>
<th>Adj usted Indirect Comparison</th>
<th>RR (95% CI)</th>
<th>Overall Hemorrhage Risk</th>
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<tr>
<td>Overall rivaroxaban vs dabigatan</td>
<td>0.37 (0.23-0.60)</td>
<td>1.25 (0.93-1.70)</td>
</tr>
<tr>
<td>Dabigatran by total daily dose</td>
<td>0.39 (0.24-0.64)</td>
<td>1.19 (0.89-1.59)</td>
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<tr>
<td>Rivaroxaban vs dabigatran 220 mg</td>
<td>0.33 (0.20-0.55)</td>
<td>1.26 (0.96-1.92)</td>
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<td>Rivaroxaban vs dabigatran 150 mg</td>
<td>0.51 (0.35-0.74)</td>
<td>1.56 (1.04-2.33)</td>
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<tr>
<td>By surgery site</td>
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<tr>
<td>Knee</td>
<td>0.25 (0.16-0.39)</td>
<td>1.02 (0.70-1.49)</td>
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<td>Hip</td>
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Abbreviations: CI, confidence interval; RR, relative risk; VTE, venous thromboembolism.


