

REVIEW ARTICLE

[Translated article] Rivaroxaban versus enoxaparin for thromboprophylaxis in orthopedic surgery: A meta-analysis



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KEYWORDS

Rivaroxaban;
Enoxaparin;
Venous
thromboembolism;
Orthopedic surgery;
Meta-analysis

Abstract

Introduction: Venous thromboembolism is highly associated with orthopedic surgery, so thromboprophylaxis is an important consideration for orthopedic surgeons. The new oral anti-coagulants have clear advantages for clinical practice.

Objectives: To analyze the efficacy and safety of rivaroxaban versus enoxaparin for thromboprophylaxis in different orthopedic surgeries.

Material and methods: Systematic electronic search of clinical trials was carried out. Data extraction of efficacy outcomes (deep venous thrombosis, pulmonary embolism and death) and safety outcomes (major bleeding and clinically relevant bleeding) was realized.

Results: Six randomized and controlled clinical trials were included in this meta-analysis. Compared with enoxaparin the risk of venous thromboembolism was lower with rivaroxaban both in different orthopedic surgeries (RR: 0.51; 95% CI: 0.36–0.73; $p = .0002$). This result was even better and more homogeneous in the analysis of symptomatic deep venous thrombosis outcome (RR: 0.43; 95% CI: 0.28–0.65; $p < .0001$; $I^2 = 0\%$; $p = .49$). The risk of bleeding was not significantly higher with rivaroxaban (RR: 1.20; 95% CI: 0.97–1.49; $p = .09$).

Conclusions: Rivaroxaban should be considerate such as a more effective alternative for thromboprophylaxis in orthopedic surgery.

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PALABRAS CLAVE

Rivaroxabán;
Enoxaparina;
Tromboembolismo
venoso;
Cirugía ortopédica;
Metaanálisis

Rivaroxabán frente a enoxaparina como tromboprofilaxis en cirugía ortopédica y traumatología: un metaanálisis

Resumen

Introducción: La enfermedad tromboembólica venosa está altamente asociada a las intervenciones ortopédicas, siendo la tromboprofilaxis una prioridad para el cirujano ortopédico. Los nuevos anticoagulantes orales presentan ventajas claras para la práctica clínica diaria.

Objetivos: Analizar la eficacia y la seguridad del rivaroxabán frente a la enoxaparina como tromboprofilaxis tras distintas intervenciones ortopédicas.

Material y métodos: Se realizó una búsqueda bibliográfica sistematizada de ensayos clínicos. Se recogieron los datos de variables de eficacia clínica (trombosis venosa profunda asintomática o sintomática, embolia pulmonar, muerte) y seguridad clínica (hemorragia mayor, hemorragia clínicamente relevante).

Resultados: Seis ensayos clínicos aleatorizados fueron seleccionados para el metaanálisis. El rivaroxabán mostró una mejor eficacia clínica tras distintas intervenciones ortopédicas (RR: 0,51; IC 95%: 0,36-0,73; $p = 0,0002$). Se observó mayor beneficio y homogeneidad en los resultados al analizar únicamente la trombosis venosa profunda sintomática (RR: 0,43; IC 95%: 0,28-0,65; $p < 0,0001$; $I^2 = 0\%$; $p = 0,49$). Además, no se apreció mayor riesgo hemorrágico estadísticamente significativo con el rivaroxabán (RR: 1,20; IC 95%: 0,97-1,49; $p = 0,09$).

Conclusiones: El rivaroxabán debería ser considerado como una alternativa terapéutica más eficaz respecto a la enoxaparina empleada de manera rutinaria en nuestro entorno.

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Introduction

Venous thromboembolism (VTE), ranging from deep vein thrombosis (DVT) to pulmonary embolism (PE), is the third leading cause of cardiovascular death after myocardial infarction (MI) and stroke.^{1,2} With no form of prophylaxis, the incidence of DVT 90 days after surgery is 60%, while the incidence of fatal PE is 1.5%.¹

In short, VTE is a disease with an enormous prevalence and mortality in our environment and is a major cause of healthcare expenditure, both for the treatment of the disease and for its sequelae.³ For each patient with VTE, European healthcare systems incur additional direct costs of €1899 over 3 months and €3220 per year of the episode.⁴

Although VTE can occur after any major surgery, the incidence of VTE is significantly higher in orthopaedic patients, particularly those undergoing hip and knee replacement surgery.⁵

Both vitamin K antagonist oral anticoagulants (VKAs) and low-molecular-weight heparins (LMWHs) have been the first choice of conventional thromboprophylaxis. VKAs are difficult to manage due to the need for blood monitoring and interactions with food and other drugs,⁶ while LMWHs require subcutaneous administration with variable outcomes in terms of adherence after hospital discharge.⁷

In response to the problems with traditional thromboprophylaxis, new oral anticoagulants (NOACs) have been intensively developed in recent years. These have more specific and effective mechanisms of action, a wider therapeutic margin so that they do not require laboratory monitoring, fewer side effects, and can be administered orally.⁸

There are currently three OACs on the market in Spain with an indication for the prevention of venous thromboembolism after hip or knee replacement surgery: dabigatran etexilate, rivaroxaban, and apixaban. The first acts on FII (thrombin) in the coagulation cascade, while the other two act on FXa.

The National Institute for Health and Care Excellence (NICE)⁹ recommends LMWH (40 mg/day) and rivaroxaban (10 mg/day) as thromboprophylaxis in patients undergoing elective THR or TKR. The use of dabigatran and apixaban would be limited to when the recommended agents are clinically contraindicated. They recommend 28-day regimens for THR and 14-day regimens for TKR.

Rivaroxaban has been shown to be clearly associated with cost savings compared to enoxaparin and dabigatran. The economic savings compared to enoxaparin are up to €160 in THR and €137 in TKR.¹⁰ In addition, a lower dropout rate and greater satisfaction has been observed in patients receiving anticoagulant thromboprophylaxis compared to conventional enoxaparin.¹¹

The main objective of this study is to compare the efficacy and safety of rivaroxaban thromboprophylaxis with enoxaparin after various orthopaedic and trauma surgical procedures. We also wanted to measure the relevance of symptomatic DVT as a variable of clinical efficacy.

Material and methods**Study design**

Analytical study in which data from different clinical trials were pooled to compare rivaroxaban at a dose of 10 mg/day with conventional European thromboprophylaxis

(enoxaparin 40 mg/day) or, failing that, with the conventional American regimen (enoxaparin 30 mg/12 h) in various orthopaedic procedures.

Literature search

An unrestricted search for articles in all languages was conducted in the following databases: PubMed, EMBASE, and the Cochrane Library. The following search terms were used without restriction until May 2020: (Enoxaparin OR Enoxaparine OR EMT966 OR EMT967 OR Clexane OR Lovenox OR PK10169) AND (BAY 597939 OR Xarelto OR Rivaroxaban) AND (Knee replacement OR Knee arthroplasty) AND (Hip replacement OR Hip arthroplasty) AND (Non major orthopedic OR Arthroscopy).

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.¹² The literature references of the retrieved articles and the references of the meta-analyses were checked to ensure that no studies of interest to the analysis were missed.

Literature selection and quality assessment

The literature was restricted to randomised controlled clinical trials comparing the efficacy and safety of the selected oral anticoagulant (rivaroxaban) with enoxaparin in any surgical procedure in orthopaedic surgery and traumatology, with an equivalent duration of treatment in both arms.

All literature identified was reviewed independently by the two investigators, and disagreements between the reviewers on the selection of literature were resolved by consensus.

The modified Jadad score^{13,14} was used to assess the quality of clinical trials. With a maximum score of 7, 1 point is awarded for each of the following variables: presence of randomisation, description of randomisation, quality of randomisation, description of double-blinding, description of method of blinding, appropriateness of blinding, description of withdrawals and dropouts. Studies with a score of less than 5 were discarded due to low scientific quality.

Inclusion criteria

- Study type and publication quality: Clinical trials with a modified Jadad score of at least 5.
- Patients were randomised to receive rivaroxaban (10 mg/day) or enoxaparin (40 mg/day or, failing that, 30 mg/12 h).
- The duration of treatment should be equivalent in both arms.
- Trials should include patients aged 18 years and older.
- Sample size: more than 200 patients.
- Follow-up time: more than 30 days from the start of treatment.
- At least the following efficacy variables had to be analysed: asymptomatic or symptomatic DVT diagnosed by imaging test, non-fatal PE, and death from any cause.
- At least the following safety variables had to be analysed: major bleeding (according to International Society

on Thrombosis and Haemostasis criteria) and clinically relevant bleeding (as defined by the investigators).

Study variables

First, to assess clinical effectiveness, data were extracted on different clinical events that occurred during the thromboprophylaxis treatment period in the different trials. The events studied were asymptomatic or symptomatic DVT (diagnosed by imaging), non-fatal PE, or death from any cause. Thus, a dichotomous variable was created that, depending on the main variable (type of thromboprophylaxis), would include all the clinical events described.

However, because of the controversy surrounding the inclusion of asymptomatic DVT as a representative variable of clinical efficacy, it was considered appropriate to perform an independent analysis of the symptomatic DVT variable.¹⁵

Secondly, to assess safety, another dependent dichotomous variable was created, consisting of the following clinical events: major haemorrhage and any clinically relevant bleeding within the parameters described by the clinical trials studied.

Data collection

After selection of the clinical trials, the following data were extracted: patient characteristics (age, sex), year of study, Jadad score, type of surgical procedure, method of diagnosis of DVT, duration of treatment, efficacy outcomes (DVT, PE, mortality), and safety outcomes (major haemorrhage or relevant bleeding).

To maintain the randomisation of the original trials, data on the per-protocol population were extracted for safety outcomes.¹⁶ The per-protocol population included all randomised patients who received at least one dose of a study drug.

For efficacy outcomes, data were used on the intention-to-treat population,¹⁶ which consisted of randomised patients who received a study drug, underwent orthopaedic surgery, and had a diagnostic test for DVT at follow-up.

Statistical analysis

This section follows the principles of the SAMPL guidelines: Reporting Basic Statistical Analyses and Methods in the Published Literature: The SAMPL Guidelines for Biomedical Journals.¹⁷

The heterogeneity of the outcomes of the selected trials was calculated using the Cochrane *Q* test and the *I*² statistic using the Mantel-Haenszel method. A value of <.05 for Cochrane's *Q* and a value of >50% for *I*² of the selected sample of studies was considered to be significantly heterogeneous.¹⁸

Depending on the degree of heterogeneity of the outcomes for each variable studied, a fixed-effects model (in the case of homogeneity) or a random-effects model (in the case of heterogeneity) was used to combine the outcomes.

A significance level of $\alpha = .05$ will be used throughout the analysis. The analysis will be carried out using Review Man-

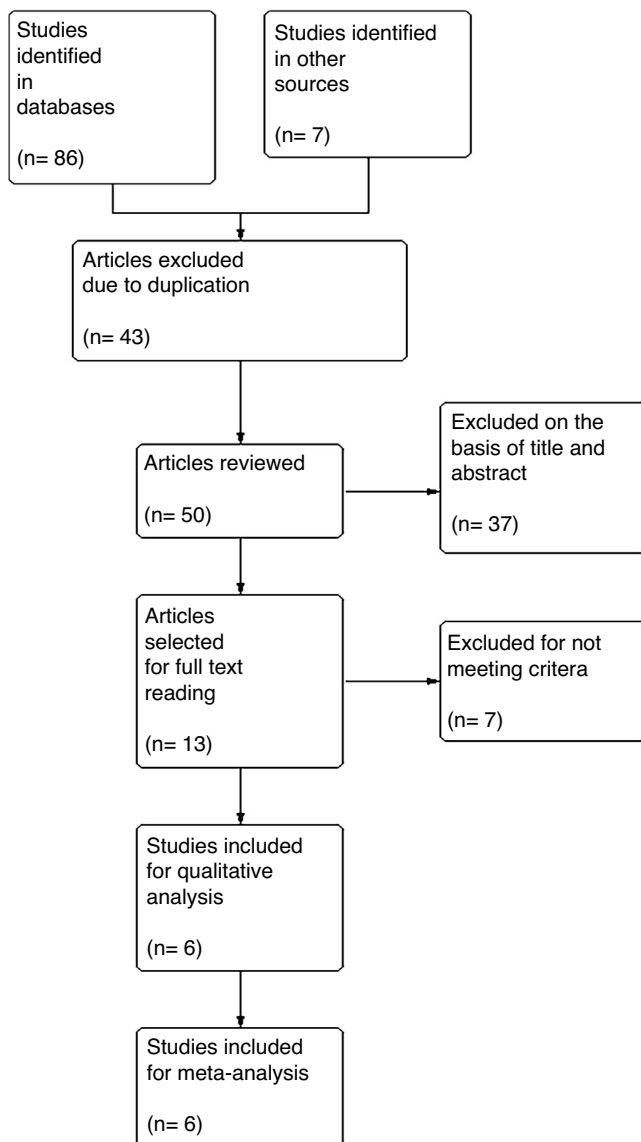


Figure 1 Flowchart of the selection of studies included in this meta-analysis.

ager version 5.3 (Cochrane Collaboration, Copenhagen: The Nordic Cochrane Centre).

The funnel plot was used to assess possible publication bias.

Results

Search results

According to the search strategy in the different electronic databases, 93 articles were identified: 49 in PubMed, 26 in Cochrane Library, 11 in EMBASE, and 7 in literature references of other meta-analyses. Forty-three articles were excluded because they were duplicates, while another 37 articles were discarded after reading the title and abstract according to the inclusion and exclusion criteria (Fig. 1).

Finally, 13 studies were selected for full-text reading. After applying the inclusion and exclusion criteria, six clin-

ical trials^{19–24} comparing rivaroxaban with enoxaparin for post-operative thromboprophylaxis were selected for statistical analysis (Table 1).

The Odixa-OD-HIP study²⁰ compared different doses of rivaroxaban with the conventional enoxaparin regimen (40 mg/24 h). For the analysis, only data from the subgroup of patients receiving the 10 mg daily dose of rivaroxaban were collected.

A single study, RECORD4,²³ which compared rivaroxaban 10 mg daily with a regimen of enoxaparin 30 mg every 12 h, was selected (Table 2).

A single study, PROMONOS,²⁴ which analysed thromboprophylaxis in procedures other than THR or TKR, was selected. This study looked at minor lower limb surgery: arthroscopy, arthrodesis, osteosynthesis, among others.

Meta-analysis of clinical efficacy outcomes

A total of 11,005 patients were allocated to the intention-to-treat population. In the group of patients receiving daily rivaroxaban, 3.74% (206/5512) experienced an event as defined by the clinical efficacy variable: asymptomatic or symptomatic DVT, non-fatal PE, or death from any cause.

In contrast, 7.12% (391/5493) of patients in the enoxaparin group experienced a clinical event. The odds of a clinical event are therefore lower in the rivaroxaban group, and this association is statistically significant (RR: .51; 95% CI: .36–.73; $p = .0002$; Fig. 2). Due to the remarkable heterogeneity of the selected data ($I^2 = 72\%$; $p = .004$; Fig. 2) a random-effects model was used for the analysis.

The heterogeneity observed in the meta-analysis could be influenced by a number of confounding factors, such as the inclusion of different surgical procedures and the use of different thromboprophylaxis regimens.

For this reason, the trials were divided into two subgroups. On the one hand, the subgroup representative of our setting included trials analysing thromboprophylaxis in THR or TKR (both included in the Summary of Product Characteristics in Spain); for thromboprophylaxis both in terms of duration (minimum 10 days in TKR and 28 days in THR) and dose (40 mg/24 h).

On the other hand, the non-representative subgroup included trials that evaluated thromboprophylaxis in interventions outside the Summary of Product Characteristics (any intervention other than THR or TKR) or in regimens other than those used in our setting.

Thus, a total of 6783 patients, selected from the intention-to-treat population, received a thromboprophylaxis regimen representative of our setting for operations within the technical specifications (THR or TKR).

In the rivaroxaban once-daily group, 4.84% (164/3388) had a clinical event as defined by the clinical efficacy variable: asymptomatic or symptomatic DVT, non-fatal PE, or death from any cause.

In contrast, 9.46% (321/3395) of patients in the enoxaparin group experienced a clinical event. The odds of experiencing a clinical event are therefore lower in the rivaroxaban group, and this association is statistically significant (RR: .50; 95% CI: .34–.72; $p = .0003$; Fig. 3). Due to the remarkable heterogeneity of the selected data ($I^2 = 73\%$;

Table 1 Characteristics of the clinical trials selected for the study.

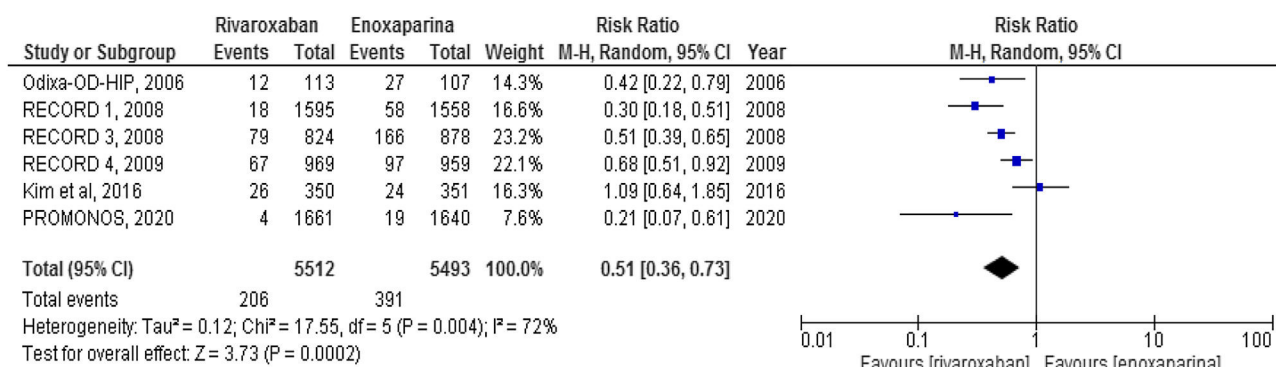
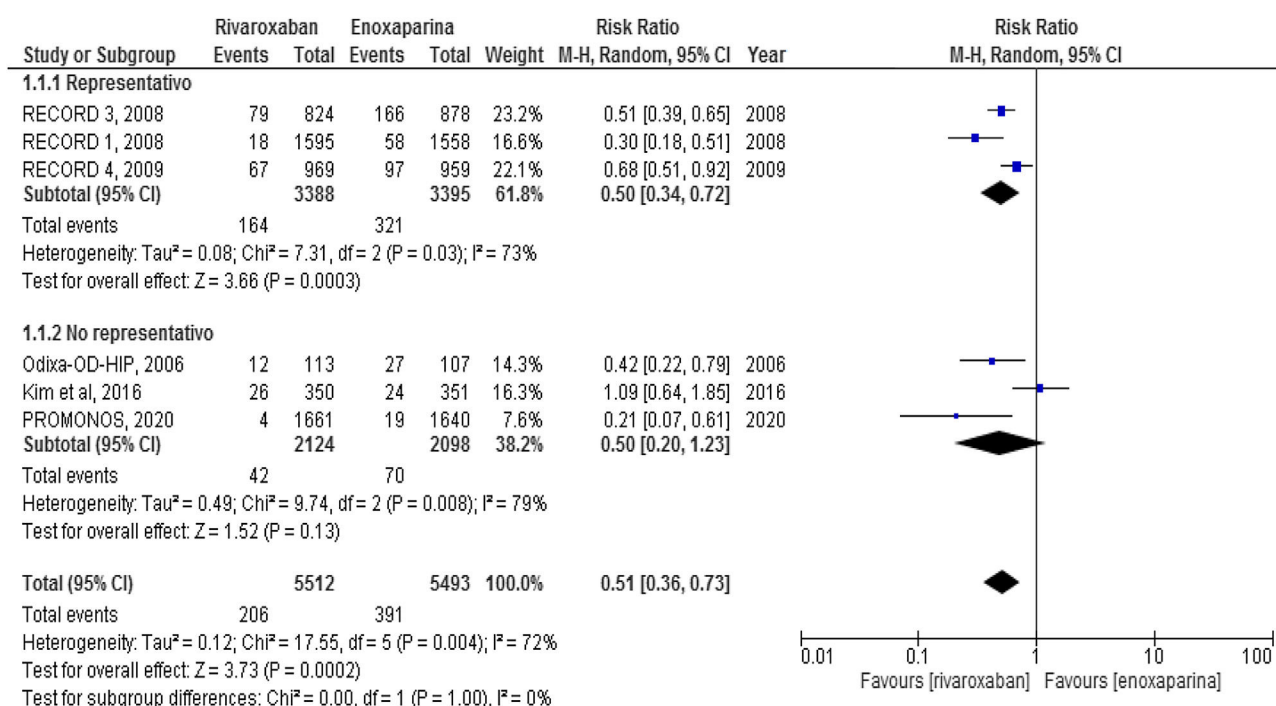
Title	Year	Jadad	SI	DVT diagnostic method	Thromboprophylaxis regimens	Per-protocol population	Mean age	Sex ^a
Kim et al. ¹⁹	2016	6	THR	Ultrasound	Rivaroxaban 10 mg orally daily, 7–12 days post-intervention	363 patients	56.5 years	53.08%
					Enoxaparin 40 mg s.c. daily; 7–12 days post-intervention	364 patients	56.7 years	52.01%
Odixa-OD-HIP ²⁰	2006	5	THR	Venogram	Rivaroxaban 5, 10, 20, 30, or 40 mg orally daily; 5–9 days post-intervention	142 patients with a 10 mg regimen	64 years	63%
					Enoxaparin 40 mg s.c. daily; 5–9 days post-intervention	157 patients	65.6 years	64%
PROMONOS ²⁴	2020	7	NMS	Ultrasound	Rivaroxaban 10 mg oral daily, 30–35 days post-intervention	1,757 patients	41 years	34%
					Enoxaparin 40 mg s.c. daily; process-dependent duration	1,739 patients	41 years	36%
RECORD 1 ²¹	2008	7	THR	Venogram	Rivaroxaban 10 mg oral daily, 30–35 days post-intervention	2,209 patients	63.1 years	55.2%
					Enoxaparin 40 mg s.c. daily; 30–35 days post-intervention	2,224 patients	63.3 years	55.8%
RECORD 3 ²²	2008	7	TKR	Venogram	Rivaroxaban 10 mg orally daily, 10–14 days post-intervention	1,220 patients	67.6 years	70.2%
					Enoxaparin 40 mg s.c. daily; 10–14 days post-intervention	1,239 patients	67.6 years	66.3%
RECORD 4 ²³	2009	7	TKR	Venogram	Rivaroxaban 10 mg orally daily, 10–14 days post-intervention	1,523 patients	64.4 years	64.4%
					Enoxaparin 30 mg s.c./12 h; 10–14 days post-intervention	1,528 patients	64.7 years	64.7%

DVT: deep vein thrombosis; THR: total hip replacement; TKR: total knee replacement; NMS: nonmajor orthopedic surgery of the lower limbs; SI: surgical intervention.

^a The qualitative variable of sex is described as the percentage of women in each population.

Table 2 Modified Jadad score of selected clinical trials.

	Randomisation	Quality of randomisation	Description of randomisation	Double-blinding	Description of method of blinding	Appropriateness of blinding	Total
Odixa-OD-HIP	1	0	0	1	1	1	5
RECORD 1	1	1	1	1	1	1	7
RECORD 3	1	1	1	1	1	1	7
RECORD 4	1	1	1	1	1	1	7
Kim et al.	1	1	0	1	1	1	6
PRONOMOS	1	1	1	1	1	1	7

**Figure 2** Clinical efficacy outcomes presented in a forest plot diagram.**Figure 3** Clinical efficacy outcomes by subgroup (representative/non-representative) presented in a forest plot diagram.

$p = .03$; Fig. 3) a random-effects model was used for the analysis.

In both the overall analysis and the subgroup analysis, there was a high degree of heterogeneity in the data from the trials included in the meta-analysis. There-

fore, it was considered appropriate to break down the outcome variable clinical efficacy into its three components: DVT (asymptomatic or symptomatic), PE, and death. Thus, it was analysed whether the heterogeneity of the data from the different studies was influenced by the

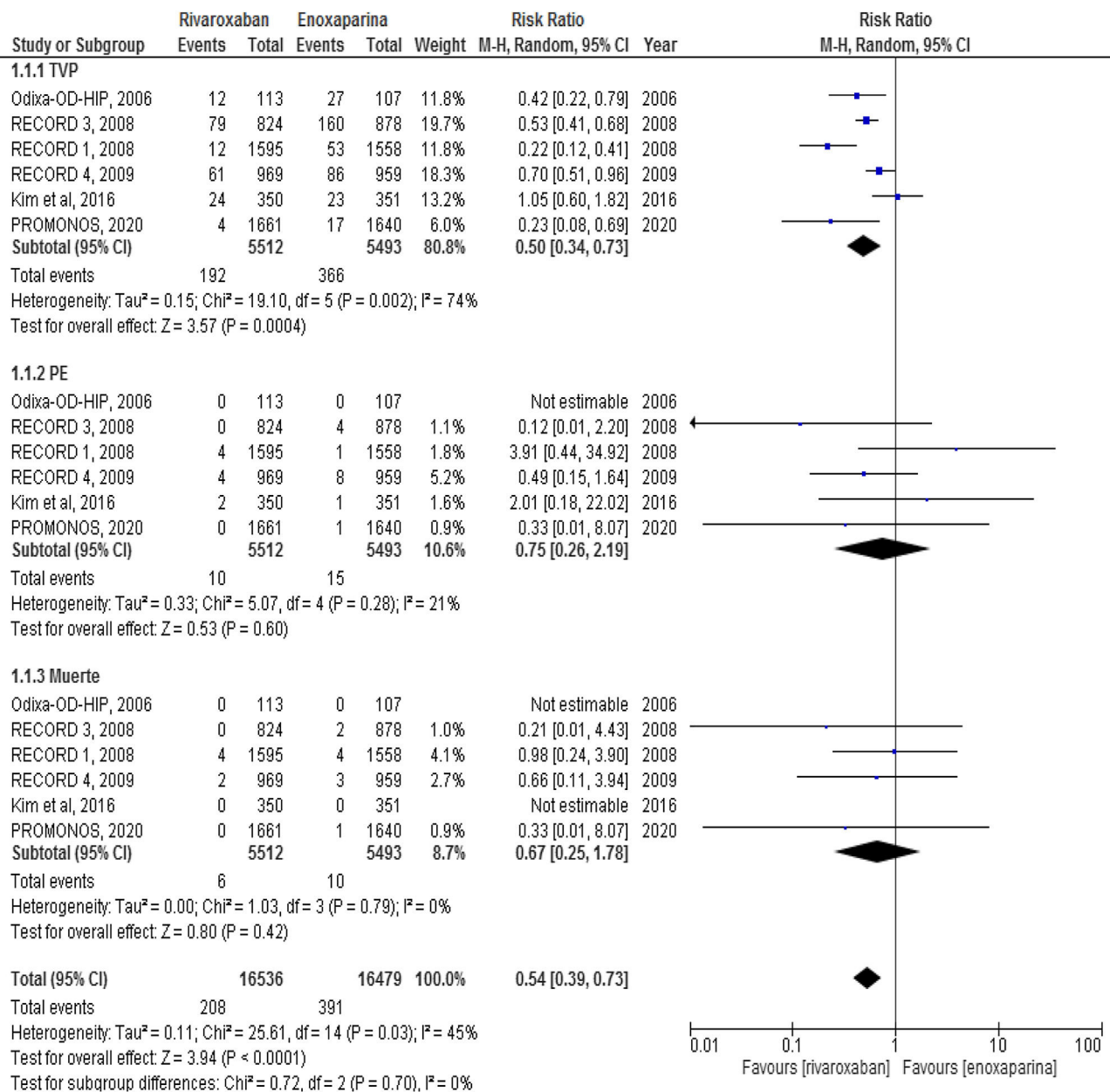


Figure 4 Results of the analysis of the clinical variables deep vein thrombosis (DVT), pulmonary embolism (PE) and death plotted on a forest plot.

grouping of different clinical events into a single variable.

It was observed that the only clinical event with a statistically significant lower incidence with rivaroxaban was the variable DVT (RR: .50; 95% CI: .34–.73; $p = .0004$; Fig. 4). The variables PE (RR: .75; 95% CI: .26–2.19; $p = .60$; Fig. 4) and death (RR: .67; 95% CI: .25–1.78; $p = .42$; Fig. 4) had a lower incidence in the rivaroxaban group but were not statistically significant.

In contrast, the DVT variable was the source of heterogeneity in the clinical efficacy variable. This is because the DVT data showed remarkable heterogeneity ($I^2 = 74\%$; $p = .002$; Fig. 4), while PE ($I^2 = 21\%$; $p = .28$; Fig. 4) and death ($I^2 = 0\%$; $p = .79$; Fig. 4) are homogenous across studies.

Meta-analysis of symptomatic deep vein thrombosis

A total of 10,785 patients from the 5 trials that recorded the variable symptomatic DVT were included in the intention-to-treat population.

In the group of patients treated with daily rivaroxaban, .57% (31/5399) had an event diagnosed as symptomatic DVT. In the group receiving enoxaparin for thromboprophylaxis, 1.36% (73/5386) suffered a symptomatic DVT.

Therefore, the probability of suffering symptomatic DVT is lower in the rivaroxaban group, this association being statistically significant (RR: .43; 95% CI: .28–.65; $p < .0001$; Fig. 5). Due to the clear homogeneity of the data in the



Figure 5 Results of the analysis of symptomatic DVT plotted on a forest plot.

variable studied ($I^2 = 0\%$; $p = .49$; Fig. 5) a fixed-effects model was used for the analysis.

Meta-analysis of safety outcomes

A total of 14,445 patients were selected in the per-protocol population. Within the group of patients who received at least one dose of rivaroxaban, 2.5% (180/7214) suffered an event described within the clinical safety variable (major haemorrhage or any clinically relevant bleeding).

In the group that received enoxaparin as thromboprophylaxis, on the other hand, 2.09% (151/7231) suffered a clinical safety event. Therefore, the probability of suffering a clinical safety event is higher in the rivaroxaban group, this association being statistically non-significant (RR: 1.20; 95% CI: .97–1.49; $p = .09$; Fig. 6). Due to the homogeneity of the selected data ($I^2 = 0\%$; $p = .82$; Fig. 6) a fixed-effects model was used for the analysis of the clinical safety variable.

Assessment of publication bias

The results of the funnel plots for both the clinical efficacy and the clinical safety meta-analyses show an inverted funnel shape or a symmetrical triangle shape (Fig. 7), thus rejecting publication bias as a serious threat to the validity of the meta-analysis outcomes.

Discussion

In patients undergoing orthopaedic surgery, the likelihood of a VTE-related event is halved when rivaroxaban is given at a dose of 10 mg as thromboprophylaxis compared with the subcutaneous dose of 40 mg (or failing that, 30 mg per 12 h) of conventional enoxaparin.

This finding is consistent with the outcomes of previous meta-analyses,^{15,25,26} despite the inclusion of a study that analysed procedures other than THR or TKR, such as the PROMONOS study.²⁴ In the latter study, patients randomised to enoxaparin had five times more clinical events than those randomised to rivaroxaban. Despite the fact that this study, published in 2020, looked at off-label use of rivaroxaban, the outcomes presented are very promising; therefore, it would not be surprising if the use of this new OAC for thromboprophylaxis in procedures other than TKR and TKR were to become widespread.

It was observed that the heterogeneity of the data for the clinical efficacy variable depended on the diagnosis of asymptomatic DVT. When only the symptomatic DVT variable was analysed, the outcomes with rivaroxaban were even better than those for the clinical efficacy variable. This result, together with the fact that there were no significant differences in the variables non-fatal PE and death, supports the current argument¹⁵ that thromboprophylaxis efficacy should be measured using the symptomatic DVT variable.

In this study, no increased risk of bleeding was observed when patients received rivaroxaban as prophylaxis compared to enoxaparin. Although previous studies^{15,25,26} have shown an increased risk of bleeding with rivaroxaban as prophylaxis, in this study the safety variable is not significantly increased in the rivaroxaban group. This finding may be due to the fact that previous meta-analyses^{15,25,26} included trials with different doses of rivaroxaban, whereas current guidelines recommend a dose of 10 mg rivaroxaban daily based on its proven efficacy.

Despite the fact that the studies included in the analysis are clinical trials, they are clearly far removed from daily clinical practice, such as the screening with imaging tests (venogram and ultrasound) to rule out DVT, which was routinely performed in the trials. A German retrospective study²⁷ investigated the efficacy of rivaroxaban in routine clinical practice by analysing data from the ORTHOTEP registry. The prevalence of thromboembolic events was half that of patients receiving rivaroxaban-based prophylaxis after THR or TKR surgery. In addition, these patients had fewer major bleeds and a lower prevalence of post-operative complications.

The literature search did not identify any clinical trials that evaluated the efficacy and safety of rivaroxaban after surgery for a condition as common as hip fracture. However, a cohort study of normal clinical practice²⁸ shows that rivaroxaban halves the rate of VTE with a lower prevalence of clinically relevant bleeding and post-operative complications in patients who have undergone surgery for hip fracture or other types of lower limb fracture.

Although the current NICE guidelines⁹ only include rivaroxaban as a therapeutic alternative to enoxaparin and this is the most cost-effective, several meta-analyses,¹⁵ have also shown greater clinical efficacy with other oral anticoagulants such as apixaban, dabigatran, or edoxaban compared with enoxaparin. For all these reasons, new oral

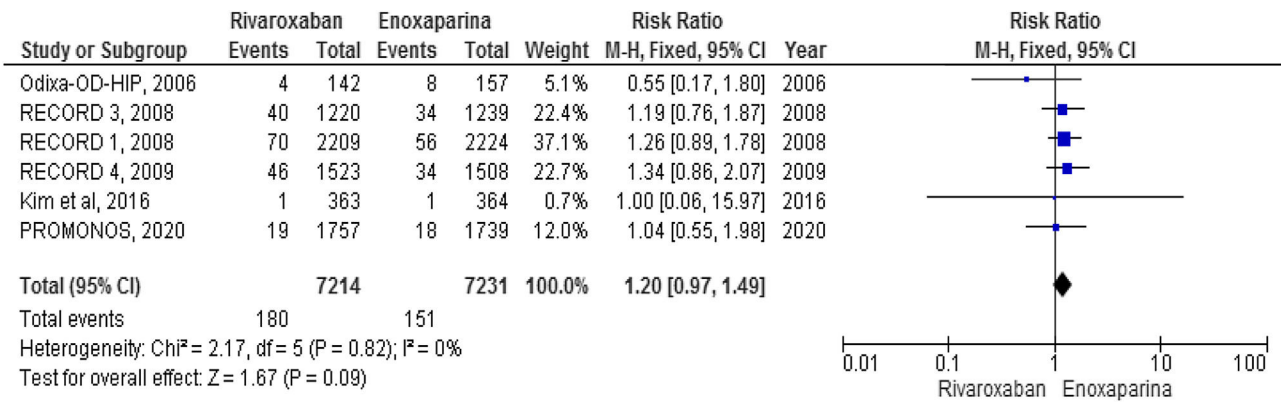


Figure 6 Clinical safety outcomes plotted on a forest plot.

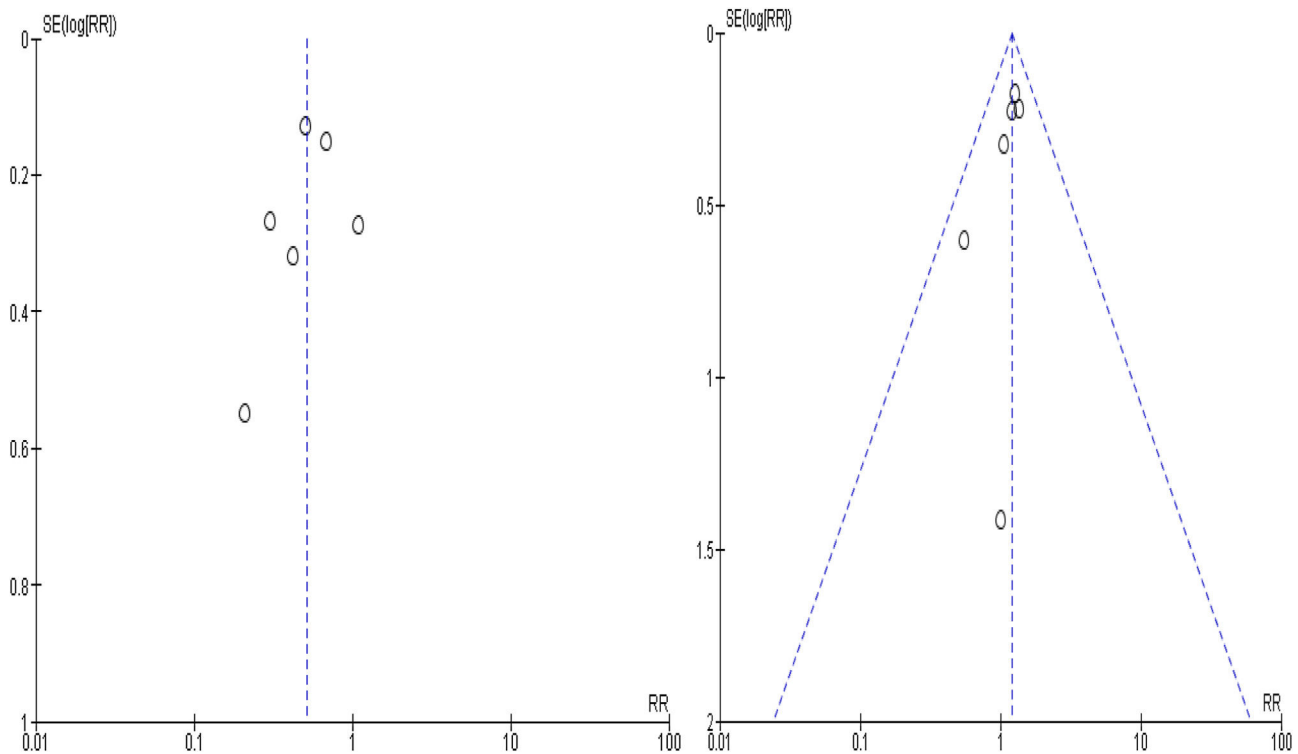


Figure 7 Funnel plot of the meta-analysis data for clinical efficacy (left) and clinical safety (right).

anticoagulants may be included in clinical guidelines as alternatives to enoxaparin in the coming years.

Study limitations

First, statistical analysis was performed on variables that grouped different clinical events to assess both clinical efficacy and safety. An example of the limitation of grouping efficacy variables is the heterogeneity found in the analysis of clinical efficacy outcomes. However, these outcomes showed homogeneity when the different events were assessed individually and symptomatic DVT was assessed alone.

Furthermore, these variables did not include secondary clinical events that were included in some clinical trials,

such as exudate from the surgical wound, which may better reflect the true risk of each drug. However, these events were not considered to be clinically relevant for assessing the safety of a drug in most of the selected clinical trials.

The number of clinical trials included (6) is relatively small. However, the small number of trials found is due to the strict selection criteria (trials with a sample size of less than 200 patients and with a follow-up of less than 30 days were not included) and the demand for high-quality clinical trials, as assessed by the Jadad system. Furthermore, both the high methodological quality of the selected trials and the large number of participants in most of the trials lend robustness to the outcomes obtained in this review. It is true, however, that future studies may strengthen and make more consistent the outcomes obtained in the present work.

The funnel plot was used to analyse publication bias that may have occurred in the selection of trials for both clinical effectiveness and clinical safety. There is controversy in the literature about the use of this plot in all types of meta-analysis, as many authors recommend its use when the number of selected trials is greater than 10. In this study, the graph took the form of a symmetrical inverted funnel, thus excluding the possibility of selection bias; the use of Begg's or Egger's tests, which assess publication bias more objectively, was not considered appropriate.

Conclusion

Although enoxaparin is the conventional thromboprophylaxis prescribed after orthopaedic surgery and trauma; rivaroxaban at a dose of 10 mg daily is more effective in preventing thromboembolic events after orthopaedic surgery. Furthermore, this anticoagulant benefit is not compromised by an increased risk of bleeding.

In addition, the efficacy was found to be even greater when only events due to symptomatic DVT were analysed, which also led to greater homogeneity in the outcomes of the trials. Therefore, symptomatic DVT should be analysed as a separate variable in future trials.

Level of evidence

Level of evidence I.

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Conflict of interests

The authors have no conflict of interests to declare.

References

- Cohen AT, Agnelli G, Anderson FA, Arcelus JI, Bergqvist D, Brecht JG, et al. Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality. *Thromb Haemost.* 2007;98:756–64.
- Geerts WH, Pineo GF, Heit JA, Bergqvist D, Lassen MR, Colwell CW, et al. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest.* 2004;126:338–400.
- Wakefield TW, Robert BM, Joann ML, Joseph AC, David LG, Marc AP. Call to action to prevent venous thromboembolism. *J Vasc Surg.* 2009;49:1620–3.
- Backman K, Carlsson P, Kentson M, Hansen S, Engquist L, Hallert C. Deep venous thrombosis: a new task for primary health care. A randomised economic study of outpatient and inpatient treatment. *Scand J Prim Health Care.* 2004;22:44–9.
- Falck-Ytter Y, Francis CW, Johanson NA, Curley CA, Dahl OE, Schulman S, et al. American College of Chest Physicians: prevention of VTE in orthopedic surgery patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141:278–325.
- Lee CJ, Ansell JE. Direct thrombin inhibitors. *Br J Clin Pharmacol.* 2011;72:92–581.
- Eriksson BI, Quinlan DJ, Weitz JI. Comparative pharmacodynamics and pharmacokinetics of oral direct thrombin and factor Xa inhibitors in development. *Clin Pharmacokinet.* 2009;48:1–22.
- Weitz JI, Hirsh J, Samama MM. New antithrombotic drugs: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest.* 2008;133:234–56.
- National Institute for Health and Care Excellence. Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism; March 2018. Available from: <https://www.nice.org.uk/guidance/ng89>
- Monreal M, Folkerts K, Diamantopoulos A, Imberti D, Brosa M. Cost-effectiveness impact of rivaroxaban versus new and existing prophylaxis for the prevention of venous thromboembolism after total hip or knee replacement surgery in France Italy and Spain. *Thromb Haemost.* 2013;110:987–94.
- Peidro L, Otero R, Lozano L. Adherencia y satisfacción en la profilaxis antitrombótica ambulatoria oral frente a la parenteral: estudio SALTO. *Rev Esp Cir Ortop Traumatol.* 2013;57:53–60.
- Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6:e1000097.
- Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials.* 1996;17:1–12.
- Moher D, Cook DJ, Jadad AR, Tugwell P, Moher M, Jones A, et al. Assessing the quality of reports of randomised trials: implications for the conduct of meta-analyses. *Health Technol Assess.* 1999;3:1–98.
- Feng W, Wu K, Liu Z, Kong G, Deng Z, Chen S, et al. Oral direct factor Xa inhibitor versus enoxaparin for thromboprophylaxis after hip or knee arthroplasty: systemic review, traditional meta-analysis, dose-response meta-analysis and network meta-analysis. *Thromb Res.* 2015;136:1133–44.
- Hollis S, Campbell F. What is meant by intention to treat analysis? Survey of published randomised controlled trials. *BMJ.* 1999;319:670–4.
- Lang TA, Altman DG. Basic statistical reporting for articles published in biomedical journals: the "Statistical Analyses and Methods in the Published Literature" or "The SAMPL Guidelines". In: Smart P, Maisonneuve H, Polderman A, editors. *Science editors' handbook.* European Association of Science Editors; 2013.
- Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* 2003;327:557–60.
- Kim SM, Moon YW, Lim SJ, Kim DW, Park YS. Effect of oral factor Xa inhibitor and low-molecular-weight heparin on surgical complications following total hip arthroplasty. *Thromb Haemost.* 2016;115:600–7.
- Eriksson BI, Borris LC, Dahl OE, Haas S, Huisman MV, Kakkar AK, et al. A once-daily, oral, direct factor Xa inhibitor, rivaroxaban (BAY 59-7939), for thromboprophylaxis after total hip replacement. *Circulation.* 2006;114:2374–81.
- Eriksson BI, Borris LC, Friedman RJ, Haas S, Huisman MV, Kakkar AK, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N Engl J Med.* 2008;358:2765–75.
- Lassen MR, Agno W, Borris LC, Lieberman JR, Rosencher N, Bandel TJ, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med.* 2008;358:2776–86.
- Turpie AG, Lassen MR, Davidson BL, Bauer KA, Gent M, Kwong LM, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. *Lancet.* 2009;373:1673–80.

24. Samama CM, Laporte S, Rosencher N, Girard P, Llau J, Mouret P, et al. Rivaroxaban or enoxaparin in nonmajor orthopedic surgery. *N Engl J Med.* 2020;382:1916–25.
25. Venker BT, Ganti BR, Lin H, Lee ED, Nunley RM, Gage BF. Safety and efficacy of new anticoagulants for the prevention of venous thromboembolism after hip and knee arthroplasty: a meta-analysis. *J Arthroplasty.* 2017;32:645–52.
26. Liu J, Zhao J, Yan Y, Su J. Effectiveness and safety of rivaroxaban for the prevention of thrombosis following total hip or knee replacement: a systematic review and meta-analysis. *Medicine (Baltimore).* 2019;98:e14539.
27. Beyer-Westendorf J, Lützner J, Donath L, Tittl L, Knoth H, Radke OC, et al. Efficacy and safety of thromboprophylaxis with low-molecular-weight heparin or rivaroxaban in hip and knee replacement surgery. Findings from the ORTHO-TEP registry. *Thromb Haemost.* 2013;109:154–63.
28. Lassen MR, Haas S, Kreutz R, Mantovani LG, Holberg G, Turpie AG. Rivaroxaban for thromboprophylaxis after fracture-related orthopedic surgery in routine clinical practice. *Clin Appl Thromb Hemost.* 2016:138–46.