

Prevention of venous thromboembolism after major orthopedic surgery: indirect comparison of three new oral anticoagulants

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In the development of innovative treatments, there is an increasing frequency of situations where two new agents (or more) have been compared with standard therapy based on a randomized controlled trial (RCT), but a head-to-head (direct) comparison between the new treatments is lacking. As a result, new techniques are being explored that generate statistical estimates of the results of these head-to-head (indirect) comparisons in the absence of a (direct) trial-based comparison.

Network meta-analysis (NETMA) is one such technique [1]. This technique can be applied using sophisticated statistical models that generate a variety of graphs (and whose design can include, in the most complex models, the so-called loops [2] and/or multivariate adjustments based on Bayesian statistics [2]). However, more simple approaches have also been reported in the past months [3] and have already been used quite extensively [4–7].

In patients at risk for venous thromboembolism (VTE) after total hip or knee arthroplasty [8], the new oral anticoagulants (dabigatran, rivaroxaban and apixaban) have been proposed as an advancement in comparison with standard therapy (e.g. enoxaparin 40 mg once daily). Numerous RCTs aimed at the prevention of VTE after this type of orthopedic surgery have shown that the oral anticoagulants can be as effective as standard treatment or possibly more effective. A PubMed search conducted on 16 June 2011 based on the keywords ‘‘prophylaxis AND venous AND (apixaban[title] OR dabigatran[title] OR rivaroxaban[title])’’ and on the limit of ‘‘Randomized Controlled Trial’’ extracted 22 articles. After excluding all papers that were not the first publication of an original RCT, a total of eight trials [9–16] were included in our analysis. Patients enrolled in these trials were aged 18 years or older, weighed at least 40 kg and were scheduled for primary elective total hip or knee replacement. The clinical endpoint was a composite of symptomatic or asymptomatic deep vein thrombosis, non-fatal pulmonary embolism and/or all-cause mortality; enoxaparin 40 mg per daily was the reference treatment.

If one applies a simplified NETMA to the above data regarding VTE prevention in major orthopedic surgery, the results derived from the eight trials can be presented through an overall analysis of this evidence-based information (with related graph), which includes both direct and indirect comparisons. For this purpose, the risk ratio (RR) for direct comparisons is determined by standard meta-analysis, while the RR for indirect comparisons is estimated through an ad-hoc NETMA statistic (namely the approach employed by the “rrc software” [17], which is the simplest form of NETMA presently available and does not include “loops”).

Figure 1 summarizes the results of these direct and indirect comparisons. In the direct comparison of apixaban 2.5 mg daily vs. enoxaparin 40 mg daily [9,10], the pooled RR for the above-mentioned endpoint was 0.56 (95% confidence interval [CI], 0.47–0.66). The values of pooled RR for the other direct comparisons were 0.39 (95% CI, 0.32–0.48) for rivaroxaban 10 mg daily vs. enoxaparin 40 mg per daily [11–13], 0.93 (95% CI, 0.81–1.07) for dabigatran 220 mg daily vs. enoxaparin 40 mg daily [14–16], and 1.12 (95% CI, 0.98–1.29) for dabigatran 150 mg daily vs. enoxaparin 40 mg daily [14,15].

In the indirect comparison of rivaroxaban 10 mg daily vs. apixaban 2.5 mg daily, the RR for our endpoint was 0.70 (95% CI, 0.53–0.90). The values of RR for the other indirect comparisons were: 2.00 (95% CI, 1.61–2.50) for dabigatran 130 mg daily vs. apixaban 2.5 mg daily; 1.66 (95% CI, 1.33–2.08) for dabigatran 220 mg daily vs. apixaban 2.5 mg daily; 2.86 (95% CI, 2.27–3.70) for dabigatran 150 mg daily vs. rivaroxaban 10 mg daily; 2.38 (95% CI, 1.85–3.03) for dabigatran 220 mg daily vs. rivaroxaban 10 mg daily; and 0.83 (95% CI, 0.67–1.02) for dabigatran 220 mg daily vs. dabigatran 150 mg daily. Further details on this analysis are presented as Data S1.

Overall, these results indicate that: apixaban and rivaroxaban are each significantly more effective than dabigatran at its two dosages; rivaroxaban is significantly more effective than apixaban or dabigatran (at any of the two dosages tested for this latter drug); and finally, no difference is apparent between the two dosages of dabigatran.

In conclusion, although a comparative assessment in this area is complex due to the multiplicity of controlled trials, the analysis shown in Fig. 1 effectively summarizes the current state of the art.

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Our results indicate that, despite the indirect nature of this type of evidence and the limitations of this technique[1,2], rivaroxaban tends to be more effective than the other two innovative oral anticoagulants (dabigatran and apixaban) and proves also to be superior to enoxaparin on the basis of a direct comparison. Of course, whether this statistical superiority translates into a clinically relevant difference still remains to be established. Finally, this comparative assessment of VTE prophylaxis confirms that these simplified graphs can be helpful in summarizing the information on efficacy when multiple innovative agents need to be compared.

**Disclosure of Conflict of interests**

The authors state that they have no conflict of interest.

**Supporting Information**

Additional Supporting Information may be found in the online version of this article.

**Data S1.** Detailed description of relative risk estimation of direct comparisons.

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**References**

3. Fadda V, Maratea D, Trippoli S, Messori A. Network meta-analysis. Results can be summarised in a simple figure. *BMJ* 2011; **342**: d1555.
CD11b+ leukocyte microparticles are associated with high-risk angiographic lesions and recurrent cardiovascular events in acute coronary syndromes

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Microparticles (MP) are markers of cell apoptosis and activation. Levels of platelet-derived MP (PMP) or endothelial-derived MP (EMP) are elevated in patients with acute coronary syndrome (ACS) [1,2]. Whereas EMP levels correlate with lesion severity [3], PMP levels are predictive of future cardiovascular events (CVE) in ACS patients [4]. Levels of leukocyte-derived MP (LeMP) correlate with cardiovascular risk factors and the number of diseased sites in asymptomatic subjects with subclinical atherosclerosis [5]. However, LeMP remain unstudied in ACS patients.

In the present study, we measured LeMP levels in patients admitted for non-ST-segment elevation (NSTE) ACS and tested whether their measurement contributed to the identification of patients at an increased risk of recurrent CVE at 1 month after coronary stenting.

One hundred and seventy-two patients with NSTE ACS including 15 with elevated troponin levels were enrolled in the present study (baseline characteristics in Table S1). NSTE ACS and exclusion criteria were defined as described elsewhere [6]. Patients received loading doses of 600 mg clopidogrel and...
Supporting information:

Prevention of venous thromboembolism after major surgery: indirect comparison between three new oral anticoagulants (Letter to the Editor) by Maratea D, Fadda V, Trippoli S, and Messori A.

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The four direct comparisons (rivaroxaban vs enoxaparin, apixaban vs enoxaparin, dabigatran 220mg vs enoxaparin, dabigatran 150mg vs enoxaparin) reported in the published graph of our network meta-analysis are based on the following clinical trials:

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<th>Comparison</th>
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For each of the four direct comparisons, the REVMan software determined the pooled value of risk ratio (with 95% confidence interval) between the intervention group and the control group. The graphs generated by this software are shown below along with the study-specific event rates extracted from each trial.