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Heparina de bajo peso molecular frente a rivaroxabán en tromboprofilaxis poscirugía. Revisión sistemática y metaanálisis

Albert González-Sagredo[1], Jaime Hospedales[1], Jesús Villoria[2], Teresa López-Sobrino[3], Sebastián Videla[4]

[1]Angiology and Vascular Surgery Department. Hospital Quironsalud del Vallés. Sabadell. Barcelona, Spain. Angiology and Vascular Surgery Department. Hospital Universitari Sagrat Cor. Barcelona, Spain. [2]Department of Design and Biometrics. Medicxact. Alpedrete. Madrid, Spain. [3]Cardiovascular Institute. Hospital Clinic. Universitat de Barcelona. Barcelona, Spain. [4]Department of Pharmacology, Therapeutics and Toxicology. Universitat Autònoma de Barcelona. Barcelona, Spain. Neuropharmacology & Pain Group. Neuroscience Program. Bellvitge Biomedical Research Institute. L'Hospitalet de Llobregat. Barcelona, Spain. Clinical Research Support Area. Hospital Universitari Germans Tries i Pujol. Badalona. Barcelona, Spain

Correspondence: Albert González-Sagredo. Angiology and Vascular Surgery Department. Hospital Quironsalud del Vallés. Passeig de Rubió i Ors, 23. 08203 Sabadell. Barcelona, Spain
e-mail: albertgonzalezsagredo@gmail.com

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ABSTRACT

Objective: the aim is to determine if rivaroxaban is comparable to low-molecular weight heparin (LMWH) in terms of venous thromboembolism (VTE) prevention after surgery, and in safety.

Methods: this meta-analysis was registered in PROSPERO (CRD420261293821) and was written in accordance with Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines. Ethical approval was not required for this work. Inclusion criteria were randomized controlled trials comparing LMWH vs. rivaroxaban for VTE prevention after surgery. MEDLINE and SCOPUS electronic databases were searched. Both common and random estimates of the overall effects were calculated with Mantel-Haenszel method. The confidence intervals of random effect estimates were calculated with the Hartung and Knapp method. Efficacy outcome was VTE incidence and safety outcome was major bleedings.

Results: of the 1063 studies identified, 985 were excluded based on tittle/abstract, and from the remaining 78, six met the inclusion criteria (four in orthopedic surgery, one in thoracic surgery, and one in gynecology). Patients receiving rivaroxaban showed a lower (statistically significant) incidence of VTE compared with LMWH (OR, 95 %CI, 0.54 [0.30;0.98]), with a higher (not statistically significant) incidence of bleeding (OR, 95 %CI, 1.72 [0.75-3.94]).

Conclusions: rivaroxaban appears to be more effective than LMWH in the prevention of postoperative VTE and may be considered an appropriate option in patients at low risk of bleeding. In contrast, in patients at higher risk - such as those with advance renal disease, liver disease, history of gastrointestinal bleeding, hematological

disorders, or concomitant use of antiplatelet therapy – LMWH should be considered.

Keywords: Venous thromboembolism. Postoperative venous thromboembolism. oral anticoagulants. Rivaroxaban. Low-molecular weight heparin.

RESUMEN

Objetivo: determinar si rivaroxabán es comparable a la heparina de bajo peso molecular (HBPM) en la prevención del tromboembolismo venoso (TEV) tras cirugía y en seguridad.

Métodos: este metaanálisis fue registrado en PROSPERO (CRD420261293821) y se redactó siguiendo las guías PRISMA. Los criterios de inclusión fueron ensayos clínicos aleatorizados que compararan HBPM con rivaroxabán en prevención de TEV tras cirugía. Se realizaron búsquedas en las bases de datos electrónicas MEDLINE y SCOPUS. Se calcularon estimaciones globales de los efectos mediante el método de Mantel-Haenszel. Los intervalos de confianza se calcularon con el método de Hartung y Knapp. El *outcome* de eficacia fue la incidencia de TEV y el de seguridad fueron las hemorragias mayores.

Resultados: de los 1063 estudios identificados, 985 fueron excluidos con base en el título/resumen, y de los 78 restantes, seis cumplieron criterios de inclusión. Los pacientes que recibieron rivaroxabán mostraron una menor incidencia de TEV (estadísticamente significativa) en comparación con HBPM (OR, IC 95 %: 0,54 [0,30; 0,98]), con una mayor incidencia de sangrado (no estadísticamente significativa; OR, IC 95 %: 1,72 [0,75-3,94]).

Conclusiones: rivaroxabán parece ser más eficaz que HBPM como tromboprofilaxis y puede considerarse una opción adecuada en pacientes con bajo riesgo de sangrado. En cambio, en pacientes con mayor riesgo (enfermedad renal avanzada, enfermedad hepática,

antecedentes de sangrado gastrointestinal o trastornos hematológicos) debería considerarse HBPM.

Palabras clave: Anticoagulante oral de acción directa. Tromboembolismo venoso. Tromboprofilaxis. Heparina de bajo peso molecular.

INTRODUCTION

Deep vein thrombosis (DVT) and pulmonary embolism (PE), collectively known as venous thromboembolism (VTE) are a life-threatening complication after surgery due to its high morbi-mortality (long-term complications, functional disability or death) (1). It is associated with up to 10 % of all hospital-related deaths, has significant healthcare costs, and it is considered the most preventable cause of death in hospitalized patients (2,3).

Surgery is a well-established risk factor for VTE, with reported risk increases ranging from 8- to 70-fold (4), largely due to activation of the coagulation cascade, platelet activation, and overproduction of procoagulant factors during and after the procedure (1). The incidence of postoperative VTE varies according to the type of surgery, ranging from less than 1 % after varicose vein surgery, to 7 % after total hip replacement (THR). Thromboprophylaxis plays a crucial role in this setting, as the 7 % incidence reported after THR refers to patients receiving appropriate anticoagulation; in patients who do not take adequate prophylaxis the reported incidence of VTE is as high as 40 % (3). Antithrombotic drugs reduce the risk of postoperative VTE but increase the risk of bleeding. Recommending drug treatment as thromboprophylaxis should depend on its expected net effect based on the expected risks of VTE and bleeding (5).

When choosing a pharmacological thromboprophylaxis agent for surgical patients -who inherently carry a higher risk of bleeding- the type of surgery and patient comorbidities play a key role in the

decision-making process. Low-molecular weight heparin (LMWH) has long been considered the cornerstone of VTE prevention and treatment. This paradigm has evolved with the introduction of direct oral anticoagulants (DOAC), which are currently recommended as first-line therapy for VTE treatment in the latest European Society for Vascular Surgery (ESVS) guidelines (6), and are increasingly replacing LMWH for VTE prophylaxis after certain surgical procedures (7-10). Guidelines from the American Society of Hematology recommend DOACs over LMWH for thromboprophylaxis after orthopedic surgery, based on a direct comparative evidence on efficacy, safety, cost effectiveness, equity, acceptability, and feasibility (11). Regarding non-orthopedic surgery, there are no strong recommendations regarding DOACs vs. LMWH due to the lack of randomized controlled trials (RCT) on this setting (5).

One of the main advantages of DOACs is their oral administration, which may improve patient adherence compared with LMWH. Subcutaneous injections of LMWH may produce pain and bruising, contributing to approximately 50 % of patients failing to adhere to treatment (1). DOACs target specific steps in the coagulation cascade and can be categorized into two groups: thrombin inhibitors (dabigatran) and factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban) (12). Among the different DOACs, a substantial body of evidence supports the use rivaroxaban and apixaban for VTE prevention after surgery, whereas data on edoxaban and dabigatran remains limited (1,7,9,12-17). Rivaroxaban may have achieved broader uptake in VTE prophylaxis, possibly due to its once-daily dosing regimen, compared with the twice-daily administration required for apixaban. Previous systematic reviews and meta-analysis have evaluated DOACs as a class (18-21); however, given that each agent has distinct pharmacokinetic and pharmacodynamic profiles, we conducted this systematic review and meta-analysis focusing exclusively on rivaroxaban, one of the most widely used DOACs in thromboprophylaxis. We have analyzed exclusively rivaroxaban as it

is the only DOAC that is given once daily and does not require bridge therapy, two factors that are essential to increase therapeutic adherence in prevention settings.

MATERIALS AND METHODS

Study registration and ethics

This meta-analysis is reported in accordance with Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines (22). The study was retrospectively registered in PROSPERO (CRD420261293821), and Ethical approval was not required for this work.

Eligibility criteria

Included studies were English-language RCTs, conducted with adult patients (≥ 18 years of age) that compared LMWH (any LMWH in prophylaxis dose) vs. rivaroxaban (10 mg once daily) as thromboprophylaxis after surgery. We excluded conference abstracts, systematic reviews, case reports, non-interventional, and pre-clinical studies.

Data sources and search criteria

MEDLINE and SCOPUS electronic databases were searched. Search terms included controlled terms (Medical Subject Headings, MeSH) in Pubmed, as well as free-text terms. All rendered results were imported to EndNote® version 20.4 (Clarivate, Philadelphia, PA, USA) and duplicates were removed. Titles and abstracts of identified articles were independently screened by two reviewers for potentially relevant studies. Those selected underwent full-text review. Discrepancies regarding inclusion were settled by a third (senior) reviewer.

Data extraction and outcome of interest

Two authors performed the data extraction using a Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA) template prepared prior to the literature search. Both reviewers extracted the data independently and discrepancies were settled by a third author. We extracted information regarding the year of publication, patients demographics (age and sex), number of patients included, treatment characteristics, and the outcome of interest. Efficacy outcome was measured as the incidence of postoperative VTE, and safety outcome was measured as major bleeding. Major bleeding was defined as overt bleeding that was associated with a decrease in the hemoglobin level of 2 g per deciliter or more, led to transfusion of 2 or more units of red cells, occurred in a critical site, or contributed to death (23).

Quality and risk of bias assessment

Two reviewers independently evaluated the included studies according to the Cochrane Handbook for Systematic Reviews of Interventions, version 6.3 (24). The risk of bias was assessed by the Cochrane risk-of-bias tool for RCTs (RoB2) (24). Seven domains were evaluated: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting bias, and other biases. Each item was classified as low-risk, high-risk, or raising some concerns.

Statistical analysis

We used odds ratios as outcome measures and calculated the study-wise 95 % asymptotic Wald confidence intervals. We then calculated the common effect estimate of the pooled odds ratio for all studies using the Mantel-Haenszel method, together with its asymptotic 95 % confidence interval based on standard normal quantiles. We also fitted a restricted maximum likelihood overall random effects estimator in a classic two-level DerSimonian-Laird model, and applied the Hartung-Knapp method, including the *ad hoc* variance correction,

to calculate its 95 % confidence interval. In addition, we calculated the corresponding prediction intervals (PI) to conservatively account for variability across studies. To quantify between-study heterogeneity we calculated the I^2 statistic based on the heterogeneity statistic *Q.* We also performed stratified (subgroup) analyses by type of surgery, as well as sensitivity analyses by sequentially excluding individual studies (leave-one-out analysis) and by removing studies identified as being at high risk of bias. Statistical analyses were conducted using R® version 4.2 for Windows® [R Foundation for Statistical Computing, Vienna, Austria).

Missing data

We attempted to contact the corresponding author in case of missing data. If no response was obtained, we ultimately excluded the study.

RESULTS

The initial search yielded a total of 1063 records. After analyzing tittle and abstract 985 were excluded, and finally six trials met inclusion criteria (1,7,8,15,17,25) as shown in figure 1.

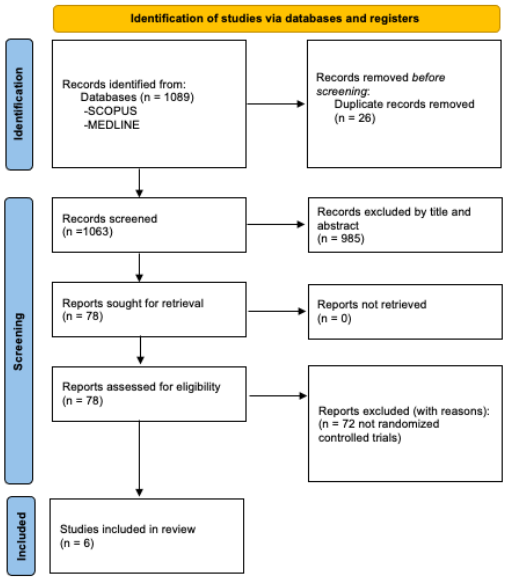

Figure 1. PRISMA Flow-diagram.

Study characteristics and risk of bias assessment

All six articles were parallel-group RCTs. Four studies were conducted in orthopedic surgery, one in thoracic surgery, and one in gynecology. Table I summarises the characteristics of the included RCTs. The inter-study heterogeneity was moderate (I^2 = 65.4 %) in the efficacy outcome, while it was low (I^2 = 0 %) in the safety outcome. All studies included as outcome of interest both symptomatic and assymptomatic VTEs.

Table I. Characteristics of the included studies

Reference	**Year**	**VTE diagnosis**	**Type of surgery**	**Intervention**	**Comparison**	**Number of patients**	**Follow-up period**
Turpie	2009	Bilateral venography	Orthopedic surgery	Rivaroxaban	LMWH	3148	35 days
Eriksson	2008	Bilateral venography	Orthopedic surgery	Rivaroxaban 10 mg for 35 days	Enoxaparin 40 IU/day for 35 days	4541	35 days
Rahman	2020	Computed tomography venography	Orthopedic surgery	Rivaroxaban 10 mg for 14 days	Enoxaparin 40 IU/day for 14 days	160	15.6 months
Lassen	2008	Bilateral venography	Orthopedic surgery	Rivaroxaban 10 mg for 14 days	Enoxaparin 40 IU/day for 14 days	2531	35 days
Zhao	2023	Duplex ultrasound	Thoracic surgery	Rivaroxaban 10 mg for 7 days	Nadroparin 57 UI/kg/day for 7 days	403	30 days
Malavasi	2022	Duplex ultrasound	Gynecological surgery	Rivaroxaban 10 mg	Enoxaparin 40 IU/day	228	30

				for 30 days	for 30 days		days

VTE: venous thromboembolism; LMWH: low-molecular weight heparin.

Figure 2 exposes the risk of bias associated with each of the trials: the RECORD trials (Eriksson, Lassen, and Turpie) were double-blinded RCTs, and therefore presented a low risk of performance and detection bias. In contrast, Zhao, Rahman, and Malavasi were open-label studies which resulted in a high risk of bias for blinding of participants and personnel. Indeed, these three open-label trials were small single-center designs, which inherently increases their risk of bias.

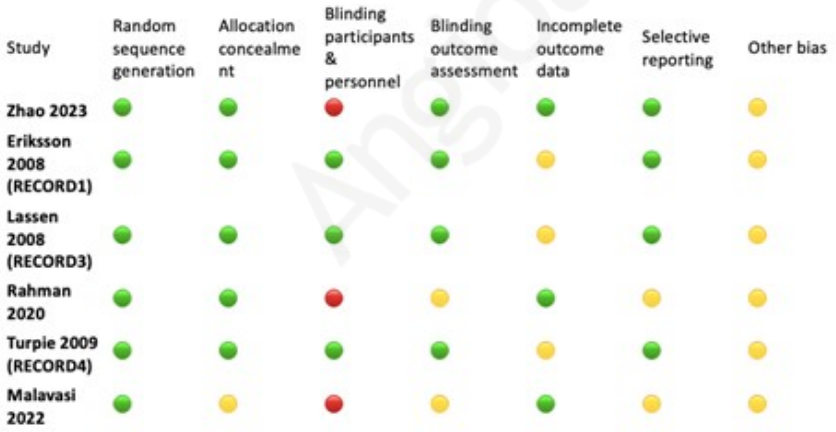

Figure 2. Risk of bias of the included trials

Outcome of interest

In terms of efficacy, figure 3 shows that patients under prophylaxis with rivaroxaban ($n = 3,778$) had a significantly lower incidence of VTE compared to those under LMWH ($n = 3,792$) (OR, 95 %CI, 0.54 [0.30-0.98]), 95 %PI: 0.23-1.26). This effect remained somewhat constant within the subgroup of four studies conducted in orthopedic surgery, although statistical significance was not retained (OR, 95 %CI, 0.51 [0.15-1.74], 95 %PI: 0.12-2.15).

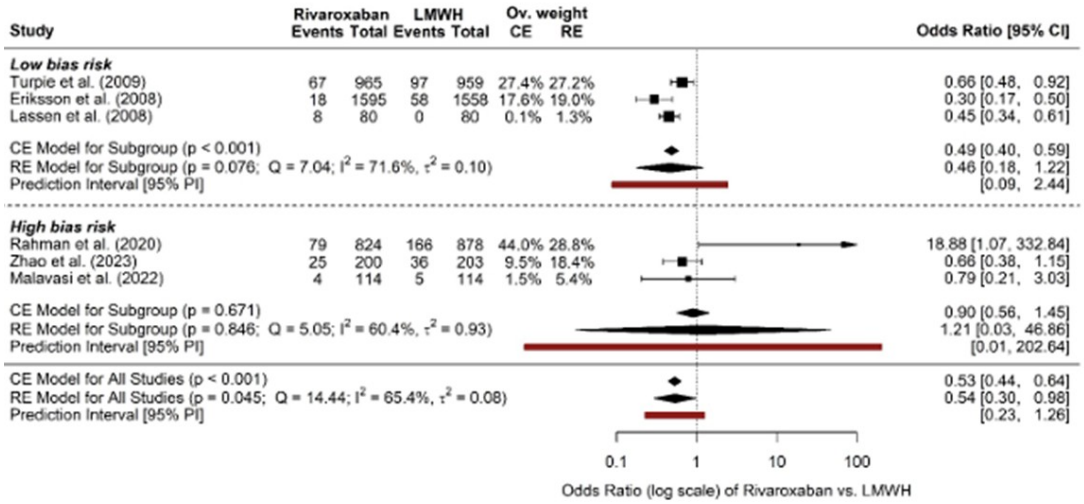

Figure 3. Forest Plot with direct contrast comparing efficacy in venous thromboembolism prevention with rivaroxaban vs. LMWH.

Leave-one-out sensitivity analyses did not reveal highly influential studies, including the one by Rahman (2020) RCT in which no VTE in the LMWH has recorded. Overall summary effect estimates (in the OR scale) remained within 0.50 and 0.60 and heterogeneity either increased or decreased slightly (the I^2 remained between 52.5 %—after excluding the aforementioned study by Rahman *et al.*- and 71.6 %—after excluding the aforementioned study by Malavasi *et al.* Overall estimates also remained constant after removing studies at high risk of bias (OR, 95 %CI 0.46 [0.18-1.22], 95 %PI: 0.09-2.44), but no whithin the latter subset (Fig. 4).

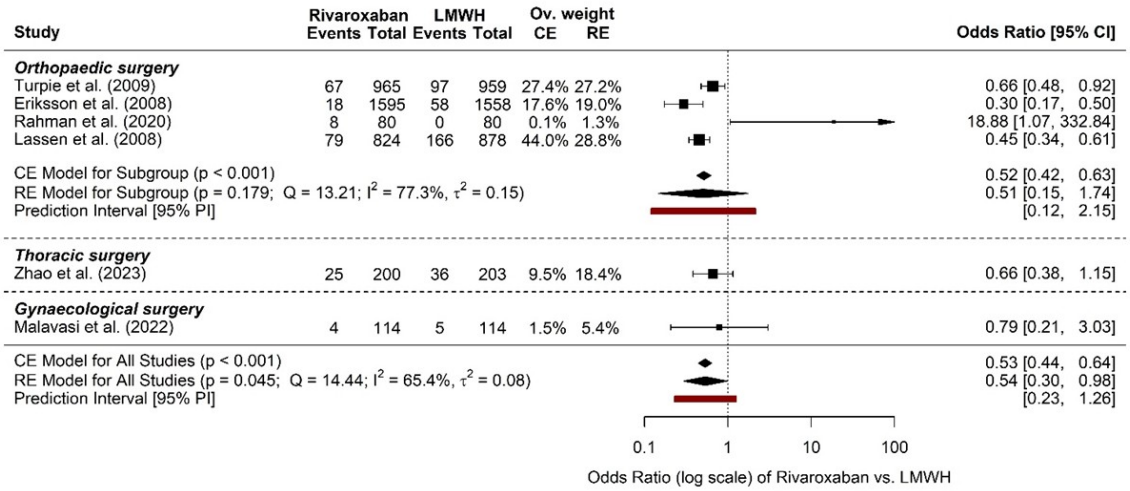

Figure 4. Forest Plot with direct contrasts comparing efficacy with rivaroxaban vs. LMWH stratified by risk of bias.

However, in terms of safety, rivaroxaban had a non-significant higher incidence of bleedings compared to LMWH (OR, 95 %CI 1.72 [0.75-3.94]), as is shown in figure 5.

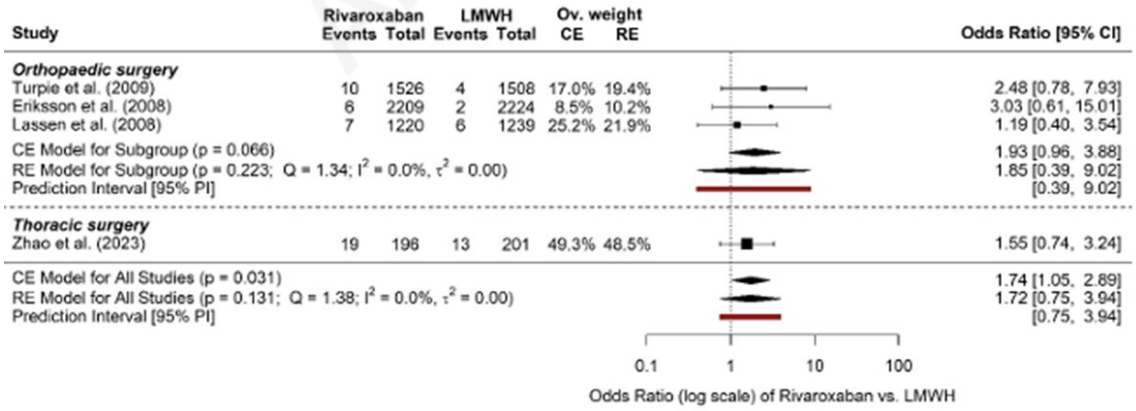

Figure 5. Forest plot with direct contrasts comparing safety with rivaroxaban vs. LMWH.

DISCUSSION

The present systematic review and meta-analysis found that patients under postoperative prophylaxis with rivaroxaban had a significant lower incidence of VTE compared to those under LMWH (OR, 95 %CI

0.54 [0.30;0.98]). However, since the prediction interval crossed the null value (1) in the OR scale (0.23-1.26), this effect may not be consistent across all study settings and populations. Regarding safety, rivaroxaban had a non-significant higher incidence of bleedings compared to LMWH (OR, 95 %CI 1.72 [0.75-3.94]).

VTE is a frightening complication after surgery due to its high morbi-mortality, and therefore pharmacological thromboprophylaxis is widely used after certain interventions (1). Classically, LMWH has been the drug of choice for VTE prevention. However, over the past decade, DOACs have been increasingly used due to their oral administration, which likely improves patient's adherence (7,8,10). Rivaroxaban, which is administered once daily and does not need bridging therapy with LMWH, has become the most widely used DOAC in prophylaxis, followed by apixaban, which although does not need bridging therapy, is administered twice daily (16,17). In a systematic review and meta-analysis exclusively conducted in thromboprophylaxis after orthopedic surgery, rivaroxaban was associated with a lower VTE incidence than with LMWH and apixaban. However, the bleeding risk was higher with rivaroxaban than with LMWH and apixaban (26). These results are consistent with those found in our study, in which rivaroxaban had a lower VTE incidence with higher bleeding rates. Beyond the prophylactic setting, in VTE treatment (both in cancer and non-cancer associated thrombosis), DOACs had a higher efficacy in preventing VTE recurrence, although rivaroxaban had shown a slightly higher incidence of bleedings, compared with other DOACs, such as apixaban (27,28).

Recently, the first RCT comparing bleeding events with rivaroxaban and apixaban in VTE treatment has been published: among patients with acute VTE, the risk of clinically relevant bleeding was significantly lower with apixaban than rivaroxaban during the 3-month treatment period (29). A possible mechanism that would explain the lower bleeding rates with apixaban would be that rivaroxaban is absorbed mainly in the stomach and requires high local

concentrations for absorption. In contrast, apixaban exhibits a more distributed absorption pattern along the gastrointestinal tract, and does not depend on high luminal peak concentrations. In addition, as apixaban is administered twice daily, it achieves more stable plasma concentrations compared with rivaroxaban, which is administered once daily (30). However, these results are not in VTE prophylaxis but in treatment; therefore, caution should be exercised when extrapolating these findings to the prophylaxis setting, as drug doses, duration, and patient populations are substantially different.

Our study has limitations. The number of included studies was only six, and three of them had high risk of bias regarding the blinding of participants and personnel. With only six studies, even using the Hartung-Knapp method, methodological limitations have to be considered. Indeed, with this number of studies no formal evaluation of publication bias with funnel plot or Egger test could be conducted. In turn, heterogeneity was substantial, and did not decrease when analyses were restricted to studies conducted in orthopedic surgery, or with a low risk of bias. Although the effects within these subgroups remained constant (and similar to the corresponding common (fixed) effect estimates), providing support to the main finding of a reduced VTE risk associated with rixaroxaban, prediction intervals spanning the value 1 caution that it may not apply to some settings or population niches, which should be investigated in future studies. Indeed, our search was limited to English language publications; thus, non-English language RCTs might have been overlooked.

CONCLUSIONS

The available evidence suggests that rivaroxaban is more effective in preventing venous thromboembolism after surgery than low molecular weight heparin, although it is associated with a higher risk of bleeding. However, the results should be interpreted with caution, and further research is needed.

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