Anticoagulantes orales de acción directa y trombosis asociada a cáncer: revisión sistemática y metaanálisis de redes

Direct oral anticoagulants and cancer associated thrombosis: systematic review and network meta-analysis

10.20960/angiologia.00837

03/02/2026

Direct oral anticoagulants and cancer associated thrombosis: systematic review and network meta-analysis

Anticoagulantes orales de acción directa y trombosis asociada a cáncer: revisión sistemática y metaanálisis de redes

Albert González-Sagredo[1,2], Jaime Hospedales[1,2], Jesús Villoria[3], Sebastián Videla[4-6,]

[1]Angiology, Vascular and Endovascular Surgery Department. Hospital Quironsalud del Vallés. Sabadell. Barcelona, Spain. [2]Angiology, Vascular and Endovascular Surgery Department. Hospital Universitari Sagrat Cor. Barcelona, Spain. [3]Department of Design and Biometrics. Medicxact. Alpedrete. Madrid, Spain. [4]Department of Pharmacology, Therapeutics and Toxicology. Universitat Autònoma de Barcelona. Bellaterra. Barcelona, Spain. [5]Neuropharmacology & Pain Group. Neuroscience Program. Bellvitge Biomedical Research Institute. L'Hospitalet de Llobregat. Barcelona, Spain. [6]Clinical Research Support Area. Clinical Pharmacology Department. Hospital Universitari Germans Trias i Pujol. Badalona. Barcelona, Spain

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

Received: 11/19/2025
Accepted: 01/12/2026

Conflicts of interest: The authors declare no conflicts of interest.
Artificial intelligence: The authors declare that no artificial intelligence (AI) or any AI-based tool was used in the preparation of this manuscript.

ABSTRACT

Introduction and objective: The aim is to analyze which is the best direct oral anticoagulant in terms of safety/efficacy for deep vein thrombosis treatment in oncological patients.

Methods: This meta-analysis is reported in accordance with Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. Ethical approval was not required for this work. Inclusion criteria were randomized controlled trials comparing low-molecular weight heparin (LMWH) vs. direct oral anticoagulant for the treatment of cancer-associated thrombosis. We included all direct oral anticoagulants independent of their mechanism of action (factor II and factor X inhibitors). MEDLINE and SCOPUS electronic databases were searched. A fixed and random effects model was performed. Efficacy outcome was rethrombosis incidence and safety outcome was major bleedings.

Results: A total of 1276 studies were analyzed, from which 1272 were excluded by tittle/abstract. 4 randomized controlled trials met inclusion criteria, with a total of 2894 patients. Apixaban ($n = 721$) was compared to low-molecular weight heparin ($n = 721$), edoxaban ($n = 522$) vs. LMWH ($n = 524$), and rivaroxaban ($n = 203$) vs. LMWH ($n = 203$). The results showed that the incidence of rethrombosis was lower with any DOAC than with LMWH, without significant differences between them. However, in terms of security, edoxaban (OR 1.77 [1.02-3.08]) and rivaroxaban (OR 1.88 [0.68-5.19]) had a higher bleeding incidence than LMWH, while apixaban showed a similar safety profile compared to LMWH (OR 0.90 [0.50-1.62].

Conclusion: Apixaban has the best profile in terms of efficacy and safety for the treatment of cancer-associated thrombosis.

Keywords: Venous thromboembolism. Cancer-associated thrombosis. Direct oral anticoagulants. Low-molecular weight heparin.

RESUMEN

Introducción y objetivo: analizar cuál es el anticoagulante oral de acción directa con mejor relación eficacia/seguridad en el tratamiento de la trombosis venosa asociada a cáncer.

Métodos: este metaanálisis ha sido reportado en adherencia a guías PRISMA. Los criterios de inclusión fueron aquellos ensayos clínicos aleatorizados que compararan heparina de bajo peso molecular (HBPM) con anticoagulante oral (NACO) para el tratamiento de la trombosis venosa profunda asociada a cáncer. Se incluyeron todos los anticoagulantes orales, independientemente de su mecanismo de acción. Se realizó la búsqueda bibliográfica en las bases de datos de MEDLINE y SCOPUS. Para el análisis estadístico se realizó un modelo de efectos fijos y aleatorios.

Resultados: se analizó un total de 1276 estudios, de los que se excluyeron 1272 por título/*abstract*. Cuatro ensayos clínicos cumplieron los criterios de inclusión, sumando un total de 2894 pacientes. Apixabán ($n = 721$) fue comparado con HBPM ($n = 721$), edoxabán ($n = 522$) con HBPM ($n = 524$) y rivaroxabán ($n = 203$) con HBPM ($n = 203$). Los resultados demostraron que la incidencia de retrombosis fue menor con cualquier NACO que con HBPM, sin diferencias estadísticamente significativas entre NACO. Sin embargo, en términos de seguridad, edoxabán (OR 1,77 [1,02-3,08]) y rivaroxabán (OR 1,88 [0,68-5,19]) presentaron una tasa mayor de sangrados que HBPM, mientras que apixabán tuvo un perfil de seguridad similar a HBPM (OR 0,90 [0,50-1,62].

Conclusión: apixabán presenta el mejor perfil de seguridad y eficacia para el tratamiento de la trombosis venosa profunda asociada a cáncer.

Palabras clave: Trombosis Venosa Profunda. Trombosis asociada a cáncer. Anticoagulantes orales de acción directa. Heparina de bajo peso molecular.

INTRODUCTION

Venous thromboembolism (VTE), which includes deep-vein thrombosis, superficial-vein thrombosis, and pulmonary embolism, is a frequent complication in patients with cancer, and it is associated with poorer prognosis (1). The primary modality treatment is anticoagulant therapy for at least 3 months (2,3). Effective treatment of VTE relies on a balance between the prevention of recurrence and the incidence of bleeding complications (4). In patients with cancer, management of VTE may be especially difficult, as this population has high risk of both recurrent events and major hemorrhages (5).

Direct oral anticoagulants (DOAC) are nowadays recommended as first line treatment for VTE in non-cancer patients (2,6-8). They can be classified between direct factor Xa inhibitors (apixaban, rivaroxaban, and edoxaban) and direct factor II inhibitor (dabigatran). They all have better safety/efficacy profile than classical ones (subcutaneous low molecular weight heparin (LMWH) or unfractioned heparin, and vitamin K antagonist) (2,6). They have a predictable effect, the administration is oral, there is no need for frequent monitoring, and the number of drug interactions is limited. This has been confirmed in several randomized controlled trials [RCT] (9-13) and meta-analysis (14-19).

However, in cancer-associated thrombosis (CAT) guidelines still recommend LMWH owing to the scarce cancer-specific data regarding the anticoagulant of choice (2,20). As an oral treatment instead of subcutaneous injection, DOACs could be specially interesting for patients with cancer, as they have higher anticoagulation interruption and discontinuation rates that people without cancer (21). During last years, different RCTs comparing CAT treatment (DOACs vs. LMWH) have been conducted (22-25), demonstrating similar efficacy between DOAC and LMWH in terms of VTE recurrence, which has been confirmed in different meta-analysis (26-28). Nonetheless, the main concern with DOACs and patients with active cancer, is that they could increase bleeding rates (8). There is a network meta-analysis in

patients without cancer suggesting that apixaban is associated with a lower risk of major or clinically relevant non-major bleeding than other (14).

To the best of our knowledge, regarding specific cancer-data, there is only one network meta-analysis published in the literature comparing different DOACs in CAT treatment (29). It studied only direct factor X inhibitors and was published in 2021. Therefore, we considered necessary to conduct this updated network meta-analysis without any exclusion criteria regarding the type of DOAC (factor X or factor II inhibitors).

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) 2020 guidelines (30). Ethical approval was not required for this work. PROSPERO registration was attempted but not accepted due to the existence of a closely related systematic review on the same topic.

Eligibility criteria

The inclusion criteria were RCTs comparing LMWH vs. DOAC for the treatment of cancer associated thrombosis. All DOACs, irrespective of their mechanism of action were included. There was no restriction on year of publication. Exclusion criteria were non-English RCTs, studies conducted in children, conference abstracts, systematic reviews, case reports, non-interventional, and pre-clinical studies.

Data sources and search criteria

A systematic literature search was performed in MEDLINE and SCOPUS based on the PRISMA 2020 guidelines. The search stratedy included controlled terms from the Medical Subject Headings (MeSH) thesaurus, as well as free-text keywords. MeSH terms and keywords were combined using Boolean operators (AND/OR). The search

strategies are presented in table I. 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. 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 (31).

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 (32). The risk of bias was assessed by the Cochrane risk-of-bias tool for RCTs (RoB2) (32). 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 (32). Each item was classified as low-risk, high-risk, or raising some concerns. Discrepancies were settled by a third reviewer.

Statistical analysis

Statistical analyses were conducted using R® version 4.2 for Windows® [R Foundation for Statistical Computing, Vienna, Austria) with the *net-meta* package (version 3.2-0). The study characteristics, and patient demographics were reported descriptively. Dichotomous data were synthesized as treatment odds ratio (OR) with asymptotic 95%CI to assess the study-wise treatment effects. We used a frequentist graph-theoretical approach for network meta-analysis based on the inverse variance method to calculate the common effect estimate. Both classic fixed-effects and, two-level DerSimonian-Laird random effects models were fitted to account for inter-study heterogeneity. For the random case, heterogeneity was assessed by calculating the I^2 index.

Unit of analysis issue

For crossover studies, we used data from the first treatment period. If the trials were assessed in more than one control group, we implemented the primary analysis to combine the data from each control group. Each patient was evaluated only once during the analyses.

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

A total of 1276 records were retrieved by literature search, and as shown in the PRISMA Flow Diagram (30) (Fig. 1), among the studies screened, four trials met inclusion criteria (9,22-25).

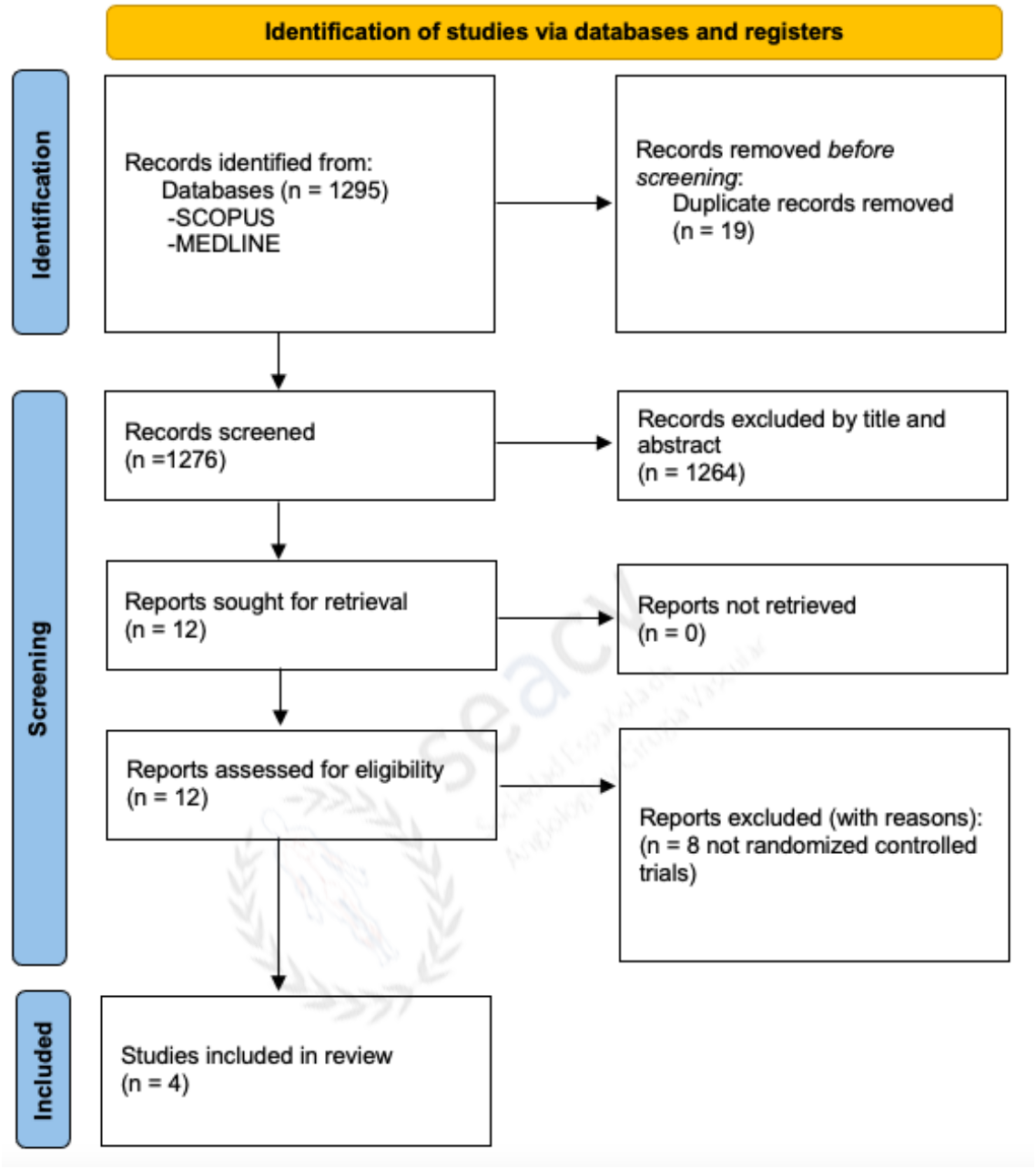

Figure 1. PRISMA flow diagram.

Study characteristics and risk of bias assessment

All four articles were parallel-group RCTs. Three studies were conducted in America, one in Europe, totalizing of 2894 patients (Fig. 2).

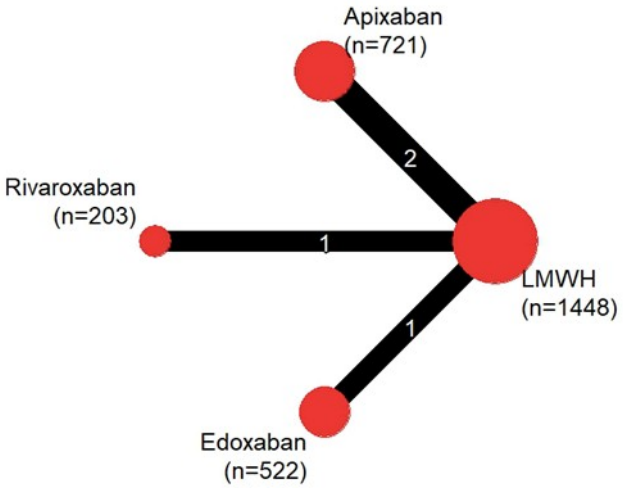

Figure 2. Network description.

Table I summarises the characteristics of the included RCTs. Inter-study heterogeneity was low (I^2 = 2.5%). In McBane's study (25), the most frequent cancers were lung (34.6%), colorectal (31.8%), pancreatic/hepatobiliary (31.8%), breast (19%), gynecologic (19.6%), genitourinary (18%), lymphoma (10.9%), and upper gastrointestinal (7.5%). In Agnellis' study (24), the most frequent cancers were colorectal (40.5%), lung (34.6%), breast (26.8%), genitourinary (24.1%), gynecological (20.6%), pancreatic or hepatobiliary (15%), hematological (14.7%), and upper gastrointestinal (9.4%). In Young's study (23), the most frequent cancers were colorectal (50%), lung (23%), breast (20%), ovarian (15%), pancreatic (14%), and hematological (14%). In Raskob's trial (22), the most frequent cancers were colorectal (31%), lung (29.1%), genitourinary (26%), breast (23.8%), gynecological (23%), hematological (21.2%), pancreatic or hepatobiliary (16%), and upper gastrointestinal (10.3%).

Table I. Characteristics of the included studies

Reference	Year	Country	Type of study	Intervention	Comparison	No of patients
McBane	**2019**	**USA**	**RCT**	**Apixaban**	**LMWH**	**287**
Agnelli	**2020**	**Italy**	**RCT**	**Apixaban**	**LMWH**	**1155**
Young	**2018**	**USA**	**RCT**	**Rivaroxaban**	**LMWH**	**406**
Raskob	**2017**	**USA**	**RCT**	**Edoxaban**	**LMWH**	**1046**

RCT: randomized clinical trial; LMWH: low-molecular weight heparin.

All trials had low risk of selection and reporting bias, while they had high risk of performance bias. One study had low risk of detection and attrition bias (23), while the other three had moderate risk (22,24,25). The overall certainty of evidence was moderate.

Outcome of interest

Apixaban ($n = 721$) was compared to low-molecular weight heparin ($n = 721$), edoxaban ($n = 522$) vs. LMWH ($n = 524$), and rivaroxaban ($n = 203$) vs. LMWH ($n = 203$). The results showed that the incidence of rethrombosis was lower with any DOAC than with LMWH, without significant differences between them, in both direct (Fig. 3) and indirect contrast (Fig. 4).

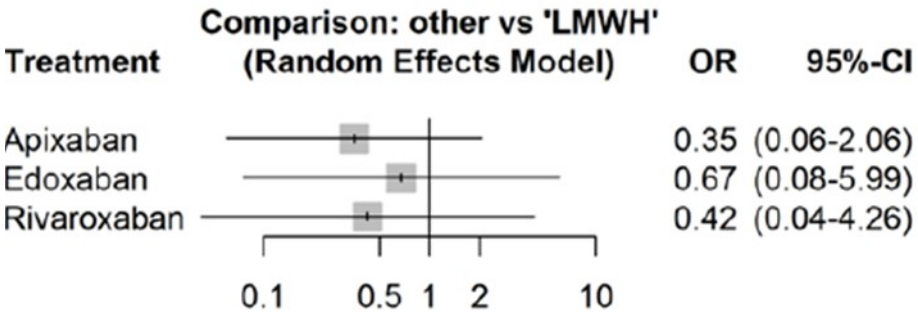

Figure 3. Forest Plot with direct contrast comparing efficacy in rethrombosis prevention with LMWH vs. DOACs.

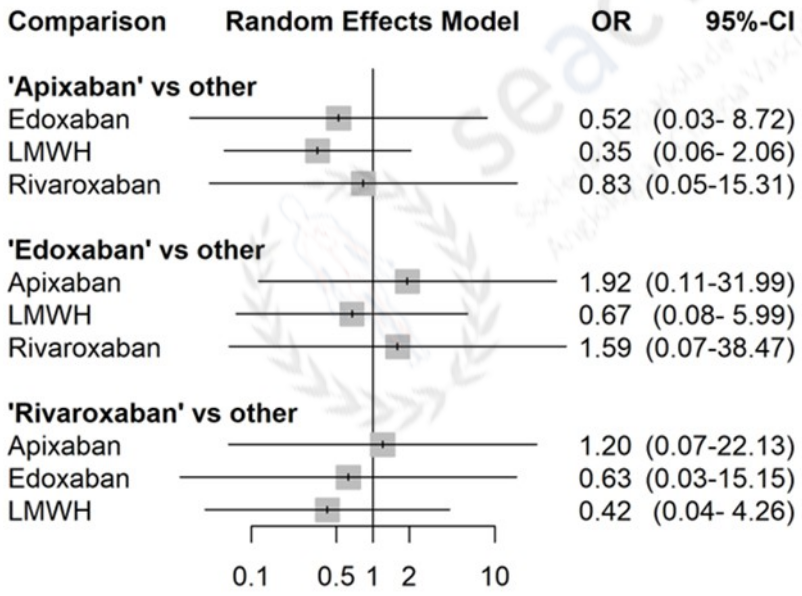

Figure 4. Forest Plot with indirect contrast comparing efficacy in rethrombosis prevention with LMWH vs. DOACs.

However, in terms of security, edoxaban (OR 1.77 [1.02-3.08]) and rivaroxaban (OR 1.88 [0.68-5.19]) had a higher bleeding incidence than LMWH, while apixaban showed a similar safety profile compared to LMWH (OR 0.90 [0.50-1.62], as we can see in both direct (Fig. 5) and indirect contrast (Fig. 6).

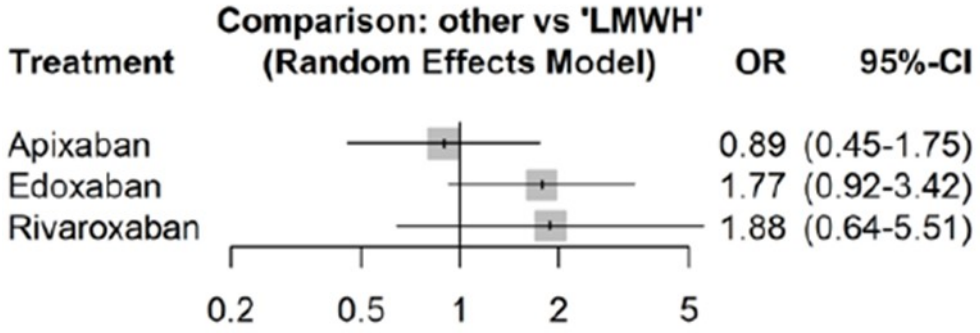

Figure 5. Forest Plot with direct contrasts comparing safety with LMWH vs. DOACs.

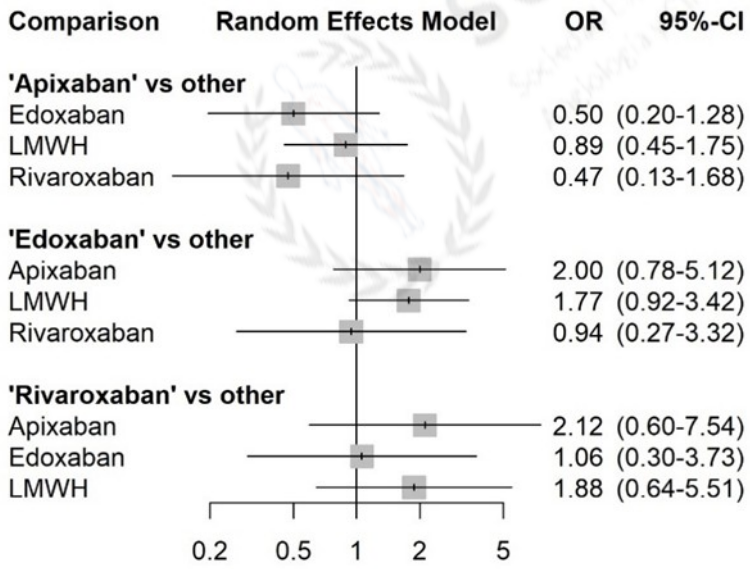

Figure 6. Forest plot with indirect contrasts comparing safety with LMWH vs. DOACs.

DISCUSSION

The present systematic review and network meta-analysis found that in cancer-associated thrombosis, DOACs have higher efficacy in rethrombosis prevention than LWMH. However, they are associated

with more bleedings except for apixaban, which has shown to be the most adequate choice in terms of efficacy and safety.
DOACs are the treatment of choice of VTE as has been reflected in recent guidelines, as they have a predictable effect, the administration is oral, there is no need for frequent monitoring, and the number of drug interactions is limited (2,6-8). Edoxaban and dabigatran required parenteral anticoagulation before being started. However, apixaban and rivaroxaban are started without initial parenteral therapy, but require higher doses (10 mg b.d for seven days, followed by 5 mg b.d for apixaban, and 15 mg b.d for three weeks, followed by 20 mg o.d for rivaroxaban).

However, for VTE in oncological patients, guidelines recommend LMWH as the treatment of choice for cancer-associated thrombosis (2,20). One of the main reasons is that LMWH is reliable in patients who have difficulty with oral therapy (eg, vomiting), and is considered safer in terms of bleedings in this subtype of patients (2), although in the past years this theoretical benefit of LMWH has not been confirmed in recent RCTs (22-25). The studies have shown that DOACs are more effective than LMWH, which has been confirmed by two systematic reviews and meta-analysis (26,28).
Nonetheless, the main concern with DOACs in oncological patients is the bleeding incidences, as they could be increased (8). In a network meta-analysis in patients without cancer they found that apixaban is the DOAC with a lower bleeding risk, comparable to LMWH (14). Afterwards, a network meta-analysis was performed by Sampaio *et al* in patients with cancer demonstrating the same results: apixaban was the drug with the best safety profile (29), although they only included studies with direct factor X inhibitors and was published in 2021. That is the reason why we have conducted this updated network meta-analysis without any exclusion criteria regarding the type of DOAC (factor X or factor II inhibitors), and our results are consistent with those previously published.

Our study has limitations. The evidence regarding this topic is scarce, as only four RCTs could be included, with an overall quality considered moderate. The absence of PROSPERO registration may be considered a limitation; however, the eligibility criteria and search strategy were defined a priori and followed throughout the study, in accordance with PRISMA recommendations. Indeed, only MEDLINE and SCOPUS were searched. Finally, our search was limited to English language publications; thus, non-English language RCTs might have been overlooked.

CONCLUSIONS

The available evidence suggests that apixaban is the drug with a higher efficacy and a lower bleeding risk for treatment of cancer-associated thrombosis. However, the results should be interpreted with caution, and further research is needed.

REFERENCES

1. Sørensen HT, Mellemkjaer L, Olsen JH, et al. Prognosis of cancers associated with venous thromboembolism. N Engl J Med 2000;343(25):1846-50. DOI: 10.1056/NEJM200012213432504
2. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest 2016;149(2):315-52. DOI: 10.1016/j.chest.2015.11.026
3. Torbicki A, Perrier A, Konstantinides S, et al. Guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J 2008;29(18):2276-315. DOI: 10.1093/eurheartj/ehn310
4. Hass B, Pooley J, Harrington AE, et al. Treatment of venous thromboembolism - effects of different therapeutic strategies on bleeding and recurrence rates and considerations for future anticoagulant management. Thromb J 2012;10(1):1. DOI: 10.1186/1477-9560-10-24
5. Napolitano M, Saccullo G, Malato A, et al. Optimal duration of low

molecular weight heparin for the treatment of cancer-related deep vein thrombosis: The cancer-DACUS study. J Clin Oncol 2014;32(32):3607-12. DOI: 10.1200/JCO.2013.51.7433

6. Kakkos SK, Gohel M, Baekgaard N, et al. Editor's Choice – European Society for Vascular Surgery (ESVS) 2021 Clinical Practice Guidelines on the Management of Venous Thrombosis. Eur J Vasc Endovasc Surg 2021;61(1):9-82. DOI: 10.1016/j.ejvs.2020.09.023
7. Ortel TL, Neumann I, Ageno W, et al. American society of hematology 2020 guidelines for management of venous thromboembolism: Treatment of deep vein thrombosis and pulmonary embolism. Blood Adv 2020;4(19):4693-738. DOI: 10.1182/bloodadvances.2020001830
8. National Institute for Health and Care Excellence. Venous thromboembolic diseases : diagnosis , management and thrombophilia testing. NICE Guidel 2015;(November):12-5.
9. Scott D, Brenner B, Buller HR, et al. Oral Rivaroxaban for Symptomatic Venous Thromboembolism. N Engl J Med 2010;363(26):2499-510. DOI: 10.1056/nejmoa1007903
10. Gallus AS, Johnson M, Masiukiewicz U, et al. Oral apixaban for the treatment of acute venous thromboembolism. Zeitschrift fur Gefassmedizin 2013;10(3):25-6. DOI: 10.1056/nejmoa1302507
11. Edoxaban versus Warfarin for the Treatment of Symptomatic Venous Thromboembolism. N Engl J Med 2013;369(15):1406-15. DOI: 10.1056/nejmoa1306638
12. Schulman S, Kearon C, Kakkar AK, et al. Extended Use of Dabigatran, Warfarin, or Placebo in Venous Thromboembolism. N Engl J Med 2013;368(8):709-18. DOI: 10.1056/nejmoa1113697
13. Liakishev AA. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. Results of the RE-COVER study. Kardiologiia 2010;50(3):80-1.
14. Cohen AT, Hamilton M, Mitchell SA, et al. Comparison of the novel oral anticoagulants apixaban, dabigatran, edoxaban, and

rivaroxaban in the initial and long-term treatment and prevention of venous thromboembolism: Systematic review and network meta-analysis. PLoS One 2015;10(12):1-14. DOI: 10.1371/journal.pone.0144856

15. Fox BD, Kahn SR, Langleben D, et al. Efficacy and safety of novel oral anticoagulants for treatment of acute venous thromboembolism: Direct and adjusted indirect meta-analysis of randomised controlled trials. BMJ 2012;345(7884):1-10. DOI: 10.1136/bmj.e7498
16. Kang N, Sobieraj DM. Indirect treatment comparison of new oral anticoagulants for the treatment of acute venous thromboembolism. Thromb Res 2014;133(6):1145-51. DOI: 10.1016/j.thromres.2014.03.035
17. Kakkos SK, Kirkilesis GI, Tsolakis IA. Editor's choice - Efficacy and safety of the new oral anticoagulants dabigatran, rivaroxaban, apixaban, and edoxaban in the treatment and secondary prevention of venous thromboembolism: A systematic review and meta-analysis of phase III trials. *E*ur J Vasc Endovasc Surg 2014;48(5):565-75. DOI: 10.1016/j.ejvs.2014.05.001
18. Van der Hulle T, Kooiman J, Den Exter PL, et al. Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: A systematic review and meta-analysis. J Thromb Haemost 2014;12(3):320-8. DOI: 10.1111/jth.12485
19. Castellucci LA, Cameron C, Le Gal G, et al. Clinical and safety outcomes associated with treatment of acute venous thromboembolism: A systematic review and meta-analysis. JAMA 2014;312(11):1122-35. DOI: 10.1001/jama.2014.10538
20. Khorana AA, Noble S, Lee AYY, et al. Role of direct oral anticoagulants in the treatment of cancer-associated venous thromboembolism: guidance from the SSC of the ISTH. J Thromb Haemost 2018;16(9):1891-4. DOI: 10.1111/jth.14219

21. Yamashita Y, Morimoto T, Amano H, et al. Anticoagulation therapy for venous thromboembolism in the real world: From the command vte registry. Circ J 2018;82(5):1262-70. DOI: 10.1253/circj.CJ-17-1128
22. Raskob GE, Van Es N, Verhamme P, et al. Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism. N Engl J Med 2018;378(7):615-24. DOI: 10.1056/NEJMoa1711948
23. Young AM, Marshall A, Thirlwall J, et al. Comparison of an oral factor xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: Results of a randomized trial (SELECT-D). J Clin Oncol 2018;36(20):2017-23. DOI: 10.1200/JCO.2018.78.8034
24. Agnelli G, Becattini C, Meyer G, et al. Apixaban for the Treatment of Venous Thromboembolism Associated with Cancer. N Engl J Med 2020;382(17):1599-607. DOI: 10.1056/nejmoa1915103
25. McBane RD, Wysokinski WE, Le-Rademacher JG, et al. Apixaban and dalteparin in active malignancy-associated venous thromboembolism: The ADAM VTE trial. J Thromb Haemost 2020;18(2):411-21. DOI: 10.1111/jth.14662
26. Mulder FI, Bosch FTM, Young AM, et al. Direct oral anticoagulants for cancer-associated venous thromboembolism: a systematic review and meta-analysis. Blood 2020;136(12):1433-41. DOI: 10.1182/blood.2020005819
27. Wang X, Ma Y, Hui X, et al. Oral direct thrombin inhibitors or oral factor Xa inhibitors versus conventional anticoagulants for the treatment of deep vein thrombosis. Cochrane Database Syst Rev 2023;2023(4). DOI: 10.1002/14651858.CD010956.pub3
28. Fujisaki T, Sueta D, Yamamoto E, et al. Comparing Anticoagulation Strategies for Venous Thromboembolism Associated With Active Cancer: A Systematic Review and Meta-Analysis. JACC CardioOncology 2024;6(1):99-113. DOI: 10.1016/j.jaccao.2023.10.009

29. Sampaio Brandão GM, Malgor RD, Vieceli T, et al. A network meta-analysis of direct factor Xa inhibitors for the treatment of cancer-associated venous thromboembolism. Vascular 2022;30(1):130-45. DOI: 10.1177/17085381211002726
30. Page MJ, Mckenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement : an updated guideline for reporting systematic reviews Systematic reviews and Meta-Analyses. BMJ 2021;372:n71. DOI: 10.1136/bmj.n71
31. Weitz JI, Lensing AWA, Prins MH, et al. Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism. N Engl J Med 2017;376(13):1211-22. DOI: 10.1056/nejmoa1700518
32. Jpt H, Thomas J, Chandler J, et al. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022). Cochrane, 2022. Disponible en: www.training.cochrane.org/handbook. 2022;3(February):2022.