Post-operative arterial thrombosis with non-vitamin K antagonist oral anticoagulants after total hip or knee arthroplasty

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Introduction

It is well established that patients undergoing total hip replacement (THR) or total knee replacement (TKR) have a high risk of post-operative venous thromboembolism (VTE), which is effectively reduced by anticoagulant drugs (1). Evidence is growing that major non-cardiac surgery is also associated with increased risk of arterial thrombosis (AT), including acute myocardial infarction (AMI) and ischaemic stroke (2, 3). Recently, two epidemiological controlled studies showed that the incidence of peri-operative AMI and ischaemic stroke is significantly higher in patients undergoing total hip replacement (THR) or total knee replacement (TKR), compared to controls not undergoing THR or TKR (4, 5). Despite the high relative risk, the absolute incidence of post-operative AT was about 0.5 % (6).

In the last 20 years, pharmacological prophylaxis of post-operative VTE with unfractionated heparin or low-molecular-weight heparin (LMWH) has been extensively studied and implemented in the routine clinical care. Between 2007 and 2012, drugs inhibiting factor Xa or factor IIa (thrombin), which are collectively termed “non-vitamin K antagonist oral anticoagulants” (NOACs) (7), were tested in high-quality randomised controlled trial (RCTs) for VTE prophylaxis in patients undergoing elective TKR or THR, and proved to be effective and safe alternatives to enoxaparin for post-operative VTE prevention.

Considering the high number of surgical interventions that are performed worldwide, prevention of post-surgical AT may be relevant in terms of reduction of morbidity and mortality. Data on the efficacy in preventing both VTE and AT are important for choosing the best pharmacological thromboprophylaxis in each

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Summary

The incidence of post-operative arterial thrombosis (AT) (acute myocardial infarction [AMI] and ischaemic stroke) is increased in patients undergoing total hip replacement (THR) or total knee replacement (TKR). We compared the incidence of post-operative AT in non-vitamin K antagonist oral anticoagulants (NOACs)-treated and enoxaparin-treated patients, performing a systematic review of phase III randomised controlled trials (RCTs) of venous thromboembolism (VTE) prophylaxis in THR and TKR. Studies were identified by electronic search of MEDLINE and EMBASE database until July 2014. Differences between NOACs and enoxaparin groups in the efficacy and safety outcomes were expressed as odds ratios (ORs) with pertinent 95 % confidence intervals (95 % CI). Statistical heterogeneity was assessed with the I² statistic. Eleven phase III RCTs for a total of 31,319 patients were included. Patients underwent TKR in six studies and THR in five studies. The NOACs under study were dabigatran (four studies), apixaban (three studies) and rivaroxaban (four studies). AT occurred in 0.23 % of patients on NOACs and in 0.27 % of patients on enoxaparin: the OR at fixed-effect model was 0.86 (95 % CI 0.53–1.40; I² 38 %). No differences in AT incidence among the three NOACs were observed. The incidence of major and clinically relevant bleeding was similar in NOACs and enoxaparin groups (OR 1.03, 95 % CI 0.92–1.15; I² 38 %). In conclusion, in RCTs of pharmacological VTE prophylaxis in patients undergoing THR or TKR, there was no difference in the incidence of post-operative AT among patients treated with NOACs, compared to those treated with enoxaparin.

Keywords

Oral anticoagulant, myocardial infarction, stroke, total hip arthroplasty, total knee arthroplasty
individual patient. This seems to be particularly appropriate considering that one of the NOACs, dabigatran, was associated with increased risk of myocardial infarction, compared with warfarin, in patients with non-valvular atrial fibrillation (8). Therefore, we performed a systematic review and meta-analysis of phase III RCTs comparing NOACs with LMWH for pharmacological VTE prophylaxis, with the aim of determining: i) the incidence of post-operative AT in NOACs-treated and LMWH-treated patients undergoing elective TKR or THR during active treatment and during follow-up; ii) the incidence of patient-relevant outcomes (i.e. prevention of major symptomatic thrombotic events and/or total mortality with minimal risk of major bleeding) with NOACs compared with standard therapy.

Methods

This systematic review was performed according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (9).

Search strategy

Using the MEDLINE and the EMBASE electronic databases (from 2004 to July 2014), we identified all published RCTs that compared the incidence of thromboembolic events, major bleeding (MB) and clinically relevant non-major bleeding (CRNMB) in patients undergoing THR or TKR, who were randomised to a NOAC (the direct anti-IIa inhibitor, dabigatran, or one of the direct anti Xa inhibitors, rivaroxaban, apixaban, edoxaban, betrixaban) or to standard pharmacological thromboprophylaxis. The search strategy was developed without any language restriction and run on www.embase.com. We used the following Medical Subject Headings (MeSH) and EMTREE terms and text words: 'oral anticoagulant', 'apixaban', 'rivaroxaban', 'dabigatran', 'edoxaban', 'betrixaban', 'knee arthroplasty', 'hip arthroplasty'; with the following limits: 'randomized controlled trial', 'Cochrane review', 'systematic review', 'meta analysis', 'humans'. We supplemented our search by manually reviewing the reference list of all retrieved articles. We also searched on the www.clinicaltrials.gov to identify unpublished trials.

Study selection

Two reviewers (AS and FL) performed study selection independently, with disagreements solved through discussion and by the opinion of a third reviewer, when necessary. Studies were considered potentially eligible for this systematic review if they met the following criteria: i) studies were phase III registration RCTs; ii) NOACs were compared with prophylactic doses of an antithrombotic drug; iii) arterial thromboembolic events were reported. In case data from a RCT were reported in more than one publication, we extracted relevant data from the paper that provided them in greatest detail.

Data extraction and quality assessment

Two reviewers independently extracted data on study (year of publication, design), population characteristics (number of patients, mean age, gender), type of intervention and comparison, duration of treatment, thromboembolic and bleeding events, and follow-up. The following thromboembolic events were recorded: AMI, ischaemic stroke, and pulmonary embolism. AMI and ischaemic stroke were combined in the single outcome “total arterial thrombosis”. AMI, ischaemic stroke and pulmonary embolism were combined in the single outcome “major vascular events”. MB and CRNMB were recorded as bleeding events. In many included studies, MB was classified, according to ISTH criteria, as bleeding causing a fall in haemoglobin levels > 2 g/dl, bleeding leading to transfusion > 2 units of whole blood or red cells, symptomatic bleeding in a critical area (intracranial, intraspinal, intraocular,
Table 1: Characteristics of the included studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Treatment duration</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advance 1</td>
<td>TKR</td>
<td>Apixaban 2.5 mg bid 12–24 h post-op</td>
<td>Enoxaparin 30 mg bid 12–24 h post-op</td>
<td>10–14 days</td>
<td>60 days</td>
</tr>
<tr>
<td>Advance 2</td>
<td>TKR</td>
<td>Apixaban 2.5 mg bid 12–24 h post-op</td>
<td>Enoxaparin 40 mg 12 h pre-op</td>
<td>10–14 days</td>
<td>60 days</td>
</tr>
<tr>
<td>Advance 3</td>
<td>THR</td>
<td>Apixaban 2.5 mg bid 12–24 h post-op</td>
<td>Enoxaparin 40 mg 12 h pre-op</td>
<td>35 days</td>
<td>60 days</td>
</tr>
<tr>
<td>Record 1</td>
<td>THR</td>
<td>Rivaroxaban 10 mg od 6–8 h post-op</td>
<td>Enoxaparin 40 mg 12 h pre-op</td>
<td>35 days</td>
<td>65–70 days</td>
</tr>
<tr>
<td>Record 2</td>
<td>THR</td>
<td>Rivaroxaban 10 mg od 6–8 h post-op</td>
<td>Enoxaparin 40 mg od 12 h pre-op</td>
<td>10–14 days (plus rivaroxaban / placebo for a total of 31–39 days)</td>
<td>30–35 days after last dose of study medication</td>
</tr>
<tr>
<td>Record 3</td>
<td>TKR</td>
<td>Rivaroxaban 10 mg od 6–8 h post-op</td>
<td>Enoxaparin 40 mg 12 h pre-op</td>
<td>10–14 days</td>
<td>40–49 days</td>
</tr>
<tr>
<td>Record 4</td>
<td>TKR</td>
<td>Rivaroxaban 10 mg od 6–8 h post-op</td>
<td>Enoxaparin 30 mg bid 12–24 h post-op</td>
<td>10–14 days</td>
<td>40–49 days</td>
</tr>
<tr>
<td>Renovate</td>
<td>THR</td>
<td>Dabigatran 220 mg od or 150 mg od 1–4 h post-op</td>
<td>Enoxaparin 40 mg od 12 h pre-op</td>
<td>28–35 days</td>
<td>90 days</td>
</tr>
<tr>
<td>Renovate II</td>
<td>THR</td>
<td>Dabigatran 220 mg od 1–4 h post-op</td>
<td>Enoxaparin 40 mg od 12 h pre-op</td>
<td>28–35 days</td>
<td>90 days</td>
</tr>
<tr>
<td>Remobilize</td>
<td>TKR</td>
<td>Dabigatran 220 mg od or 150 mg od 6–12 h post-op</td>
<td>Enoxaparin 30 mg bid 12–24 h post-op</td>
<td>10–12 days</td>
<td>90 days</td>
</tr>
<tr>
<td>Remodel</td>
<td>TKR</td>
<td>Dabigatran 220 mg od or 150 mg od 1–4 h post-op</td>
<td>Enoxaparin 40 mg od 12 h pre-op</td>
<td>6–10 days</td>
<td>90 days</td>
</tr>
</tbody>
</table>

TKR, total knee replacement; THR, total hip replacement; post-op, post-operatively; pre-op, pre-operatively.

Statistical analysis

Statistical analysis was carried out using Review Manager (RevMan. Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012). Differences in the outcomes among groups were expressed as pooled odds ratio (OR) and corresponding 95% confidence interval (CI), which were calculated using a fixed-effects and a random-effects model (DerSimonian and Laird method) (12). Statistical heterogeneity was evaluated using the I² statistic, which assesses the appropriateness of pooling the individual study results (13). The I² value provides an estimate of the amount of variance across the studies as a result of heterogeneity rather than chance: I² < 30% indicates mild, 30–50% moderate and > 50% severe heterogeneity (13). Random-effects model was used in case of moderate or severe heterogeneity. Publication bias was graphically represented by funnel plots of the effect size versus the standard error.

Results

Study identification and selection

We identified 312 potentially relevant studies from MEDLINE and EMBASE. A total of 299 studies were excluded, based on title and abstract, because were duplicate publications or did not meet our predefined inclusion criteria. Three extra studies were identified by additional strategies. The remaining 16 studies were retrieved in full for detailed evaluation and 11 were included in the final analysis (Table 1). Three studies were excluded, based on our predefined inclusion criteria: no study was a phase III registration RCTs (14–16) and, in addition, two did not provide data on AT.

retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome), or bleeding events leading to death (10). However, no attempt was made to reclassify bleeding events.

All outcomes occurring during active treatment and during follow-up period were collected.

The same two reviewers assessed the methodological quality of selected studies on the basis of Cochrane criteria (11). Each of the following points was scored as 'low,' 'high,' or 'unclear' (where 'low' indicates that the study is less open to bias) and reported in a risk of bias table (Figure 1). Additionally, reporting of arterial thromboembolic events as pre-specified secondary outcome was scored as 'low risk of bias.'
events (15, 16). Two studies on the efficacy and safety of edoxaban vs enoxaparin that had been published in abstract form only were excluded because no data on arterial thrombosis were available (17). Searching in www.clinicaltrials.gov and reviewing the reference lists of included studies did not lead to the identification of additional studies.

Eleven phase III RCTs (18–28), encompassing a total of 31,319 patients, were therefore included in this systematic review. Six studies were in patients undergoing TKR (20, 21, 23, 25–27) and five in patients undergoing THR (18,19,22,24,28); 4 evaluated the safety and the efficacy of dabigatran compared to enoxaparin (22–25), three apixaban compared to enoxaparin (26–28), and four rivaroxaban compared to enoxaparin (18–21). Two doses of dabigatran, i.e. 220 mg od and 150 mg od, were tested in three RCTs (Table 1) (22, 23, 25). For the purpose of this review, as 220 mg od was the only dose tested in all four RCTs and was the approved dose for clinical use, we analysed data only from the 220 mg groups.

Quality assessment

Quality assessment items are summarised in Figure 1. According to Cochrane criteria (11), all the included studies were of high quality.

### Table 1: Arterial thrombosis events of NOACs vs enoxaparin in orthopaedic surgery

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>NOAs</th>
<th>Enoxaparin</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td><strong>8.1.1 Dabigatran</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Re-Novate</td>
<td>5</td>
<td>1146</td>
<td>9</td>
<td>1154</td>
</tr>
<tr>
<td>Re-Novate II</td>
<td>1</td>
<td>1010</td>
<td>1</td>
<td>1003</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>2156</td>
<td>2157</td>
<td>38.7%</td>
<td>0.60 [0.22, 1.67]</td>
</tr>
<tr>
<td>Total events</td>
<td>6</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.14; df = 1 (P = 0.70); I^2 = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.97 (P = 0.33)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>8.1.2 Rivaroxaban</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Record 1</td>
<td>3</td>
<td>2209</td>
<td>6</td>
<td>2224</td>
</tr>
<tr>
<td>Record 2</td>
<td>6</td>
<td>1228</td>
<td>3</td>
<td>1229</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>3437</td>
<td>3453</td>
<td>41.7%</td>
<td>1.00 [0.26, 3.90]</td>
</tr>
<tr>
<td>Total events</td>
<td>9</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.46; Chi^2 = 1.91; df = 1 (P = 0.17); I^2 = 48%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.01 (P = 1.00)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>8.1.3 Apixaban</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advance 3</td>
<td>5</td>
<td>2673</td>
<td>3</td>
<td>2659</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>2673</td>
<td>2659</td>
<td>19.6%</td>
<td>1.66 [0.40, 6.95]</td>
</tr>
<tr>
<td>Total events</td>
<td>5</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.69 (P = 0.49)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>8266</td>
<td>8269</td>
<td>100.0%</td>
<td>0.91 [0.48, 1.71]</td>
</tr>
<tr>
<td>Total events</td>
<td>20</td>
<td>22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.00; Chi^2 = 3.40; df = 4 (P = 0.49); I^2 = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.29 (P = 0.77)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Chi^2 = 1.32; df = 2 (P = 0.52); I^2 = 0%</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Total hip replacement**

Five studies, totalling 16,355 patients undergoing THR, were included in the analysis (Table 1). The experimental drug was dabigatran in two studies (23, 24), apixaban in one (28), and rivaroxaban in two (18, 19). In all studies enoxaparin 40 mg once daily, starting 12 hours (h) pre-operatively, was used as comparator. Both the study drug and the comparator were administered for a total 28–35 days in all studies, with the exception of RECORD 2 (19), in which rivaroxaban was compared to enoxaparin in the first 10 to 14 days, and then compared to placebo for up to 35 days. Follow-up periods ranged from 60 to 90 days. For the purpose of the meta-analysis we pooled all the studies together.

In the whole population pooled analysis, the use of NOACs was associated to a similar incidence of arterial thrombosis compared to enoxaparin at fixed-effect model. NOACs were associated with a non-statistically significant reduction of AMI (OR=0.91; 95%CI 0.50, 1.67; I^2=0) and ischaemic stroke (OR=0.50; 95%CI 0.15, 1.66; I^2=0) compared to enoxaparin during active treatment, and with an OR=1.00 (95%CI 0.56, 1.79; I^2=0) for AMI and an OR=0.65 (95%CI 0.22, 1.89; I^2=14) for ischaemic stroke including the follow-up period.

During active treatment, AMI occurred in 0.24% of patients on NOACs and 0.27% of patients on enoxaparin, and ischaemic stroke in 0.06% and 0.11%. Including the follow-up period, the incidence of AMI was 0.33% in patients on NOACs and 0.33% in...
patients on enoxaparin, and that of ischaemic stroke 0.08 % and 0.14 %.

Drug-related risk of arterial thrombosis

Arterial thrombotic risk of each NOAC, compared to enoxaparin was as follows at random-effect model during active treatment (Figure 2): dabigatran, OR 0.60 (95 %CI 0.22, 1.67; I²=0) for AMI (the risk of stroke was not estimable due to the lack of events in both groups); apixaban, OR 1.66 (95 %CI 0.40, 6.95) for AMI and 0.25 (95 %CI, 0.03, 2.22) for ischaemic stroke (the test of heterogeneity was not applicable as only one study was available); rivaroxaban, OR 1.00 (95 %CI, 0.26, 3.90; I²=48) for AMI and 0.78 (95 %CI, 0.14, 4.50; I²=11) for ischaemic stroke.

Arterial thrombotic risk for all combined anti-Xa inhibitors (i.e. apixaban and rivaroxaban) was OR 1.17 (95 %CI, 0.54, 2.53; I²=10) for AMI and 0.50 (95 %CI, 0.15, 1.66; I²=0) for ischaemic stroke, at fixed-effect model.

Additional outcomes

NOACs and enoxaparin were similar at the fixed-effect model in the risk of pulmonary embolism (OR 0.94; 95 %CI, 0.47, 1.85; I²=23), major vascular events (OR 0.97; 95 %CI, 0.61, 1.55; I²=0), MB plus CRNMB (OR 1.12; 95 %CI, 0.96,1.31; I²=0), and total mortality (OR 0.99; 95 %CI, 0.46,2.15; I²=17) during active treatment.

Total knee replacement

Six studies (20, 21, 23, 25–27), totalling 14,792 patients undergoing TKR, were included in the analysis (►Table 1). The experimental drug was dabigatran in two studies (23,25), apixaban in two (26, 27), and rivaroxaban in two (20, 21). For each NOAC, enoxaparin 40 mg once daily, starting 12 h pre-operatively, was the comparator in one study, while enoxaparin 30 mg twice daily, starting 12–24 h post-operatively was the comparator in the other study. The study drug and the comparator were administered for a total 10–14 days in all studies, with the exception of REMODEL (23), in which dabigatran and enoxaparin were administered for 6–10 days. Follow-up periods ranged from 40 to 90 days.

In the whole population pooled analysis, the use of NOACs was associated with a similar incidence of arterial thrombosis compared to enoxaparin at fixed-effect model. NOACs were associated with a non-statistically significant difference in the risk of AMI (OR 0.50; 95 %CI 0.20, 1.24; I²=0) and ischaemic stroke (OR, 1.37; 95 %CI 0.45, 4.10; I²=27) compared to enoxaparin during active treatment; the corresponding OR values during the overall follow-up period were 1.19 (95 %CI 0.36, 3.91; I²=11) for stroke and 0.41 (95 %CI 0.17, 0.99; I²=0) for AMI, which was statistically significant.

During active treatment, AMI occurred in 0.11 % of patients on NOACs and 0.21 % of patients on enoxaparin, and ischaemic stroke in 0.09 % and 0.07 %. During the overall follow-up period, the incidence of AMI was 0.13 % in patients on NOACs and 0.32 %
Drug-related risk of arterial thrombosis

Arterial thrombotic risk of each single NOAC compared to enoxaparin was as follows, at random-effect model during active treatment (Figure 3): dabigatran, OR 0.76 (95% CI 0.17, 3.41; \( I^2 = \) the test of heterogeneity was not applicable as only one study was available) for AMI and not estimable for ischaemic stroke due to the lack of data; apixaban, OR 0.43 (95% CI 0.08, 2.37; \( I^2 = 0 \)) and 1.00 (95% CI, 0.04, 23.72; \( I^2 = 54 \)); rivaroxaban, OR 0.40 (95% CI, 0.08, 2.10; \( I^2 = 0 \)) and 1.63 (95% CI, 0.12, 22.88; \( I^2 = 49 \)).

The OR values for all combined direct anti-Xa inhibitors (i.e. apixaban and rivaroxaban) were 0.40 (95% CI, 0.13, 1.27; \( I^2 = 0 \)) for AMI and 1.37 (95% CI, 0.45, 4.10; \( I^2 = 27 \)) for ischaemic stroke, at fixed-effect model.

Additional outcomes

NOACs and enoxaparin were similar at the fixed-effect model in the risk of pulmonary embolism (OR 1.27; 95% CI, 0.76, 2.11; \( I^2 = 40 \)), major vascular events (OR 1.06; 95% CI, 0.66, 1.71; \( I^2 = 51 \)), MB plus CNRMB (OR 0.93; 95% CI, 0.78, 1.10; \( I^2 = 52 \)), and total mortality (OR 1.00; 95% CI, 0.43, 2.36; \( I^2 = 0 \)) during active treatment.

Subanalysis of studies using different enoxaparin dosages

Different dosages of enoxaparin (40 mg od and 30 mg bid) were used in patients undergoing TKR. At fixed-effect model, the major efficacy and safety outcomes did not differ significantly between NOACs and enoxaparin, independently of its dosage, except for a lower risk of total arterial thrombosis during treatment with NOACs compared to enoxaparin 30 mg bid (OR 0.27; 95% CI, 0.08, 0.97; \( I^2 = 0 \)). Moreover, a statistically significant increase in the risk of major vascular events during follow-up was associated with apixaban compared to enoxaparin 40 mg od (OR 5.03; 95% CI, 1.10, 22.99; \( I^2 = \) the test for heterogeneity was not applicable as only one study, ADVANCE 2, provided data).

Outcomes combining data from THR and TKR studies

When we combined data from THR and TKR studies, NOACs and enoxaparin were similar at fixed-effect model in the risk of major efficacy and safety outcomes, in particular in the risk of total arterial thrombosis (OR 0.86; 95% CI, 0.53, 1.40; \( I^2 = 11 \)), major vascular events (OR 0.97; 95% CI, 0.69, 1.36; \( I^2 = 0 \)) (Figure 4), MB plus CNRMB (OR 1.03; 95% CI, 0.92, 1.15; \( I^2 = 38 \)), and total mortality (OR 1.00; 95% CI, 0.56, 1.77; \( I^2 = 0 \)) (Figure 5) during treatment period.

Publication bias

The included RCTs for each outcome are less than 10 in most outcomes. Despite this limitation, the funnel plots (available from the authors on request) appeared quite symmetrical, suggesting the absence of publication bias.

Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis of all phase III RCTs for VTE prevention in patients undergoing elective TKR or THR that was performed with the primary aim to evaluate the incidence of post-operative AMI, stroke and clinically relevant events (mortality, pulmonary embolism, and major and clinically relevant bleeding) in patients treated with NOACs compared to those treated with enoxaparin. Our large meta-analysis, incorporating 31,319 patients, showed that the incidence of post-operative AT was about 0.5%, similar to that reported in previous studies (4–6).

Despite the relatively low frequency of post-operative AT, the relative risk compared to subjects not undergoing surgery is very high (4, 5). Moreover, considering the high number of surgical
interventions that are performed, it may be calculated that up to about one million patients suffer post-surgical cardiovascular complications worldwide every year (29). Thus, prevention of post-surgical AT remains a relevant objective in terms of reduction of morbidity and mortality worldwide. In this regard, our analysis reveals a global similar profile of NOACs, compared to LMWH in terms of incidence of post-operative AT, and these results are consistent for all three studied NOACs: dabigatran, rivaroxaban and apixaban.

No statistically significant differences in the incidence of the composite measurement of patient-relevant outcomes, such as pulmonary embolism, AT, total mortality and major and clinically relevant bleeding between NOACs and enoxaparin groups was detected. These results are in line with those of previous meta-analyses (30, 31) which, however, did not consider the incidence of post-operative AT.

In our meta-analysis there was no difference among the three NOACs in terms of incidence of post-operative AMI. This is in contrast with the results of the RELY (8) study and those of two meta-analyses, which showed that the use of dabigatran was associated with an increased risk for AMI (32, 33). However, this effect of dabigatran was evident only in trials in which the drug was compared to warfarin in the prevention of stroke and systemic embolism in patients with atrial fibrillation (8, 32), likely due to differences in patient characteristics, in the daily doses of dabigatran used and in treatment duration.

Based on the results of our analysis, NOACs appear to reduce the incidence of AMI (OR 0.41; 95% CI 0.17, 0.99; I²=0) during 40–90 days following TKR, compared to all dosages of enoxaparin, and to reduce the incidence of total arterial thrombosis (OR 0.27; 95% CI, 0.08, 0.97; I²=0) during the treatment period, compared to enoxaparin 30 mg bid. Given the low incidence of AT, statistical casualty might account for the observed difference.

Our study has some limitations. First, we combined results of trials carried out with three different NOACs: a direct thrombin inhibitor (dabigatran etexilate) and two direct factor Xa inhibitors (rivaroxaban and apixaban). However, the combined results were quite homogeneous without signs of heterogeneity for the different outcomes, suggesting that the similarities between these compounds are greater than the differences. Moreover, subanalyses, for each single NOAC and for the two direct factor Xa inhibitors considered as a group, did not reveal relevant disparities in efficacy and safety. The second limitation, differences among the studies, including those in the dosage of the comparator (enoxaparin), may limit definitive conclusions. However, a subanalysis failed to reveal relevant different results with different doses of enoxaparin (40 mg od vs 30 mg bid). Last, potential differences between NOACs and enoxaparin might have emerged for patients at high risk of AT, such as those older than 80 years, or with an AMI in the six months before surgery, peripheral vascular disease, diabetes mellitus or congestive heart failure (4, 34). Unfortunately, we were unable to consider these variables separately, because our analysis was performed on data composed of aggregate values from studies rather than from individual patients. On the other hand, the strengths of this study include the rigorous methodological approach, the selection of all phase III studies performed with the three NOACs considered and the consistency of the results of sub-analyses. Furthermore, our analysis provides the treating physician with important safety and efficacy information because we confined our analysis to clinically relevant events and, because all the studies were performed as a component of product registration, it is likely that all reported outcome events were objectively confirmed.

In conclusion, in the setting of THR and TKR, NOACs do not differ from enoxaparin in terms of patient-relevant post-operative outcomes, such as arterial thrombosis, mortality, pulmonary embolism, or bleeding. Inferences about the relative efficacy or safety of individual NOACs cannot be made due to the lack of head-to-head comparisons.

Conflict of interest
Alessandro Squizzato has received lecture fees from Bayer Healthcare and Pfizer. No other conflicts of interest are declared.
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References


