REVIEW

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The Role of Anticoagulation on Venous Thromboembolism Primary Prophylaxis in Low- to Intermediate-Risk Ambulatory Cancer Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract

Background: The role of anticoagulants in the primary prevention of venous Thromboembolism(VTE) in high-risk cancer patients has been proven in previous studies; however, the routine use of thromboprophylaxis in cancer patients with Khorana score≤ 2 is still debated. This systematic review and meta-analysis aimed to investigate the role of prophylaxis with anticoagulants in cancer patients with low to moderate risk for first time. **Methods:** PubMed, Scopus, Google Scholar, and Web of Science databases were searched with Mesh terms to find Randomized controlled trial studies (RCTs) that evaluated the effect of thromboprophylaxis against placebo on VTE up to January 2024 in low-risk cancer patients. This systematic review was conducted based on the PRISMA guidelines. Heterogeneity between studies was evaluated using the I^2 test. Egger's test was used to check publication bias. In general, 21 studies with 9985 participants were included. **Results:** The majority of studies had high quality and low risk of bias. The pooled estimate showed that using anticoagulants compared to placebo significantly reduces the risk of VTE (HR: 0.53, 95% CI: 0.43, 0.60, I^2: 8.1%). Analysis of subgroups based on the class of anticoagulants showed that both direct oral anticoagulants (DOACs) (HR: 0.46, 95% CI: 0.36, 0.56, I^2:8.5%) and Low molecular weight heparin (LMWH) (HR: 0.60, 95% CI: 0.51, 70, I^2:0%) were significantly related to VTE risk compared to placebo. A pooled estimate of 18 studies did not show a significant association between increased major bleeding and anticoagulant prophylaxis. (HR: 1.25, 95% CI: 0.96, 1.54, I^2: 4%). **Conclusion:** Anticoagulant prophylaxis with both classes of LMWHs and DOACs compared to placebo can be associated with a reduction in VTE risk in low-to-intermediate risk cancer patients. DOACs were associated with a greater reduction in VTE risk. Anticoagulant prophylaxis had no significant relationship with increased major bleeding.

Keywords: Venous Thromboembolism- Anticoagulants- Khorana score- Prophylaxis- Cancer

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Introduction

In recent decades, due to the development of treatment methods, the life expectancy of cancer patients has increased significantly [1-4]. The association between cancer and its treatments with an increased risk of venous Thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), has been demonstrated [4, 5] .Studies have shown that the risk of VTE in cancer patients is up to 7 times higher than in the general population .[6, 7] The risk of VTE varies based on the primary site of the tumor, histological type, and duration of treatment (e.g., chemotherapy and antiangiogenic agents) [8, 9, 5]. The risk of VTE in advanced stages of cancer and pancreatitis and stomach cancers is significantly higher than in other cancers [10, 11]. Based on the Khorana classification, pancreatic and stomach cancers are classified as very high risk according to the primary site of the tumor [12].

VTE is one of the most common causes of increased morbidity and mortality in cancer patients, so reducing the incidence of VTE can lead to a reduction in mortality in these patients [13, 7]. Studies have shown that treatment and primary thromboprophylaxis with anticoagulants after assessing the risk of bleeding associated with anticoagulant treatment may be very useful and are considered the first line of VTE treatment and prevention [14-17]. The main goal of primary thromboprophylaxis is to reduce the risk of VTE and, consequently, its short-term and long-term consequences [12]. Various scoring systems have been

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introduced to classify patients regarding VTE risk [18, 19]. Khorana score has been one of the most common systems used in the stratification of patients [19, 20]. This score classifies cancer patients in terms of VTE risk based on five clinical variables into three risk categories: low risk (0 points), moderate (1-2 points), or high risk (≥3 points) [21]. In this classification, based on the sub-dimension of the primary site of the tumor, pancreatic and stomach cancers are classified as high risk regardless of other variables [21]. While it is recommended that high-risk patients (Khorana score>3) should receive VTE prophylaxis, the routine use of thromboprophylaxis in cancer patients with Khorana score ≤2 is still debated [22]. Inconsistent results have been reported on the role of primary prophylaxis with anticoagulants in moderate-to-high-risk cancers. Several studies showed that in cancer patients with moderate risk, primary prevention with anticoagulants was associated with a reduction in the risk of VTE. Several studies did not report a significant relationship to reducing the risk of VTE with thromboprophylaxis [23-25]. While several studies did not report a significant relationship between reducing the risk of VTE with thromboprophylaxis in cancer patients with low to moderate risk, and in addition, they showed that thromboprophylaxis with anticoagulants may even be associated with an increased risk of bleeding [26-28].

Therefore, considering the subject's importance, this systematic review and meta-analysis aimed to investigate the role of prophylaxis with anticoagulants in cancer patients with low to moderate risk.

Materials and Methods

Literature search

In this systematic review and meta-analysis, we reviewed all randomized clinical trial studies (RCTs) that evaluated the effect of using anticoagulants to prevent VTE in cancer patients with a Khorana score ≤2 from the beginning to 2024. The last search was done on January 20, 2024. The design of this systematic review study was based on the checklist of guidelines for systematic review studies (PRISMA) [29].

To find the articles, after specifying the search strategy, PubMed, Scopus, Google Scholar, Web of Science, and Cochrane databases were searched by two independent researchers (AA) and (AY). The mesh terms were determined by the PICO (population, intervention, comparison, and outcome) format to search the datasets. The search was conducted using the following mesh terms: ((‘’ Cancer’’ OR ‘’ malignancy “ OR ‘’ Tumor’’ OR’’ Neoplasm’’) and (“Venous thromboembolism’’ OR’’ Deep vein thrombosis” OR “Pulmonary embolism’’) and (“Prophylaxis’’ OR’’ “prevention’’ OR ‘Primary’’ OR ‘thromboprophylaxis’’)). The references of the included trials and published meta-analyses and systematic reviews were also assessed for further potential trials to include.

Inclusion and Exclusion criteria

In this study, we included only RCTs that evaluated the effect of anticoagulants versus placebo as the primary prevention of VTE in ambulatory cancer patients with a Khorana score ≤2 [21] or tumors whose primary site was not the Pancreas or stomach (Very high-risk cancer), in this met analysis. We also included only RCTs in the study that clearly examined the type of tumor in the title or clearly defined the risk group of patients with Khorana a Score in the method.

The outcomes that were examined in these studies included the occurrence of primary VTE and major bleeding. The study's eligibility was evaluated by screening titles and, if necessary, by reviewing the abstract and full text of the article. Later, the full texts were evaluated according to the inclusion and exclusion criteria. Studies published in a language other than English, review articles, Observational studies, laboratory or animal studies, studies whose comparison group was one of the anticoagulant drugs, studies that evaluated the effect of anticoagulants in stomach cancers and Pancreas (high risk based on Khorana score), and lack of access to the full text of the article were defined as exclusion criteria.

Data extraction

After the search, duplicate studies were removed, and then the articles were cleaned to find relevant articles using Endnote version 20 software. Two independent researchers performed the initial screening of studies based on the title and abstract. In the initial search, 3024 studies were found. Then, 2745 studies were excluded. The full text of 278 studies was evaluated. Twenty-one RCTs were included in this meta-analysis (Figure 1).

A checklist was designed by experts in cardio-oncology and epidemiology to extract data based on the literature review. All data, including the first author, year, type of anticoagulant, number of subjects in the intervention and control group, number of outcomes in the intervention and control group, effect size (HR), 95% confidence interval, mean age, Gender distribution, study country, number of total deaths, duration of follow-up, major bleeding and its effect size and quality of studies were extracted. Two independent researchers (SFH) and (RY) used Excel software to extract data. A third independent investigator resolved any discrepancies between investigators.

Quality assessment

To assess the methodological quality and risk of bias of RCT studies from the revised Cochrane risk-of-bias tool for randomized trials (RoB 2) [30] tool, for random sequence generation, allocation concealment, blinding of participants and health care personnel, blinded outcome assessment, completeness of data Outcome, selective reporting evidence or other cases were used. Based on this tool, the quality of studies was classified into three levels: low, some concerns, and high.

Statistical analyses

Data were analyzed using Stata 17 software. Effect size indices were estimated with random models to control the effects of the study sample size. Pooled results estimates were presented with risk ratios (RRs) and 95% confidence intervals (CIs) based on the Mantel-Haenszel random effects model. The I^2 test was used to estimate heterogeneity between studies. Egger's test was

used to evaluate the publication bias, and the results of the publication bias were expressed with funnel plots. Sensitivity analysis was used to evaluate the individual effect of each study on the overall outcome.Due to the absence of publication bias in various studies, there was no need to use trim and fill analysis to solve publication bias. P<0.05 was considered significant.

Results

In this meta-analysis, Twenty-one RCTs [31, 32, 27, 33-36, 23, 37, 28, 38, 39, 24, 25, 40-46], including 9,985 patients (4561 in the intervention group and 4748 in the placebo group) with cancer with a Khorana score ≤2 were examined. The mean age of the patients was 62.8 ± 5.1 years. In all studies, 56% of patients were male. Based on the study evaluation checklist, most studies had high quality and low risk of bias. LMWH was the most common drug group investigated. In 13 studies, the effect of the DOACs drug class and in 8 studies, the effect of the drug class DOACs were evaluated compared to placebo (Table 1).

The effect of anticoagulants on the prevention of VTE

The pooled estimation of the studies showed that using anticoagulants compared to placebo significantly reduces the risk of VTE in cancer patients with low to moderate risk (HR: 0.53, 95% CI: 0.43, 0.60, I^2: 8.1 %). (Figure 2) Subgroup analyses based on the anticoagulant groups showed that both LMWHs and DOACs anticoagulant groups were significantly associated with VTE complications compared to placebo. The rate of reduction of VTE in patients who use DOACs was higher than in patients who use LMWHs (0.46 vs. 0.6) (Figure 3).

The effect of anticoagulants on major bleeding

A pooled estimate of 18 studies [31, 32, 27, 33-36, 23, 37, 28, 38, 39, 24, 25, 40-43] showed that although the use of anticoagulants compared to placebo increased the risk of major bleeding in low-to-intermediate risk cancer patients, this difference was not statistically significant (HR: 1.25, 95% CI: 0.96, 1.54, I^2:4%). (Figure 4) Subgroup analysis based on the class of anticoagulants showed that both LMWHs and DOACs groups increased the risk of major bleeding compared to placebo, and the increased risk of bleeding was higher in the LMWHs

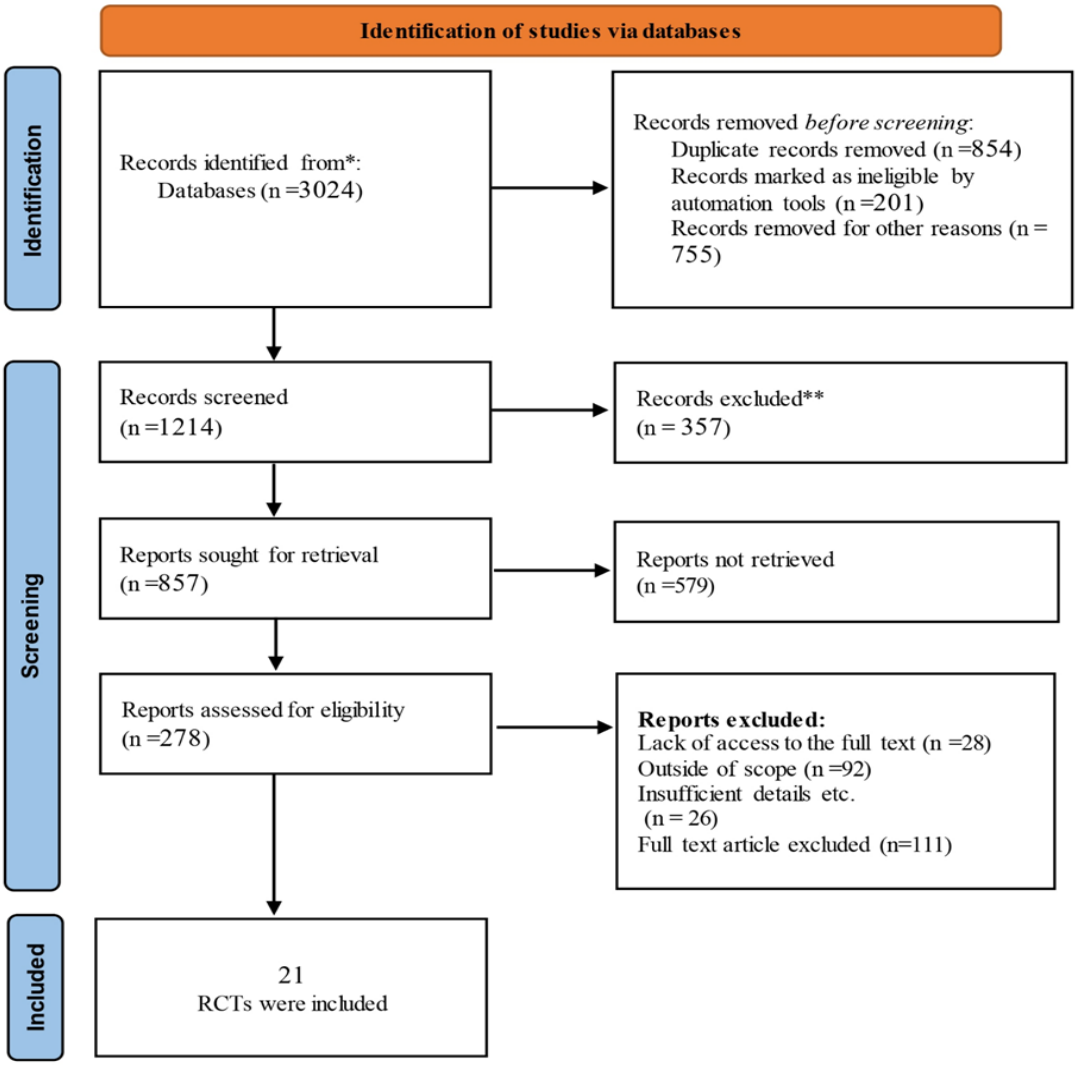

Figure 1. Flowchart Page of Studies based on PRISMA 2020.

Table 1. Characteristics of Study Participants

Author(Year)	Country	comparison group	Sample size (Total)	No. Intervention/ control	Mean Age	Sex (Male)	Follow-up (Week)	Risk of bias
Mitchell [45]	Canada	Antithrombin Vs. Placebo	85	25/60	65	46	4	High
Kakkar [31]	Canada	Dalteparin Vs. Placebo	330	172/160	62	113	13	Low
M Altinbas [46]	Turkey	Dalteparin Vs. Placebo	84	42/42	58	53	14	High
Sideras [32]	USA	Dalteparin Vs. Placebo	138	68/70	63.8	71	13	Low
perry [27]	Canada	Dalteparin Vs. Placebo	186	99/87	57	111	13	Low
Haas (2012)[52]	Germany	Certoparin Vs. Placebo	898	447/451	78.1	481	13	Low
G Agnelli [33]	Canada	Semuloparin Vs. Placebo	2547	1278/1269	62	1301	14	Low
Levine [35]	Canada	Apixaban Vs. Placebo	125	95/30	63	65	12	Moderate
R Lecumberri [36]	Spain	Bemiparin Vs. Placebo	38	20/89	62.8	20	26	Moderate
F Macbeth [23]	USA	Dalteparin Vs. Placebo	2202	1101/1101	65	661	24	Low
Meyer [37]	France	Tinzaparin Vs. Placebo	359	185/174	61.6	285	26	Low
M Carrier [38]	Canada	Apixaban Vs. Placebo	376	186/190	62	274	26	Low
B Pegourie [28]	France	Apixaban Vs. Placebo	208	104/104	69.8	56	26	Moderate
W Knoll [24]	Canada	Apixaban Vs. Placebo	227	107/120	60.25	114	26	Low
Y Shargall [39]	Canada	Enoxaparin Vs. Placebo	219	116/109	58	111	13	Low
W Brandt [25]	Australia	Enoxaparin Vs. Placebo	128	42/86	65	176	13	Moderate
M Alexander [44]	China	Rivaroxaban Vs. Placebo	203	100/103	61.2	101	4	Moderate
M Zhao [42]	USA	Apixaban Vs. Placebo	512	256/256	NA	290	14	Low
N Potere [41]	Italy	Apixaban Vs. Placebo	357	154/203	61	266	26	Low
L Girardi [40]	Canada	Tinzaparin Vs. Placebo	614	307/307	61	368	6	Low
SH O'Brien [43]	Canada	Apixaban Vs. Placebo	149	88/61	59.4	57	26	Moderat

group, but this relationship was not statistically significant (Figure 5).

Publication bias

Egger's test analysis did not show a significant estimate for the publication bias of the studies. (Egger test: 0.37, p: 0.47, 95%CI: -0.71, 1.45) The publication distribution of the studies is shown in Figure 6.

Discussion

The role of anticoagulants in the primary prevention of VTE in high-risk cancer patients and patients with pancreatic and gastric cancers has been proven in previous studies [15, 47, 48][15, 47, 48][15, 47, 48] [48-50]. However, the routine use of thromboprophylaxis in cancer patients with a Khorana score ≤2 is still under discussion, and their preventive and safety aspects are still not clearly defined in these patients. In this meta-analysis, we evaluated the effect of anticoagulants on the primary prevention of VTE and also their relationship with the risk of major bleeding in 21 RCTs [24-25, 28-29, 32-47] in 9,985 low- and moderate-risk cancer patients. We also evaluated the effect of two anticoagulant groups, LMWHs, and DOACs, on the primary prevention of VTE and major bleeding in these patients.

The results of this meta-analysis showed that in patients with low to moderate risk of cancer, the use of anticoagulants was associated with a 47% reduction in the risk of VTE compared to placebo, regardless of

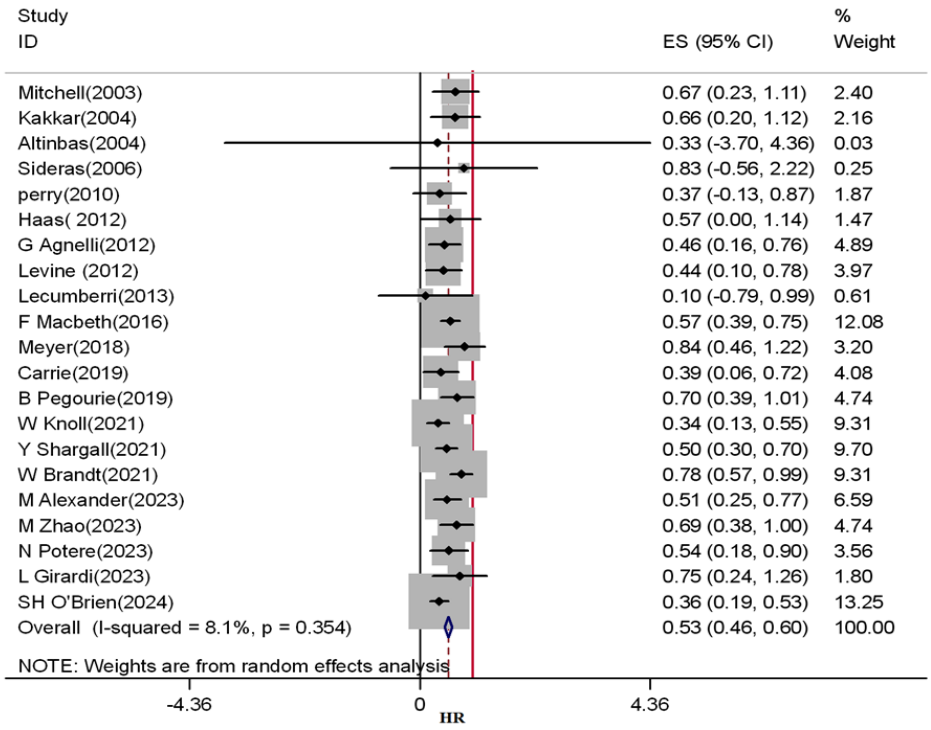

Figure 2. The Effect of Anticoagulants on the Prevention of VTE

the duration of use and the group of drugs used. The subgroup analysis showed that the use of LMWHs and DOACs drugs reduced the risk of VTE by 40 and 86%, respectively. The effect of anticoagulants on the risk of major bleeding was investigated in 18 studies [24-25, 28-29, 33, 35-42,44-47]. The pooled estimation showed that although the use of both categories of LMWHs and DOACs drugs increased the risk of major bleeding in

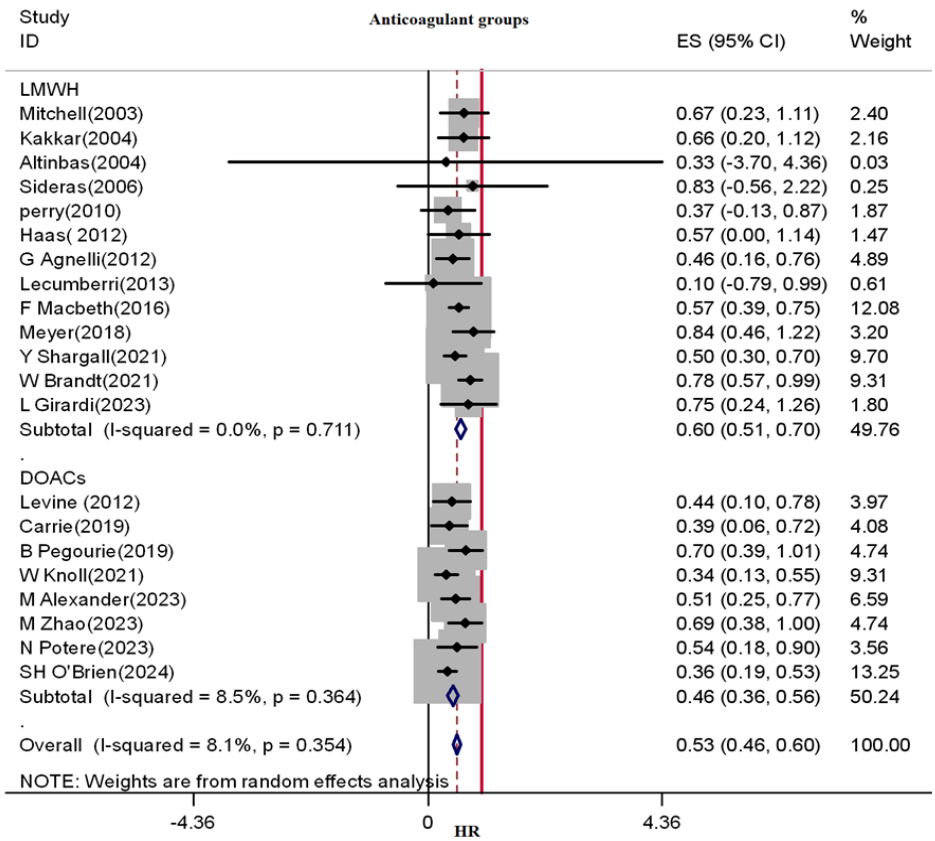

Figure 3. The Effect of Anticoagulants on the Prevention of VTE base on Anticoagulant Groups

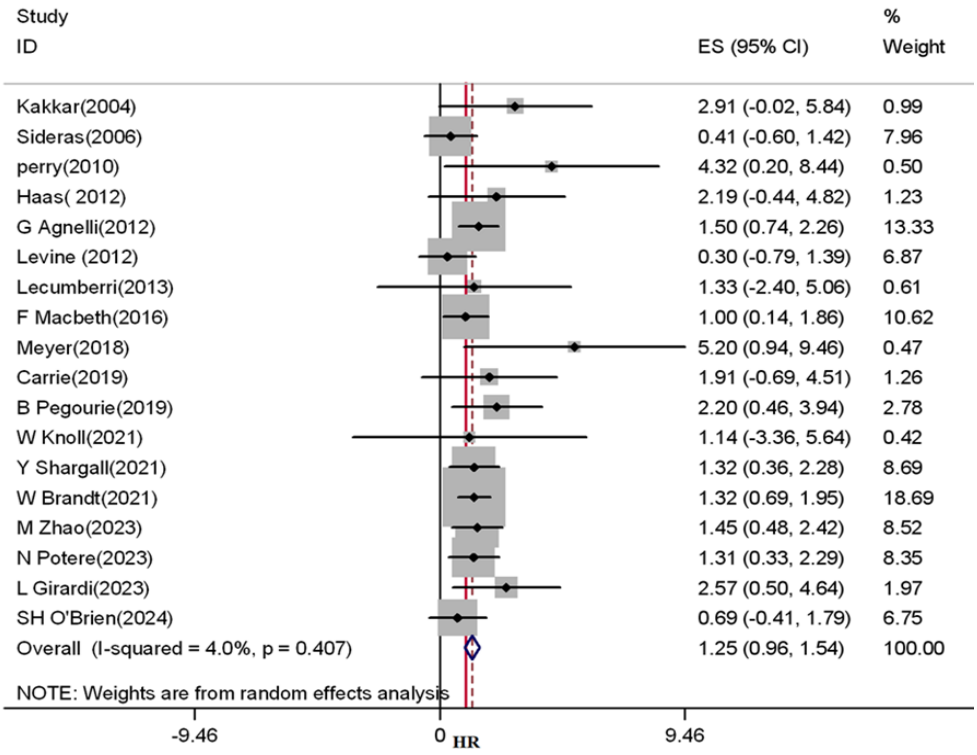

Figure 4. The Effect of Anticoagulants on the Risk of Major Bleeding

cancer patients with low to moderate risk by nearly 25%, this difference was not statistically significant. Most of the studies included in this meta-analysis were of high quality, and the heterogeneity rate for estimating both outcomes was very low and close to zero. Our meta-analysis and literature review [15, 49, 50] show that in cancer patients, anticoagulants can reduce the risk of VTE regardless of the risk level, primary tumor site, type of anticoagulant, tumor characteristics, and the type of drug regimen received for cancer treatment. The amount of reduction in the risk of

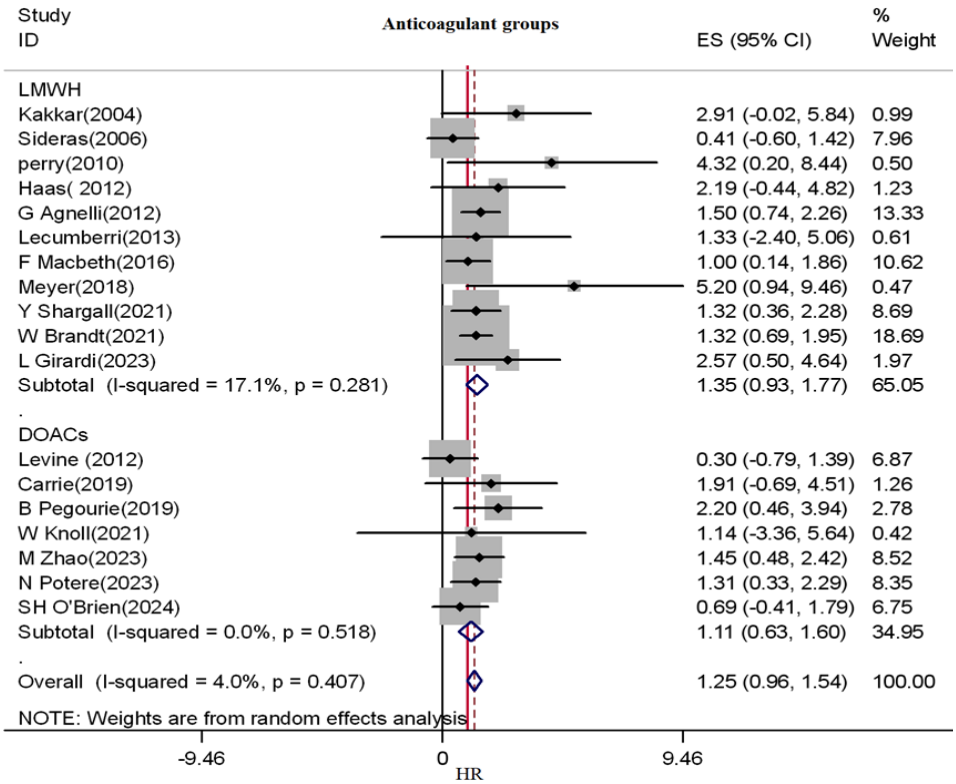

Figure 5. The Effect of Anticoagulants on the Risk of Major Bleeding base on Anticoagulant Groups

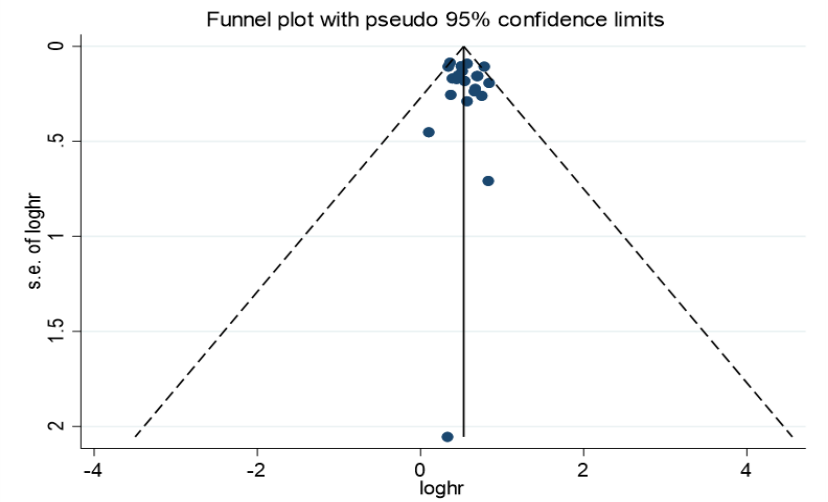

Figure 6. Funnel Plot of Publication bias of Studies

VTE is different based on the type of anticoagulant drug, and DOACs reduce the risk of VTE more than LMWHs, without having a significant difference in the rate of major bleeding in low- and moderate-risk cancer patients.

In 2019, in a meta-analysis, M Barbarawi et al. [15], by evaluating the role of anticoagulants in the primary prevention of venous Thromboembolism in cancer patients, showed that both LMWH and direct Xa inhibitors compared to placebo significantly reduced VTE events and reduced the risk of VTE by 40%. They reported no significant difference in the rate of major bleeding in the two anticoagulation groups, which confirmed the results of our study. They also estimated all-cause mortality in their study, which we could not estimate in this meta-analysis because the mortality rate was not assessed in the majority of studies in the primary studies; however, assuming this is that the reduction of VTE can be associated with the reduction of mortality. In 2017, in a meta-analysis, HE Fuentes et al. [51] reviewed seven studies and showed that primary prevention with LMWH can significantly reduce the incidence of VTE without an apparent increase in bleeding risk in outpatients with lung cancer. In our study, in addition to evaluating the role of primary prevention with LMWHs and DOACs in patients with low to moderate-risk lung cancer, we also evaluated the prevention effect of both drug groups on other low to moderate-risk cancers apart from pancreatic and stomach cancers. In line with the results of our study, H Chen et al. [48] investigated the prevention of venous Thromboembolism in cancer patients with direct oral anticoagulants in 6 studies and showed that the efficiency of DOACs was higher compared to LMWH to reduce VTE, without significant difference in the rate of major bleeding.

Limitations

Our study had limitations that need to be mentioned: 1; In this meta-analysis, we included studies that had a low to moderate risk level, and the classification of these patients in the studies was based on the Khorana Score, which may be a number of studies that have been misclassified.2; We were unable to assess a number of outcomes, such as total mortality, due to limitations in the primary studies.3; The anticoagulant drug use period, follow-up period, and doses used differed in the included articles and may have affected the final result, although we had a sensitivity analysis based on anticoagulant groups. 4; Most studies were conducted in developed countries with specific characteristics and may not be generalizable to different populations.

In Conclusion, our meta-analysis showed that anticoagulant prophylaxis with both classes of LMWHs and DOACs compared to placebo can be associated with a reduction in VTE risk in low-to-intermediate risk cancer patients. The amount of VTE risk reduction varies based on the type of anticoagulant drug, and DOACs were associated with a great reduction in VTE risk.Although anticoagulant treatment with both classes of LMWHs and DOACs increased the rate of major bleeding, this difference was not statistically significant. No significant difference was observed in the risk of major bleeding in the two classes of LMWHs and DOACs.

Author Contribution Statement

Conceptualization: AA and AY; methodology: SFH, SF, YA, and RY; software: AY, HH; validation: MMS and YA; Qualitative data collection and analysis: AA, AY, and SFH; investigation: SF, MM, and AY; resources, AA; data curation: AA, SFM, YA, and AY; writing—review and editing: AA, YA, and AY; supervision: AA; project administration. All authors have read and agreed to the published version of the manuscript.

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Availability of data and materials

The datasets created and analyzed during this study are publicly available due to their availability. They can be obtained from the corresponding author upon request.

Competing interests

The authors declare no potential conflict of interest.

How the ethical issue was handled

Not required as data is not individualized, and primary data need to be collected.

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