Systematic Review / Meta-analysis

ANNALS OF MEDICINE & SURGERY

OPEN

Apixaban versus low molecular weight heparin in patients with cancer-associated venous thromboembolism: a systematic review and meta-analysis

Anam Amin, MBBS[a], Muhammad Omar Naeem, MBBS[c], Laraib Amin, MBBS[d], Saad Ul Khaliq, MBBS[b], Athar Ahmad, MBBS[e], Rimsha Rahim Vohra, MBBS[f], Sayed Jawad, MBBS[g,*]

Background: The optimal treatment regimen for patients with cancer-associated venous thromboembolism (CA-VTE) remains unclear. Therefore, the authors sought to compare the outcomes of (VKAs) versus direct apixaban and low molecular weight heparin (LMWH) in patients with CA-VTE.

Methods: MEDLINE, Embase, and Cochrane Central databases were searched for randomized controlled trials (RCTs) and observational studies comparing the efficacy and safety of apixaban and LMWH in patients with CA-VTE. Major bleeding, clinically relevant non-major bleeding (CRNMB), recurrence of pulmonary embolism (PE), deep venous thrombosis (DVT) and bleeding-related mortality were among outcomes of interest. Mantel-Haenszel weighted random-effects model was used to calculate relative risks (RRs) with 95% CIs.

Results: The analysis included 12 011 patients from 3 RCTs and 2 observational studies. Compared to LMWH, apixaban significantly decreased the risk of major bleeding [RR 0.67 (95% CI 0.54, 0.83); $P = 0.0003$, $I^2 = 0\%$] without significantly changing the risk of clinically relevant non-major bleeding [RR 0.96 (95% CI 0.64, 0.1.45); $P = 0.85$, $I^2 = 57\%$]. Patients on apixaban had a noticeably reduced the risk of recurrence of PE than those taking LMWH, according to a meta-analysis [RR 0.56 (95% CI 0.32, 0.99); $P = 0.05$, $I^2 = 0\%$]. There was no discernible difference between apixaban and LMWH in bleeding-related mortality events [RR 0.20 (95% CI 0.01, 4.18); $P = 0.30$, $I^2 = NA\%$], and recurrence of DVT [RR 0.60 (95% CI 0.22, 1.59); $P = 0.23$, $I^2 = 32\%$],

Conclusion: Due to its lower risk of severe bleeding and reduced PE recurrence, apixaban may be a preferable treatment option for CA-VTE, but additional research is required to validate these conclusions and evaluate its long-term efficacy and safety.

Keywords: apixaban, factor Xa inhibitors, low molecular heparin, venous thromboembolism

Introduction

Venous thromboembolism (VTE) is a major health problem that has been on the rise in recent years[1]. VTE is a growing concern in healthcare, and its incidence has been increasing. Notably, individuals with cancer face a sevenfold higher risk of developing VTE. Approximately 15% of cancer patients experience at least one episode of cancer-associated venous thromboembolism (CA-VTE)../[2] This increased risk is caused by a number of things, such as being unable to move, having surgery, and taking anti-cancer drugs[3].

Parenteral low molecular heparin (LMWH) used to be the usual way to treat CA-VTE[4]. However, using LMWH in this vulnerable group is not without risks. Cost, the need for daily parenteral injections, weight-based dose modifications, reduced adherence, and build-up in patients with low glomerular filtration rate are all issues that have long been raised[5]. Factor Xa inhibitors are a possible option that has only recently come to light.

Departments of [a]Medicine, [b]Surgery, Northwest General Hospital and Research Center, [c]Department of Pathology, Northwest General Hospital, [d]Department of Medicine, Northwest School of Medicine, [e]Department of Surgery, MTI—Lady Reading Hospital, Peshawar, [f]Department of Medicine, Dow University of Health Sciences, Karachi, Pakistan and [g]Department of Medicine, Kabul University of Medical Sciences, Kabul, Afghanistan

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

**Corresponding author. Address: Kabul University of Medical Sciences, Kabul, Afghanistan. Tel.: +92 335 350 6888. E-mail: SayedJawad12345@outlook.com (S. Jawad).*

Annals of Medicine & Surgery (2024) 86:4675–4683

Received 7 June 2023; Accepted 14 April 2024

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.lww.com/annals-of-medicine-and-surgery.

Published online 4 June 2024

http://dx.doi.org/10.1097/MS9.0000000000002147

Even though we know a little bit about how well they work and how safe they are new information has come to light that may show very different results. In their 2021 recommendations, the American Society of Haematology recommended the use of Factor Xa inhibitor therapy as a possible alternative to LMWH for short-term treatment of CA-VTE[6]. Although multiple meta-analyses have been conducted to determine the efficacy and safety of Factor Xa inhibitors and rivaroxaban alone versus LMWH[7,8]. None of the previous meta-analysis have been conducted to determine the efficacy of apixaban versus LMWH. On the other hand, the evidence for effectiveness of apixaban is not very strong or certain because of scant pool of studies.

Multiple new studies that have been published may help make this more likely by giving us a bigger body of evidence to look at[8,9]. Therefore, in this meta-analysis we aimed to evaluate the effectiveness of apixaban compared with LMWH in patients with CA-VTE patients by pooling the evidence from all clinical trials to date. This study aimed to compare the outcomes of vitamin K antagonists (VKAs) versus direct apixaban and low molecular weight heparin in patients with CA-VTE.

Selecting the optimal treatment regimen for CA-VTE in cancer patients is of paramount importance. Patients with cancer are particularly susceptible to VTE due to various factors such as immobility, surgical interventions, and the prothrombotic effects of cancer itself. Moreover, anti-cancer drugs, while crucial for treating malignancies, can further increase the risk of VTE. Historically, LMWH was the standard treatment for CA-VTE. However, this approach presents several challenges for cancer patients. It involves daily parenteral injections, weight-based dose adjustments, and potential issues with patient adherence. Furthermore, in individuals with reduced kidney function, LMWH can accumulate and lead to complications. The American Society of Hematology's 2021 recommendations acknowledged Factor Xa inhibitor therapy as a viable short-term treatment option for CA-VTE. Despite previous meta-analyses evaluating the effectiveness of Factor Xa inhibitors, notably rivaroxaban, compared to LMWH, there remains a critical gap in knowledge regarding the performance of apixaban in this context. The limited available evidence on apixaban's effectiveness underscores the need for further research to guide clinical decisions. Hence, this research is crucial for enhancing our understanding of the optimal treatment approach in this high-risk population and ultimately improving patient outcomes.

Methods

The Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA, Supplemental Digital Content 1, http://links.lww.com/MS9/A502) guidelines and the Risk of Bias in Systematic reviews and assessment of multiple systematic reviews (AMSTAR, Supplemental Digital Content 2, http://links.lww.com/MS9/A503) 2 were both followed when doing this meta-analysis[10,11]. The International Prospective Register of Systematic Reviews (PROSPERO), maintained by the National Institute for Health Research (NIHR), contains information about this study. Since the information was accessible to the general public, institutional review board (IRB) approval was not necessary.

HIGHLIGHTS

- Multiple meta-analysis have demonstrated varying findings of previous for the treatment of patients with cancer-associated venous thromboembolism.
- The primary choice of regimen for the treatment of cancer-associated venous thromboembolism depends primarily on reducing the risk of major bleeding, while minimizing the risk of clinically relevant non-major bleeding.
- In the current meta-analysis, apixaban was noted to significantly reduce the risk of major bleeding, and recurrence of pulmonary embolism, without significantly altering the risk of clinically relevant non-major bleeding.

Data sources and search strategy

MEDLINE, EMBASE and Cochrane CENTRAL were comprehensively searched from inception through April 2023 by two independent reviewers (A.A. and G.F.). We extracted studies based on abstracts and titles. A full-text appraisal was sought when required. MeSH phrases and keywords were used to find generic and brand names for apixaban, LMWH and CA-VTE symptoms. Supplemental Table 1, Supplemental Digital Content 3, http://links.lww.com/MS9/A504 provides the detailed search strategy for both databases.

Study selection

We included studies if they were: (1) randomized controlled trials (RCTs) or observational studies including patients at risk of CA-VTE, (2) had apixaban as intervention group, (3) LMWH as a comparator group, and (4) reported any thrombotic or bleeding event, any adverse event or reaction including recurrence of PE or DVT. A third investigator (V.K.) was consulted in case of any disagreement regarding study selection. All articles were then uploaded to Endnote Reference Library (Version X7.5; Clarivate Analytics) software to remove any duplicates.

Data extraction and assessment of study quality

Two reviewers (A.A. and G.F.) independently extracted from the selected studies, including characteristics of the studies, patient demographics, summary events, number of events, sample sizes and treatment type. Summary events were also extracted for outcomes of interest, and risk ratios (ORs) with 95% CIs were calculated from them. We also extracted the year of publication, follow-up duration, and mean/median ages. The quality of studies across six categories [selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias] was evaluated using the Cochrane Risk of Bias Tool (CRBT). The Risk of Bias (ROB) assessment conducted in our systematic review plays a pivotal role in determining the overall confidence in the results. This assessment serves as a critical lens through which we evaluate the methodological rigour of the included studies and the potential impact of bias on the outcomes.

To determine the risk of bias in the selection of study participants, we meticulously examined several key factors. This involved assessing the adequacy of randomization methods. The potential risk of performance bias was evaluated by assessing whether the intervention was administered in a manner that could introduce bias in the study. We also assessed detection bias that

involved close examination of the methods used for outcome measurement and the presence of blinding among the outcome assessors. To evaluate the risk of attrition bias associated with incomplete outcome data, we examined the presence of differential loss to follow-up or missing data in the included studies. The potential risk of bias related to selective outcome reporting was also scrutinized. This aspect involved ensuring that all prespecified outcomes were reported in the published studies.

Statistical analysis

RevMan (version 5.3; Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration) was used for all statistical calculations. We pooled ORs with 95% CI with Mantel-Haenszel (MH) random-effects weighted methods. Random-effects model in our meta-analysis is driven by our commitment to provide a more cautious and comprehensive synthesis of the data. It acknowledges and accommodates the expected heterogeneity among the included studies, thereby yielding a more conservative and robust estimate of the overall treatment effect. We assessed heterogeneity across studies by using Higgins I^2. Two outcomes, clinically relevant non-major bleeding and major bleeding events were stratified into subgroups based on the type of study design to minimise the risk of bias. Egger's regression test was conducted to evaluate the risk of publication bias. Due to the small number of studies, we did not evaluate publication bias using funnel plots.

Results

Literature search and characteristics of included studies

PRISMA flow diagrams describe the literature search and research selection procedure (Fig. 1). Of the 1728 articles were found initially, 3 RCTs and 2 observational studies containing 12 011 patients were finalized for this analysis[12–16]. Table 1 lists the demographic and baseline characteristics. Patients' average

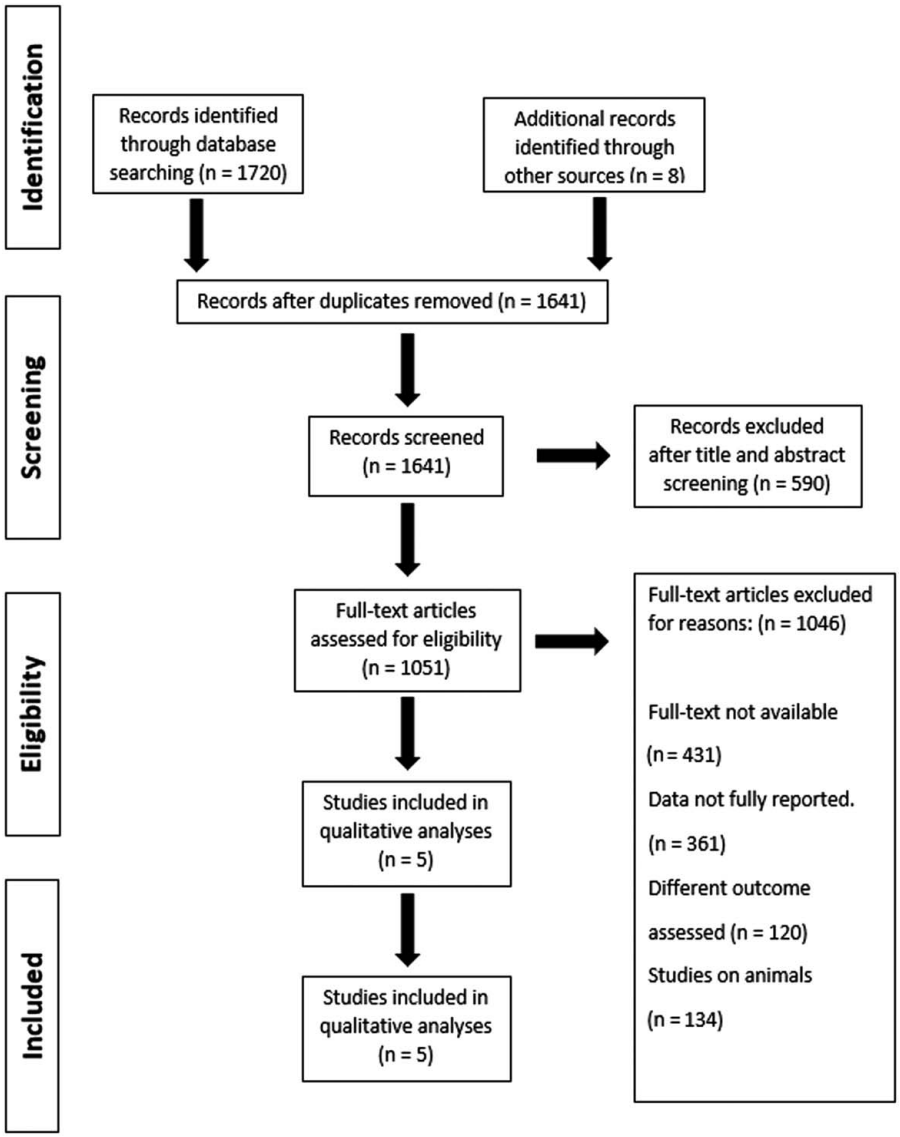

Figure 1. PRISMA flow diagram of study identification for meta-analysis. PRISMA, Preferred Reporting Items for Systematic review and Meta-Analyses.

Table 1

Baseline characteristics of included studies

Author	Country	Study duration	Study design	Cancer type	Drug	Age (mean ± SD)	Total sample (*N*)	Females (*N*)
McBane *et al.* 2020[12]	USA	Nov 2015–Oct 2017	Multicenter, randomized, open-label trial	Mixed	NOAC	64.4 (11.3)	145	78
					LMWH	64.0 (10.8)	142	77
Agnelli *et al.* 2020[13]	Nine European countries, Israel and USA	Apr 2017–Jun 2019	Randomized, controlled, open-label, noninferiority trial	Mixed	NOAC	67.2 ± 11.3	576	284
					LMWH	67.2 ± 10.9	579	303
Houghton *et al.* 2021[14]	USA	1 March 2013, and 20 April 2020	Prospective, single centre	Mixed	NOAC	64.8 (12.1)	474	229
					LMWH	62.4 (11.9)	494	204
Cohen *et al.* 2021	USA	1 March 2014–31 March 2018	Retrospective	Mixed	NOAC	64.6 (12.6)	3393	1772
					LMWH	63.7 (13.2)	6108	3237
Mokadem *et al.* 2021[16]	Egypt	Follow-up of 6 months	Single centre, randomized controlled trial	Mixed	NOAC	61.26 ± 11.23	50	30
					LMWH	59.94 ± 9.71	50	28

LMWH, low molecular weight heparin; NOAC, novel oral anticoagulants

ages varied from 59.94 to 67.2. Egger's regression test was not significant for publication bias ($t = 1.30$, $P = 0.712$).

Major bleeding

Five studies (3 RCTs, 2 observational studies) reported the outcome of major bleeding. (Figs. 2, 3). Compared to LMWH, apixaban significantly decreased the risk of major bleeding VKAs with no heterogeneity [RR 0.67 (95% CI 0.54, 0.83); $P = 0.0003$, $I^2 = 0\%$]. Upon conducting subgroup analysis by type of study design, a significant reduction was noted in observational studies [RR 0.63 (95% CI 0.49, 1.48); $P = 0.0003$, $I^2 = 0\%$] but not in RCTs [RR 0.85 (95% CI 0.49, 1,48); $P = 0.0003$, $I^2 = 0\%$].

Clinically relevant non-major bleeding

Five studies (3 RCTs, 2 observational studies) reported the outcome of clinically relevant non-major bleeding (CRNMB). (Fig. 2). Compared to LMWH, apixaban significantly did not significantly decrease the risk of clinically relevant non-major

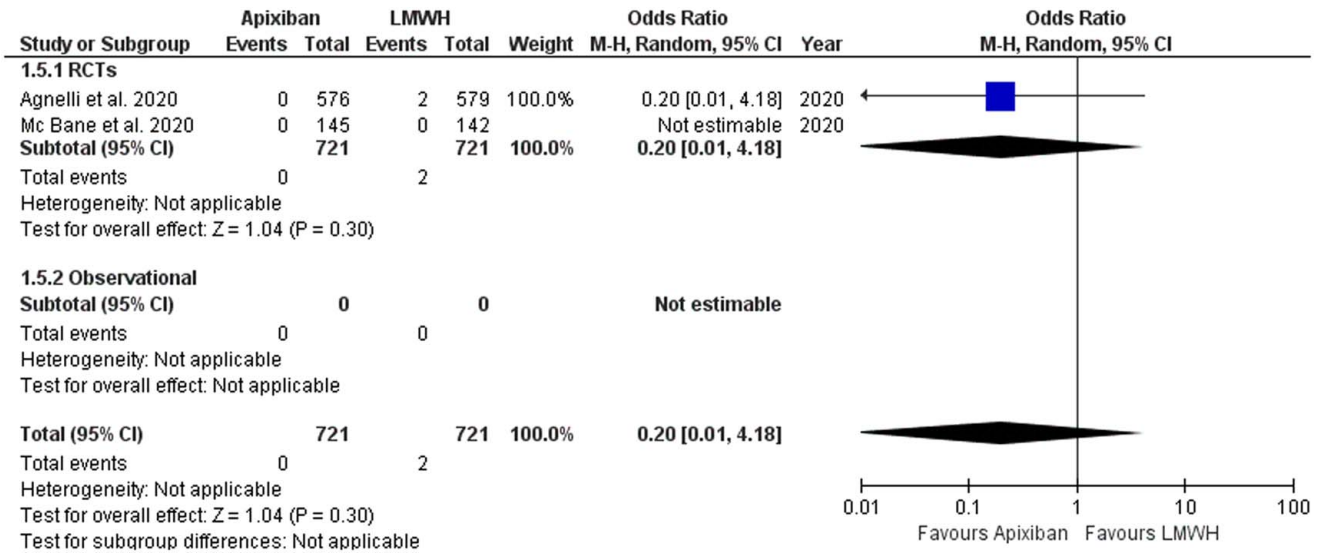

Figure 2. Forest plot showing results of Apixaban vs. LMWH on recurrence of major bleeding events. LMWH, low molecular weight heparin; RCT, randomized controlled trial.

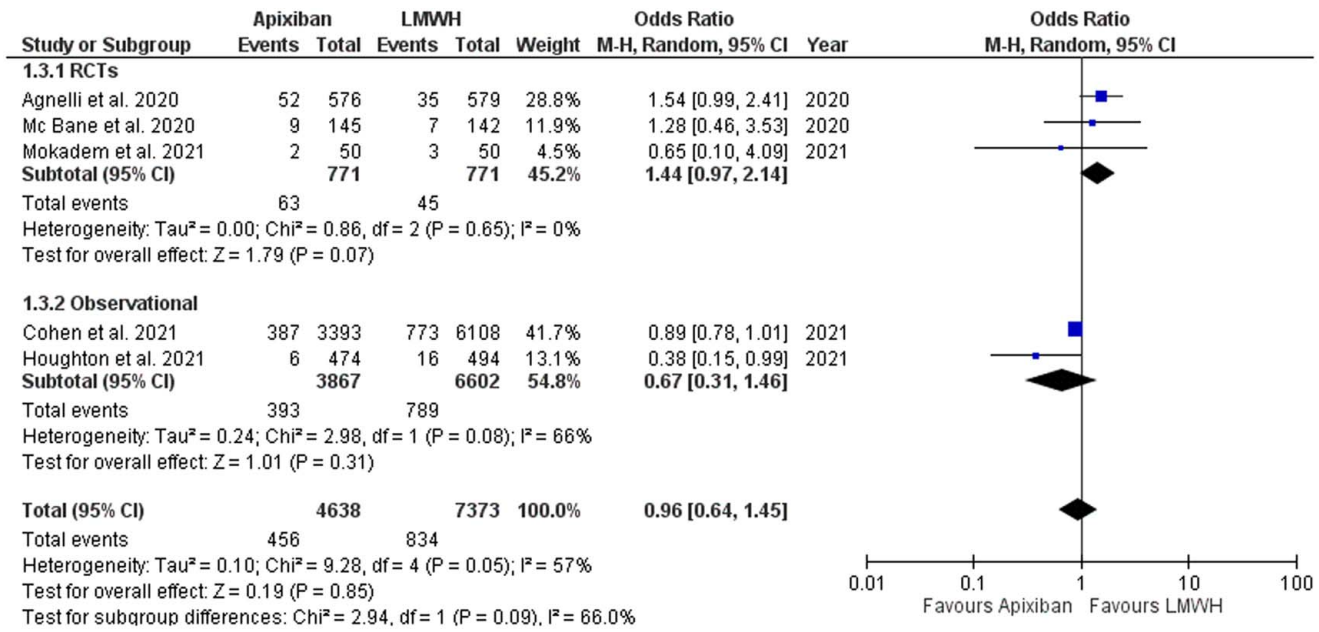

Figure 3. Forest plot showing results of Apixaban vs. LMWH on clinically non-relevant major bleeding recurrence of pulmonary embolism. LMWH, low molecular weight heparin; RCT, randomized controlled trial.

bleeding with high heterogeneity [RR 0.96 (95% CI 0.64, 0.1.45); $P = 0.85$, $I^2 = 57\%$]. Upon conducting subgroup analysis by type of study design, no significant difference was noted in observational studies [RR 0.67 (95% CI 0.31, 1.46); $P = 0.31$, $I^2 = 66\%$] or [RR 1.44 (95% CI 0.97, 2.14); $P = 0.07$, $I^2 = 0\%$].

Bleeding-related mortality

Two studies (2 RCTs) reported events on bleeding-related mortality. In terms of preventing bleeding-related mortality, there was no discernible difference between apixaban and LMWH [RR 0.20 (95% CI 0.01, 4.18); $P = 0.30$, $I^2 = NA\%$]. (Fig. 4)

Recurrence of DVT

Three studies (3 RCTs) reported recurrence of DVT (Fig. 5). Between apixaban and LMWH, no discernible difference was seen with moderate heterogeneity [RR 0.60 (95% CI 0.22, 1.59); $P = 0.23$, $I^2 = 32\%$].

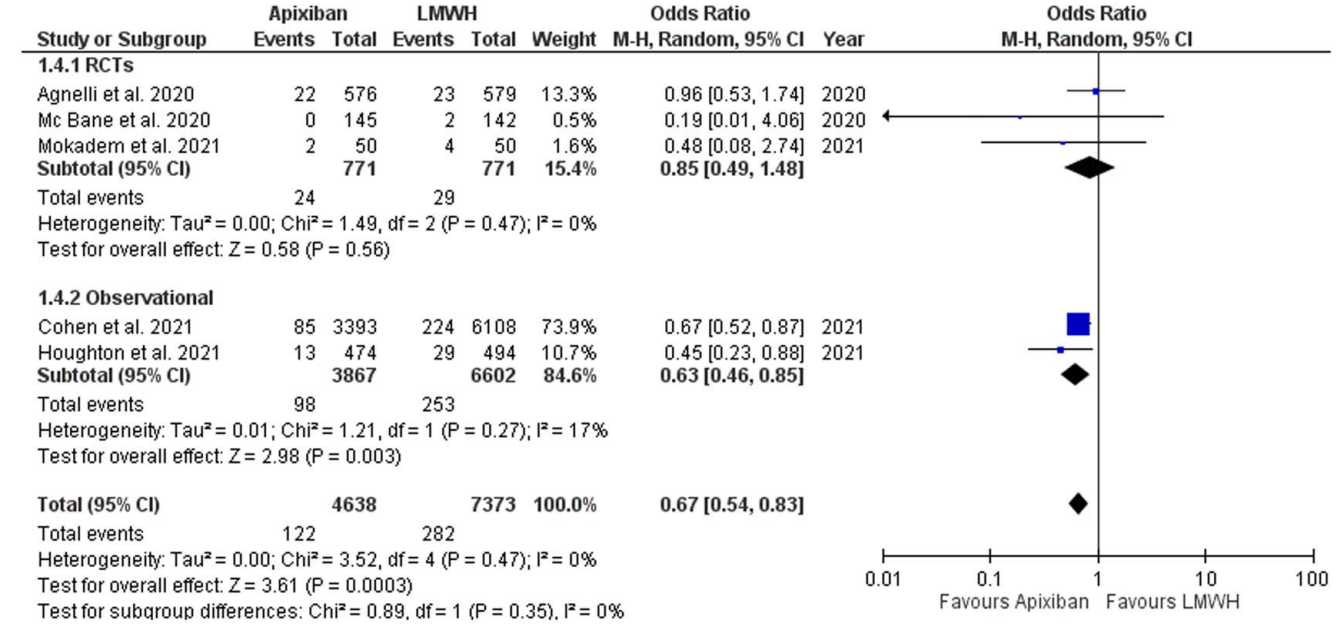

Figure 4. Forest plot showing results of Apixaban vs. LMWH on bleeding-related mortality. LMWH, low molecular weight heparin; RCT, randomized controlled trial.

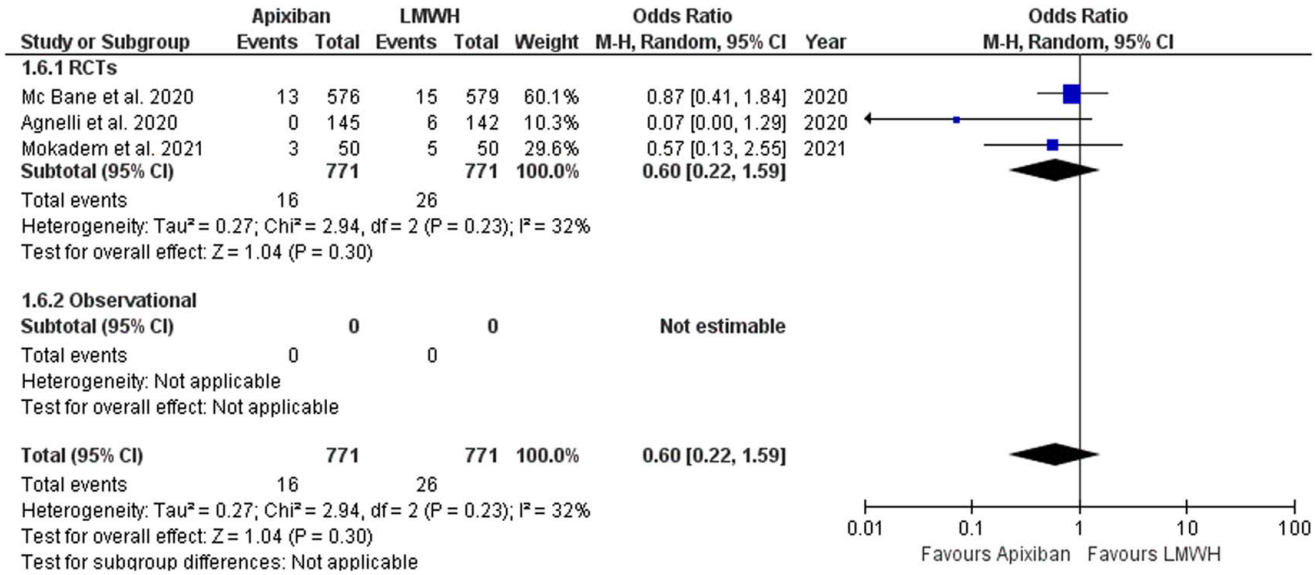

Figure 5. Forest plot showing results of Apixaban vs. LMWH on recurrence of deep venous thrombosis. LMWH, low molecular weight heparin; RCT, randomized controlled trial.

Recurrence of pulmonary embolism (PE)

Two RCTs provided data on the recurrence of PE (Fig. 6). Patients on apixaban had a significant reduction the risk of recurrence of PE than those taking LMWH without heterogeneity, according to a meta-analysis [RR 0.56 (95% CI 0.32, 0.99); $P = 0.05$, $I^2 = 0\%$].

Quality assessment

According to the Cochrane risk-of-bias methodology for randomised trials and New Castle Ottawa Scale, RCTs and observational studies were rated as having a moderate risk of bias. (Supplemental Table 2 and 3, Supplemental Digital Content 3, http://links.lww.com/MS9/A504).

Discussion

In this study assessing the effectiveness of apixaban in patients with CA-VTE, we report several key findings. Apixaban reduced the risk of major bleeding in patients with CA-VTE. However, this finding was noted only in observational studies and not RCTs. Moreover, a reduced risk of recurrence of PE was noted among patients with apixaban compared with LMWH. Lastly,

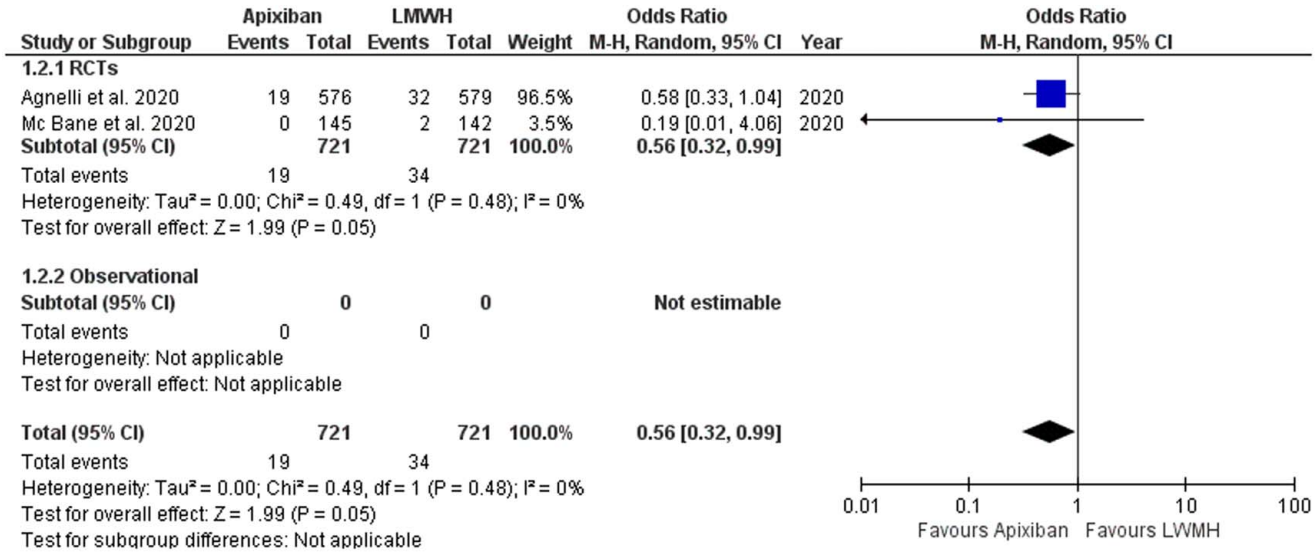

Figure 6. Forest plot showing results of Apixaban vs. LMWH on recurrence of pulmonary embolism. LMWH, low molecular weight heparin; RCT, randomized controlled trial.

patients on apixaban had a reduced risk of CRNMB compared with patients on LMWH.

This study emphasizes that patients on factor Xa inhibitors had a lower risk of major bleeding problems than people taking LMWH. In addition, when compared to LMWH, the risk of clinically relevant non-major bleeding was not significantly higher with Apixaban, but in fact was lower among observational studies. These findings support the practicality of this intervention as a secure substitute for the conventional administration of LMWH[8]. We can draw the conclusion that apixaban reduces the risk of major bleeding events without increasing the risk of non-major bleeding events. These findings are in contrast with previous meta-analysis on overall DOAC and rivaroxaban alone that have demonstrated increased risk of non-major bleeding events among patients compared with LMWH[17]. The association of use of DOAC and non-major bleeding events is well-established. However, our findings demonstrate that the use apixaban can help dismantle the risk of non-major bleeding adverse events that can allow it to be use at higher dosages thus maximizing its efficacy.

We determined that the risk of PE recurrence was substantially lower when apixaban inhibitors were administered as opposed to LMWH. These results were driven by evidence from RCTs[12,13,16]. These findings are in conjunction finding with of previous meta-analysis to this purpose, establishing its fidelity and demonstrating the efficacy of apixaban in the treatment of PE associated with cancer[18]. A decreased risk of recurrent PE events is directly correlated with the potential for a more favourable prognosis for these patients.

Apart from being more effective than LMWH, apixaban can also be administered orally, whereas LMWH must be administered intravenously. This is a significant advance in terms of patient prescription adherence and the quality of care provided to patients[19]. Adoption of apixaban as standard treatment for CA-VTE would provide a substantially more cost-effective, convenient, and comfortable alternative to the routine parenteral administration of LMWH[20]. Apixaban inhibits factor Xa directly in the coagulation cascade. As a result, their mechanism of action is considerably more predictable, meaning they do not require routine laboratory monitoring and have fewer drug interactions than their counterparts[21]. This is especially useful in the case of CA-VTE, as these patients are likely to be receiving chemotherapy or other medications concurrently[22]. In contrast, LMWH affects parameters IIa, Xa, and to a lesser extent IXa and XIIa. This indirect mode of action necessitates intensive laboratory monitoring to ensure that the INR remains within the therapeutic range[22]. As such, apixaban would not only be safer but also considerably more comfortable, convenient, and practicable for these patients, vastly enhancing the quality of care they receive. As such, apixaban are more beneficial for outpatient use than LMWH, which are primarily prescribed to hospitalized patients[15].

One of the most significant clinical implications of this study is the observed reduction in major bleeding events associated with apixaban compared to LMWH. Cancer patients are at an increased risk of bleeding due to their underlying disease and the potential need for invasive procedures. By significantly decreasing the risk of major bleeding, apixaban may offer a safer option for the management of CA-VTE. This finding is particularly important because it may allow healthcare providers to provide more aggressive anticoagulation therapy when needed, potentially reducing the risk of recurrent thrombotic events. Another important clinical implication is the lower risk of recurrence of pulmonary embolism (PE) with apixaban compared to LMWH. PE is a severe and potentially life-threatening complication of VTE, and preventing its recurrence is a critical aspect of CA-VTE management. The reduced risk of PE recurrence observed in this meta-analysis suggests that apixaban may be more effective in preventing this serious complication, ultimately contributing to better patient outcomes. Furthermore, the convenience of oral administration of apixaban compared to LMWH's injectable route may improve patient adherence and overall treatment compliance. This is especially relevant in the outpatient setting, where many cancer patients receive their treatment. The switch to an oral anticoagulant like apixaban may enhance patients' quality of life and reduce the burden of frequent injections.

Despite the fact that our results were largely consistent with previous findings and that the majority of the included studies were of high quality, our research had some limitations[18,23]. Due to the small sample size and small number of studies evaluating these populations, the results cannot be exhaustively or rigorously verified or authenticated. Larger-scale RCTs are needed to confirm these findings and provide more robust evidence. Next, there were insufficient data to compare the numerous apixaban with other Factor Xa inhibitors in order to determine the most effective one for the treatment of CA-VTE. The potential for publication bias should also be acknowledged. Although Egger's regression test did not detect significant publication bias, small study effects could still exist due to the limited number of studies included in this analysis. Heterogeneity, both clinical and methodological, among the included studies is another limitation. Variability in patient populations, treatment protocols, and study designs may introduce bias and impact the consistency of the results., Although our study investigated efficacy in terms of VTE event recurrence and safety in terms of bleeding events in patients, these findings do not inherently translate to a meaningful improvement in patients' quality of life. These outcomes were not investigated in our study. More information is required regarding the differences in quality of life between patients receiving apixaban and LMWH therapies. In addition, additional research is required to determine whether this increased efficacy translates into improved prognostic outcomes for patients, such as decreased mortality or morbidity. Lastly, the relatively short follow-up duration in some of the included studies may not capture long-term outcomes and safety profiles. Cancer patients often require extended anticoagulation therapy, and the long-term effects of apixaban in this population remain uncertain.

Methodological inconsistencies and biases are introduced by many study designs, including RCTs and observational studies. Heterogeneity can also be increased by patient groups with a variety of demographics, medical problems, and genetic profiles. Different interventions, outcome metrics, and environmental factors are also important. Researchers can evaluate the validity and generalizability of findings by transparently addressing various sources of variability while taking into account the target population and particular subgroups. Measurement of heterogeneity and assessments of the overall coherence and robustness of the evidence are made possible by methods like meta-analysis and systematic reviews. Since meta-analyses include multiple studies, there is a potential of several types of biases that may impact the results. By employing objective measurements or validated scales and blinding outcome assessors, detection bias

can be eliminated. It is critical to determine whether there was a significant loss to follow-up and whether attrition was balanced among intervention groups since attrition bias might impact the representativeness of the sample under analysis. By comparing pre-specified results with reported results to make sure all pertinent information is included, reporting bias can be eliminated.

Further investigation into the potential function of apixaban in these are patients. This analysis's accuracy was hindered by a lack of relevant data, and additional RCTs with greater statistical power are required in this particular subgroup to produce a more accurate conclusion. To determine the most effective Factor Xa inhibitor for the treatment of CA-VTE, additional research is required. To achieve this objective, high-powered RCTs that could serve as the premise for future guideline revision recommendations are required. Lastly, it is necessary to determine whether the increased efficacy of Factor Xa inhibitors over LMWH correlates to an improvement in patients' quality of life and prognosis. Due to the limits of the available evidence, long-term effectiveness and safety study of apixaban in patients with cancer-associated venous thromboembolism (CA-VTE) is essential. Although apixaban may have short-term advantages, the lack of long-term data places serious restrictions on its use. Apixaban's long-term effects on recurrent VTE, bleeding issues, and general survival in the CA-VTE group are still unknown. Without thorough long-term analysis, there is a chance of exaggerating the advantages of continued apixaban treatment or understating the potential dangers. In order to provide a more solid evidence foundation, guide therapeutic decision-making, and guarantee the best possible patient outcomes, more studies examining the long-term efficacy and safety of apixaban in CA-VTE patients are required.

Conclusions

In this meta-analysis comparing apixaban and LMWH for treating CA-VTE, apixaban was found to be superior to LMWH. As evidenced by both RCTs and observational studies, apixaban substantially reduced the risk of major bleeding events and a reduced recurrence of pulmonary embolism (PE) compared to LMWH, making it potentially safer and effective choice for CA-VTE management in cancer patients. Based on available RCTs, there was no significant difference between apixaban and LMWH in terms of the recurrence of DVT. In contrast to LMWH, apixaban was associated with a reduced incidence of recurrent PE. The quality assessment revealed that the included RCTs and observational studies posed a moderate risk of bias. Due to its lower risk of severe bleeding and reduced PE recurrence, apixaban may be a preferable treatment option for CA-VTE. Future research should focus on assessing the long-term efficacy and safety of apixaban, comparing it with other Factor Xa inhibitors, evaluating its impact on patients' quality of life, and exploring its potential to improve prognostic outcomes. These findings offer valuable guidance for clinicians and highlight the need for further research to optimize treatment strategies for this high-risk patient population.

Ethical approval

Since all the data used in this study are publicly available in the trials referenced within the manuscript, ethical approval was not required.

Consent

Since all the data used in this study are publicly available in the trials referenced within the manuscript, no patient was directly involved in this study. Hence, there was no need to obtain consent from patients. However, the trials included in this study did obtain patients' consent prior to their enrolment.

Source of funding

Not applicable.

Author contribution

A. Amin and M.O.N. conceived the idea and designed the study. L.A., and S.U.K. the data and analysed it. A. Ahmad drafted the manuscript. R.R.V. created the illustrations. S.J. critically revised the manuscript.

Conflicts of interest disclosure

Not applicable.

Research registration unique identifying number (UIN)

1. Name of the registry: National Institute for Health Research (NIHR) International prospective register of systematic reviews (PROSPERO)
2. Unique Identifying number or registration ID: CRD4202-3429253 Hyperlink to your specific registration (must be publicly accessible and will be checked): crd.york.ac.uk/PROSPERO/display_record.php?RecordID=429253.

Guarantor

Sayed Jawad.

Data availability statement

All the data used in this study are publicly available in the trials, which are referenced in the bibliography.

Provenance and peer review

Not commissioned, externally peer-reviewed.

References

[1] Lutsey PL, Zakai NA. Epidemiology and prevention of venous thromboembolism. Nat Rev Cardiol 2023;20:248–62.
[2] Horsted F, West J, Grainge MJ. Risk of venous thromboembolism in patients with cancer: a systematic review and meta-analysis. PLoS Med 2012;9:e1001275.
[3] Biedka M, Ziółkowska E, Windorbska W. Acute pulmonary embolus in the course of cancer. Contemp Oncol (Pozn) 2012;165:388–93.
[4] Lyman GH. Thromboprophylaxis with low-molecular-weight heparin in medical patients with cancer. Cancer 2009;115:5637–50.
[5] Fabbian F, De Giorgi A, Pala M, *et al*. Low molecular weight heparins and glomerular filtration rate: a report to be considered. Curr Vasc Pharmacol 2011;9:693–7.

[6] Witt DM, Nieuwlaat R, Clark NP, *et al*. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. Blood Adv 2018;2:3257–91.
[7] Yang M, Li J, Sun R, *et al*. Comparison between direct factor Xa inhibitors and low-molecular-weight heparin for efficacy and safety in the treatment of cancer-associated venous thromboembolism: a meta-analysis. J Cancer Res Ther 2019;15:1541–6.
[8] Cohen AT, Keshishian A, Lee T, *et al*. Effectiveness and safety of apixaban, LMWH, and warfarin among high-risk subgroups of VTE patients with active cancer. Curr Med Res Opin 2021;121:383–95.
[9] Fernández-Ruiz I. Apixaban therapy is effective and safe for cancer-associated VTE. Nat Rev Cardiol 2020;17:322.
[10] Shea BJ, Reeves BC, Wells G, *et al*. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 2017;358:j4008.
[11] Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
[12] McBane RD II, Wysokinski WE, Le-Rademacher JG, *et al*. Apixaban and dalteparin in active malignancy-associated venous thromboembolism: The ADAM VTE trial. J Thromb Haemost 2020;18:411–21.
[13] Agnelli G, Becattini C, Meyer G, *et al*. Apixaban for the treatment of venous thromboembolism associated with cancer. N Engl J Med 2020; 382:1599–607.
[14] Houghton DE, Vlazny DT, Casanegra AI, *et al*. Bleeding in patients with gastrointestinal cancer compared with nongastrointestinal cancer treated with apixaban, rivaroxaban, or enoxaparin for acute venous thromboembolism. Mayo Clin Proc 2021;96:2793–805.
[15] Cohen AT, Pan S, Byon W, *et al*. Efficacy, safety, and exposure of apixaban in patients with high body weight or obesity and venous thromboembolism: insights from AMPLIFY. Adv Ther 2021;38:3003–18.
[16] Mokadem ME, Hassan A, Algaby AZ. Efficacy and safety of apixaban in patients with active malignancy and acute deep venous thrombosis. Vascular 2021;29:745–50.
[17] Yamani N, Unzek S, Almas T, *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 2022;79:103925.
[18] Samaranayake CB, Anderson J, McCabe C, *et al*. Direct oral anticoagulants for cancer-associated venous thromboembolisms: a systematic review and network meta-analysis. Intern Med J 2022;52:272–81.
[19] Rachidi S, Aldin ES, Greenberg C, *et al*. The use of novel oral anticoagulants for thromboprophylaxis after elective major orthopedic surgery. Expert Rev Hematol 2013;6:677–95.
[20] Lanitis T, Leipold R, Hamilton M, *et al*. Cost-effectiveness of apixaban versus other oral anticoagulants for the initial treatment of venous thromboembolism and prevention of recurrence. Clin Ther 2016;38: 478–93.
[21] Jiménez D, Yusen RD, Ramacciotti E. Apixaban: an oral direct factor-xa inhibitor. Adv Ther 2012;29:187–201.
[22] Carrier M, Abou-Nassar K, Mallick R, *et al*. Apixaban to prevent venous thromboembolism in patients with cancer. N Engl J Med 2018;380: 711–9.
[23] Wu S, Lv M, Chen J, *et al*. Direct oral anticoagulants for venous thromboembolism in cancer patients: a systematic review and network meta-analysis. Support Care Cancer 2022;30:10407–20.