



FACULTAD DE CIENCIAS DE LA SALUD
CARRERA PROFESIONAL DE MEDICINA HUMANA

**“EFICACIA DEL APIXABAN VERSUS DALTEPARINA COMO
TRATAMIENTO DE LA TROMBOEMBOLIA VENOSA
ASOCIADA AL CÁNCER: REVISIÓN SISTEMÁTICA”**

Tesis para optar el grado académico de:

**MAESTRO EN EPIDEMIOLOGÍA CLÍNICA Y
BIOESTADÍSTICA**

Presentado por:

Miguel Angel Arce Huamani (0000-0003-3185-4861)

Asesor:

Jorge Luis Maguiña Quispe (0000-0002-4136-7795)

Lima – Perú

2024

ACTA DE SUSTENTACIÓN

Lima, 19 de enero de 2024.

Los integrantes del Jurado de tesis:

Presidente: Dra. Leda Yamileé Hurtado Roca
Miembro: Maestro Franco Ronald Romaní Romaní
Miembro: Maestro Fernando Miguel Runzer Colmenares

Se reúnen para evaluar la tesis titulada: **“EFICACIA DEL APIXABAN VERSUS DALTEPARINA COMO TRATAMIENTO DE LA TROMBOEMBOLIA VENOSA ASOCIADA AL CÁNCER: REVISIÓN SISTEMÁTICA”**

Presentada por **Miguel Angel Arce Huamaní** .

Para optar por el Grado de **Maestro en Epidemiología Clínica y Bioestadística**.

Con la asesoría de: **Maestro Jorge Luis Maguiña Quispe**.

Luego de haber evaluado el informe final de tesis y evaluado su desempeño en la sustentación, concluyen de manera unánime calificar a:

Tesis: Miguel Angel Arce Huamaní .			Nota (en letras): QUINCE
Aprobado (X)	Aprobado - Muy buena ()	Aprobado - Sobresaliente ()	Desaprobado ()

Los miembros del jurado firman en señal de conformidad.



Dra. Leda Yamileé Hurtado Roca
Presidente del Jurado



Maestro Jorge Luis Maguiña Quispe
Asesor



Maestro Fernando Miguel Runzer Colmenares
Miembro



Maestro Franco Ronald Romaní Romaní
Miembro

UNIVERSIDAD CIENTÍFICA DEL SUR
DECLARACIÓN DE ORIGINALIDAD DE CONTENIDO DE INFORME FINAL
DE TESIS¹³

Lima, 23 de octubre del 2023

Señor,
Carlos Zavalaga
Director General de Investigación, Desarrollo e Innovación
Universidad Científica del Sur
Presente. –

De nuestra consideración,

Yo: Miguel Angel Arce Huamani, egresado de la Maestría en Epidemiología Clínica y Bioestadística de la Universidad Científica del Sur, en conjunto con el asesor de tesis Jorge Luis Maguiña Quispe, declaramos que este informe final de tesis titulado: Eficacia del Apixaban versus Dalteparina como Tratamiento de la Tromboembolia Venosa Asociada al Cáncer: Revisión Sistemática, sustentado para obtener el grado de Magister es original.

Es decir, no contiene plagio parcial ni total, cuando se utilizó información de fuentes externas se reconoció la autoría mediante la adecuada citación y los resultados obtenidos son producto entero de mi investigación y no han sido falseados ni fabricados. Todo esto en cumplimiento del Código de ética en la investigación, Reglamento del Comité de Integridad Científica, Reglamento de Propiedad Intelectual, Normas y procedimientos de los trabajos de investigación para la obtención de títulos profesionales y grados académicos ¹⁴, que afirmamos conocer en su totalidad.

Por ello, en caso de identificarse alguna situación de plagio, falsificación o fabricación de resultados, nos allanamos al proceso de investigación que establezca la Universidad y las posibles sanciones que pudieran surgir.

Firmamos en conformidad con lo declarado,



Firma tesista
DNI: 71469125



Firma del asesor de tesis
DNI: 42381675

¹³ En conformidad con la Resolución del Consejo Directivo N° 084-2022-SUNEDU/CD

¹⁴ Los documentos están en: <https://investigacion.cientifica.edu.pe/reglamentos/>

INFORME DE REVISIÓN DE ORIGINALIDAD

Título del documento evaluado. Eficacia del apixaban versus dalteparina como tratamiento de la tromboembolia venosa asociada al cáncer: revisión sistemática

Autores. Miguel Angel Arce Huamani

Mecanismo de revisión de originalidad. Evaluación con Turnitin (ID 2301801227).

Resultado de la evaluación. 9%

Revisado por. Magaly Kelly Guerrero Huaracallo.

Comentarios sobre la revisión. Filtros usados: excluir fuentes de menos de 12 palabras.



Índice

Índice	5
Resumen	6
Abstract	7
Versión aprobada para publicar en revista	8
Versión inicial enviada a publicar a revista	24
Copias de cartas de respuesta a las observaciones	42
Versión final posterior al levantamiento de las observaciones de los jurados en español	44
Anexos	62

Resumen

Antecedentes y objetivos

El tromboembolismo venoso (TEV) es común en pacientes con cáncer. La terapia anticoagulante con heparinas de bajo peso molecular (HBPM) y los anticoagulantes orales directos (ACOD), como dalteparina y apixaban, han demostrado eficacia y seguridad. Sin embargo, todavía se necesita más investigación comparativa sobre estos fármacos. Este estudio tuvo como objetivo sintetizar la evidencia sobre la eficacia de apixaban en comparación con dalteparina para reducir el TEV recurrente, el sangrado mayor y el sangrado no mayor clínicamente relevante asociado con el cáncer.

Materiales y métodos

Realizamos búsquedas sistemáticas en las bases de datos PubMed, Scopus, Web of Science, Embase, Cochrane Library y ClinicalTrials hasta el 5 de enero de 2023 para ensayos controlados aleatorizados que compararan apixaban frente a dalteparina como tratamiento para el TEV asociado al cáncer. Se incluyeron cinco estudios. Los efectos según los metaanálisis se informaron como riesgos relativos (RR) y sus intervalos de confianza del 95% (IC).

Resultados

Se encontró que 33 de 734 (4.5%) pacientes tratados con apixaban y 56 de 767 (7.3%) con dalteparina tuvieron TEV recurrente como un resultado de eficacia (RR 0.49, IC 95% 0.15–1.58, I² 38%). El sangrado mayor ocurrió en 25 de 734 pacientes tratados con apixaban (3.4%) y en 27 de 767 pacientes tratados con dalteparina (3.5%) (RR 1.29, IC 95% 0.31–5.27, I² 59%). De igual manera, el sangrado no mayor clínicamente relevante ocurrió en 64 de 734 pacientes tratados con apixaban (8.7%) y en 46 de 767 (5.9%) pacientes tratados con dalteparina (RR 1.52, IC 95% 1.05–2.19, I² 0%).

Conclusiones

El apixaban mostró un menor riesgo de TEV recurrente que la dalteparina en pacientes con TEV asociado al cáncer, aunque sin diferencia estadística. Se observó significación estadística para el sangrado no mayor clínicamente relevante pero no para el sangrado mayor.

Abstract

Background and Objectives: Venous thromboembolism (VTE) is common in cancer patients. Anticoagulant therapy with low-molecular-weight heparins (LMWHs) and direct oral anticoagulants (DOACs), such as dalteparin and apixaban, have demonstrated efficacy and safety. However, more comparative research on these drugs is still needed. This study aimed to synthesize evidence on the efficacy of apixaban compared to dalteparin in reducing recurrent VTE, major bleeding, and clinically relevant non-major bleeding associated with cancer.

Materials and Methods: We systematically searched the PubMed, Scopus, Web of Science, Embase, Cochrane Library, and ClinicalTrials databases up to 5 January 2023 for randomized controlled trials comparing apixaban versus dalteparin as a treatment for cancer-associated VTE. Five studies were included. Effects according to meta-analyses were reported as relative risks (RRs) and their 95% confidence intervals (CIs).

Results: It was found that 33 of 734 (4.5%) patients treated with apixaban and 56 of 767 (7.3%) with dalteparin had recurrent VTE as an efficacy outcome (RR 0.49, 95% CI 0.15–1.58, I² 38%). Major bleeding occurred in 25 of 734 patients treated with apixaban (3.4%) and 27 of 767 patients treated with dalteparin (3.5%) (RR 1.29, 95% CI 0.31–5.27, I² 59%). Likewise, clinically relevant non-major bleeding occurred in 64 of 734 patients treated with apixaban (8.7%) and 46 of 767 (5.9%) patients treated with dalteparin (RR 1.52, 95% CI 1.05–2.19, I² 0%).

Conclusions: Apixaban showed a lower risk of recurrent VTE than dalteparin in patients with cancer-associated VTE, albeit with no statistical difference. Statistical significance was observed for no major clinically relevant bleeding but not for major bleeding.

Versión aprobada para publicar en revista

1. Introduction

Venous thromboembolism (VTE) is the third most important vascular disease in the general population. Cancer patients are 4 to 7 times more likely to develop VTE, with it being the second cause of death among these patients [1,2]. The incidence of recurrent VTE is 9.6%, reaching 22.1% in the first 6 months after the initial diagnosis of cancer [3]. Anticoagulant therapy is recommended to prevent VTE in high-risk patients (KHORANA score >2) and to treat those who have already had a thrombotic event [4]. However, this therapy carries a significant risk of bleeding, the most serious adverse reaction. Low- molecular-weight heparins (LMWHs) and direct oral anticoagulants (DOACs) are the most widely used anticoagulant treatments [3,5]. Dalteparin, an LMWH, is recommended in patients with cancer-related VTE, as it has been associated with a lower incidence of osteoporosis and heparin-induced thrombocytopenia [6]. Among DOACs, apixaban has been shown to have a lower risk of systemic cerebrovascular disease/embolism and major bleeding [7]. However, the cost of the aforementioned drugs is approximately USD 64 and USD 106 for apixaban and dalteparin, respectively, making access by the general public difficult [8,9]. Therefore, it is necessary to propose strategies for their acquisition.

Various studies have addressed DOACs and LMWHs as treatment for cancer-associated VTE [10,11], with new drugs such as apixaban and dalteparin having demonstrated efficacy and safety compared to other common treatments [12,13]. Regarding thromboprophylaxis, the efficacy and safety of apixaban have been reported in a randomized clinical trial (RCT) with 130 patients with gastrointestinal cancer, in whom it was shown to reduce the incidence of thromboembolism to 4.6% compared to 20% in the placebo group [14]. In another RCT, in 365 patients stratified according to the presence or absence of metastatic cancer, thromboprophylaxis with apixaban was associated with a significantly lower rate of VTE, with a hazard ratio of 0.55 and 0.34, respectively, compared to the placebo [15]. For its part, in an RCT in patients with VTE associated with gynecological cancer, dalteparin showed a lower occurrence of major bleeding in 5% compared to 7.8% in those who received rivaroxaban as treatment [16]. However, no study has synthesized the results of treatment with apixaban and dalteparin for VTE in cancer patients, which is important information.

Consequently, the study authors note that evaluation of the efficacy and safety of the treatment of VTE associated with cancer remains challenging due to the various studies available that expand the treatment options. Likewise, the adverse reactions of these treatments can be harmful for patients, making it important to synthesize the evidence between them. Apixaban and dalteparin have undergone several studies demonstrating their capacity to reduce major bleeding and the recurrence of VTE in cancer patients. However, despite the number of RCTs comparing these drugs with other LMWHs and DOACs, no study has compared the efficacy and safety of apixaban and dalteparin.

Therefore, the purpose of our study was to synthesize evidence on the efficacy and safety of apixaban versus dalteparin in reducing recurrent VTE, major bleeding, and

clinically relevant non-major bleeding associated with cancer.

2. Materials and Methods

We used the PRISMA report for systematic reviews, and meta-analyses [17] for writing our systematic review. The version of our protocol was registered in the International Prospective Register of Systematic Review (PROSPERO) with the code CRD42021275583.

2.1 Data Sources and Searches

From inception to 5 January 2023, we searched the following databases: PubMed, Scopus, Web of Science, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) for studies evaluating the efficacy of apixaban versus dalteparin as a treatment for cancer-associated VTE and conducted a search of ClinicalTrials to identify ongoing or completed RCTs related to our review. The decision was made to include dalteparin as the sole LMWH (control group) due to the lack of studies that exclusively compared these two drugs, both of which have shown promising results in cancer-associated VTE. This choice aims to maintain consistency within the comparison and reduce result variability by standardizing the comparison, thus avoiding differences between different low-molecular-weight heparins.

In the search strategy, we used the terms “Apixaban”, “Dalteparin” and “Venous thromboembolism” and their MESH synonyms using the Peer Review of Electronic Search Strategies Checklist [18]. Our team developed the search strategy in PubMed, and it was adapted to the different bibliographic databases that were mentioned (Supporting Information). No language restrictions were applied.

2.2. Selection of Studies and Data Extraction

Studies that met the following criteria were included: (1) experimental study RCT, phase 2 or 3, parallel or crossover; (2) studies that included patients with cancer of any etiology and presenting with VTE; (3) treatment with apixaban as experimental/intervention group with a duration of 6 months; and (4) dalteparin as a control group with a duration of 6 months of treatment. Likewise, studies conducted in animals, duplicates, conference abstracts, case reports and series, observational studies, review articles, systematic reviews, and editorials or comments were excluded. The outcomes were classified in terms of efficacy and safety, which are used in RCTs; the efficacy outcomes were prevention of venous thrombosis and the safety outcomes were bleeding [19]. In our study, the efficacy outcome was recurrent VTE, which was defined as thrombosis of a venous site that was not previously affected, or a previous history of resolution interval of the incident thrombus [20]. On the other hand, the safety outcomes were major bleeding, defined as obvious bleeding accompanied by a decrease in hemoglobin of ≥ 2 g/dL; or transfusion of ≥ 2 red cell packet units; or intracranial, intraspinal/epidural, intraocular, retroperitoneal, pericardial, intraarticular, intramuscular hemorrhage with compartment syndrome or fatal [21]; and clinically relevant non-major bleeding was defined as overt bleeding that does not meet the definition of major bleeding but is associated with medical intervention, unscheduled medical attention, or temporary discontinuation of

anticoagulant therapy [22].

Two reviewers (MAAH and JJB) independently screened the titles and abstracts of the selected articles to choose potentially relevant articles. After finding potential studies to be included, four authors (MAH, JJB, JSTR, and JFMH) independently read the full text of each selected article. If an article did not meet one or more selection criteria, it was excluded from the study. Discrepancies were resolved by consensus among the team of researchers at each stage. We used Rayyan QCRI software Version 1.2.1 (Qatar Computing Research Institute, Doha, Qatar) to carry out the study selection process [23]. Finally, two authors (MAH and JJB) extracted data from the studies using a standardized data extraction sheet performed in Microsoft Excel. The following information was extracted: author, year, country, study design, number of participants, intervention, comparator, duration of treatment, efficacy and safety outcomes, mean age, percentage male, active cancer, metastatic cancer, ECOG status greater than or equal to 2, solid tumor, hematological malignancy, body weight—median (standard deviation), creatinine clearance 30–50 mL/min, platelet count 50–100,000/mm³ and incidental pulmonary embolism at the time of diagnosis.

2.3. Assessment of the Certainty of the Study Evidence and Risk of Bias of the Studies

The certainty of the evidence was assessed using the GRADE methodology [24], covering all five aspects: risk of bias, inconsistency, indirect evidence, imprecision, and publication bias. The certainty of the evidence was assessed by the outcome, and we used the GRADEpro GDT software version 2021 because it allows for summarizing and presenting information for healthcare decision making by creating summary of findings (SoF) tables.

We used the 2019 Risk of Bias (RoB) 2.0 tool to assess the risk of bias of the RCTs included in this study [25]. This tool assessed several domains from which bias may arise: Risk of bias by domain follows an algorithm to conclude low risk, some concerns, or high risk per domain and per trial. The evaluation of the RoB 2.0 was carried out independently by two authors (MAH and JJB), and discrepancies were resolved by discussion or the consultation of a third author (JMQ).

2.4. Data Synthesis and Analysis

Statistical analyses were performed with Review Manager 5.3 (RevMan 5.3) (The Cochrane Collaboration, Copenhagen, Denmark). An inverse-variance random effects metaanalysis evaluating the effect of apixaban versus dalteparin on outcomes was performed. The treatment effects were reported as relative risks (RRs) and their 95% confidence intervals (CIs). CIs for effects were adjusted using the Hartung–Knapp method, and between-study tau² variance was calculated using the Paule–Mandel method. The heterogeneity of the effects between the studies was quantified with the I² statistic (an I² > 60% corresponds to moderate heterogeneity) [26].

We performed an outcomes analysis according to the following criteria: apixaban dose (10 mg dose twice daily for the first 7 days, followed by 5 mg twice daily) and dalteparin dose (200 IU dose per kilogram of body weight once daily for the first month, followed by 150 IU per kilogram once daily) and recurrence of VTE, major bleeding, and no

major clinically relevant bleeding; the interaction test was used where the p-value < 0.05 indicates an effect modification by outcomes [27]. Review Manager 5.3 (RevMan 5.3) software (The Cochrane Collaboration, Copenhagen, Denmark) was used for the meta-analysis.

3. Results

3.1. Subsection

3.1.1. Selection of Studies

The flowchart summarizing the study selection process is shown in Figure 1. In the initial search, we found a total of 75 records. After excluding duplicate studies, 36 studies were retained. Subsequently, during the evaluation of titles and abstracts, 27 more records were excluded. Finally, during the full-text evaluation, four articles were excluded due to having another outcome, another study design, not being available in full text, or due to the protocol design. Finally, three studies published in the five articles selected for the synthesis of the information, with three corresponding to the Caravaggio study [28–30], one study corresponding to the ADAM TVE trial (VTE) [31], and one phase II study corresponding to the PRIORITY trial [32].

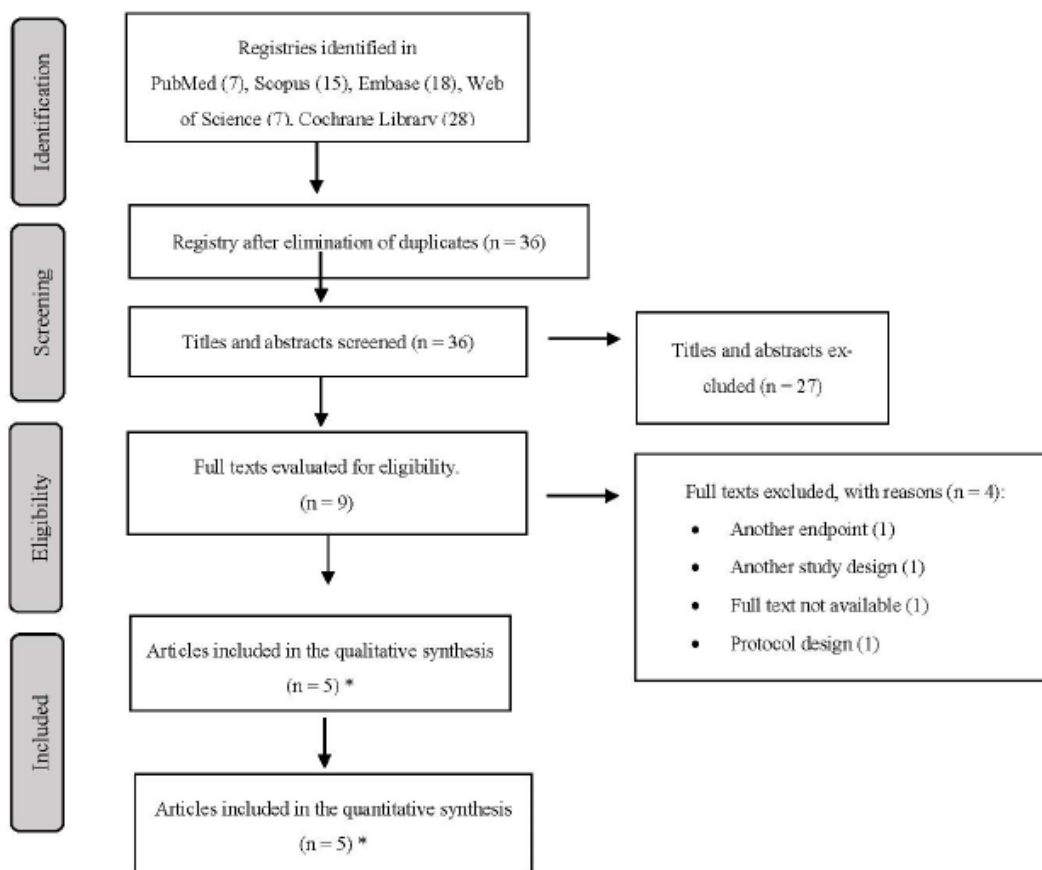


Figure 1. PRISMA 2009 flow chart. * 5 articles: 3 on the Caravaggi study, 1 on the ADAM study and 1 on the PRIORITY study.

3.1.2. Description and Characteristics of the Studies

The characteristics of the studies included are presented in Table 1. For this systematic review, three studies were included; these were open label RCTs. The efficacy outcome (recurrent VTE) and safety outcomes (major bleeding and clinically relevant non-major bleeding) were reported by all three studies. The doses in the intervention and comparator were the same in the three clinical trials (Caravaggio, ADAM, and PRIORITY) with a duration of 6 months of treatment. The mean and median age ranged from 64 to 67 years, the male-to-female ratio was similar, and more than 60% of the patients had metastatic cancer.

3.1.3. Assessment of the Certainty of the Study Evidence and Risk of Bias of the Studies

For the risk of bias, the Cochrane RoB 2.0 tool presented in Figure 2 was used. All three trials had some concerns in one dimension (deviations from planned interventions) and high risk in another (outcome measurement), and thus, overall, all three studies had a high risk of bias. The high risk of bias rating in outcome measurement and deviations from planned intervention was based on several factors. This includes insufficient blinding, for both participants and researchers, which can allow for unconscious influence on the results. Deviations from the planned intervention, such as treatment non-compliance or unforeseen changes, can bias the results. Furthermore, inadequate follow-up can contribute to an increased risk of bias in the research.

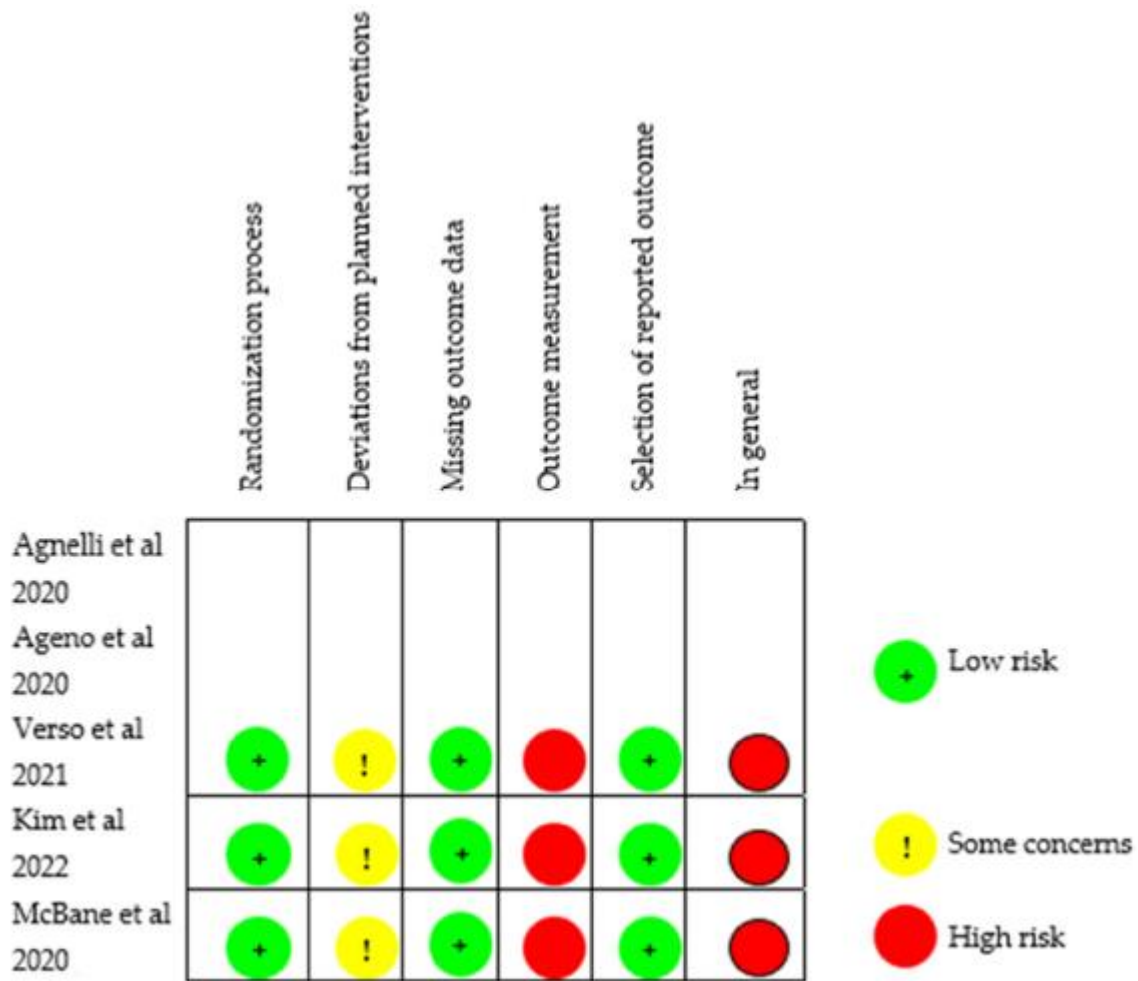


Figure 2. 2019 Cochrane risk of bias (RoB) Tool 2.0 [25,28–32].

Table 1. Characteristics of the studies included.

Author, Year	Study Design	Number of Participants	Intervention and Comparator	Dose	Treatment Duration	Efficacy and Safety Outcomes	Average Age	Male Gender	Metastatic Cancer	Creatinine Clearance 30–50 mL/min	Platelet Count, 50–100,000/mm ³
Agnelli et al., 2020 [28]; Ageno et al., 2020 [29]; Verso et al., 2021 [30]	Randomized and open trial	1155	Apixaban	Apixaban 10 mg orally twice daily for the first 7 days and 5 mg twice daily.	6 months	Efficacy outcome: - recurrent VTE Safety outcome: - Major bleeding - No major clinically relevant bleeding	67.2	50.7%	67.5%	8.9%	3.6%
			Dalteparin	Subcutaneous dalteparin (200 IU/kg for 1 month followed by 150 IU/kg once daily).			67.2	47.7%	68.4%	10.5%	3.8%
Kim et al., 2022 [32]	Multicenter, open label, randomized, controlled phase II trial	90	Apixaban	Apixaban 10 mg orally twice daily for the first 7 days and 5 mg twice daily.	6 months	Efficacy outcome: - recurrent VTE Safety outcome: - Major bleeding - Clinically relevant bleeding	64 (39–77) *	56.8%	86.4%	NR	NR
			Dalteparin	Subcutaneous dalteparin (200 IU/kg for 1 month followed by 150 IU/kg once daily).			63 (42–78) *	50.0%	71.7%	NR	NR
McBane et al., 2020 [31]	Randomized and open trial	287	Apixaban	Apixaban 10 mg orally twice daily for the first 7 days and 5 mg twice daily.	6 months	Efficacy outcome: - recurrent VTE Safety outcome: - Major bleeding - No major clinically relevant bleeding	64.4	48.0%	65.3%	9.3%	6.7%
			Dalteparin	Subcutaneous dalteparin (200 IU/kg for 1 month followed by 150 IU/kg once daily).			64.0	48.7%	66.0%	9.3%	8.7%

Abbreviations: PE, pulmonary embolism; VTE: venous thromboembolism; NR: Not reported; * Median (range).

We used the GRADEpro GDT software version 2021 to create the summary table of the outcomes shown in Table 2. Three outcomes (one of efficacy and two of safety) were evaluated. The degree of certainty of the evidence was very low in these studies since the participants knew which drug they were receiving by the route of administration, and therefore, the blinding was lost. The relative effect with a 95% CI was not statistically significant for two outcomes (recurrent VTE and major bleeding).

Table 2. Summary of GRADE results.

Outcome	Anticipated Absolute Effects * (95% CI)		Relative Effect (95% CI)	N°. of Participants (Studies)	Certainty of the Evidence (GRADE)
	Risk with Dalteparin	Risk with Apixaban			
Efficacy: Recurrent venous thromboembolism	73 for 1000	37 for 1000 (12 to 112)	RR 0.50 (0.16 to 1.53)	1501 (3 Randomized Controlled Experiments)	⊕○○○ Very low ^{a,b}
Safety: - Major bleeding	35 for 1000	45 for 1000 (11 to 186)	RR 1.29 (0.31 to 5.27)	1501 (3 Randomized Controlled Experiments)	⊕○○○ Very low ^{a,b}
- No major clinically relevant bleeding	60 for 1000	91 for 1000 (63 to 131)	RR 1.52 (1.05 to 2.19)	1501 (3 Randomized Controlled Experiments)	⊕○○○ Very low ^{a,b}

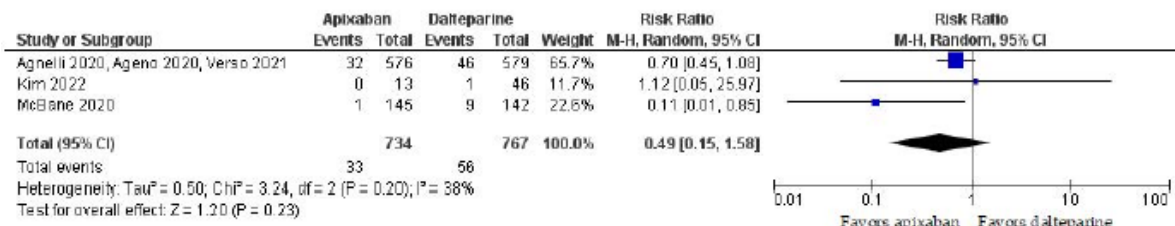
* The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% confidence interval). CI: confidence interval; RR: Risk ratio. “⊕” There is certainty of the evidence. “○” There is no certainty of the evidence. GRADE Working Group grades of evidence. High certainty: We are very confident that the true effect is close to that of the estimate of effect. Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the effect estimate, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: the actual effect may be substantially different from the effect estimate. Very low certainty: We have very little confidence in the estimate of effect: The actual effect is likely to be substantially different from the estimate of effect. Explanations: a. The participant knows which drug they are receiving due to its route of administration; therefore, blinding is lost. b. The effects in the evaluated studies are not significant and have a high risk of bias.

3.1.4. Outcomes Analysis

The outcome analysis was performed according to the efficacy (primary) and safety (secondary) outcomes using the Forest plot presented in Figure 3. Thirty-three of the 734 (4.5%) patients treated with apixaban and 56 of 767 (7.3%) receiving dalteparin had recurrent VTE as the efficacy outcome (RR 0.49, 95% CI 0.15–1.58, I² 38%). Major bleeding occurred in 25/734 patients treated with apixaban (3.4%) and 27/767 with dalteparin (3.5%) (RR 1.29, 95% CI 0.31–5.27, I² 59%). Likewise, clinically relevant non-major bleeding occurred in 64/734 patients treated with apixaban (8.7%) and 46/767 (5.9%) with dalteparin (RR 1.52, 95% CI 1.05–2.19, I² 0%).

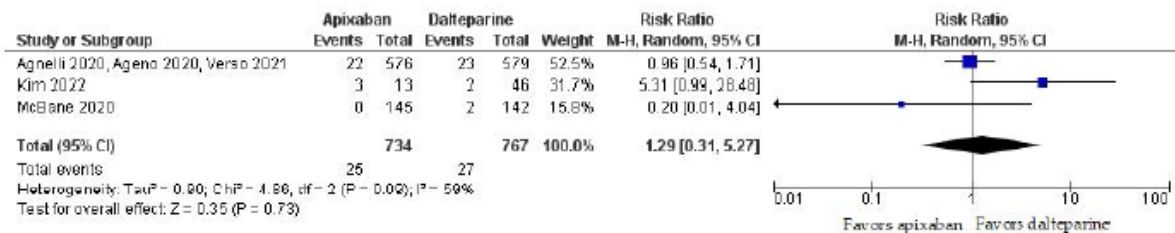
Efficacy outcome:

- Recurrent venous thromboembolism



Safety outcomes:

- Major bleeding



- No major clinically relevant bleeding

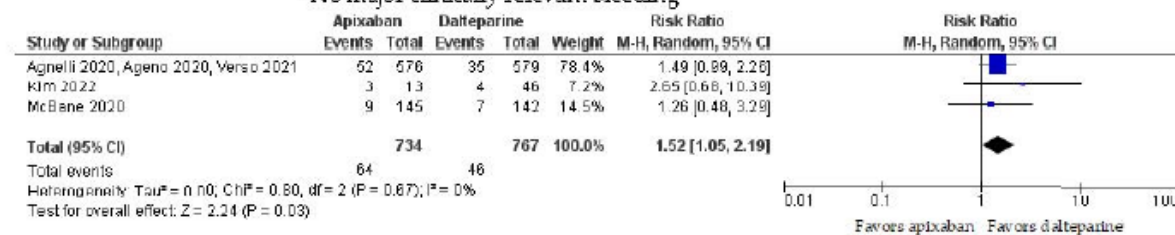


Figure 3. Forest plot of studies comparing apixaban and dalteparin [26,28–32].

4. Discussion

According to the results of our systematic review, apixaban and dalteparin did not significantly reduce the RR of recurrent VTE and major bleeding in patients with cancer-associated VTE. However, dalteparin safely reduced the RR of clinically relevant non-major bleeding with anticoagulant therapy compared to apixaban. Analysis by outcomes due to recurrent VTE was the main finding, and clinically major bleeding and non-major bleeding were the secondary findings of the present study. The risk of bias was high in the three studies.

Various guidelines have established DOACs and LMWHs as an alternative to usual treatment to counteract side effects, such as bleeding and thrombocytopenia, in the prophylaxis and treatment of vascular diseases in cancer patients [33,34], with DOACs being more accepted due to their oral administration [35,36]. Multiple meta-analyses comparing LMWH and DOAC treatments were performed [37–43]. Some outcomes evaluated in each treatment showed no significant differences between LMWH and DOAC, with the latter being used as another treatment option for cancer-associated VTE [37–43]. Other studies have concluded that among the drugs used for the prevention and treatment of VTE in cancer patients, DOACs have a greater efficacy

and a relatively low risk of bleeding, and apixaban is the most effective and has the lowest risk of bleeding [37–44]. However, some studies have reported that DOACs have an increased risk of major bleeding in patients with gastrointestinal and genitourinary malignancies [37–43].

A meta-analysis of four RCTs concluded that DOACs are more effective in the treatment of VTE associated with malignancy compared to LMWH, although an increased risk of clinically relevant combined major or non-major bleeding was observed [45]. Another meta-analysis of eight RCTs comparing DOACs with LMWH and vitamin K antagonists (VKAs) concluded that DOACs are the optimal treatment for cancer-associated VTE, have a similar or slightly increased risk of bleeding compared to LMWH, are a safer alternative to VKAs, and have a promising lowering effect on mortality, regardless of cancer status in these patients [46]. The recently published phase II PRIORITY RCT involving 90 patients with active cancer reported that DOAC therapy further increased the risk of bleeding compared to dalteparin in patients with active advanced upper gastrointestinal, hepatobiliary, or pancreatic cancer. Therefore, great care is needed when selecting anticoagulant therapy for cancer-associated VTE in high-risk patients [32]. Two meta-analyses had similar conclusions to those of our study, describing that LMWH drugs had fewer bleeding episodes compared to DOACs [47,48]. However, our results included two additional components, an assessment of the quality and certainty of the evidence, and an outcomes analysis of efficacy and safety according to the type of bleeding and in patients with cancer.

In our analysis using the GRADE summary results table, we found that patients receiving apixaban presented statistically significant, clinically relevant non-major bleeding, with an anticipated absolute effect greater than 91 per 1000 compared to those receiving dalteparin with 60 per 1000 (RR 1.52; 95% CI, 1.05 to 2.19). On the other hand, there was no statistical difference in major bleeding for patients using both drugs. However, recurrent VTE was non-significantly lower in patients with apixaban compared to dalteparin. The number of participants in the RCTs evaluated add up to 1501, which is a considerable number for the synthesis of evidence for the two drugs. However, based on the very-lowcertainty evidence, the effect of the drugs is uncertain; therefore, the use of apixaban cannot be recommended because it may increase the risk of clinically relevant non-major bleeding compared to dalteparin.

In the various meta-analyses evaluating DOACs versus LMWH described above for the treatment of cancer-associated VTE, the evaluation was carried out jointly and not directly between each drug. Therefore, in our study, we chose the most effective and safest DOACs and LMWH drugs, apixaban and dalteparin, with the results showing the efficacy and safety of these drugs in the different types of bleeding and encouraging the need for more RCTs and a subsequent meta-analysis of these trials.

The various factors that contribute to the risk of bleeding in cancer patients are a challenge for physicians administering anticoagulation treatment in this population. These factors involve the pathophysiology of cancer, thrombocytopenia, chemotherapy treatment, and subsequent renal failure, which generate hemostatic instability. Taking all these factors into account the evidence as to whether LMWH and DOACs have a similar efficacy and safety remains insufficient and thus, more RCTs

on the use of these drugs is necessary to achieve more solid and significant conclusions.

Our study has some limitations that must be considered. The small number of studies available comparing apixaban and dalteparin did not allow for a greater synthesis of the results; however, the number of participants in the studies evaluated provide the relative risks with respect to each outcome. A strength of this study is the methodology used, describing the certainty of the study evidence and risk of bias of the studies included in a systematic review and meta-analysis. Another strength is that the PRIORITY study was added, for the first time, to a meta-analysis for the summary of its results. Furthermore, it is important to mention that it is not the time to contemplate the inclusion of these medications in the national cancer plan when the evidence of their efficacy and safety is still unclear.

5. Conclusions

Patients with cancer-associated VTE treated with apixaban showed a lower risk of recurrent VTE (safety outcome) compared to dalteparin, albeit with no statistical difference. In the evaluation of clinically relevant non-major bleeding, there were statistical differences between the two drugs. Likewise, the certainty of the evidence of the studies was very low and the risk of bias was high; thus, it is still not possible to suggest that one of the evaluated treatments is more effective and safer than the other.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/medicina59101867/s1>. Research approach format.

Author Contributions: M.A.A.-H.: Conceptualization, methodology, software, formal analysis, research, methodology, writing—original draft preparation, writing—review and editing. J.J.B.: Conceptualization, data curation, methodology, writing—original draft preparation, writing—review and editing. J.F.M.-H.: Supervision, writing—review and editing. J.S.T.-R.: Methodology, writing—original draft preparation, writing—review and editing. J.L.M.: Conceptualization, original draft writing, and supervision. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Universidad Científica del Sur through the “Concurso Fondo Becas Cabies—Proyectos de Tesis de Grado y Posgrado 2022-1” approved by Directorial Resolution no. 019-DGIDI-CIENTÍFICA-2021.

Institutional Review Board Statement: The study was carried out in accordance with the Declaration of Helsinki, approved by the ethics committee of the Universidad Científica del Sur, the 23 September 2021 through certificate no. 341-CIEI-CIENTÍFICA-2021 and registration code 667-2021-POS50.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data are available in the Supporting Information.

Acknowledgments: This article was prepared by MA Arce-Huamani in partial compliance with the requirements to obtain the academic degree of master's in clinical epidemiology and biostatistics from the Universidad Científica del Sur. Therefore, the support provided during the execution of the article is appreciated.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Albertsen, I.E.; Nielsen, P.B.; Søgaard, M.; Goldhaber, S.Z.; Overvad, T.F.; Rasmussen, L.H.; Larsen, T.B. Risk of Recurrent Venous Thromboembolism: A Danish Nationwide Cohort Study. *Am. J. Med.* **2018**, *131*, 1067–1074.e4. [CrossRef]
2. Caputo, R.; Pyle, J.; Kuriakose, P.; Lekura, J. A systematic review of apixaban in prevention and treatment of cancer-associated venous thromboembolism. *J. Am. Pharm. Assoc.* **2021**, *61*, e26–e38. [CrossRef] [PubMed]
3. Song, X.; Liu, Z.; Zeng, R.; Shao, J.; Liu, B.; Zheng, Y.; Liu, C.; Ye, W. Treatment of venous thromboembolism in cancer patients: A systematic review and meta-analysis on the efficacy and safety of different direct oral anticoagulants (DOACs). *Ann. Transl. Med.* **2021**, *9*, 162. [CrossRef] [PubMed]
4. Key, N.S.; Bohlke, K.; Falanga, A. Venous Thromboembolism Prophylaxis and Treatment in Patients with Cancer: ASCO Clinical Practice Guideline Update Summary. *J. Oncol. Pract.* **2019**, *15*, 661–664. [CrossRef]
5. Lloyd, A.J.; Dewilde, S.; Noble, S.; Reimer, E.; Lee, A.Y.Y. What Impact Does Venous Thromboembolism and Bleeding Have on Cancer Patients' Quality of Life? *Value Health J. Int. Soc. Pharmacoecon. Outcomes Res.* **2018**, *21*, 449–455. [CrossRef] [PubMed]
6. Hao, C.; Sun, M.; Wang, H.; Zhang, L.; Wang, W. Chapter Two—Low molecular weight heparins and their clinical applications. In *Progress in Molecular Biology and Translational Science*; Zhang, L., Ed.; Glycans and Glycosaminoglycans as Clinical Biomarkers and Therapeutics—Part B; Academic Press: Cambridge, MA, USA, 2019; Volume 163, pp. 21–39. [CrossRef]
7. Amin, A.; Keshishian, A.; Dina, O.; Dhamane, A.; Nadkarni, A.; Carda, E.; Russ, C.; Rosenblatt, L.; Mardekian, J.; Yuce, H.; et al. Comparative clinical outcomes between direct oral anticoagulants and warfarin among elderly patients with non-valvular atrial fibrillation in the CMS medicare population. *J. Thromb. Thrombolysis* **2019**, *48*, 240–249. [CrossRef] [PubMed]
8. Li, A.; Manohar, P.M.; Garcia, D.A.; Lyman, G.H.; Steuten, L.M. Cost Effectiveness Analysis of Direct Oral Anticoagulant (DOAC) versus Dalteparin for the Treatment of Cancer Associated Thrombosis (CAT) in the United States. *Thromb. Res.* **2019**, *180*, 37–42. [CrossRef]
9. Liao, C.T.; Lee, M.C.; Chen, Z.C.; Ku, L.J.E.; Wang, J.D.; Toh, H.S. Cost-

Effectiveness Analysis of Oral Anticoagulants in Stroke Prevention among Patients with Atrial Fibrillation in Taiwan. *Acta Cardiol. Sin.* **2020**, 36, 50–61. [CrossRef]

10. Ay, C.; Beyer-Westendorf, J.; Pabinger, I. Treatment of cancer-associated venous thromboembolism in the age of direct oral anticoagulants. *Ann. Oncol. Off. J. Eur. Soc. Med. Oncol.* **2019**, 30, 897–907. [CrossRef]

11. O'Connell, C.; Escalante, C.P.; Goldhaber, S.Z.; McBane, R.; Connors, J.M.; Raskob, G.E. Treatment of Cancer-Associated Venous Thromboembolism with Low-Molecular-Weight Heparin or Direct Oral Anticoagulants: Patient Selection, Controversies, and Caveats. *Oncologist* **2021**, 26, e8–e16. [CrossRef]

12. Carrier, M.; Abou-Nassar, K.; Mallick, R.; Tagalakis, V.; Shivakumar, S.; Schattner, A.; Kuruvilla, P.; Hill, D.; Spadafora, S.; Marquis, K.; et al. Apixaban to Prevent Venous Thromboembolism in Patients with Cancer. *N. Engl. J. Med.* **2019**, 380, 711–719. [CrossRef] [PubMed]

13. Frere, C.; Benzidia, I.; Marjanovic, Z.; Farge, D. Recent Advances in the Management of Cancer-Associated Thrombosis: New Hopes but New Challenges. *Cancers* **2019**, 11, 71. [CrossRef] [PubMed]

14. Ladha, D.; Mallick, R.; Wang, T.F.; Caiano, L.; Wells, P.S.; Carrier, M. Efficacy, and safety of apixaban for primary prevention in gastrointestinal cancers: A post-hoc analysis of the AVERT trial. *Thromb. Res.* **2021**, 202, 151–154. [CrossRef]

15. Knoll, W.; Mallick, R.; Wells, P.S.; Carrier, M. Safety, and efficacy of apixaban thromboprophylaxis in cancer patients with metastatic disease: A post-hoc analysis of the AVERT trial. *Thromb. Res.* **2021**, 197, 13–15. [CrossRef]

16. Lee, J.H.; Lee, J.H.; Jo, K.W.; Huh, J.W.; Oh, Y.M.; Lee, J.S. Comparison of rivaroxaban and dalteparin for the long-term treatment of venous thromboembolism in patients with gynecologic cancers. *J. Gynecol. Oncol.* **2020**, 31, e10. [CrossRef]

17. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* **2021**, 372, n71. [CrossRef]

18. Saif-Ur-Rahman, K.M. Transparency of reporting search strategies in systematic reviews. *Hypertens. Res.* **2022**, 45, 1838–1839. [CrossRef]

19. Tabares, D.H.; Carrillo, V.P.; Gómez, J.H.D. Clasificación de los desenlaces en los ensayos clínicos. *Med. UPB* **2019**, 38, 147–157. [CrossRef]

20. Khan, F.; Tritschler, T.; Kimpton, M.; Wells, P.S.; Kearon, C.; Weitz, J.I.; Büller, H.R.; Raskob, G.E.; Ageno, W.; Couturaud, F.; et al. Long-term risk of recurrent venous thromboembolism among patients receiving extended oral anticoagulant therapy for first unprovoked venous thromboembolism: A systematic review and meta-analysis. *J. Thromb. Haemost.* **2021**, 19, 2801–2813. [CrossRef] [PubMed]

21. Franco, L.; Becattini, C.; Beyer-Westendorf, J.; Vanni, S.; Nitti, C.; Re, R.; Manina, G.; Pomero, F.; Cappelli, R.; Conti, A.; et al. Definition of major bleeding: Prognostic classification. *J. Thromb. Haemost.* **2020**, *18*, 2852–2860. [CrossRef]
22. Yee, M.K.; Gibson, C.M.; Nafee, T.; Kerneis, M.; Daaboul, Y.; Korjian, S.; Chi, G.; AlKhalfan, F.; Hernandez, A.F.; Hull, R.D.; et al. Characterization of Major and Clinically Relevant Non-Major Bleeds in the APEX Trial. *TH Open Companion J. Thromb. Haemost.* **2019**, *3*, e103–e108. [CrossRef]
23. Valizadeh, A.; Moassefi, M.; Nakhostin-Ansari, A.; Hosseini Asl, S.H.; Saghab Torbati, M.; Aghajani, R.; Maleki Ghorbani, Z.; Faghani, S. Abstract screening using the automated tool Rayyan: Results of effectiveness in three diagnostic test accuracy systematic reviews. *BMC Med. Res. Methodol.* **2022**, *22*, 160. [CrossRef] [PubMed]
24. Brozek, J.L.; Canelo-Aybar, C.; Akl, E.A.; Bowen, J.M.; Bucher, J.; Chiu, W.A.; Cronin, M.; Djulbegovic, B.; Falavigna, M.; Guyatt, G.H.; et al. GRADE Guidelines 30: The GRADE approach to assessing the certainty of modeled evidence—An overview in the context of health decision-making. *J. Clin. Epidemiol.* **2021**, *129*, 138–150. [CrossRef] [PubMed]
25. Lee, L.L. Application of the Risk of Bias 2 Tool. *Hu Li Za Zhi* **2021**, *68*, 85–91. [CrossRef]
26. Lin, L. Comparison of four heterogeneity measures for meta-analysis. *J. Eval. Clin. Pract.* **2020**, *26*, 376–384. [CrossRef] [PubMed]
27. Kilpeläinen, T.P.; Tikkinen, K.A.O.; Guyatt, G.H.; Vernooij, R.W.M. Evidence-based Urology: Subgroup Analysis in Randomized Controlled Trials. *Eur. Urol. Focus* **2021**, *7*, 1237–1239. [CrossRef]
28. Agnelli, G.; Becattini, C.; Meyer, G.; Muñoz, A.; Huisman, M.; Connors, J.; Cohen, A.; Bauersachs, R.; Brenner, B.; Torbicki, A.; et al. Apixaban for the Treatment of Venous Thromboembolism Associated with Cancer. *N. Engl. J. Med.* **2020**, *382*, 1599–1607. [CrossRef]
29. Agno, W.; Vedovati, M.; Cohen, A.; Huisman, M.; Bauersachs, R.; Gussoni, G.; Becattini, C.; Agnelli, G. Bleeding with Apixaban and Dalteparin in Patients with Cancer-Associated Venous Thromboembolism: Results from the Caravaggio Study. *Thromb. Haemost.* **2021**, *121*, 616–624. [CrossRef]
30. Verso, M.; Muñoz, A.; Bauersachs, R.; Huisman, M.; Mandalà, M.; Vescovo, G.; Becattini, C.; Agnelli, G. Effects of concomitant administration of anticancer agents and apixaban or dalteparin on recurrence and bleeding in patients with cancer-associated venous thromboembolism. *Eur. J. Cancer* **2021**, *148*, 371–381. [CrossRef]
31. McBane, R.D.; Wysokinski, W.E.; Le-Rademacher, J.G.; Zemla, T.; Ashrani, A.; Tafur, A.; Perepu, U.; Anderson, D.; Gundabolu, K.; Kuzma, C.; et al. Apixaban and dalteparin in active malignancy-associated venous thromboembolism: The ADAM VTE trial. *J. Thromb. Haemost.* **2020**, *18*, 411–421. [CrossRef]

32. Kim, J.H.; Yoo, C.; Seo, S.; Jeong, J.H.; Ryoo, B.Y.; Kim, K.P.; Lee, J.B.; Lee, K.W.; Kim, J.W.; Kim, I.H.; et al. A Phase II Study to Compare the Safety and Efficacy of Direct Oral Anticoagulants versus Subcutaneous Dalteparin for Cancer-Associated Venous Thromboembolism in Patients with Advanced Upper Gastrointestinal, Hepatobiliary and Pancreatic Cancer: PRIORITY. *Cancers* **2022**, *14*, 559. [CrossRef] [PubMed]
33. Farge, D.; Frere, C.; Connors, J.M.; Khorana, A.A.; Kakkar, A.; Ay, C.; Muñoz, A.; Brenner, B.; Prata, P.H.; Brilhante, D.; et al. 2022 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer, including patients with COVID-19. *Lancet Oncol.* **2022**, *23*, e334–e347. [CrossRef]
34. Frere, C.; Farge, D.; Douketis, J.; Connors, J.M. The 2022 ITAC evidence-based clinical practice guidelines: New update from the International Initiative on Thrombosis and Cancer to improve the care in patients with cancer-associated thrombosis. *J. Med. Vasc.* **2022**, *47*, 113–115. [CrossRef]
35. Hutchinson, A.; Rees, S.; Young, A.; Maraveyas, A.; Date, K.; Johnson, M.J. Oral anticoagulation is preferable to injected, but only if it is safe and effective: An interview study of patient and carer experience of oral and injected anticoagulant therapy for cancer-associated thrombosis in the select-d trial. *Palliat. Med.* **2019**, *33*, 510–517. [CrossRef] [PubMed]
36. Hendriks, T.; McGregor, S.; Rakesh, S.; Robinson, J.; Ho, K.M.; Baker, R. Patient satisfaction after conversion from warfarin to direct oral anticoagulants for patients on extended duration of anticoagulation for venous thromboembolism—The SWAN Study. *PLoS ONE* **2020**, *15*, e0234048. [CrossRef]
37. Mareev, V.Y.; Mareev, Y.V. Role of anticoagulants in therapy and prevention of recurrent venous thromboembolism in patients with cancer: A meta-analysis of randomized trials with apixaban. *Kardiologija* **2022**, *62*, 4–15. [CrossRef]
38. Wu, S.; Lv, M.; Chen, J.; Jiang, S.; Chen, M.; Fang, Z.; Zeng, Z.; Qian, J.; Xu, W.; Guan, C.; et al. Direct oral anticoagulants for venous thromboembolism in cancer patients: A systematic review and network meta-analysis. *Support. Care Cancer Off. J. Multinatl. Assoc. Support. Care Cancer* **2022**, *30*, 10407–10420. [CrossRef] [PubMed]
39. Frere, C.; Farge, D.; Schrag, D.; Prata, P.H.; Connors, J.M. Direct oral anticoagulant versus low molecular weight heparin for the treatment of cancer-associated venous thromboembolism: 2022 updated systematic review and meta-analysis of randomized controlled trials. *J. Hematol. Oncol.* **2022**, *15*, 69. [CrossRef]
40. Hussain, M.R.; Ali, F.S.; Verghese, D.; Myint, P.T.; Ahmed, M.; Gong, Z.; Gerails, Y.; Siddiqui, M.; Lin, J.J.; Troy, K. Factor Xa inhibitors versus low molecular weight heparin for the treatment of cancer associated venous thromboembolism; A meta-analysis of randomized controlled trials and non-randomized studies. *Crit. Rev. Oncol. Hematol.* **2022**, *169*, 103526. [CrossRef]

41. Murphy, A.C.; Koshy, A.N.; Farouque, O.; Yeo, B.; Raman, J.; Kearney, L.; Yudi, M.B. Factor Xa Inhibition for the Treatment of Venous Thromboembolism Associated with Cancer: A Meta-Analysis of the Randomised Controlled Trials. *Heart Lung Circ.* **2022**, *31*, 716–725. [CrossRef]
42. Mohamed, M.F.H.; ElShafei, M.N.; Ahmed, M.B.; Abdalla, L.O.; Ahmed, I.; Elzouki, A.N.; Danjuma, M.I.M.U. The Net Clinical Benefit of Rivaroxaban Compared to Low-Molecular-Weight Heparin in the Treatment of Cancer-Associated Thrombosis: Systematic Review and Meta-Analysis. *Clin. Appl. Thromb. Off. J. Int. Acad. Clin. Appl. Thromb.* **2021**, *27*, 1076029620940046.
43. Riaz, I.B.; Fuentes, H.E.; Naqvi, S.A.A.; He, H.; Sipra, Q.U.A.R.; Tafur, A.J.; Padranos, L.; Wysokinski, W.E.; Marshall, A.L.; Vandvik, P.O.; et al. Direct Oral Anticoagulants Compared with Dalteparin for Treatment of Cancer-Associated Thrombosis: A Living, Interactive Systematic Review and Network Meta-analysis. *Mayo Clin. Proc.* **2022**, *97*, 308–324. [CrossRef]
44. Ning, H.; Yang, N.; Ding, Y.; Chen, H.; Wang, L.; Han, Y.; Cheng, G.; Zou, M. Efficacy and safety of direct oral anticoagulants for the treatment of cancer-associated venous thromboembolism: A systematic review and Bayesian network meta-analysis. *Med. Clin.* **2023**, *160*, 245–252. [CrossRef]
45. Samaranayake, C.B.; Anderson, J.; McCabe, C.; Zahir, S.F.; Upham, J.W.; Keir, G. Direct oral anticoagulants for cancer-associated venous thromboembolisms: A systematic review and network meta-analysis. *Intern. Med. J.* **2022**, *52*, 272–281. [CrossRef]
46. Yamani, N.; Unzek, S.; Almas, T.; Musheer, A.; Ejaz, A.; Paracha, A.A.; Shahid, I.; Mookadam, F. DOACs or VKAs or LMWH—What is the optimal regimen for cancer-associated venous thromboembolism? A systematic review and meta-analysis. *Ann. Med. Surg.* **2022**, *79*, 103925. [CrossRef] [PubMed]
47. Mai, V.; Tanguay, V.F.; Guay, C.A.; Bertoletti, L.; Magnan, S.; Turgeon, A.F.; Lacasse, Y.; Lega, J.C.; Provencher, S. DOAC compared to LMWH in the treatment of cancer related-venous thromboembolism: A systematic review and meta-analysis. *J. Thromb. Thrombolysis* **2020**, *50*, 661–667. [CrossRef]
48. Moik, F.; Posch, F.; Zielinski, C.; Pabinger, I.; Ay, C. Direct oral anticoagulants compared to low-molecular-weight heparin for the treatment of cancer-associated thrombosis: Updated systematic review and meta-analysis of randomized controlled trials. *Res. Pract. Thromb. Haemost.* **2020**, *4*, 550–561. [CrossRef] [PubMed]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.

Versión inicial enviada a publicar a revista

1. Introduction

Venous thromboembolism (VTE) is the third most important vascular disease in the general population. Cancer patients are 4 to 7 times more likely to develop VTE, being the second cause of death in these patients [1,2]. The incidence of recurrent VTE is 9.6%, reaching 22.1% in the first 6 months after the initial diagnosis of cancer [3]. To prevent VTE in high-risk patients (KHORANA score >2) and to treat those who have already had a thrombotic event, anticoagulant therapy is recommended [4]. However, this therapy carries a significant risk of bleeding, the most serious adverse reaction. Low molecular weight heparins (LMWH) and direct oral anticoagulants (DOAC) are the most widely used anticoagulant treatments [3,5]. Dalteparin, an LMWH, is recommended in patients with cancer-related VTE, as it has been associated with a lower incidence of osteoporosis and heparin-induced thrombocytopenia [6]. In DOACs, apixaban has been shown to have a lower risk of systemic cerebrovascular disease/embolism and major bleeding [7]. However, the aforementioned drugs cost approximately \$64 to \$106 for Apixaban and Dalteparin, respectively, making them difficult to access for the general public [8,9]. Therefore, it is necessary to propose strategies for its acquisition.

Various studies have addressed DOACs and LMWHs as treatment for cancer-associated VTE [10,11], where new drugs such as Apixaban and Dalteparin have demonstrated efficacy and safety compared to other common treatments [12,13]. Regarding thromboprophylaxis, the efficacy and safety of Apixaban has been reported in a randomized clinical trial (RCT) with 130 patients with gastrointestinal cancer, where it was shown to reduce the incidence of thromboembolism to 4.6% compared to 20% in the placebo group [14]. In another RCT in 365 patients stratified according to the presence or absence of metastatic cancer, thromboprophylaxis with Apixaban was found to be associated with a significantly lower rate of VTE with a Hazard Ratio (HR) 0.55 and 0.34, respectively, compared to placebo [15]. For its part, dalteparin in an RCT in patients with VTE associated with gynecological cancer showed a lower occurrence of major bleeding in 5% compared to 7.8% of those who had rivaroxaban as treatment [16]. However, the studies do not synthesize results of treatment with Apixaban and Dalteparin for VTE in cancer patients, so it is important to have this information.

Consequently, the study authors note that the evaluation of the efficacy and safety of the treatment of VTE associated with cancer remains a challenge due to the various studies available that expand the treatment options. Likewise, the adverse reactions of these treatments can be harmful for patients, so it is important to synthesize the evidence between them. Apixaban and Dalteparin being the drugs that have various studies, proving to reduce major bleeding and recurrence of VTE in cancer patients. Likewise, we identified that there is a knowledge gap in the synthesis of the evidence that compares these two drugs, even though they are the two drugs with the most randomized clinical trials compared to other LMWH and DOAC.

Therefore, the purpose of our study was to synthesize the evidence on the efficacy

and safety of apixaban versus dalteparin in reducing recurrent venous thromboembolism, major bleeding, and clinically relevant non-major bleeding associated with cancer.

2. Materials and Methods

We used the PRISMA report for systematic reviews and meta-analyses [17] for writing our systematic review. The version of our protocol was registered in the International Prospective Register of Systematic Review (PROSPERO) with the code CRD42021275583.

Data sources and searches

From inception to January 5, 2023, we searched the following databases: PubMed, Scopus, Web of Science, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) for studies evaluating the efficacy of apixaban versus dalteparin as a treatment for cancer-associated venous thromboembolism and conducted a search of ClinicalTrials to identify ongoing or completed randomized clinical trials. related to our study.

In the search strategy we used the terms "Apixaban", "Dalteparin" and "Venous thromboembolism" and their MESH synonyms using the Peer Review of Electronic Search Strategies Checklist. [18]. Our team developed the search strategy in PubMed, and it was adapted to the different bibliographic databases that were mentioned (Supporting Information 1). No language restrictions applied.

Selection of studies and data extraction

Studies that met the following criteria were included: (1) experimental study randomized controlled trial, phase 2 or 3, parallel or crossover, (2) studies that included patients with cancer of any etiology and presenting with venous thromboembolism, (3) treatment with Apixaban as experimental/intervention group with a duration of 6 months and (4) Dalteparin as a control group with a duration of 6 months of treatment. Likewise, studies conducted in animals, duplicates, conference abstracts, case reports and series, observational studies, review articles, systematic reviews, and editorials or comments were excluded. The outcomes were classified in terms of efficacy and safety, which are used in randomized clinical trials; the efficacy outcomes are prevention of venous thrombosis and the safety outcomes are bleeding [19]. In our study, the efficacy outcome was recurrent venous thromboembolism, which was defined as thrombosis of a venous site that was not previously affected or had a previous history of resolution interval of the incident thrombus [20]. On the other hand, the safety outcomes were major bleeding, defined as obvious bleeding accompanied by a decrease in hemoglobin of ≥ 2 g/dL; or transfusion of ≥ 2 red cell packet units; or intracranial, intraspinal/epidural, intraocular, retroperitoneal, pericardial, intraarticular, intramuscular hemorrhage with compartment syndrome or fatal; and Clinically relevant non-major bleeding is defined as overt bleeding that does not meet the definition of major bleeding but is associated with medical intervention, unscheduled medical attention, or temporary discontinuation of anticoagulant therapy.

Two reviewers (MAAH and JJB) independently screened the titles and abstracts of the selected articles to choose potentially relevant articles. After finding potential studies to be included, four authors (MAH, JJB, JSTR, and JFMH) independently read the full text of each selected article. If an article did not meet one or more selection criteria, it was excluded from our study. Discrepancies were resolved by consensus among the team of researchers at each stage. We use Rayyan QCRI software (Qatar Computing Research Institute, Doha, Qatar) to carry out the study selection process [21]. Finally, two authors (MAH and JJB) extracted data from the studies using a standardized data extraction sheet performed in Microsoft Excel. The following information was extracted: author, year, country, study design, number of participants, intervention, comparator, duration of treatment, efficacy and safety outcomes, mean age, percentage male, active cancer, metastatic cancer, ECOG status greater than or equal to 2, solid tumor, hematological malignancy, body weight – median (SD), creatinine clearance 30-50 mL/min, platelet count 50-10 0.000/mm³ and Incidental pulmonary embolism at the time of diagnosis.

Assessment of the certainty of the study evidence and risk of bias of the studies

The certainty of the evidence was assessed using the GRADE methodology [22], covering all five aspects: risk of bias, inconsistency, indirect evidence, imprecision, and publication bias. The certainty of the evidence was assessed by outcome, and we used the GRADEpro GDT software because it allows summarizing and presenting information for healthcare decision-making by creating summary of findings (SoF) tables.

We used the 2019 Risk of Bias (RoB) 2.0 tool to assess the risk of bias of the RCTs included in this study [23]. This tool assessed several domains from which bias may arise: Risk of bias by domain follows an algorithm to conclude low risk, some concerns, or high risk per domain and per trial. The evaluation of the RoB 2.0 was carried out independently by two authors (MAH and JJB), and discrepancies were resolved by discussion or with the consultation of a third author (JMQ).

Data synthesis analysis

Statistical analyzes were performed with Review Manager 5.3 (RevMan 5.3) (The Cochrane Collaboration, Copenhagen, Denmark). An inverse variance random effects meta-analysis evaluating the effect of Apixaban versus Dalteparin on outcomes was performed. Treatment effects were reported as relative risks (RR) and their 95% confidence intervals (CI). CIs for effects were adjusted using the Hartung-Knapp method and between-study tau² variance was calculated using the Pau-le-Mandel method. The heterogeneity of the effects between the studies was quantified with the I² statistic (an I² > 60% corresponds to moderate heterogeneity) [24].

We performed a subgroup analysis according to the following criteria: Apixaban dose (10 mg dose twice daily for the first 7 days, followed by 5 mg twice daily) and Dalteparin dose (200 IU dose per kilogram of body weight once daily for the first month, followed by 150 IU per kilogram once daily) between recurrence of venous thromboembolism, major bleeding, and no major bleeding. relevant mind; the interaction test was used where a p value < 0.05 will indicate an effect modification by subgroup [25]. Review

Manager 5.3 (RevMan 5.3) software (The Cochrane Collaboration, Copenhagen, Denmark) was used for the meta-analysis.

3. Results

3.1. Subsection

Selection of studies

The flowchart summarizing the study selection process is shown in Figure 1. In the initial search, we found a total of 75 records. After excluding duplicate studies, 36 studies were retained. Subsequently, during the evaluation of titles and abstracts, 27 more records were excluded. Finally, during the full text evaluation, 4 articles were excluded because of having another outcome, another study design, not being available in full text, protocol design. Finally, 3 studies published in 5 articles were selected for the synthesis of the information, 3 corresponding to the Caravaggio study. [26–28], 1 study corresponding to the ADAM TVE trial (venous thromboembolism) [29] and 1 phase II study corresponding to the PRIORITY trial [30].

Description and characteristics of the study

The characteristics of the included studies are presented in Table 1. For this systematic review, 3 studies were included, these were open label randomized controlled trials. The efficacy outcome (recurrent venous thromboembolism) and safety outcomes (major bleeding and clinically relevant non-major bleeding) were reported by all 3 studies. The doses in the intervention and comparator were the same in the three clinical trials (Caravaggio, ADAM, and PRIORITY) with a duration of 6 months of treatment. The mean and median age ranged from 64 to 67 years, the male to female ratio was similar, and more than 60% of the patients had metastatic cancer.

Assessment of the certainty of the study evidence and risk of bias of the studies

We used the GRADEpro GDT software to create the summary table of outcomes that is presented in Table 2. The three outcomes (one of efficacy and two of safety) where the degree of certainty of the evidence was very low in these were evaluated since the participant when receiving the treatment knows the drug by its route of administration, therefore the blinding is lost. The relative effect with a 95% confidence interval was not statistically significant for two outcomes (recurrent venous thromboembolism and major bleeding).

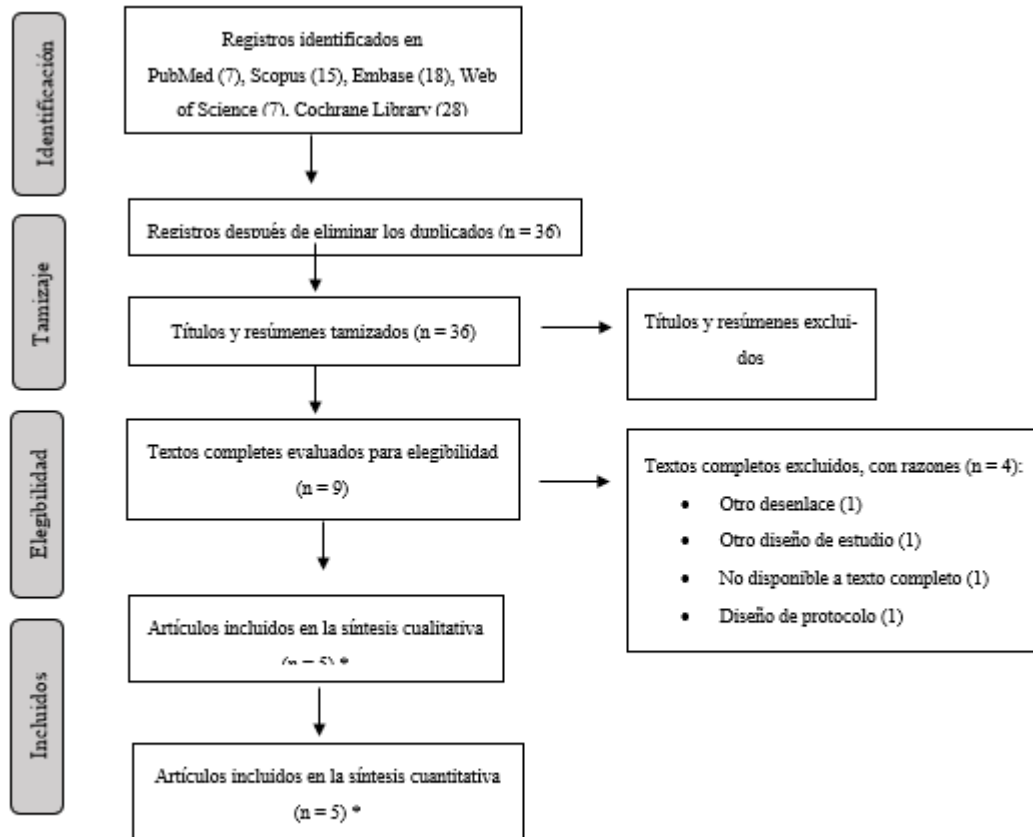
For risk of bias, the Cochrane RoB 2.0 tool presented in Figure 2 was used. All three trials had some concerns in one dimension (Deviations from planned interventions) and high risk in another (Outcome measurement), so overall all three studies are at high risk of bias.

Subgroup analysis

Subgroup analysis was performed according to the efficacy (primary) and safety (secondary) outcomes using the Forest plot presented in Figure 3. 33 of 734 (4.5%)

patients treated with Apixaban and 56 of 767 (7.3%) with Dalteparin had recurrent venous thromboembolism as the efficacy outcome (RR 0.49, 95% CI 0.15). -1.58, I² 38%). Major bleeding occurred in 25 of 734 patients treated with Apixaban (3.4%) and 27 of 767 with Dalteparin (3.5%) (RR 1.29, 95% CI 0.31-5.27, I² 59%). Likewise, clinically relevant non-major bleeding occurred in 64 of 734 patients treated with Apixaban (8.7%) and 46 of 767 (5.9%) with dalteparin (RR 1.52, 95% CI 1.05-2.19, I² 0%).

3.2. Figures, Tables and Schemes



* 5 artículos: 3 artículos sobre el estudio Caravaggio, 1 artículo sobre el estudio ADAM y 1 artículo sobre el estudio PRIORITY

Figure 1. PRISMA 2009 flow chart.

Table 1. Characteristics of included studies.

Author, year	Study design	Number of participants	Intervention and comparator	Dose	Treatment duration	Efficacy and Safety Outcomes	Average age	Male gender	Metastatic cancer	Creatinine clearance 30–50 mL/min	Platelet count 50–100,000/r
Agnelli et al., 2020; Ageno et al., 2020; Verso et al., 2021	Randomized and open trial	1155	Apixaban	Apixaban 10 mg orally twice daily for the first 7 days and 5 mg twice daily.	6 months	Efficacy outcome: - recurrent VTE	67.2	50.7%	67.5%	8.9%	3.6%
			Dalteparin	Subcutaneous dalteparin (200 IU/kg for 1 month followed by 150 IU/kg once daily).		Safety outcome: - Major bleeding - No major clinically relevant bleeding	67.2	47.7%	68.4%	10.5%	3.8%
Kim et al. 2022	Multicenter, open label, randomized, controlled phase II trial	90	Apixaban	Apixaban 10 mg orally twice daily for the first 7 days and 5 mg twice daily.	6 months	Efficacy outcome: - recurrent VTE	64 (39-77) *	56.8%	86.4%	NR	NR
			Dalteparin	Subcutaneous dalteparin (200 IU/kg for 1 month followed by		Safety outcome: - Major bleeding	63 (42-78) *	50.0%	71.7%	NR	NR

			150 IU/kg once daily).		- Clinically relevant bleeding					
			Apixaban 10 mg orally twice daily for the first 7 days and 5 mg twice daily.		Efficacy outcome: - recurrent VTE	64.4	48.0%	65.3%	9.3%	6.7%
McBane et al., 2020	Randomized and open trial	287	Subcutaneous dalteparin (200 IU/kg for 1 month followed by 150 IU/kg once daily).	6 months	Safety outcome: - Major bleeding - No major clinically relevant bleeding - Major bleeding plus clinically relevant non-major bleeding	64.0	48.7%	66.0%	9.3%	8.7%

Abbreviation: ISTH, International Society for Thrombosis and Haemostasis; PE, pulmonary embolism; VTE: venous thromboembolism; DVT: deep vein thrombosis; NR: Not reported; * Median (range)

Table 2. Summary of GRADE results

Outcomes	Anticipated Absolute Effects * (95% CI) Risk with Dalteparin	Risk with Apixaban	Relative effect (95% CI)	N°. of participants (studies)	Certainty of the evidence (GRADE)
Efficacy: Recurrent venous thromboembolism	73 for 1000	37 for 1000 (12 to 112)	RR 0.50 (0.16 to 1.53)	1501 (3 Randomized Controlled Experiments [RCTs])	⊕○○○ Very low a,b
Safety: - Major bleeding	35 for 1000	45 for 1000 (11 to 186)	RR 1.29 (0.31 to 5.27)	1501 (3 Randomized Controlled Experiments [RCTs])	⊕○○○ Very low a,b
- No major clinically relevant bleeding	60 for 1000	91 for 1000 (63 to 131)	RR 1.52 (1.05 to 2.19)	1501 (3 Randomized Controlled Experiments [RCTs])	⊕○○○ Very low a,b

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% confidence interval).

CI: confidence interval; RR: Risk ratio

GRADE Working Group grades of evidence.

High certainty: We are very confident that the true effect is close to that of the estimate of effect.

Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the effect estimate, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: the actual effect may be substantially different from the effect estimate.

Very low certainty: We have very little confidence in the estimate of effect: The actual effect is likely to be substantially different from the estimate of effect

Explanations

5

a. The participant when receiving the treatment knows the drug due to its route of administration, therefore, the blinding is lost.

6

b. The effects in the evaluated studies are not significant and have a high risk of bias.

7

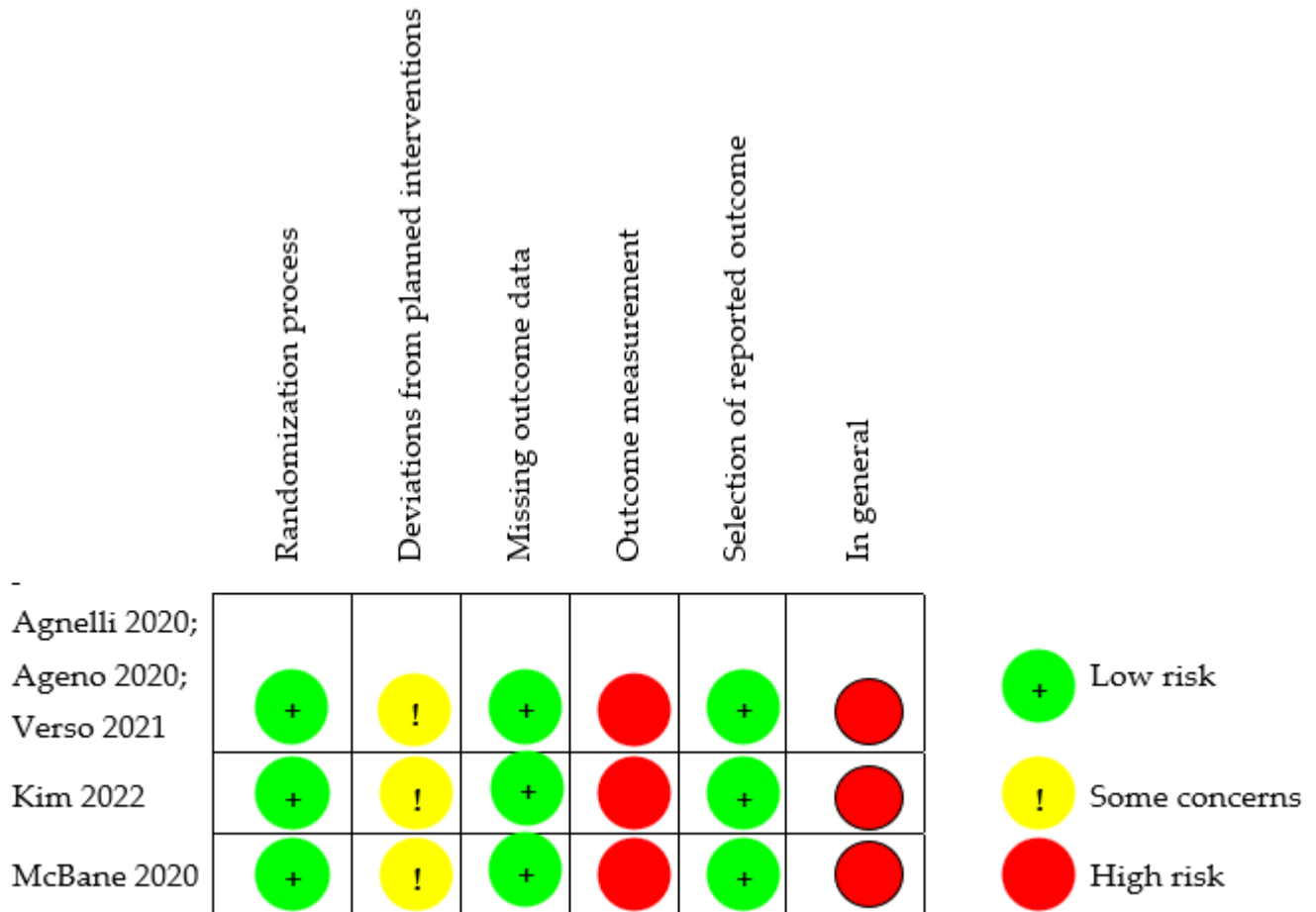
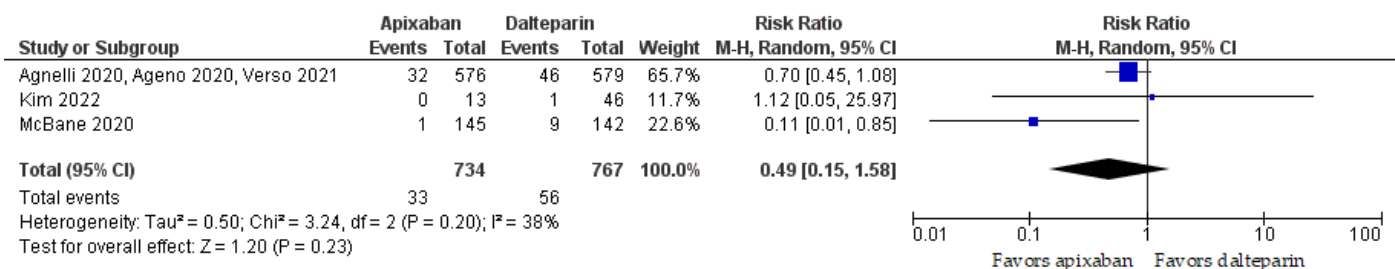


Figure 2. 2019 Cochrane Risk of Bias (RoB) Tool 2.0

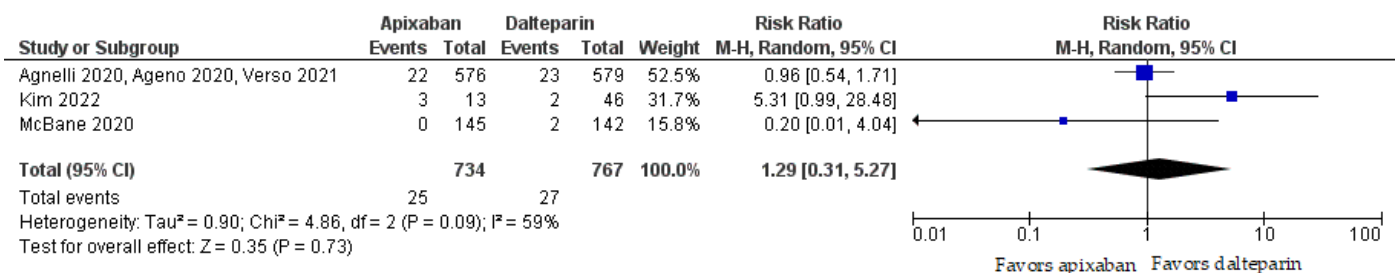
Efficacy outcome:

- Recurrent venous thromboembolism



Safety outcomes:

- Major bleeding



- No major clinically relevant bleeding

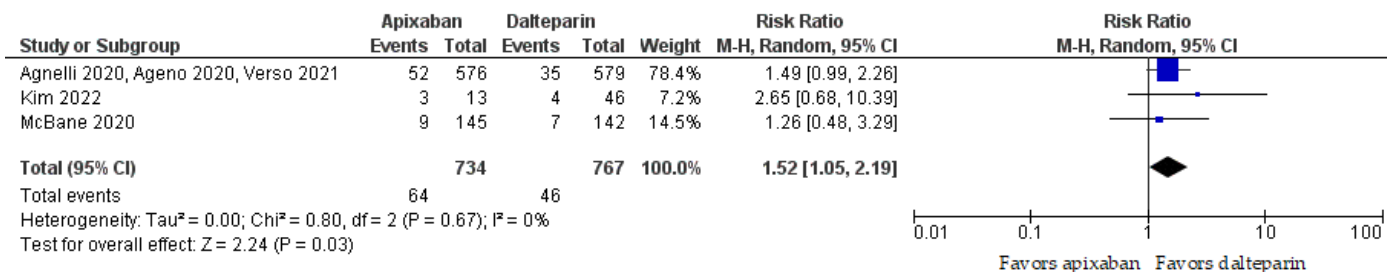


Figure 3. Forest plot of studies comparing apixaban and dalteparin.

4. Discussion

In our systematic review in patients with cancer-associated venous thromboembolism, apixaban and dalteparin were not statistically significant in reducing the relative risk of recurrent VTE and major bleeding. However, dalteparin was safe in reducing the relative risk of clinically relevant non-major bleeding in anticoagulant therapy compared to apixaban. Analysis by subgroup due to recurrent VTE was the main finding, clinically major bleeding and non-major bleeding were the secondary findings of the study. The risk of bias was high in the three studies evaluated. The degree of certainty of the evidence was very low in all three studies.

Various guidelines have established DOACs and LMWHs as an alternative to usual treatment in the prophylaxis and treatment of vascular diseases in cancer patients to counteract side effects such as bleeding and thrombocytopenia [31,32], where DOACs are more accepted for their oral therapy [33,34]. Multiple meta-analyses have been performed that have compared both treatment groups [35–41]. Some outcomes evaluated in each treatment have concluded that there is no significant difference between LMWH and DOAC, where the latter can be used as another treatment option for VTE associated with cancer [35–41]. Other outcomes have concluded that DOACs have greater efficacy and a relatively low risk of bleeding among drugs for the prevention and treatment of VTE in cancer patients, where Apixaban is the most effective and with the lowest risk of bleeding [35–42]. However, some results mentioned that DOACs had an increased risk of major bleeding in patients with gastrointestinal and genitourinary malignancies [35–41].

A meta-analysis of four RCTs concluded that DOACs are effective in the treatment of VTE associated with malignancy compared to LMWH; however, an increased risk of clinically relevant combined major or non-major bleeding was observed [43]. Another meta-analysis of eight RCTs comparing DOACs with LMWH and vitamin K antagonists (VKAs) concluded that DOACs are the optimal treatment for cancer-associated VTE, have a similar or slightly increased bleeding risk compared to LMWH and are a safer alternative to VKAs, and have a promising lowering effect on mortality, regardless of cancer status in these patients [44]. The recently published phase II PRIORITY RCT involving 90 patients with active cancer mentions that DOAC therapy further increased the risk of bleeding compared to Dalteparin in patients with active advanced upper GI, hepatobiliary, or pancreatic cancer. Therefore, great care is necessary when selecting

anticoagulant therapy for CA-VTE in high-risk patients [30]. Two meta-analyses had similar conclusions to our study, where LMWH drugs had fewer bleeding episodes compared to DOACs [45,46]. However, our results include two additional components, an assessment of the quality and certainty of the evidence; and a subgroup analysis of efficacy and safety according to the type of bleeding and in patients with cancer.

In our analysis performed in the GRADE summary results table, we found that patients receiving Apixaban had clinically relevant non-major bleeding with an anticipated absolute effect greater than 91 per 1000 compared to those receiving Dalteparin with 60 per 1000, this being statistically significant (RR 1.52; 95% CI, 1.05 to 2.19). Likewise, there was no statistical difference in major bleeding for patients who used both drugs. On the other hand, recurrent VTE was lower in patients with apixaban compared to dalteparin, but there was no statistical difference. These results of the RCTs evaluated add up to 1501 participants, which is a considerable number for the synthesis of evidence for two drugs. However, based on very low-certainty evidence, it is uncertain about the effect of the drugs, therefore, the use of Apixaban cannot be recommended because it may increase the risk of clinically relevant non-major bleeding compared to dalteparin.

In the various meta-analyses described above that evaluated DOACs versus LMWH as a treatment for cancer associated VTE, the evaluation was carried out jointly and not directly between each drug, this being little studied, therefore, in our study we chose the most effective and safe drug of DOACs and LMWH, with Apixaban and Dalteparin, respectively, being selected. Consequently, the exposed results leave evidence of the efficacy and safety of these drugs in the different types of bleeding, thus encouraging more randomized clinical trials and a subsequent meta-analysis of them.

The increase in various factors that contribute to the risk of bleeding in cancer patients is a challenge faced by every physician who performs anticoagulation treatment in this population. These are since the pathophysiology of cancer, thrombocytopenia, chemotherapy treatment and subsequent renal failure, generate instability in the hemostasis of everyone. In this sense, the evidence is still insufficient for a conclusion that LMWH and DOAC have similar efficacy and safety, therefore, carrying out more RCTs could bring us closer to a more solid and significant conclusion, since the small amount in each one can be attributed to a type 2 statistical error (false negative).

Our study has some limitations that must be considered. It was not possible to carry out a greater synthesis of the results of the different studies due to the little evidence of these, however, the number of participants can guide us the relative risks with respect to each outcome. The strength of the study is the methodology used where the results of the evaluation of the certainty of the study evidence and risk of bias of the studies included in the systematic review and meta-analysis were obtained, likewise the PRIORITY study was added for the first time to a meta-analysis for the summary of its results. The next step in the research is to carry out an economic evaluation of both therapies so that they are included in the national cancer plan and are more accessible to low-income populations.

5. Conclusions

Patients with cancer associated VTE who were treated with apixaban had a lower risk of recurrent VTE (safety outcome) compared to dalteparin. However, there was no statistical difference. Similarly, in the evaluation of major bleeding and clinically relevant non-major bleeding, there were no statistical differences between the two drugs. Likewise, the certainty of the evidence of the studies was found to be very low and the risk of bias high. Therefore, the evaluated treatments cannot be recommended because there is a very low certainty of evidence related to a non-significant effect in all clinical outcomes, in addition to a high risk of bias in the trials found.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, Figure S1: title; Table S1: title; Video S1: title.

Author Contributions:

Miguel A. Arce-Huamani: Conceptualization, methodology, software, formal analysis, research, methodology, writing—original draft preparation, writing—review and editing.

Joshuan J Barboza: Conceptualization, data curation, methodology, writing—original draft preparation, writing—review and editing.

José F. Martínez-Herrera: Supervision, writing—review and editing.

J. Smith Torres-Román: Methodology, writing—original draft preparation, writing—review and editing.

Jorge L. Maguiña: Conceptualization, original draft writing, and supervision.

All authors have read and agreed to the published version of the manuscript.

Funding: Please add: This research was funded by the Universidad Científica del Sur through the "Concurso Fondo Becas Cabies - Proyectos de Tesis de Grado y Posgrado 2022 - 1" approved by Directorial Resolution No. 019-DGIDI-CIENTÍFICA-2021.

Institutional Review Board Statement: The study was carried out in accordance with the Declaration of Helsinki, approved by the ethics committee of the Universidad Científica del Sur, through Certificate No. 341-CIEI-CIENTÍFICA-2021 and registration code 667-2021-POS50.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data is available in the supporting information.

Acknowledgments: Acknowledgments: This article was prepared by MA Arce-Huamani in partial compliance with the requirements to obtain the academic degree of master's in clinical Epidemiology and Biostatistics from the Universidad Científica del Sur. Therefore, the support provided during the execution of the article is appreciated.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Albertsen IE, Nielsen PB, Søgaard M, Goldhaber SZ, Overvad TF, Rasmussen LH, et al. Risk of Recurrent Venous Thromboembolism: A Danish Nationwide Cohort Study. *Am J Med.* 2018;131(9):1067-1074.e4. <https://doi.org/10.1016/j.amjmed.2018.04.042>
2. Caputo R, Pyle J, Kuriakose P, Lekura J. A systematic review of apixaban in prevention and treatment of cancer-associated venous thromboembolism. *J Am Pharm Assoc.* 2021; 61(5): e26-38. <https://doi.org/10.1016/j.japh.2021.06.005>
3. Song X, Liu Z, Zeng R, Shao J, Liu B, Zheng Y, et al. Treatment of venous thromboembolism in cancer patients: a systematic review and meta-analysis on the efficacy and safety of different direct oral anticoagulants (DOACs). *Ann Transl Med.* 2021; 9(2):162. <https://doi.org/10.21037/atm-20-8156>
4. Key NS, Bohlke K, Falanga A. Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Clinical Practice Guideline Update Summary. *J Oncol Pract.* 2019; 15(12):661-4. Disponible en: <https://ascopubs.org/doi/full/10.1200/JOP.19.00368>
5. Lloyd AJ, Dewilde S, Noble S, Reimer E, Lee AYY. What Impact Does Venous Thromboembolism and Bleeding Have on Cancer Patients' Quality of Life?. *Value Health J Int Soc Pharmacoeconomics Outcomes Res.* 2018; 21(4):449-55. <https://doi.org/10.1016/j.jval.2017.09.015>
6. Hao C, Sun M, Wang H, Zhang L, Wang W. Chapter Two - Low molecular weight heparins and their clinical applications. En: Zhang L, editor. *Progress in Molecular Biology and Translational Science.* Academic Press; 2019. p. 21-39. (Glycans and Glycosaminoglycans as Clinical Biomarkers and Therapeutics - Part B; vol. 163). <https://doi.org/10.1016/bs.pmbts.2019.02.003>
7. Amin A, Keshishian A, Dina O, Dhamane A, Nadkarni A, Carda E, et al. Comparative clinical outcomes between direct oral anticoagulants and warfarin among elderly patients with non-valvular atrial fibrillation in the CMS medicare population. *J Thromb Thrombolysis.* 2019; 48(2):240-9. <https://doi.org/10.1007%2Fs11239-019-01838-5>
8. Li A, Manohar PM, Garcia DA, Lyman GH, Steuten LM. Cost Effectiveness Analysis of Direct Oral Anticoagulant (DOAC) versus Dalteparin for the Treatment of Cancer Associated Thrombosis (CAT) in the United States. *Thromb Res.* 2019; 180:37-42. <https://doi.org/10.1016%2Fj.thromres.2019.05.012>

9. Liao CT, Lee MC, Chen ZC, Ku LJE, Wang JD, Toh HS. Cost-Effectiveness Analysis of Oral Anticoagulants in Stroke Prevention among Patients with Atrial Fibrillation in Taiwan. *Acta Cardiol Sin.* 2020; 36(1):50-61. [https://doi.org/10.6515%2FACS.202001_36\(1\).20190511A](https://doi.org/10.6515%2FACS.202001_36(1).20190511A)
10. Ay C, Beyer-Westendorf J, Pabinger I. Treatment of cancer-associated venous thromboembolism in the age of direct oral anticoagulants. *Ann Oncol Off J Eur Soc Med Oncol.* 2019;30(6):897-907. <https://doi.org/10.1093/annonc/mdz111>
11. O'Connell C, Escalante CP, Goldhaber SZ, McBane R, Connors JM, Raskob GE. Treatment of Cancer-Associated Venous Thromboembolism with Low-Molecular-Weight Heparin or Direct Oral Anticoagulants: Patient Selection, Controversies, and Caveats. *The Oncologist.* 2021;26(1): e8-16. <https://doi.org/10.1002/onco.13584>
12. Carrier M, Abou-Nassar K, Mallick R, Tagalakis V, Shivakumar S, Schattner A, et al. Apixaban to Prevent Venous Thromboembolism in Patients with Cancer. *N Engl J Med.* 2019; 380(8):711-9. <https://doi.org/10.1056/NEJMoa1814468>
13. Frere C, Benzidia I, Marjanovic Z, Farge D. Recent Advances in the Management of Cancer-Associated Thrombosis: New Hopes but New Challenges. *Cancers.* 2019; 11(1):71. <https://doi.org/10.3390%2Fcancers11010071>
14. Ladha D, Mallick R, Wang TF, Caiano L, Wells PS, Carrier M. Efficacy, and safety of apixaban for primary prevention in gastrointestinal cancers: A post-hoc analysis of the AVERT trial. *Thromb Res.* 2021; 202:151-4. <https://doi.org/10.1016/j.thromres.2021.03.013>
15. Knoll W, Mallick R, Wells PS, Carrier M. Safety, and efficacy of apixaban thromboprophylaxis in cancer patients with metastatic disease: A post-hoc analysis of the AVERT trial. *Thromb Res.* 2021; 197:13-5. <https://doi.org/10.1016/j.thromres.2020.10.026>
16. Lee JH, Lee JH, Jo KW, Huh JW, Oh YM, Lee JS. Comparison of rivaroxaban and dalteparin for the long-term treatment of venous thromboembolism in patients with gynecologic cancers. *J Gynecol Oncol.* 2020;31(1): e10. <https://doi.org/10.3802%2Fjgo.2020.31.e10>
17. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* 2021; 372: n71. <https://doi.org/10.1136/bmj.n71>
18. Saif-Ur-Rahman KM. Transparency of reporting search strategies in systematic reviews. *Hypertens Res.* 2022; 45(11):1838-9. <https://doi.org/10.1038/s41440-022-01003-1>

19. Tabares DH, Carrillo VP, Gómez JHD. Clasificación de los desenlaces en los ensayos clínicos. *Med UPB*. 2019; 38(2):147-57.
<https://doi.org/10.18566/medupb.v38n2.a07>
20. Khan F, Tritschler T, Kimpton M, Wells PS, Kearon C, Weitz JI, et al. Long-term risk of recurrent venous thromboembolism among patients receiving extended oral anticoagulant therapy for first unprovoked venous thromboembolism: A systematic review and meta-analysis. *J Thromb Haemost JTH*. 2021; 19(11):2801-13. <https://doi.org/10.1111/jth.15491>
21. Valizadeh A, Moassefi M, Nakhostin-Ansari A, Hosseini Asl SH, Saghab Torbati M, Aghajani R, et al. Abstract screening using the automated tool Rayyan: results of effectiveness in three diagnostic test accuracy systematic reviews. *BMC Med Res Methodol*. 2022;22(1):160.
<https://doi.org/10.1186/s12874-022-01631-8>
22. Brozek JL, Canelo-Aybar C, Akl EA, Bowen JM, Bucher J, Chiu WA, et al. GRADE Guidelines 30: the GRADE approach to assessing the certainty of modeled evidence-An overview in the context of health decision-making. *J Clin Epidemiol*. 2021; 129:138-50.
<https://doi.org/10.1016/j.jclinepi.2020.09.018>
23. Lee LL. [Application of the Risk of Bias 2 Tool]. *Hu Li Za Zhi*. 2021;68(2):85-91. [https://doi.org/10.6224/jn.202104_68\(2\).11](https://doi.org/10.6224/jn.202104_68(2).11)
24. Lin L. Comparison of four heterogeneity measures for meta-analysis. *J Eval Clin Pract*. 2020; 26(1):376-84. <https://doi.org/10.1111/jep.13159>
25. Kilpeläinen TP, Tikkinen KAO, Guyatt GH, Vernooij RWM. Evidence-based Urology: Subgroup Analysis in Randomized Controlled Trials. *Eur Urol Focus*. 2021; 7(6):1237-9. <https://doi.org/10.1016/j.euf.2021.10.001>
26. Agnelli G, Becattini C, Meyer G, Muñoz A, Huisman M, Connors J, et al. Apixaban for the Treatment of Venous Thromboembolism Associated with Cancer. *N Engl J Med*. 2020; 382(17):1599-1607.
<https://doi.org/10.1056/NEJMoa1915103>
27. Ageno W, Vedovati M, Cohen A, Huisman M, Bauersachs R, Gussoni G, et al. Bleeding with Apixaban and Dalteparin in Patients with Cancer-Associated Venous Thromboembolism: results from the Caravaggio Study. *Thromb Haemost*. 2021; 121(5):616-624. <https://doi.org/10.1055/s-0040-1720975>
28. Verso M, Munoz A, Bauersachs R, Huisman M, Mandalà M, Vescovo G, et al. Effects of concomitant administration of anticancer agents and apixaban or dalteparin on recurrence and bleeding in patients with cancer-associated venous thromboembolism. *Eur J Cancer Oxf Engl 1990*. 2021; 148:371-381.
<https://doi.org/10.1016/j.ejca.2021.02.026>
29. 29. McBane RD, Wysokinski WE, Le-Rademacher JG, Zemla T, Ashrani A,

- Tafur A, et al. Apixaban and dalteparin in active malignancy-associated venous thromboembolism: The ADAM VTE trial. *J Thromb Haemost JTH*. 2020; 18(2):411-21. <https://doi.org/10.1111/jth.14662>
30. Kim JH, Yoo C, Seo S, Jeong JH, Ryoo BY, Kim KP, et al. A Phase II Study to Compare the Safety and Efficacy of Direct Oral Anticoagulants versus Subcutaneous Dalteparin for Cancer-Associated Venous Thromboembolism in Patients with Advanced Upper Gastrointestinal, Hepatobiliary and Pancreatic Cancer: PRIORITY. *Cancers*. 2022; 14(3):559. <https://doi.org/10.3390/cancers14030559>
 31. Farge D, Frere C, Connors JM, Khorana AA, Kakkar A, Ay C, et al. 2022 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer, including patients with COVID-19. *Lancet Oncol*. 2022;23(7): e334-47. [https://doi.org/10.1016/s1470-2045\(22\)00160-7](https://doi.org/10.1016/s1470-2045(22)00160-7)
 32. Frere C, Farge D, Douketis J, Connors JM. The 2022 ITAC evidence-based clinical practice guidelines: New update from the International Initiative on Thrombosis and Cancer to improve the care in patients with cancer-associated thrombosis. *J Med Vasc*. 2022; 47(3):113-5. <https://doi.org/10.1016/j.jdmv.2022.08.002>
 33. Hutchinson A, Rees S, Young A, Maraveyas A, Date K, Johnson MJ. Oral anticoagulation is preferable to injected, but only if it is safe and effective: An interview study of patient and carer experience of oral and injected anticoagulant therapy for cancer-associated thrombosis in the select-d trial. *Palliat Med*. 2019; 33(5):510-7. <https://doi.org/10.1177/0269216318815377>
 34. Hendriks T, McGregor S, Rakesh S, Robinson J, Ho KM, Baker R. Patient satisfaction after conversion from warfarin to direct oral anticoagulants for patients on extended duration of anticoagulation for venous thromboembolism – The SWAN Study. *PLoS ONE*. 2020; 15(6): e0234048. <https://doi.org/10.1371/journal.pone.0234048>
 35. Mareev VY, Mareev YV. Role of anticoagulants in therapy and prevention of recurrent venous thromboembolism in patients with cancer: a meta-analysis of randomized trials with apixaban. *Kardiologija*. 2022;62(3):4-15. <https://doi.org/10.18087/cardio.2022.3.n1987>
 36. Wu S, Lv M, Chen J, Jiang S, Chen M, Fang Z, et al. Direct oral anticoagulants for venous thromboembolism in cancer patients: a systematic review and network meta-analysis. *Support Care Cancer Off J Multinatl Assoc Support Care Cancer*. 2022;30(12):10407-20. <https://doi.org/10.1007/s00520-022-07433-4>
 37. Frere C, Farge D, Schrag D, Prata PH, Connors JM. Direct oral anticoagulant versus low molecular weight heparin for the treatment of cancer-associated venous thromboembolism: 2022 updated systematic review and meta-

- analysis of randomized controlled trials. *J Hematol Oncol*. 2022; 15(1):69. <https://doi.org/10.1186/s13045-022-01289-1>
38. Hussain MR, Ali FS, Verghese D, Myint PT, Ahmed M, Gong Z, et al. Factor Xa inhibitors versus low molecular weight heparin for the treatment of cancer associated venous thromboembolism; A meta-analysis of randomized controlled trials and non-randomized studies. *Crit Rev Oncol Hematol*. 2022; 169:103526. <https://doi.org/10.1016/j.critrevonc.2021.103526>
 39. Murphy AC, Koshy AN, Farouque O, Yeo B, Raman J, Kearney L, et al. Factor Xa Inhibition for the Treatment of Venous Thromboembolism Associated With Cancer: A Meta-Analysis of the Randomised Controlled Trials. *Heart Lung Circ*. 2022; 31(5):716-25. <https://doi.org/10.1016/j.hlc.2021.10.024>
 40. Mohamed MFH, ElShafei MN, Ahmed MB, Abdalla LO, Ahmed I, Elzouki AN, et al. The Net Clinical Benefit of Rivaroxaban Compared to Low-Molecular-Weight Heparin in the Treatment of Cancer-Associated Thrombosis: Systematic Review and Meta-Analysis. *Clin Appl Thromb Off J Int Acad Clin Appl Thromb*. 2021; 27:1076029620940046. <https://doi.org/10.1177/1076029620940046>
 41. Riaz IB, Fuentes HE, Naqvi SAA, He H, Sipra QUAR, Tafur AJ, et al. Direct Oral Anticoagulants Compared With Dalteparin for Treatment of Cancer-Associated Thrombosis: A Living, Interactive Systematic Review and Network Meta-analysis. *Mayo Clin Proc*. 2022;97(2):308-24. <https://doi.org/10.1016/j.mayocp.2020.10.041>
 42. Ning H, Yang N, Ding Y, Chen H, Wang L, Han Y, et al. Efficacy and safety of direct oral anticoagulants for the treatment of cancer-associated venous thromboembolism: A systematic review and Bayesian network meta-analysis. *Med Clin (Barc)*. 2023;160(6):245-52. <https://doi.org/10.1016/j.medcli.2022.06.022>
 43. Samaranayake CB, Anderson J, McCabe C, Zahir SF, W Upham J, Keir G. Direct oral anticoagulants for cancer-associated venous thromboembolisms: a systematic review and network meta-analysis. *Intern Med J*. 2022;52(2):272-81. <https://doi.org/10.1111/imj.15049>
 44. Yamani N, Unzek S, Almas T, Musheer A, Ejaz A, Paracha AA, et al. DOACs or VKAs or LMWH - What is the optimal regimen for cancer-associated venous thromboembolism? A systematic review and meta-analysis. *Ann Med Surg* 2012. 2022; 79:103925. <https://doi.org/10.1016/j.amsu.2022.103925>
 45. Mai V, Tanguay VF, Guay CA, Bertoletti L, Magnan S, Turgeon AF, et al. DOAC compared to LMWH in the treatment of cancer related-venous thromboembolism: a systematic review and meta-analysis. *J Thromb Thrombolysis*. 2020; 50(3):661-7. <https://doi.org/10.1007/s11239-020-02055-1>

46. Moik F, Posch F, Zielinski C, Pabinger I, Ay C. Direct oral anticoagulants compared to low-molecular-weight heparin for the treatment of cancer-associated thrombosis: Updated systematic review and meta-analysis of randomized controlled trials. *Res Pract Thromb Haemost.* 2020;4(4):550-61. <https://doi.org/10.1002/rth2.12359>

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions, or products referred to in the content.

Copias de cartas de respuesta a las observaciones

- Respuesta observaciones del primer revisor:

Dear reviewer,

In accordance with the provided feedback, the following changes have been implemented, as detailed below:

1. Abstract: The number of studies included in the meta-analysis has been added to the abstract.
2. Methods: An explanation has been provided for why only studies with dalteparin as a control were included in the analysis and not other types of LMWH in the systematic review.
3. Methods: Appropriate citations have been included for the definition of major bleeding and clinically non-relevant major bleeding.
4. The suggested change has been accepted, and the section previously named "Subgroup Analysis" has been renamed to "Outcome Analysis."
5. Results: The rationale for classifying the risk of high bias in outcome measurement and deviations from planned intervention has been provided.
6. The order of the GRADE assessment and RoB evaluation has been revised.

Furthermore, these changes have been highlighted in yellow in the attached document of the article.

Sincerely,

- Respuesta del primer revisor:

Review Report Form					
Quality of English Language	<input type="checkbox"/> I am not qualified to assess the quality of English in this paper <input type="checkbox"/> English very difficult to understand/incomprehensible <input type="checkbox"/> Extensive editing of English language required <input type="checkbox"/> Moderate editing of English language required <input type="checkbox"/> Minor editing of English language required <input checked="" type="checkbox"/> English language fine. No issues detected				
	<table style="margin: auto;"> <thead> <tr> <th style="padding: 2px 10px;">Yes</th> <th style="padding: 2px 10px;">Can be improved</th> <th style="padding: 2px 10px;">Must be improved</th> <th style="padding: 2px 10px;">Not applicable</th> </tr> </thead> </table>	Yes	Can be improved	Must be improved	Not applicable
Yes	Can be improved	Must be improved	Not applicable		
Does the introduction provide sufficient background and include all relevant references?	<table style="margin: auto;"> <tr> <td style="padding: 2px 10px;">(x)</td> <td style="padding: 2px 10px;">()</td> <td style="padding: 2px 10px;">()</td> <td style="padding: 2px 10px;">()</td> </tr> </table>	(x)	()	()	()
(x)	()	()	()		
Are all the cited references relevant to the research?	<table style="margin: auto;"> <tr> <td style="padding: 2px 10px;">(x)</td> <td style="padding: 2px 10px;">()</td> <td style="padding: 2px 10px;">()</td> <td style="padding: 2px 10px;">()</td> </tr> </table>	(x)	()	()	()
(x)	()	()	()		
Is the research design appropriate?	<table style="margin: auto;"> <tr> <td style="padding: 2px 10px;">(x)</td> <td style="padding: 2px 10px;">()</td> <td style="padding: 2px 10px;">()</td> <td style="padding: 2px 10px;">()</td> </tr> </table>	(x)	()	()	()
(x)	()	()	()		
Are the methods adequately described?	<table style="margin: auto;"> <tr> <td style="padding: 2px 10px;">(x)</td> <td style="padding: 2px 10px;">()</td> <td style="padding: 2px 10px;">()</td> <td style="padding: 2px 10px;">()</td> </tr> </table>	(x)	()	()	()
(x)	()	()	()		
Are the results clearly presented?	<table style="margin: auto;"> <tr> <td style="padding: 2px 10px;">(x)</td> <td style="padding: 2px 10px;">()</td> <td style="padding: 2px 10px;">()</td> <td style="padding: 2px 10px;">()</td> </tr> </table>	(x)	()	()	()
(x)	()	()	()		
Are the conclusions supported by the results?	<table style="margin: auto;"> <tr> <td style="padding: 2px 10px;">(x)</td> <td style="padding: 2px 10px;">()</td> <td style="padding: 2px 10px;">()</td> <td style="padding: 2px 10px;">()</td> </tr> </table>	(x)	()	()	()
(x)	()	()	()		
Comments and Suggestions for Authors	I am satisfied with authors' responses.				
Submission Date	06 September 2023				
Date of this review	13 Oct 2023 09:01:11				

- **Respuesta observaciones del segundo revisor:**

Dear reviewer,

Figure 1 can be viewed, and you can also verify it in the attached document of the article. Furthermore, we accept your recommendation that it is not the time to contemplate the inclusion of these medications in the national cancer plan when the evidence of their effectiveness and safety is still unclear.

Additionally, these changes have been highlighted in yellow in the attached document of the article.

Sincerely,

- **Respuesta observaciones del tercer revisor:**

Dear reviewer,

We appreciate your observation where you mentioned that from a clinical standpoint, both apixaban and dalteparin are suitable therapeutic options. Therefore, we have modified and added the following statement to the conclusion: "It is still not possible to recommend that one of the evaluated treatments is more effective and safer than the other."

Furthermore, these changes have been highlighted in yellow in the attached document of the article.

Sincerely,

1. Introducción

La tromboembolia venosa (TEV) es la tercera enfermedad vascular más importante en la población general. Los pacientes con cáncer tienen entre 4 y 7 veces más probabilidades de desarrollar TEV, siendo la segunda causa de muerte entre estos pacientes [1,2]. La incidencia de TEV recurrente es del 9,6%, alcanzando el 22,1% en los primeros 6 meses tras el diagnóstico inicial de cáncer [3]. El riesgo de TEV varía entre los diferentes tipos de cáncer, pacientes con cáncer de páncreas o gástrico debido a su alto potencial trombogénico, asimismo, pacientes con cáncer de riñón, ovario, pulmón y estómago son los más propensos [4-6] y factores individuales como la edad, la obesidad y comorbilidades médicas también contribuyen al riesgo. Tratamientos como quimioterapias a base de platino y terapias antiangiogénicas se asocian con un mayor riesgo de TEV [7-8].

El tratamiento anticoagulante se recomienda para prevenir la TEV en pacientes de alto riesgo (puntuación KHORANA >2) y para tratar a los que ya han sufrido un evento trombótico [9]. Sin embargo, esta terapia conlleva un riesgo significativo de hemorragia, la reacción adversa más grave. Las heparinas de bajo peso molecular (HBPM) y los anticoagulantes orales directos (ACOD) son los tratamientos anticoagulantes más utilizados [3,10]. La Dalteparina, una HBPM, se recomienda en pacientes con TEV relacionada con el cáncer, ya que se ha asociado a una menor incidencia de osteoporosis y trombocitopenia inducida por la heparina [11]. Entre los ACOD, el Apixaban ha demostrado tener un menor riesgo de enfermedad/embolia cerebrovascular sistémica y de hemorragia grave [12]. Sin embargo, el coste de dichos fármacos es de aproximadamente 64 USD y 106 USD para el Apixaban y la Dalteparina, respectivamente, lo que dificulta el acceso del público en general [13,14]. Por lo tanto, es necesario proponer estrategias para su adquisición.

Diversos estudios han abordado los ACOD y las HBPM como tratamiento de la ETV asociada al cáncer [15,16], y nuevos fármacos como el Apixaban y la Dalteparina han demostrado su eficacia y seguridad en comparación con otros tratamientos habituales [17,18]. En cuanto a la trombopprofilaxis, se ha informado de la eficacia y seguridad de Apixaban en un ensayo clínico randomizado (ECA) con 130 pacientes con cáncer gastrointestinal, en los que demostró reducir la incidencia de tromboembolismo al 4,6% frente al 20% en el grupo placebo [19]. En otro ECA, en 365 pacientes estratificados según la presencia o ausencia de cáncer metastásico, la trombopprofilaxis con Apixaban se asoció a una tasa significativamente menor de TEV, con una Hazard ratio de 0,55 y 0,34, respectivamente, en comparación con el placebo [20]. Por su parte, en un ECA en pacientes con TEV asociada a cáncer ginecológico, la Dalteparina mostró una menor aparición de hemorragias mayores en el 5% frente al 7,8% en las que recibieron rivaroxabán como tratamiento [21]. Sin embargo, ningún estudio ha sintetizado los desenlaces del tratamiento con Apixaban y Dalteparina para la TEV en pacientes con cáncer, lo que constituye una información importante.

En consecuencia, los autores del estudio señalan que la evaluación de la eficacia y la seguridad del tratamiento de la ETV asociada al cáncer sigue siendo un reto debido a los diversos estudios disponibles que amplían las opciones terapéuticas. Asimismo, las reacciones adversas de estos tratamientos pueden ser perjudiciales para los pacientes, por lo que es importante sintetizar la evidencia entre ellos. El Apixaban y la

Dalteparina han sido objeto de varios estudios que demuestran su capacidad para reducir las hemorragias mayores y la recurrencia de la TEV en pacientes con cáncer. Sin embargo, a pesar del número de ECA que comparan estos fármacos con otras HBPM y ACOD, ningún estudio ha comparado la eficacia y seguridad de Apixaban y Dalteparina.

Por lo tanto, el objetivo de nuestro estudio fue sintetizar la evidencia sobre la eficacia y la seguridad de Apixaban frente a Dalteparina en la reducción de la TEV recurrente, las hemorragias graves y las hemorragias no graves clínicamente relevantes asociadas al cáncer.

2. Materiales y métodos

Utilizamos el informe PRISMA para revisiones sistemáticas y metaanálisis [22] para redactar nuestra revisión sistemática. La versión de nuestro protocolo se registró en el Registro Prospectivo Internacional de Revisiones Sistemáticas (PROSPERO) con el código CRD42021275583.

2.1. Fuentes de datos y búsquedas

Desde el inicio hasta el 5 de enero de 2023, se realizaron búsquedas en las siguientes bases de datos: PubMed, Scopus, Web of Science, Embase y Registro Cochrane Central de Ensayos Controlados (Cochrane Central Register of Controlled Trials, CENTRAL) en busca de estudios que evaluaran la eficacia de Apixaban frente a Dalteparina como tratamiento de la ETV asociada al cáncer, y se realizó una búsqueda en ClinicalTrials para identificar ECA en curso o finalizados relacionados con nuestra revisión. Se tomó la decisión de incluir la Dalteparina como única HBPM (grupo de control) debido a la falta de estudios que compararan exclusivamente estos dos fármacos, los cuales han mostrado resultados prometedores en la TEV asociada al cáncer. Esta elección tiene como objetivo mantener la coherencia dentro de la comparación y reducir la variabilidad de los resultados mediante la estandarización de la comparación, evitando así las diferencias entre las diferentes heparinas de bajo peso molecular.

En la estrategia de búsqueda, se utilizaron los términos "Apixaban", "Dalteparin" y "Venous thromboembolism" y sus sinónimos MESH utilizando la lista de comprobación Peer Review of Electronic Search Strategies [23]. Nuestro equipo desarrolló la estrategia de búsqueda en PubMed, y se adaptó a las diferentes bases de datos bibliográficas mencionadas (Información de Soporte 1). No se aplicaron restricciones de idioma.

2.2. Selección de estudios y extracción de datos

Se incluyeron los estudios que cumplían los siguientes criterios (1) estudio experimental ECA, fase 2 o 3, paralelo o cruzado; (2) estudios que incluyeran pacientes con cáncer de cualquier etiología y que presentaran TEV; (3) tratamiento con Apixaban como grupo experimental/de intervención con una duración de 6 meses; y (4) Dalteparina como grupo control con una duración de 6 meses de tratamiento. Asimismo, se excluyeron los estudios realizados en animales, las duplicaciones, los

resúmenes de congresos, los informes de casos y series, los estudios observacionales, los artículos de revisión, las revisiones sistemáticas y los editoriales o comentarios. Los desenlaces se clasificaron en términos de eficacia y seguridad, que se utilizan en los ECA; los desenlaces de eficacia fueron la prevención de la trombosis venosa y los resultados de seguridad fueron las hemorragias [24]. En nuestro estudio, el resultado de eficacia fue la TEV recurrente, que se definió como la trombosis de un sitio venoso que no estaba afectado previamente, o un historial previo de intervalo de resolución del trombo incidente [25]. Por otra parte, los desenlaces de seguridad fueron hemorragia grave, definida como hemorragia visible acompañada de una disminución de la hemoglobina de ≥ 2 g/dL; o transfusión de ≥ 2 unidades de paquete de hematíes; o hemorragia intracraneal, intraespinal/epidural, intraocular, retroperitoneal, pericárdica, intraarticular, intramuscular con síndrome compartimental o mortal [26]; y la hemorragia no grave clínicamente relevante se definió como una hemorragia manifiesta que no se ajusta a la definición de hemorragia grave pero que se asocia a intervención médica, atención médica no programada o interrupción temporal del tratamiento anticoagulante [27].

Dos revisores (MAAH y JJB) examinaron de forma independiente los títulos y resúmenes de los artículos seleccionados para elegir los artículos potencialmente relevantes. Una vez encontrados los posibles estudios a incluir, cuatro autores (MAH, JJB, JSTR y JFMH) leyeron de forma independiente el texto completo de cada artículo seleccionado. Si un artículo no cumplía uno o más criterios de selección, se excluía del estudio. Las discrepancias se resolvieron por consenso entre el equipo de investigadores en cada fase. Se utilizó el software Rayyan QCRI Versión 1.2.1 (Qatar Computing Research Institute, Doha, Qatar) para llevar a cabo el proceso de selección de estudios [28]. Por último, dos autores (MAH y JJB) extrajeron los datos de los estudios mediante una hoja de extracción de datos estandarizada realizada en Microsoft Excel. Se extrajo la siguiente información: autor, año, país, diseño del estudio, número de participantes, intervención, comparador, duración del tratamiento, desenlace de eficacia y seguridad, edad media, porcentaje de varones, cáncer activo, cáncer metastásico, estado ECOG mayor o igual a 2, tumor sólido, neoplasia hematológica, peso corporal medio (desviación estándar), aclaramiento de creatinina de 30-50 ml/min, recuento de plaquetas de 50-100.000/mm³ y embolia pulmonar incidental en el momento del diagnóstico.

2.3. Evaluación de la certeza de la evidencia del estudio y riesgo de sesgo de los estudios

La evaluación de la certeza de la evidencia se realizó utilizando la metodología GRADE [29], considerando cinco criterios: riesgo de sesgo, inconsistencia, evidencia indirecta, imprecisión y sesgo de publicación, este último no se presentó resultado porque el sesgo de publicación es difícil de evaluar entre revisiones de 10 o menos estudios (debido a la falta de poder estadístico) [30-32]. La certeza de la evidencia se determinó en función de los resultados empleando el programada GRADEpro GDT versión 2021, que facilita la síntesis y presentación de los datos para apoyar la toma de decisiones en el ámbito de la salud, a través de la elaboración de tablas de resumen de resultados (SoF).

La versión 2019 de la herramienta Risk of Bias (RoB) 2.0 se empleó para analizar el riesgo de sesgo presente en los estudios controlados aleatorios (ECAs) considerados en esta investigación [33]. Dicha herramienta abordó distintas áreas potenciales de sesgo, empleando un algoritmo para asignar una categorización de riesgo como bajo, de preocupación intermedia o alto, tanto por cada área específica como por estudio. Dos autores (MAH y JJB) realizaron la evaluación con RoB 2.0 de forma independiente, y las diferencias que surgieron se manejaron a través de debates o la consulta a un tercer investigador (JMQ) para su resolución.

2.4. Síntesis y análisis de datos

Se empleó el programa Review Manager 5.3 (RevMan 5.3), desarrollado por The Cochrane Collaboration en Copenhague, Dinamarca, para llevar a cabo los análisis estadísticos. Se optó por un modelo de meta-análisis de efectos aleatorios con varianza inversa para examinar la diferencia en la eficacia de Apixaban en comparación con Dalteparina. Los efectos del tratamiento se calcularon como riesgos relativos (RR) acompañados de sus intervalos de confianza (IC) del 95%. Para ajustar los IC de los resultados, se utilizó el método Hartung-Knapp, y la dispersión tau² entre los estudios se determinó mediante el método de Paule-Mandel. La variabilidad entre los resultados de los estudios se midió con el índice I², interpretando un I² mayor al 60% como una señal de heterogeneidad moderada [34].

Se procedió con un análisis detallado siguiendo parámetros establecidos: para Apixaban, se administró una dosis de 10 mg dos veces diarias durante los siete días iniciales, pasando a 5 mg dos veces diarias posteriormente, y para Dalteparina, se prescribió una dosis inicial de 200 unidades internacionales (UI) por kilogramo de peso corporal al día durante el primer mes, que luego se ajustó a 150 UI por kilogramo diariamente. Se examinaron la recurrencia de tromboembolismo venoso (TEV), sangrado mayor y sangrado no mayor clínicamente relevante; se empleó el análisis de interacción, considerando $p < 0.05$ como indicativo de una influencia significativa de los resultados en la efectividad del tratamiento [35]. Para realizar el metaanálisis, se utilizó el software Review Manager 5.3 (RevMan 5.3) de The Cochrane Collaboration, ubicado en Copenhague, Dinamarca.

3. Resultados

3.1. Subsección

3.1.1. Selección de estudios

El diagrama de flujo que resume el proceso de selección de estudios se muestra en la Figura 1. En la búsqueda inicial se encontraron un total de 75 registros. Tras excluir los estudios duplicados, se conservaron 36 estudios. Posteriormente, durante la evaluación de títulos y resúmenes, se excluyeron 27 registros más. Por último, durante la evaluación del texto completo, se excluyeron cuatro artículos debido a que tenían otro resultado, otro diseño de estudio, no estaban disponibles en texto completo o debido al diseño del protocolo. Finalmente, de los cinco artículos seleccionados para

la síntesis de la información, tres correspondían al estudio Caravaggio [36-38], uno al ensayo ADAM TVE (ETV) [39] y uno de fase II al ensayo PRIORITY [40]. Se considero los tres artículos del estudio Caravaggio para tener información completa del este.

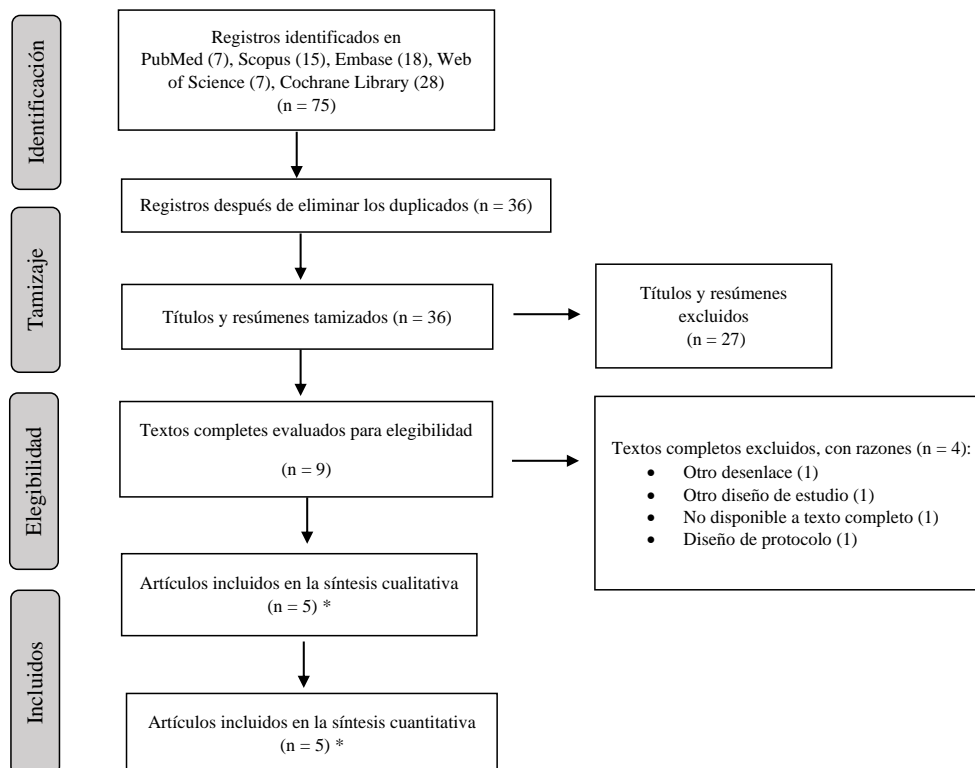


Figura 1. Diagrama de flujo PRISMA 2009. * 5 artículos: 3 sobre el estudio Caravaggi, 1 sobre el estudio ADAM y 1 sobre el estudio PRIORITY.

3.1.2. Descripción y Características de los Estudios

Las características de los estudios incluidos se presentan en la Tabla 1. Para esta revisión sistemática, se incluyeron tres estudios; se trataba de ECA abiertos. Los tres estudios informaron sobre el desenlace de eficacia (TEV recurrente) y los desenlaces de seguridad (hemorragia grave y hemorragia no grave clínicamente relevante). Las dosis en la intervención y el comparador fueron las mismas en los tres ensayos clínicos (Caravaggio, ADAM y PRIORITY) con una duración de 6 meses de tratamiento. La media y la mediana de edad oscilaron entre 64 y 67 años, la proporción entre hombres y mujeres fue similar y más del 60% de los pacientes tenían cáncer metastásico.

Tabla 1. Características de los estudios incluidos.

Autor, Año	Diseño del estudio	Número de Participantes	Intervención y comparador	Dosis	Duración del tratamiento	Desenlaces de eficacia y seguridad	Edad promedio	Género masculino	Cáncer metastásico	Aclaramiento de creatinina 30-50 ml/min	Recuento de plaquetas 50-100.000/mm ³
Agnelli et al., 2020 [28]; Ageno et al., 2020 [29]; Verso et al., 2021 [30]	Ensayo aleatorizado y abierto.	1155	Apixaban	Apixaban 10 mg por vía oral dos veces al día durante los primeros 7 días y 5 mg dos veces al día.	6 meses	Desenlaces de eficacia: - TEV recurrente	67.2	50.7%	67.5%	8.9%	3.6%
			Dalteparina	Dalteparina subcutánea (200 UI/kg durante 1 mes seguido de 150 UI/kg una vez al día).		Desenlaces de seguridad: - Sangrado importante - Sin hemorragia importante clínicamente relevante					
Kim et al., 2022 [32]	Ensayo de fase II multicéntrico, abierto, aleatorizado y controlado	90	Apixaban	Apixaban 10 mg por vía oral dos veces al día durante los primeros 7 días y 5 mg dos veces al día.	6 meses	Desenlaces de eficacia: - TEV recurrente	64 (39-77) *	56.8%	86.4%	NR	NR
			Dalteparina	Dalteparina subcutánea (200 UI/kg durante 1 mes seguido de 150 UI/kg una vez al día).		- Sangrado clínicamente relevante					
McBane et al., 2020 [31]	Ensayo aleatorizado y abierto.	287	Apixaban	Apixaban 10 mg por vía oral dos veces al día durante los primeros 7 días y 5 mg dos veces al día.	6 meses	Desenlaces de eficacia: - TEV recurrente	64.4	48.0%	65.3%	9.3%	6.7%
			Dalteparina	Dalteparina subcutánea (200 UI/kg durante 1 mes seguido de 150 UI/kg una vez al día).		- Sangrado importante - Sin hemorragia importante clínicamente relevante - Sangrado mayor más sangrado no mayor clínicamente relevante					

Abreviaturas: PE, embolia pulmonar; TEV: tromboembolismo venoso; NR: No informado; * Mediana (rango)

3.1.3. Evaluación de la certeza de la evidencia del estudio y riesgo de sesgo de los estudios

Para el riesgo de sesgo, se utilizó la herramienta Cochrane RoB 2.0 presentada en la figura 2. Los tres ensayos presentaban cierta preocupación en una dimensión (desviaciones de las intervenciones planificadas) y alto riesgo en otra (medición de resultados), por lo que, en conjunto, los tres estudios tenían un alto riesgo de sesgo. La calificación de alto riesgo de sesgo en la medición de resultados y las desviaciones de la intervención planificada se basó en varios factores. En lo que respecta al alto riesgo de sesgo en la medición de resultados se debe a un cegamiento insuficiente, tanto para los participantes como para los investigadores, que puede permitir una influencia inconsciente en la medición o determinación de los resultados, porque ambos tratamientos tienen vía de administración distinta. Asimismo, los evaluadores y participantes (pacientes) sabían el tratamiento que recibían al momento de la administración. Las desviaciones de la intervención planificada, como el incumplimiento del tratamiento o los cambios imprevistos, pueden sesgar los resultados. Además, un seguimiento inadecuado puede contribuir a aumentar el riesgo de sesgo en la investigación.

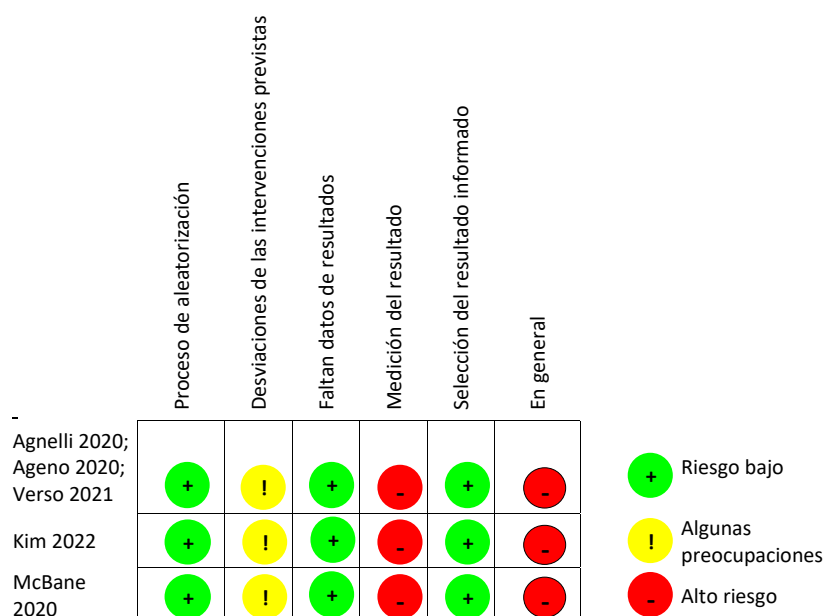


Figura 2. 2019 Herramienta Cochrane de riesgo de sesgo (RoB) 2.0 [33, 36-40].

Se utilizó el programa informático GRADEpro GDT versión 2021 para crear la tabla resumen de los resultados que se muestra en la Tabla 2. Se evaluaron tres resultados (uno de eficacia y dos de seguridad). El grado de certeza de la evidencia fue muy bajo en estos estudios, ya que los participantes sabían qué fármaco estaban recibiendo por la vía de administración y, por lo tanto, se perdió el cegamiento. El efecto relativo con un IC del 95% no fue estadísticamente significativo para dos resultados (TEV recurrente y hemorragia grave).

Tabla 2. Resumen de resultados de GRADE.

Resultado	Efectos absolutos previstos* (95% IC)		Efecto relativo (95% IC)	N°. Participantes (Estudios)	deCerteza de la evidencia (GRADE)
	Riesgo Dalteparina	conRiesgo Apixaban			
Eficacia: Tromboembolis mo venoso recurrente	73 por 1000	37 por (12 a 112)	1000RR (0.16 a 1.53)	1501 (3 experimentos controlados aleatoriamente)	⊕○○○ Muy bajo ^{a,b}
Seguridad: - Sangrado importante	35 por 1000	45 por (11 a 186)	1000RR (0.31 a 5.27)	1501 (3 experimentos controlados aleatoriamente)	⊕○○○ Muy bajo ^{a,b}
- Sin hemorragia clínicamente relevante	60 por 1000	91 por (63 a 131)	1000RR (1.05 a 2.19)	1501 (3 experimentos controlados aleatoriamente)	⊕○○○ Muy bajo ^{a,b}

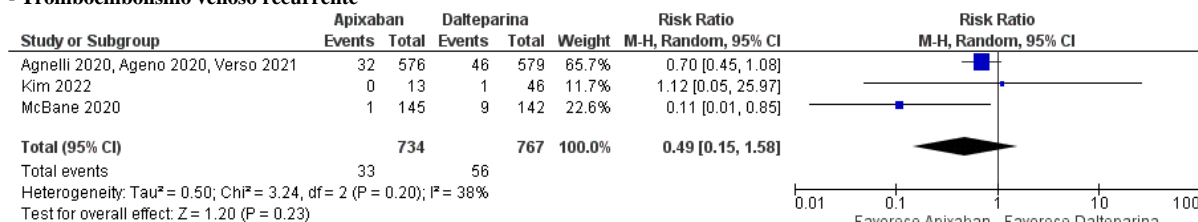
*La estimación del riesgo para el grupo sometido a la intervención (junto con su intervalo de confianza del 95%) se determina a partir del riesgo previsto en el grupo de control y el impacto relativo de la intervención (incluido su intervalo de confianza del 95%). El término IC se refiere al intervalo de confianza, y RR a la razón de riesgo. El símbolo “⊕” indica certeza en la evidencia proporcionada, mientras que “○” refleja la falta de certeza en la evidencia. Los niveles de certeza de la evidencia de acuerdo con el enfoque GRADE se describen de la siguiente forma: Certeza alta significa que hay mucha seguridad en que el efecto real se acerque a la estimación de efecto. Con certeza moderada, se tiene una confianza razonable en la estimación del efecto, aceptando la posibilidad de que el efecto real se diferencie en algún grado significativo. La certeza baja implica que la confianza en la estimación del efecto es reducida, y el efecto real podría diferir de manera notable de la estimación. La certeza muy baja señala escasa confianza en la estimación del efecto, siendo muy probable que el efecto real se desvíe significativamente de la estimación. Se añaden las siguientes notas explicativas: a) La conciencia del participante sobre el fármaco que se administra, debido a su método de administración, anula el efecto de enmascaramiento. b) Los resultados observados en los estudios considerados no son concluyentes y presentan un elevado riesgo de sesgo.

3.1.4. Análisis de desenlaces

El análisis de desenlaces se realizó en función de los desenlaces de eficacia (primarios) y seguridad (secundarios) mediante el diagrama de Forest presentado en la figura 3. Treinta y tres de los 734 (4,5%) pacientes tratados con Apixaban y 56 de los 767 (7,3%) que recibieron Dalteparina presentaron TEV recurrente como desenlace de eficacia (RR 0,49; IC 95%: 0,15). -1.58, I² 38%). Se produjeron hemorragias graves en 25/734 pacientes tratados con Apixaban (3,4%) y 27/767 con Dalteparina (3,5%) (RR 1,29; IC del 95%: 0,31-5,27; I² 59%). Asimismo, se produjeron hemorragias no graves clínicamente relevantes en 64/734 pacientes tratados con Apixaban (8,7%) y 46/767 (5,9%) con Dalteparina (RR 1,52; IC 95%: 1,05-2,19; I² 0%).

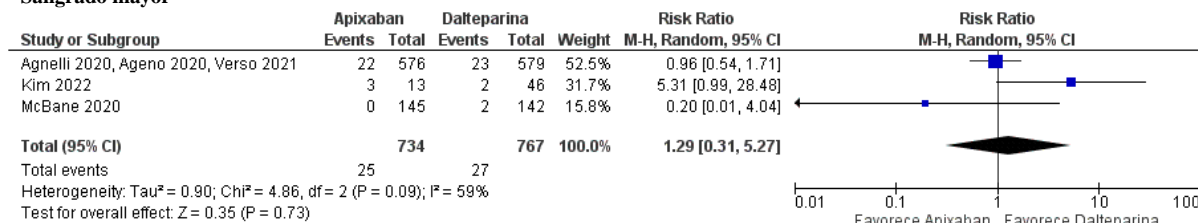
Desenlace de eficacia:

- Tromboembolismo venoso recurrente



Desenlaces de seguridad:

- Sangrado mayor



- Sangrado no mayor clínicamente relevante

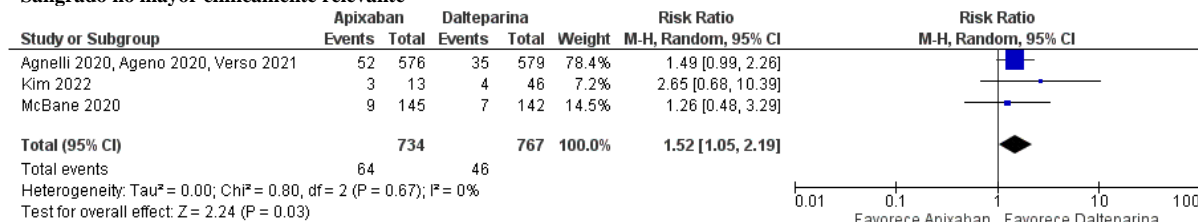


Figura 3. Diagrama de bosque de los estudios que comparan Apixaban y Dalteparina [26, 28-32].

4. Discusión

Según los desenlaces de nuestra revisión sistemática, el Apixaban y la Dalteparina no redujeron significativamente el RR de TEV recurrente y hemorragia grave en pacientes con TEV asociada a cáncer. Sin embargo, la Dalteparina redujo de forma segura el RR de hemorragias no graves clínicamente relevantes con el tratamiento anticoagulante en comparación con el Apixaban. El análisis según los desenlaces debidos a TEV recurrente fue el desenlace de eficacia, y las hemorragias clínicamente importantes y las hemorragias no importantes fueron los desenlaces de seguridad del presente estudio. El riesgo de sesgo fue alto en los tres estudios evaluados, mientras que el grado de certeza de las pruebas fue muy bajo en los tres estudios.

Diversas directrices han establecido los ACOD y las HBPM como alternativa al tratamiento habitual para contrarrestar los efectos secundarios, como hemorragias y trombocitopenia, en la profilaxis y el tratamiento de enfermedades vasculares en pacientes con cáncer [41,42], siendo los ACOD más aceptados debido a su administración oral [43,44]. Se realizaron múltiples metaanálisis comparando los tratamientos con HBPM y ACOD [45-51]. Algunos desenlaces evaluados en cada tratamiento no mostraron diferencias significativas entre HBPM y ACOD, utilizándose este último como otra opción de tratamiento para la ETV asociada al cáncer [45-51]. Otros estudios han concluido que entre los fármacos utilizados para la prevención y

el tratamiento de la TEV en pacientes con cáncer, los ACOD tienen una mayor eficacia y un riesgo relativamente bajo de hemorragia, y Apixaban es el más eficaz y tiene el menor riesgo de hemorragia [45-52]. Sin embargo, algunos estudios han informado de que los ACOD tienen un mayor riesgo de hemorragia grave en pacientes con neoplasias gastrointestinales y genitourinarias [45-51].

Un metaanálisis de cuatro ECA concluyó que los ACOD son más eficaces en el tratamiento de la TEV asociada a neoplasia que la HBPM, aunque se observó un mayor riesgo de hemorragia grave o no grave combinada clínicamente relevante [53]. Otro metaanálisis de ocho ECA que compararon los ACOD con la HBPM y los antagonistas de la vitamina K (AVK) concluyó que los ACOD son el tratamiento óptimo para la TEV asociada al cáncer, tienen un riesgo de hemorragia similar o ligeramente superior al de la HBPM, son una alternativa más segura a los AVK y tienen un efecto prometedor de reducción de la mortalidad, independientemente del estado del cáncer en estos pacientes [54]. El ECA PRIORITY de fase II publicado recientemente, en el que participaron 90 pacientes con cáncer activo, informó de que el tratamiento con ACOD aumentaba aún más el riesgo de hemorragia en comparación con la Dalteparina en pacientes con cáncer avanzado activo gastrointestinal superior, hepatobiliar o pancreático. Por lo tanto, hay que tener mucho cuidado al seleccionar el tratamiento anticoagulante para la TEV asociada al cáncer en pacientes de alto riesgo [40]. Dos metaanálisis llegaron a conclusiones similares a las de nuestro estudio, describiendo que los fármacos HBPM presentaban menos episodios hemorrágicos en comparación con los ACOD [55,56]. Sin embargo, nuestros resultados incluyeron dos componentes adicionales, una evaluación de la calidad y certeza de la evidencia, y un análisis de desenlaces de eficacia y seguridad según el tipo de hemorragia y en pacientes con cáncer.

En nuestro análisis mediante la tabla de resultados resumidos GRADE, encontramos que los pacientes que volvieron a recibir Apixaban presentaron hemorragias no mayores estadísticamente significativas y clínicamente relevantes, con un efecto absoluto anticipado superior a 91 por 1000 en comparación con los que recibieron Dalteparina con 60 por 1000 (RR 1,52; IC 95%, 1,05 a 2,19). Por otra parte, no hubo diferencias estadísticas en las hemorragias mayores para los pacientes que utilizaron ambos fármacos. De similar manera, el TEV recurrente fue no concluyente en los pacientes tratados con Apixaban que con Dalteparina. El número de participantes en los ECA evaluados asciende a 1.501, un número considerable para la síntesis de las pruebas de ambos fármacos. Sin embargo, en base a las pruebas de muy baja certeza, el efecto de los fármacos es incierto; por lo tanto, no puede recomendarse el uso de Apixaban porque puede aumentar el riesgo de hemorragias no graves clínicamente relevantes en comparación con la Dalteparina.

En los distintos metaanálisis que evalúan ACODs frente a HBPM descritos anteriormente para el tratamiento de la ETV asociada al cáncer, la evaluación se realizó de forma conjunta y no directamente entre cada fármaco. Por ello, en nuestro estudio, elegimos los fármacos ACODs y HBPM más eficaces y seguros, Apixaban y Dalteparina, mostrando desenlaces de eficacia y seguridad de estos fármacos en los diferentes tipos de hemorragia y fomentando la necesidad de realizar más ECAs y un posterior metaanálisis de estos ensayos.

Los diversos factores que contribuyen al riesgo de hemorragia en los pacientes con cáncer constituyen un reto para los médicos que administran tratamiento anticoagulante a esta población. Estos factores incluyen la fisiopatología del cáncer, la trombocitopenia, el tratamiento quimioterápico y la posterior insuficiencia renal, que generan inestabilidad hemostática. Teniendo en cuenta todos estos factores, las pruebas sobre si las HBPM y los ACOD tienen una eficacia y seguridad similares siguen siendo insuficientes y, por lo tanto, son necesarios más ECA sobre el uso de estos fármacos para alcanzar conclusiones más sólidas y significativas.

Nuestro estudio tiene algunas limitaciones que deben tenerse en cuenta. El reducido número de estudios disponibles que comparaban Apixaban y Dalteparina no permitió una mayor síntesis de los desenlaces; sin embargo, el número de participantes en los estudios evaluados proporciona los riesgos relativos con respecto a cada resultado. Asimismo, no se realizó un análisis estratificado por tipo de cáncer, debido a que los ECA mencionados no brindaban suficiente información para realizar el análisis, los resultados de sesgos de publicación no se pudieron realizar debido al bajo poder estadístico por la cantidad de estudios. Otra limitación fue el alto riesgo de sesgo en la medición de resultados, esto se debió a un cegamiento insuficiente tanto en participantes como en investigadores, lo que podría influir inconscientemente en los resultados debido a las diferentes vías de administración de ambos tratamientos. La falta de cegamiento también implica que los evaluadores y los participantes conocían el tratamiento durante la administración. Desviaciones de la intervención planeada, como incumplimientos o cambios imprevistos, pueden sesgar los resultados, y un seguimiento inadecuado contribuye a aumentar el riesgo de sesgo en la investigación.

Uno de los puntos fuertes de este estudio es la metodología utilizada, que describe la certeza de la evidencia de los estudios y el riesgo de sesgo de los estudios incluidos en una revisión sistemática y un metaanálisis. Asimismo, durante la selección de estudios se encontró que tres artículos pertenecían al estudio Caravaggio, por lo que, se decidió considerar los tres por ser importantes para la obtención completa de información del estudio en mención los cuales tenían la misma cantidad en cada brazo. Otro punto fuerte es que el estudio PRIORITY se añadió, por primera vez, a un meta-análisis para el resumen de sus desenlaces. Además, es importante mencionar que no es el momento de contemplar la inclusión de estos medicamentos en el plan nacional contra el cáncer cuando las pruebas de su eficacia y seguridad aún no están claras.

5. Conclusiones

Los pacientes con TEV asociada al cáncer tratados con Apixaban mostraron un menor riesgo de TEV recurrente (resultado de seguridad) en comparación con Dalteparina, aunque sin diferencias estadísticas. En la evaluación de hemorragias no graves clínicamente relevantes, tuvo diferencias estadísticas entre los dos fármacos. Asimismo, la certeza de la evidencia de los estudios fue muy baja y el riesgo de sesgo alto; por lo tanto, todavía no es posible sugerir que uno de los tratamientos evaluados sea más eficaz y seguro que el otro.

Materiales complementarios: La siguiente información complementaria puede

descargarse en: www.mdpi.com/xxx/s1. Formato del enfoque de la investigación
Título.

Contribución de los autores: M.A.A.-H.: Conceptualización, metodología, software, análisis formal, investigación, metodología, redacción del borrador original, redacción-revisión y edición. J.J.B.: Conceptualización, recopilación de datos, metodología, redacción del borrador original, redacción, revisión y edición. J.F.M.-H.: Supervisión, redacción-revisión y edición. J.S.T.-R.: Metodología, redacción del borrador original, redacción, revisión y edición. J.L.M.: Conceptualización, redacción del borrador original y supervisión. Todos los autores han leído y aceptado la versión publicada del manuscrito.

Financiación: Esta investigación fue financiada por la Universidad Científica del Sur a través del "Concurso Fondo Becas Cabies-Proyectos de Tesis de Grado y Posgrado 2022-1" aprobado por Resolución Directoral no. 019-DGIDI-CIENTÍFICA-2021.

Declaración de la Junta de Revisión Institucional: El estudio se realizó de acuerdo con la Declaración de Helsinki, aprobado por el comité de ética de la Universidad Científica del Sur, el 23 de sep-tiembre de 2021 mediante certificado no. 341-CIEI-CIENTÍFICA-2021 y código de registro 667-2021-POS50.

Declaración de Consentimiento Informado: No procede.

Declaración de disponibilidad de datos: Los datos están disponibles en la información complementaria.

Agradecimientos: Este artículo fue elaborado por MA Arce-Huamani en cumplimiento parcial de los requisitos para obtener el grado académico de maestría en epidemiología clínica y bioestadística de la Universidad Científica del Sur. Por lo tanto, se agradece el apoyo brindado durante la realización del artículo.

Conflictos de interés: Los autores declaran no tener conflictos de interés.

Referencias

1. Albertsen, I.E.; Nielsen, P.B.; Søgaard, M.; Goldhaber, S.Z.; Overvad, T.F.; Rasmussen, L.H.; Larsen, T.B. Risk of Recurrent Venous Thromboembolism: A Danish Nationwide Cohort Study. *Am. J. Med.* 2018, *131*, 1067–1074.e4. <https://doi.org/10.1016/j.amjmed.2018.04.042>.
2. Caputo, R.; Pyle, J.; Kuriakose, P.; Lekura, J. A systematic review of apixaban in prevention and treatment of cancer-associated venous thromboembolism. *J. Am. Pharm. Assoc.* 2021, *61*, e26–e38. <https://doi.org/10.1016/j.japh.2021.06.005>.
3. Song, X.; Liu, Z.; Zeng, R.; Shao, J.; Liu, B.; Zheng, Y.; Liu, C.; Ye, W. Treatment of venous thromboembolism in cancer patients: A systematic review and meta-analysis on the efficacy and safety of different direct oral anticoagulants (DOACs). *Ann. Transl. Med.* 2021, *9*, 162. <https://doi.org/10.21037/atm-20-8156>.
4. Liu Y, Ma R, Li Y, Gao L. Clinical and laboratory features of different types of cancer-associated thrombosis. *J Cancer.* 2023; *14*(18):3561-3565. <https://doi.org/10.7150%2Fjca.89231>
5. Cohen A.T., Katholing A., Rietbrock S., Bamber L., Martinez C. Epidemiology of first and recurrent venous thromboembolism in patients with active cancer. *Thromb Haemost.* 2016; *117*: 57-65. <https://doi.org/10.1160/th15-08-0686>
6. Di Nisio M, Candeloro M, Rutjes AWS, Porreca E. Venous thromboembolism in cancer patients receiving neoadjuvant chemotherapy: a systematic review and meta-analysis. *J Thromb Haemost.* 2018 Jul;*16*(7):1336-1346. <https://doi.org/10.1111/jth.14149>
7. Costa J, Araújo A. Cancer-Related Venous Thromboembolism: From Pathogenesis to Risk Assessment. *Semin Thromb Hemost.* 2021; *47*(6):669-676. <https://doi.org/10.1055/s-0040-1718926>
8. Ay C., Pabinger I., Cohen A.T. Cancer-associated venous thromboembolism: burden, mechanisms, and management. *Thromb Haemost.* 2017; *117*: 219-30. <https://doi.org/10.1160/th16-08-0615>
9. Key, N.S.; Bohlke, K.; Falanga, A. Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Clinical Practice Guideline Update Summary. *J. Oncol. Pract.* 2019, *15*, 661–664. <https://doi.org/10.1200/JOP.19.00368>.
10. Lloyd, A.J.; Dewilde, S.; Noble, S.; Reimer, E.; Lee, A.Y.Y. What Impact Does Venous Thromboembolism and Bleeding Have on Cancer Patients' Quality of Life? *Value Health J. Int. Soc. Pharmacoecon. Outcomes Res.* 2018, *21*, 449–455. <https://doi.org/10.1016/j.jval.2017.09.015>.
11. Hao, C.; Sun, M.; Wang, H.; Zhang, L.; Wang, W. Chapter Two—Low molecular weight heparins and their clinical applications. In *Progress in Molecular Biology*

- and Translational Science*; Zhang, L., Ed.; Glycans and Glycosaminoglycans as Clinical Biomarkers and Therapeutics—Part B; Academic Press: Cambridge, MA, USA, 2019; Volume 163, pp. 21–39. <https://doi.org/10.1016/bs.pmbts.2019.02.003>.
12. Amin, A.; Keshishian, A.; Dina, O.; Dhamane, A.; Nadkarni, A.; Carda, E.; Russ, C.; Rosenblatt, L.; Mardekian, J.; Yuce, H.; et al. Comparative clinical outcomes between direct oral anticoagulants and warfarin among elderly patients with non-valvular atrial fibrillation in the CMS medicare population. *J. Thromb. Thrombolysis* 2019, *48*, 240–249. <https://doi.org/10.1007%2Fs11239-019-01838-5>.
 13. Li, A.; Manohar, P.M.; Garcia, D.A.; Lyman, G.H.; Steuten, L.M. Cost Effectiveness Analysis of Direct Oral Anticoagulant (DOAC) versus Dalteparin for the Treatment of Cancer Associated Thrombosis (CAT) in the United States. *Thromb. Res.* 2019, *180*, 37–42. <https://doi.org/10.1016%2Fj.thromres.2019.05.012>.
 14. Liao, C.T.; Lee, M.C.; Chen, Z.C.; Ku, L.J.E.; Wang, J.D.; Toh, H.S. Cost-Effectiveness Analysis of Oral Anticoagulants in Stroke Prevention among Patients with Atrial Fibrillation in Taiwan. *Acta Cardiol. Sin.* 2020, *36*, 50–61. [https://doi.org/10.6515%2FACS.202001_36\(1\).20190511A](https://doi.org/10.6515%2FACS.202001_36(1).20190511A).
 15. Ay, C.; Beyer-Westendorf, J.; Pabinger, I. Treatment of cancer-associated venous thromboembolism in the age of direct oral anticoagulants. *Ann. Oncol. Off. J. Eur. Soc. Med. Oncol.* 2019, *30*, 897–907. <https://doi.org/10.1093/annonc/mdz111>.
 16. O’Connell, C.; Escalante, C.P.; Goldhaber, S.Z.; McBane, R.; Connors, J.M.; Raskob, G.E. Treatment of Cancer-Associated Venous Thromboembolism with Low-Molecular-Weight Heparin or Direct Oral Anticoagulants: Patient Selection, Controversies, and Caveats. *Oncologist* 2021, *26*, e8–e16. <https://doi.org/10.1002/onco.13584>.
 17. Carrier, M.; Abou-Nassar, K.; Mallick, R.; Tagalakis, V.; Shivakumar, S.; Schattner, A.; Kuruvilla, P.; Hill, D.; Spadafora, S.; Marquis, K.; et al. Apixaban to Prevent Venous Thromboembolism in Patients with Cancer. *N. Engl. J. Med.* 2019, *380*, 711–719. <https://doi.org/10.1056/NEJMoa1814468>.
 18. Frere, C.; Benzidia, I.; Marjanovic, Z.; Farge, D. Recent Advances in the Management of Cancer-Associated Thrombosis: New Hopes but New Challenges. *Cancers* 2019, *11*, 71. <https://doi.org/10.3390%2Fcancers11010071>.
 19. Ladha, D.; Mallick, R.; Wang, T.F.; Caiano, L.; Wells, P.S.; Carrier, M. Efficacy, and safety of apixaban for primary prevention in gastrointestinal cancers: A post-hoc analysis of the AVERT trial. *Thromb. Res.* 2021, *202*, 151–154. <https://doi.org/10.1016/j.thromres.2021.03.013>.
 20. Knoll, W.; Mallick, R.; Wells, P.S.; Carrier, M. Safety, and efficacy of apixaban thromboprophylaxis in cancer patients with metastatic disease: A post-hoc analysis of the AVERT trial. *Thromb. Res.* 2021, *197*, 13–15. <https://doi.org/10.1016/j.thromres.2020.10.026>.

21. Lee, J.H.; Lee, J.H.; Jo, K.W.; Huh, J.W.; Oh, Y.M.; Lee, J.S. Comparison of rivaroxaban and dalteparin for the long-term treatment of venous thromboembolism in patients with gynecologic cancers. *J. Gynecol. Oncol.* 2020, 31, e10. <https://doi.org/10.3802%2Fjgo.2020.31.e10>.
22. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* 2021, 372, n71. <https://doi.org/10.1136/bmj.n71>.
23. Saif-Ur-Rahman, K.M. Transparency of reporting search strategies in systematic reviews. *Hypertens. Res.* 2022, 45, 1838–1839. <https://doi.org/10.1038/s41440-022-01003-1>.
24. Tabares, D.H.; Carrillo, V.P.; Gómez, J.H.D. Clasificación de los desenlaces en los ensayos clínicos. *Med. UPB* 2019, 38, 147–157. <https://doi.org/10.18566/medupb.v38n2.a07>.
25. Khan, F.; Tritschler, T.; Kimpton, M.; Wells, P.S.; Kearon, C.; Weitz, J.I.; Büller, H.R.; Raskob, G.E.; Ageno, W.; Couturaud, F.; et al. Long-term risk of recurrent venous thromboembolism among patients receiving extended oral anticoagulant therapy for first unprovoked venous thromboembolism: A systematic review and meta-analysis. *J. Thromb. Haemost.* 2021, 19, 2801–2813. <https://doi.org/10.1111/jth.15491>.
26. Franco, L.; Becattini, C.; Beyer-Westendorf, J.; Vanni, S.; Nitti, C.; Re, R.; Manina, G.; Pomero, F.; Cappelli, R.; Conti, A.; et al. Definition of major bleeding: Prognostic classification. *J. Thromb. Haemost.* 2020, 18, 2852–2860. <https://doi.org/10.1111/jth.15048>.
27. Yee, M.K.; Gibson, C.M.; Nafee, T.; Kerneis, M.; Daaboul, Y.; Korjian, S.; Chi, G.; AlKhalfan, F.; Hernandez, A.F.; Hull, R.D.; et al. Characterization of Major and Clinically Relevant Non-Major Bleeds in the APEX Trial. *TH Open Companion J. Thromb. Haemost.* 2019, 3, e103–e108. <https://doi.org/10.1055%2Fs-0039-1685496>.
28. Valizadeh, A.; Moassefi, M.; Nakhostin-Ansari, A.; Hosseini Asl, S.H.; Saghab Torbati, M.; Aghajani, R.; Maleki Ghorbani, Z.; Faghani, S. Abstract screening using the automated tool Rayyan: Results of effectiveness in three diagnostic test accuracy systematic reviews. *BMC Med. Res. Methodol.* 2022, 22, 160. <https://doi.org/10.1186/s12874-022-01631-8>.
29. Brozek, J.L.; Canelo-Aybar, C.; Akl, E.A.; Bowen, J.M.; Bucher, J.; Chiu, W.A.; Cronin, M.; Djulbegovic, B.; Falavigna, M.; Guyatt, G.H.; et al. GRADE Guidelines 30: The GRADE approach to assessing the certainty of modeled evidence—An overview in the context of health decision-making. *J. Clin. Epidemiol.* 2021, 129, 138–150. <https://doi.org/10.1016/j.jclinepi.2020.09.018>.
30. Dalton JE, Bolen SD, Mascha EJ. Publication Bias: The Elephant in the Review.

- Anesth Analg.* 2016; 123(4):812-3.
<https://doi.org/10.1213/ane.0000000000001596>
31. Lin L, Chu H, Murad MH, Hong C, Qu Z, Cole SR, Chen Y. Empirical Comparison of Publication Bias Tests in Meta-Analysis. *J Gen Intern Med.* 2018; 33(8):1260-1267. <https://doi.org/10.1007/s11606-018-4425-7>
 32. Tang JL, Liu JL. Misleading funnel plot for detection of bias in meta-analysis. *J Clin Epidemiol.* 2000; 53(5):477-84. [https://doi.org/10.1016/s0895-4356\(99\)00204-8](https://doi.org/10.1016/s0895-4356(99)00204-8)
 33. Lee, L.L. Application of the Risk of Bias 2 Tool. *Hu Li Za Zhi* 2021, 68, 85–91. [https://doi.org/10.6224/jn.202104_68\(2\).11](https://doi.org/10.6224/jn.202104_68(2).11).
 34. Lin, L. Comparison of four heterogeneity measures for meta-analysis. *J. Eval. Clin. Pract.* 2020, 26, 376–384. <https://doi.org/10.1111/jep.13159>.
 35. Kilpeläinen, T.P.; Tikkinen, K.A.O.; Guyatt, G.H.; Vernooij, R.W.M. Evidence-based Urology: Subgroup Analysis in Randomized Controlled Trials. *Eur. Urol. Focus* 2021, 7, 1237–1239. <https://doi.org/10.1016/j.euf.2021.10.001>.
 36. Agnelli, G.; Becattini, C.; Meyer, G.; Muñoz, A.; Huisman, M.; Connors, J.; Cohen, A.; Bauersachs, R.; Brenner, B.; Torbicki, A.; et al. Apixaban for the Treatment of Venous Thromboembolism Associated with Cancer. *N. Engl. J. Med.* 2020, 382, 1599–1607. <https://doi.org/10.1056/NEJMoa1915103>.
 37. Ageno, W.; Vedovati, M.; Cohen, A.; Huisman, M.; Bauersachs, R.; Gussoni, G.; Becattini, C.; Agnelli, G. Bleeding with Apixaban and Dalteparin in Patients with Cancer-Associated Venous Thromboembolism: Results from the Caravaggio Study. *Thromb. Haemost.* 2021, 121, 616–624. <https://doi.org/10.1055/s-0040-1720975>.
 38. Verso, M.; Muñoz, A.; Bauersachs, R.; Huisman, M.; Mandalà, M.; Vescovo, G.; Becattini, C.; Agnelli, G. Effects of concomitant administration of anticancer agents and apixaban or dalteparin on recurrence and bleeding in patients with cancer-associated venous thromboembolism. *Eur. J. Cancer* 2021, 148, 371–381. <https://doi.org/10.1016/j.ejca.2021.02.026>.
 39. McBane, R.D.; Wysokinski, W.E.; Le-Rademacher, J.G.; Zemla, T.; Ashrani, A.; Tafur, A.; Perepu, U.; Anderson, D.; Gundabolu, K.; Kuzma, C.; et al. Apixaban and dalteparin in active malignancy-associated venous thromboembolism: The ADAM VTE trial. *J. Thromb. Haemost.* 2020, 18, 411–421. <https://doi.org/10.1111/jth.14662>.
 40. Kim, J.H.; Yoo, C.; Seo, S.; Jeong, J.H.; Ryoo, B.Y.; Kim, K.P.; Lee, J.B.; Lee, K.W.; Kim, J.W.; Kim, I.H.; et al. A Phase II Study to Compare the Safety and Efficacy of Direct Oral Anticoagulants versus Subcutaneous Dalteparin for Cancer-Associated Venous Thromboembolism in Patients with Advanced Upper Gastrointestinal, Hepatobiliary and Pancreatic Cancer: PRIORITY. *Cancers* 2022, 14, 559. <https://doi.org/10.3390/cancers14030559>.

41. Farge, D.; Frere, C.; Connors, J.M.; Khorana, A.A.; Kakkar, A.; Ay, C.; Muñoz, A.; Brenner, B.; Prata, P.H.; Brilhante, D.; et al. 2022 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer, including patients with COVID-19. *Lancet Oncol.* 2022, 23, e334–e347. [https://doi.org/10.1016/s1470-2045\(22\)00160-7](https://doi.org/10.1016/s1470-2045(22)00160-7).
42. Frere, C.; Farge, D.; Douketis, J.; Connors, J.M. The 2022 ITAC evidence-based clinical practice guidelines: New update from the International Initiative on Thrombosis and Cancer to improve the care in patients with cancer-associated thrombosis. *J. Med. Vasc.* 2022, 47, 113–115. <https://doi.org/10.1016/j.jdmv.2022.08.002>.
43. Hutchinson, A.; Rees, S.; Young, A.; Maraveyas, A.; Date, K.; Johnson, M.J. Oral anticoagulation is preferable to injected, but only if it is safe and effective: An interview study of patient and carer experience of oral and injected anticoagulant therapy for cancer-associated thrombosis in the select-d trial. *Palliat. Med.* 2019, 33, 510–517. <https://doi.org/10.1177/0269216318815377>.
44. Hendriks, T.; McGregor, S.; Rakesh, S.; Robinson, J.; Ho, K.M.; Baker, R. Patient satisfaction after conversion from warfarin to direct oral anticoagulants for patients on extended duration of anticoagulation for venous thromboembolism—The SWAN Study. *PLoS ONE* 2020, 15, e0234048. <https://doi.org/10.1371/journal.pone.0234048>.
45. Mareev, V.Y.; Mareev, Y.V. Role of anticoagulants in therapy and prevention of recurrent venous thromboembolism in patients with cancer: A meta-analysis of randomized trials with apixaban. *Kardiologija* 2022, 62, 4–15. <https://doi.org/10.18087/cardio.2022.3.n1987>.
46. Wu, S.; Lv, M.; Chen, J.; Jiang, S.; Chen, M.; Fang, Z.; Zeng, Z.; Qian, J.; Xu, W.; Guan, C.; et al. Direct oral anticoagulants for venous thromboembolism in cancer patients: A systematic review and network meta-analysis. *Support. Care Cancer Off. J. Multinat. Assoc. Support. Care Cancer* 2022, 30, 10407–10420. <https://doi.org/10.1007/s00520-022-07433-4>.
47. Frere, C.; Farge, D.; Schrag, D.; Prata, P.H.; Connors, J.M. Direct oral anticoagulant versus low molecular weight heparin for the treatment of cancer-associated venous thromboembolism: 2022 updated systematic review and meta-analysis of randomized controlled trials. *J. Hematol. Oncol.* 2022, 15, 69. <https://doi.org/10.1186/s13045-022-01289-1>.
48. Hussain, M.R.; Ali, F.S.; Verghese, D.; Myint, P.T.; Ahmed, M.; Gong, Z.; Gerais, Y.; Siddiqui, M.; Lin, J.J.; Troy, K. Factor Xa inhibitors versus low molecular weight heparin for the treatment of cancer associated venous thromboembolism; A meta-analysis of randomized controlled trials and non-randomized studies. *Crit. Rev. Oncol. Hematol.* 2022, 169, 103526. <https://doi.org/10.1016/j.critrevonc.2021.103526>.
49. Murphy, A.C.; Koshy, A.N.; Farouque, O.; Yeo, B.; Raman, J.; Kearney, L.; Yudi,

- M.B. Factor Xa Inhibition for the Treatment of Venous Thromboembolism Associated With Cancer: A Meta-Analysis of the Randomised Controlled Trials. *Heart Lung Circ.* 2022, 31, 716–725. <https://doi.org/10.1016/j.hlc.2021.10.024>.
50. Mohamed, M.F.H.; ElShafei, M.N.; Ahmed, M.B.; Abdalla, L.O.; Ahmed, I.; Elzouki, A.N.; Danjuma, M.I.M.U. The Net Clinical Benefit of Rivaroxaban Compared to Low-Molecular-Weight Heparin in the Treatment of Cancer-Associated Thrombosis: Systematic Review and Meta-Analysis. *Clin. Appl. Thromb. Off. J. Int. Acad. Clin. Appl. Thromb.* 2021, 27, 1076029620940046. <https://doi.org/10.1177/1076029620940046>.
 51. Riaz, I.B.; Fuentes, H.E.; Naqvi, S.A.A.; He, H.; Sipra, Q.U.A.R.; Tafur, A.J.; Padranos, L.; Wysokinski, W.E.; Marshall, A.L.; Vandvik, P.O.; et al. Direct Oral Anticoagulants Compared With Dalteparin for Treatment of Cancer-Associated Thrombosis: A Living, Interactive Systematic Review and Network Meta-analysis. *Mayo Clin. Proc.* 2022, 97, 308–324. <https://doi.org/10.1016/j.mayocp.2020.10.041>.
 52. Ning, H.; Yang, N.; Ding, Y.; Chen, H.; Wang, L.; Han, Y.; Cheng, G.; Zou, M. Efficacy and safety of direct oral anticoagulants for the treatment of cancer-associated venous thromboembolism: A systematic review and Bayesian network meta-analysis. *Med. Clin.* 2023, 160, 245–252. <https://doi.org/10.1016/j.medcli.2022.06.022>.
 53. Samaranayake, C.B.; Anderson, J.; McCabe, C.; Zahir, S.F.; Upham, J.W.; Keir, G. Direct oral anticoagulants for cancer-associated venous thromboembolisms: A systematic review and network meta-analysis. *Intern. Med. J.* 2022, 52, 272–281. <https://doi.org/10.1111/imj.15049>.
 54. Yamani, N.; Unzek, S.; Almas, T.; Musheer, A.; Ejaz, A.; Paracha, A.A.; Shahid, I.; Mookadam, F. DOACs or VKAs or LMWH—What is the optimal regimen for cancer-associated venous thromboembolism? A systematic review and meta-analysis. *Ann. Med. Surg.* 2022, 79, 103925. <https://doi.org/10.1016%2Fj.amsu.2022.103925>.
 55. Mai, V.; Tanguay, V.F.; Guay, C.A.; Bertolotti, L.; Magnan, S.; Turgeon, A.F.; Lacasse, Y.; Lega, J.C.; Provencher, S. DOAC compared to LMWH in the treatment of cancer related-venous thromboembolism: A systematic review and meta-analysis. *J. Thromb. Thrombolysis* 2020, 50, 661–667. <https://doi.org/10.1007/s11239-020-02055-1>.
 56. Moik, F.; Posch, F.; Zielinski, C.; Pabinger, I.; Ay, C. Direct oral anticoagulants compared to low-molecular-weight heparin for the treatment of cancer-associated thrombosis: Updated systematic review and meta-analysis of randomized controlled trials. *Res. Pract. Thromb. Haemost.* 2020, 4, 550–561. <https://doi.org/10.1002/rth2.12359>.

Anexos

Carta de aceptación de artículo



medicina

an Open Access Journal by MDPI

Indexed in:
PubMed

CITESCORE
3.6

IMPACT FACTOR
2.6



CERTIFICATE OF ACCEPTANCE

Certificate of acceptance for the manuscript (medicina-2623469) titled:
Efficacy and safety of apixaban versus dalteparin as a treatment for cancer-associated venous thromboembolism: a systematic review and meta-analysis

Authored by:
Miguel A. Arce-Huamani; Joshuan J Barboza; José Fabián Martínez-Herrera; J. Smith Torres-Roman; Jorge L. Maguiña

has been accepted in *Medicina* (ISSN 1648-9144) on 18 October 2023



Academic Open Access Publishing
since 1996

Basel, October 2023

Prueba impresa del artículo



Systematic Review

Efficacy and Safety of Apixaban versus Dalteparin as a Treatment for Cancer-Associated Venous Thromboembolism: A Systematic Review and Meta-Analysis

Miguel A. Arce-Huamani ^{1,2,*}, Joshuan J. Barboza ³, José Fabián Martínez-Herrera ^{2,4}, J. Smith Torres-Roman ^{2,5} and Jorge L. Maguina ¹

¹ Facultad de Ciencias de la Salud, Universidad Científica del Sur, Lima 15067, Peru; jorge.luis.maguina@gmail.com

² Cancer Research Networking, Universidad Científica del Sur, Lima 15067, Peru; jfabianmd@gmail.com (J.F.M.-H.); jstorresroman@gmail.com (J.S.T.-R.)

³ Centro de Investigación en Epidemiología y Medicina Basada en Evidencia, Universidad Norbert Wiener, Lima 13007, Peru; jbarbozameca@gmail.com

⁴ Cancer Center, Medical Center American British Cowdray, Mexico City 01120, Mexico

⁵ Latin American Network for Cancer Research (LAN-CANCER), Lima 11702, Peru

* Correspondence: maarcehuamani@gmail.com; Tel.: +51-926-896-694



Citation: Arce-Huamani, M.A.; Barboza, J.J.; Martínez-Herrera, J.F.; Torres-Roman, J.S.; Maguina, J.L. Efficacy and Safety of Apixaban versus Dalteparin as a Treatment for Cancer-Associated Venous Thromboembolism: A Systematic Review and Meta-Analysis. *Medicina* **2023**, *59*, 1867. <https://doi.org/10.3390/medicina59101867>

Received: 6 September 2023

Revised: 6 October 2023

Accepted: 18 October 2023

Published: 20 October 2023



Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

Abstract: *Background and Objectives:* Venous thromboembolism (VTE) is common in cancer patients. Anticoagulant therapy with low-molecular-weight heparins (LMWHs) and direct oral anticoagulants (DOACs), such as dalteparin and apixaban, have demonstrated efficacy and safety. However, more comparative research of these drugs is still needed. This study aimed to synthesize evidence on the efficacy of apixaban compared to dalteparin in reducing recurrent VTE, major bleeding, and clinically relevant non-major bleeding associated with cancer. *Materials and Methods:* We systematically searched the PubMed, Scopus, Web of Science, Embase, Cochrane Library, and ClinicalTrials databases up to 5 January 2023, for randomized controlled trials comparing apixaban versus dalteparin as treatment for cancer-associated VTE. Five studies were included. Effects according to meta-analyses were reported as relative risks (RRs) and their 95% confidence intervals (CIs). *Results:* It was found that 33 of 734 (4.5%) patients treated with apixaban and 56 of 767 (7.3%) with dalteparin had recurrent VTE as the efficacy outcome (RR 0.49, 95% CI 0.15–1.58, I² 38%). Major bleeding occurred in 25 of 734 patients treated with apixaban (3.4%) and 27 of 767 with dalteparin (3.5%) (RR 1.29, 95% CI 0.31–5.27, I² 59%). Likewise, clinically relevant non-major bleeding occurred in 64 of 734 patients treated with apixaban (8.7%) and 46 of 767 (5.9%) with dalteparin (RR 1.52, 95% CI 1.05–2.19, I² 0%). *Conclusions:* Apixaban showed a lower risk of recurrent VTE than dalteparin in patients with cancer-associated VTE, but without statistical significance. No statistical significance was observed in clinically relevant major or non-major bleeding.

Keywords: apixaban; dalteparin; meta-analysis; venous thromboembolism; cancer

1. Introduction

Venous thromboembolism (VTE) is the third most important vascular disease in the general population. Cancer patients are 4 to 7 times more likely to develop VTE, with it being the second cause of death among these patients [1,2]. The incidence of recurrent VTE is 9.6%, reaching 22.1% in the first 6 months after the initial diagnosis of cancer [3]. Anticoagulant therapy is recommended to prevent VTE in high-risk patients (KHORANA score >2) and to treat those who have already had a thrombotic event [4]. However, this therapy carries a significant risk of bleeding, the most serious adverse reaction. Low-molecular-weight heparins (LMWHs) and direct oral anticoagulants (DOACs) are the most widely used anticoagulant treatments [3,5]. Dalteparin, an LMWH, is recommended

Constancia de Aprobación del comité de ética

COMITÉ INSTITUCIONAL DE ÉTICA EN INVESTIGACIÓN



CONSTANCIA N° 341-CIEI-CIENTÍFICA-2021

El presidente del Comité Institucional de Ética en Investigación de la Universidad Científica del Sur (CIEI-CIENTÍFICA) da constancia que el proyecto de investigación, cuyos datos se registran a continuación, ha sido **aprobado** por el CIEI-CIENTÍFICA.

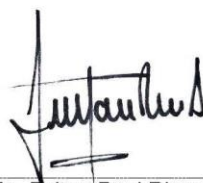
Código de registro: **667-2021-POS50**
 Título: **Eficacia del apixaban versus dalteparina como tratamiento de la tromboembolia venosa asociada al cáncer: revisión sistemática**
 Investigador(a): **Miguel Angel Arce Huamani**

La aprobación del proyecto de investigación implica que el documento presentado a evaluación cumple con los lineamientos de Universidad en materia de investigación y ética, los cuales se sustentan en la normativa internacional vigente. Adicionalmente, en el contexto de la pandemia de enfermedad por COVID-19, le recomendamos cumplir con las normas publicadas por el estado peruano (accesos, medidas de bioseguridad, etc.) y tener los permisos de las instituciones en las que realizará el estudio antes de ejecutarlo.

En tal sentido, esta aprobación carecerá de valor si es que el proyecto de investigación arriba indicado es modificado de cualquier forma. Toda enmienda, añadido, eliminación o eventualidad (eventos adversos, etc.) posterior a la fecha de aprobación debe ser reportado al CIEI-CIENTÍFICA.

La vigencia de la aprobación de este documento es de dieciocho (18) meses (**hasta el 22 de marzo del 2023**), periodo en el que puede desarrollarse el proyecto. Cualquier trámite para su renovación deberá ser enviado antes del término de la vigencia de este documento, debiendo suspenderse todo desarrollo hasta que la renovación sea aprobada.

Villa El Salvador, 23 de setiembre de 2021




Mg. Fulton Paul Rivera Albinagorta
 Presidente
 Comité Institucional de Ética en Investigación

Constancia de extensión de plazo

COMITÉ INSTITUCIONAL DE ÉTICA EN
INVESTIGACIÓN



Constancia

Luego de la revisión de la solicitud, el presidente del Comité Institucional de Ética en Investigación de la Universidad Científica del Sur (CIEI-CIENTÍFICA) hace constar que el CIE-CIENTÍFICA ha aprobado de forma expedita la **extensión** del proyecto de investigación que se detalla continuación:

Código de registro: **667-2021-POS50**

Título: **Eficacia del apixaban versus dalteparina como tratamiento de la tromboembolia venosa asociada al cáncer: revisión sistemática**

Investigador(es): **Miguel Angel Arce Huamani**

Constancia de aprobación: **CONSTANCIA N° 341-CIEI-CIENTÍFICA-2021**

Por consiguiente, se otorga:

Extensión de vigencia del periodo de aprobación ética. Vista la solicitud, **se da la ampliación** de la vigencia de la aprobación del proyecto de investigación por un periodo de seis meses; es decir, hasta el 21 de septiembre del 2023. El proyecto solo podrá ejecutarse entre los periodos detallados en este documento y el **tesista/investigador** tendrá que realizar la solicitud de una nueva ampliación 30 días antes de finalizar esta esta extensión de tiempo.

Todas las demás características de la investigación descritas en el proyecto original permanecen; por lo que cualquier otra modificación deberá informarse a este Comité, para su evaluación.

Lima, 24 de febrero de 2023



Mg. Cinthya Ruth Chipana Herquinio
Presidente
Comité Institucional de Ética en Investigación

Constancia de Renovación de plazo

COMITÉ INSTITUCIONAL DE ÉTICA EN
INVESTIGACIÓN



Constancia

Luego de la revisión de la solicitud, el presidente del Comité Institucional de Ética en Investigación de la Universidad Científica del Sur (CIEI-CIENTÍFICA) hace constar que el CIEI-CIENTÍFICA ha aprobado de forma expedita la **renovación** del proyecto de investigación que se detalla continuación:

Código de registro: **667-2021-POS50**

Título: **Eficacia del apixaban versus dalteparina como tratamiento de la tromboembolia venosa asociada al cáncer: revisión sistemática**

Investigador(es): **Miguel Angel Arce Huamani**

Constancia de aprobación: **CONSTANCIA N° 341-CIEI-CIENTÍFICA-2021**

Por consiguiente, se otorga:

Renovación de vigencia del periodo de aprobación ética. Vista la solicitud, **se renueva** la vigencia de la aprobación ética por un periodo de seis meses; es decir, hasta el **19 de mayo del 2024**. El proyecto solo podrá ejecutarse entre los periodos detallados en este documento y el **investigador** tendrá que realizar la solicitud de una nueva ampliación 30 días antes de finalizar esta renovación de la aprobación.

Dejando constancia que hay un periodo de ventana (entre el 22 de marzo del 2023 hasta el 20 de noviembre del 2023) que toda actividad de investigación estuvo suspendida, sin el amparo del comité. El CIEI no se hace responsable de lo desarrollado en la margen de tiempo en donde no se contaba con la aprobación.

Todas las demás características de la investigación descritas en el proyecto original permanecen; por lo que cualquier otra modificación deberá informarse a este Comité, para su evaluación.

Lima, 20 de noviembre del 2023



Mg. Cinthya Ruth Chipana Herquinio
Presidente
Comité Institucional de Ética en Investigación

Resolución de aprobación por comité de ética



RESOLUCIÓN DIRECTORAL ACADÉMICA DE CARRERA No. 642 - DACMH-DAFCS-U. CIENTIFICA-2021

Lima, 04 de octubre del 2021

VISTO:

El informe de revisión independiente académica y la aprobación de un Comité de Ética del proyecto de investigación titulado: **"EFICACIA DEL APIXABAN VERSUS DALTEPARINA COMO TRATAMIENTO DE LA TROMBOEMBOLIA VENOSA ASOCIADA AL CÁNCER: REVISIÓN SISTEMÁTICA"**.

CONSIDERANDO:

Que, de acuerdo al Reglamento General de la Universidad Científica del Sur y el reglamento y Procedimientos de trabajos de Investigación para obtener el **Grado de Maestro**.

Que, de acuerdo a la normativa vigente de la Universidad Científica del Sur, en uso de las atribuciones conferidas al Director Académico de la Carrera.

SE RESUELVE:

ART. 1° Aprobar, en vías de regularización e inscribir el proyecto de tesis titulado **"EFICACIA DEL APIXABAN VERSUS DALTEPARINA COMO TRATAMIENTO DE LA TROMBOEMBOLIA VENOSA ASOCIADA AL CÁNCER: REVISIÓN SISTEMÁTICA"**, presentado por el alumno **MIGUEL ANGEL ARCE HUAMANI** con N° de registro: **667-2021-POS50**.

ART. 2° Nombrar al Docente Jorge Luis Maguiña Quispe, como asesor para el desarrollo de la tesis en cuestión.

Regístrese, comuníquese y archívese.



Mg. JORDI GRAU MONGE
Director Académico (e)
Carrera de Medicina Humana



c.c. Archiva

Resolución de la extensión de plazo



RESOLUCIÓN DIRECTORAL ACADÉMICA DE CARRERA No. 197 - DACMH-DAFCS-U. CIENTÍFICA-2023

Villa el Salvador, 30 de marzo del 2023

VISTO:

El informe de revisión independiente académica y la aprobación de un Comité de Ética del proyecto de investigación titulado: “EFICACIA DEL APIXABAN VERSUS DALTEPARINA COMO TRATAMIENTO DE LA TROMBOEMBOLIA VENOSA ASOCIADA AL CÁNCER: REVISION SISTEMATICA”.

CONSIDERANDO:

Que, de acuerdo al Reglamento General de la Universidad Científica del Sur y el reglamento y Procedimientos de trabajos de Investigación para obtener el **Grado de Maestro**.

Que, de acuerdo a la normativa vigente de la Universidad Científica del Sur, en uso de las atribuciones conferidas al Director Académico de la Carrera.

SE RESUELVE:

ART. 1° Aprobar, en vías de regularización e inscribir el proyecto de tesis titulado “EFICACIA DEL APIXABAN VERSUS DALTEPARINA COMO TRATAMIENTO DE LA TROMBOEMBOLIA VENOSA ASOCIADA AL CÁNCER: REVISION SISTEMATICA”, presentado por el alumno Miguel Angel Arce Huamani con N° de registro: **667-2021-PO50**

ART. 2° Nombrar al Docente Jorge Luis Maguiña Quispe como asesor para el desarrollo de la tesis en cuestión.

Regístrese, comuníquese y archívese.


Mg. JORDI GRAU MONGE
Director Académico (e)
Carrera de Medicina Humana



Resolución de Renovación de plazo



RESOLUCIÓN DIRECTORAL ACADÉMICA DE CARRERA No. 688 - DACMH-DAFCS-U. CIENTIFICA-2023

Lima, 24 de noviembre del 2023

VISTO:

El informe de revisión independiente académica y la aprobación de un Comité de Ética del proyecto de tesis titulado: **"EFICACIA DEL APIXABAN VERSUS DALTEPARINA COMO TRATAMIENTO DE LA TROMBOEMBOLIA VENOSA ASOCIADA AL CÁNCER: REVISION SISTEMATICA"**.

CONSIDERANDO:

Que, de acuerdo al Reglamento General de la Universidad Científica del Sur y el reglamento y Procedimientos de trabajos de Investigación para obtener el **Grado de Maestro**.

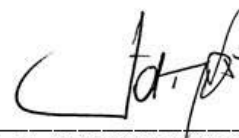
Que, de acuerdo a la normativa vigente de la Universidad Científica del Sur, en uso de las atribuciones conferidas al Director Académico de la Carrera.

SE RESUELVE:

ART. 1° Aprobar e inscribir el proyecto de tesis titulado: **"EFICACIA DEL APIXABAN VERSUS DALTEPARINA COMO TRATAMIENTO DE LA TROMBOEMBOLIA VENOSA ASOCIADA AL CÁNCER: REVISION SISTEMATICA"**, presentado por el alumno Miguel Angel Arce Huamani con N° de registro: **667-2021-POS50**.

ART. 2° Nombrar al docente: Jorge Luis Maguiña Quispe, como asesor para el desarrollo de la tesis en cuestión.

Regístrese, comuníquese y archívese.



Mg. JORDI GRAU MONGE
DECANO
CARRERA DE MEDICINA HUMANA



c.c. Archivo