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META-ANALYSIS

Direct Oral Anticoagulants for the Prevention and Treatment of Venous Thromboembolic Events in Cancer Patients: A Meta-analysis of Randomized Controlled Trials

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Abstract: ***Introduction*:** Cancer is associated with a higher risk of venous thromboembolic events compared to the general population. About one-fifth of patients diagnosed with venous thromboembolic events have underlying cancer. The guidelines recommend both low molecular weight heparin and direct oral anticoagulants for the prevention and treatment of venous thromboembolic events. Further evidence is required to adequately characterize the exact role of direct oral anticoagulants.

***Methods*:** A systematic review of the literature was done by searching the databases of Medline, Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov. The analysis included only randomized controlled trials enrolling adult patients with cancer and venous thromboembolic events comparing low molecular weight heparin versus direct oral anticoagulants. Duration of follow-up of at least 6 months was considered as a minimum. The studies had to assess the risk of thromboembolic recurrence rate, all-cause mortality, and risk of bleeding.

***Results*:** The final search results led to the inclusion of five randomized controlled trials. The analysis showed a similar risk of recurrence of venous thrombotic events (RR 0.71, 95% CI 0.44-1.17; $p = 0.18$), mortality risk (RR 1.02, 95% CI 0.88-1.17; $p = 0.8$), and major bleeding (RR 1.05, 95% CI 0.69-1.62; $p = 0.81$) between the two treatment groups.

***Conclusion*:** The use of direct oral anticoagulants is a feasible and practical option in ambulatory cancer patients with venous thromboembolic events. The efficacy and safety are similar to that of low molecular weight heparin.

Keywords: Direct oral anticoagulants, cancer, neoplasm, thromboembolism, pulmonary embolism, deep venous thrombosis, low molecular weight heparin.

1. INTRODUCTION

Cancer is associated with a risk of venous thromboembolic events (VTE) that is up to six folds higher than that of the general population, as well as with a higher VTE-related mortality rate. In about 20% of patients diagnosed with VTE, cancer is identified as the main underlying precipitating factor [1]. Patients with cancer are faced with both an increased risk of VTE recurrence and risk of bleeding secondary to treatment effects, which especially complicate therapeutic decisions in patients with high-risk features associated with an increased risk of complications [2]. Risk factors for an increased risk of complications [2]. Risk factors for the development of VTE in patients with cancer are variable and can be related to the type of cancer (primary site and histologic type), the clinical characteristics of the patient (age, racial/ethnic group, and comorbidities), and treatment type (type of chemotherapy, type of supportive therapy) [3]. The underlying mechanism driving the increased incidence of VTE in patients with cancer is partly explained by increased activation of coagulation pathways (cancer-associated procoagulants), increased stimulation of the inflammatory response (increased circulating proinflammatory cytokines

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and neutrophil extracellular traps (NETs)), and inhibition of the fibrinolysis system (elevated plasminogen activator inhibitor-1 (PAI-1)) [4].

The management of VTE in patients with cancer is directed toward relieving thrombosis and preventing recurrences. Guidelines issued by the American Society of Clinical Oncology (ASCO) recommend VTE primary prophylaxis for all patients with cancer who are undergoing surgery, and for hospitalized patients with cancer and acute medical conditions. The ASCO guidelines recommend both low molecular weight heparin (LMWH) and direct oral anticoagulants (DOACs) for the prevention and treatment of VTE [5]. Although DOACs have been recently adopted as the preferred option for the treatment of VTE in many scenarios, further evidence is required to adequately characterize the exact role of DOACs in the management of patients with cancer.

Therefore, the objective of this meta-analysis is to evaluate the available evidence regarding the effectiveness and safety of DAOC in the treatment of VTE in patients with cancer, with a focus on studies comparing their use with LMWH, which is considered the standard of care.

2. METHODS

The methodology of this meta-analysis is based on the Preferred Reporting Items for Systematic Reviews and MetaAnalyses (PRISMA) statement [6]. A systematic review of the literature was done by searching the databases of Medline, Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov.

The search terms used included various combinations of cancer, thromboembolic events, pulmonary embolism, deep venous thrombosis, low molecular weight heparin, and direct oral anticoagulants. The search was limited to human studies published in the English language between the years 2000 and 2021. Two reviewers (Loma A. and Firas A.) screened the databases for eligible studies by identifying the titles, abstracts, and then full-texts for the included studies. Any disagreements between the two reviewers were solved by consensus. The authors included those studies that met the inclusion criteria for the analysis. A third reviewer was responsible for the extraction of data and analysis of the results. Each study was evaluated for quality and bias.

2.1. Inclusion Criteria

This meta-analysis included only randomized controlled trials (RCT) enrolling adult patients with cancer and VTE. The RCT compared treatment with LMWH against DOACs (dabigatran etexilate, apixaban, edoxaban, or rivaroxaban) as an alternative treatment. Duration of the follow-up of at least 6 months was considered as a minimum timeframe for inclusion. Studies had to include an assessment of the VTE recurrence rate, all-cause mortality, and risk of bleeding.

2.2. Outcomes

We assessed the included studies for the efficacy of DOACs against LWMH by analyzing the rate of recurrence of VTE (deep vein thrombosis [DVT] of lower and/or upper limbs and/or pulmonary embolism [PE] [symptomatic or incidental]). We assessed the safety of the DOACs by analyzing the rate of major bleeding (fatal bleeding, decrease in hemoglobin $\geq$ 2g/dL, need for transfusion of $\geq$ 2 units of blood, or bleeding in a major site [intracranial, intraspinal, retroperitoneal, intraarticular, intraocular, and other major sites]).

2.3. Statistical Analysis

The clinical outcomes were compared between the DOAC and LMWH groups by measuring the risk ratios (RRs) and 95% confidence intervals (CIs) for each outcome. The analysis used the random-effect model to address the heterogeneity between the enrolled studies with the MantelHaenszel method used for dichotomous data.

The Cochrane's Q statistic and I2 statistic test were used to measure the heterogeneity of studies, which was categorized as low (I_2=25%), moderate ($I_{2=}$50%), or high (I_2=75%).

A p-value of less than 0.05 was considered statistically significant. Publication bias was assessed by visual inspection of the funnel plot. We used the software *The Review Manager* (RevMan) v5.3, (The Cochrane Collaboration, Oxford, UK) for all statistical analyses.

3. RESULTS

The selected databases were searched for eligible studies, and their titles and abstracts were evaluated, which was followed by a review of the full-text of selected studies. The final search results led to the inclusion of five RCTs meeting all inclusion criteria. The five RCTs were Hokusai, SELECT-D, ADAM VTE, Caravaggio, and CANVAS trials [7-11]. The search strategy and search results are shown in Fig. (**1**).

The included studies were all published in the full-text except for one study (abstract presentation), which was included due to the significant data provided. All included studies were RCT, and their detailed characteristics are shown in Table **1**. The total number of patients enrolled across all studies was 3597. All studies compared DOACs with LMWH for the treatment and prevention of VTE in patients with different types of cancer. The outcomes of the studies evaluated the non-inferiority of DOACs as an effective and safe alternative for VTE treatment in patients with cancer.

Effectiveness outcomes were represented by the rate of recurrent VTE across all studies. The pooled analysis of the data provided by the five RCTs showed that DOACs led to a numerically lower rate of recurrent VTE events compared to LMHW. However, the difference did not reach statistical significance. In total, there were 136 VTE events among patients treated with DOACs compared to 167 events among those treated with LMWH (RR 0.71, 95% CI 0.44-1.17; p = 0.18). The heterogeneity between studies was found to be moderate, I^2 = 73% (Fig. **2**).

The mortality rate was observed to be similar between the two groups. The number of events was 483 in the DOACs group and 472 in the LMWH group, with no significant difference between the treatments (RR 1.02, 95% CI 0.881.17; p = 0.8). The heterogeneity between the studies was moderate, I^2 = 31% (Fig. **3**).

Safety outcomes were represented by the occurrence of major bleeding events. The rate of major bleeding events

Fig. (1). PRISMA flow chart of the identification and screening process

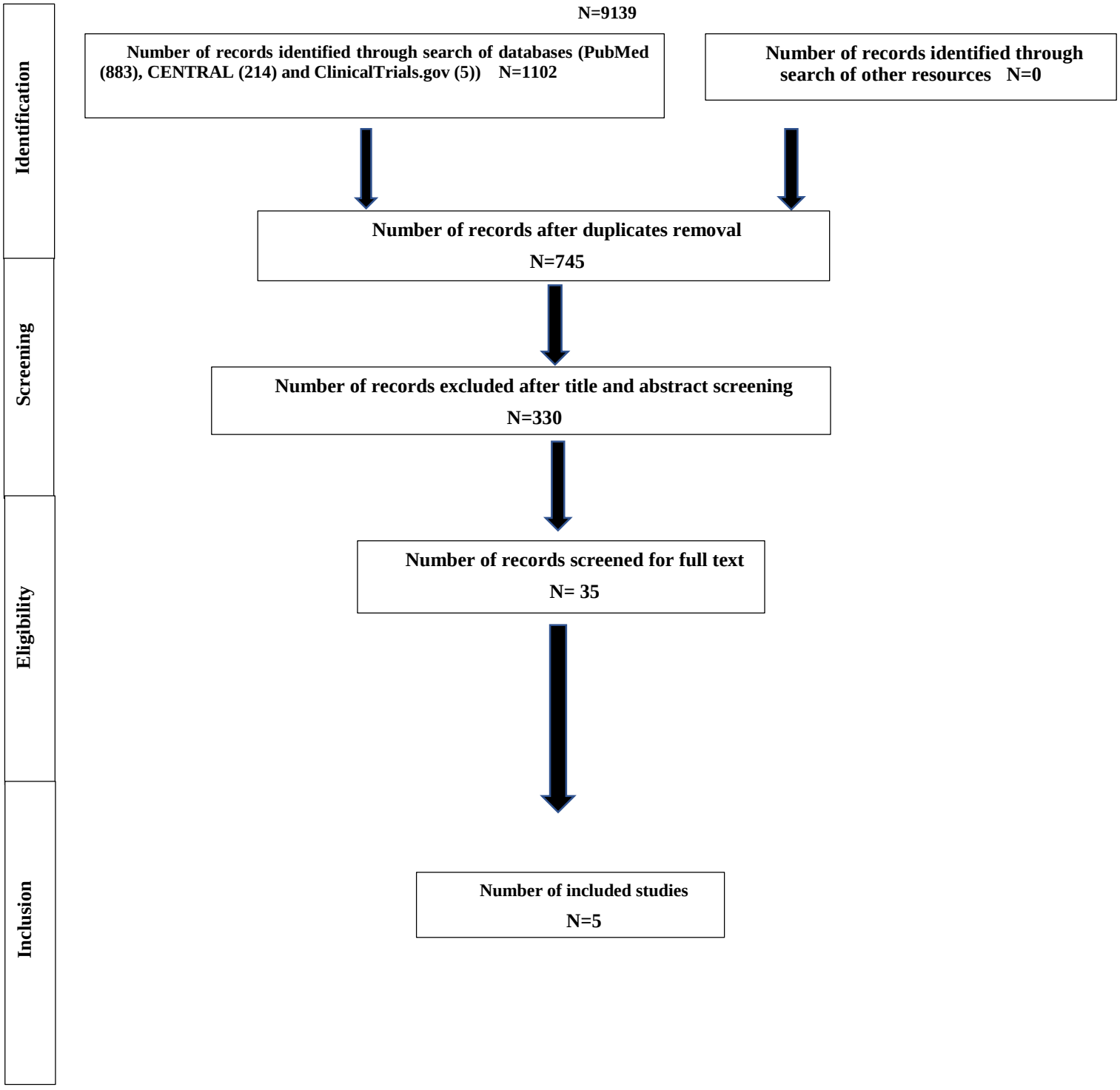


Table-1: Basic characteristics of the included studies

Study	Year	Type of Study	Total number of patients	Interventional arm	Control arm	Duration of follow up	Trial registration number
Hokusai (Raskob et al.)	2018	Open-label, non-inferiority RCT	1050	Edoxaban (522 patients)	Dalteparin (524 patients)	12 months	NCT02073682
SELECT-D (Young et al.)	2018	Open-label, pilot RCT	406	Rivaroxaban (203 patients)	Dalteparin (203 patients)	24 months	ISRCTN86712308
ADAM VTE (McBane II et al.)	2019	Open-label RCT	300	Apixaban (145 patients)	Dalteparin (142 patients)	6 months	NCT02585713
Caravaggio (Agnelli et al)	2020	Open-label, non-inferiority RCT	1170	Apixaban (576 patients)	Dalteparin (579 patients)	7 months	NCT03045406
CANVAS (Schrag et al.)	2021	Unblinded, Non inferiority RCT	671	Any (330 patients)	Any (308 patients)	6 months	NCT02744092

Fig. (2). Forest plot showing the rate of recurrent VTE comparison between DOACs vs LMWH in patients with cancer

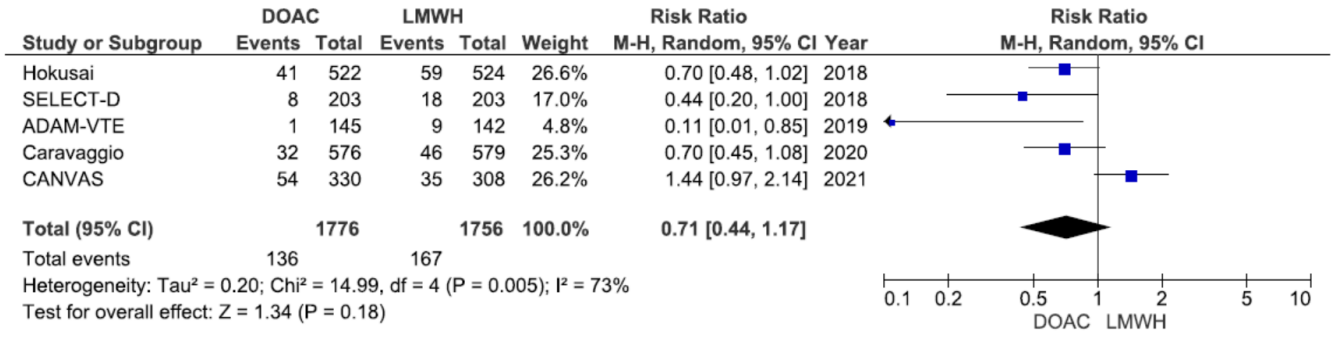


Figure-3: Forest plot showing the over-all mortality comparison between DOACs vs LMWH in patients with cancer

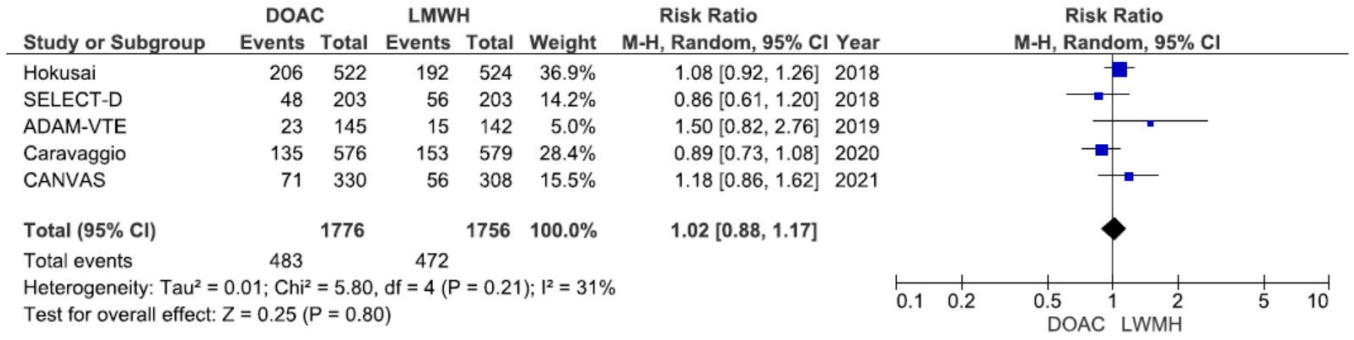
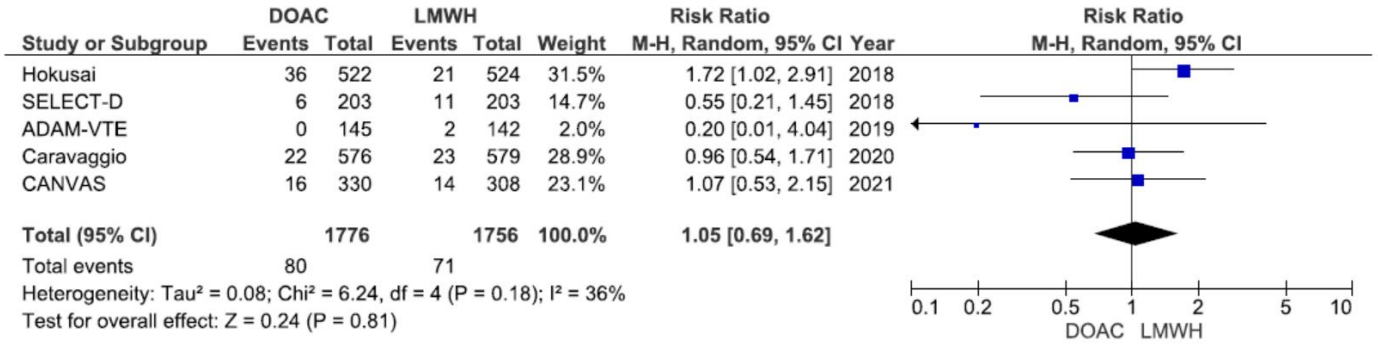


Figure-4: Forest plot showing rate of major bleeding comparison between DOACs vs LMWH in patients with cancer



4. DISCUSSION

The prevention of VTE in patients with cancer, as well as the choice of antithrombotic agents, represents a major challenge for clinicians worldwide. The results of the present meta-analysis of available RCTs comparing DOACs with

rin) [12, 13]. However, the technical difficulties associated with the parenteral route, as well as the cost of LMWH injection for a long duration, were reported as limitations to its widespread use in patients with cancer. Therefore, subsequent studies have focused on finding a simpler and similarly effective treatment approach, with DOACs representing a promising option that could fill the gaps in the treatment strategy.

Currently, DOACs are considered a first-line option for the treatment and prevention of VTE in patients without a diagnosis of cancer [14]. Likewise, their role in the management of patients with cancer has been the subject of several recent studies, such as the trials included in this metaanalysis. Because of these trials, ASCO guidelines recommend the use of the DOACs (apixaban, rivaroxaban) as equivalent to LMWH for the primary prevention of VTE in high-risk non-hospitalized patients with cancer [5]. Likewise, the American Society of Hematology (ASH) recommends the use of DOACs for the treatment and secondary prophylaxis of VTE in patients with cancer for short- and long-term duration [15]. However, the recommendations have low certainty, with more data needed to adequately support the evidence.

In this meta-analysis, we searched the literature for all RCTs evaluating DOACs as an alternative to LMWH for the secondary prophylaxis of VTE in patients with different types of cancers. Our search resulted in five RCTs (Hokusai, SELECT-D, ADAM VTE, Caravaggio, and CANVAS trials) [7-11]. This meta-analysis is updated and has included all the randomized controlled trials that have compared DOAC with LMWH and involved at least 6 months of follow-up duration. Our results indicated that DOACs have a similar rate of recurrent VTE events and overall mortality in comparison to LMWH. The analysis has also assessed the rate of major bleeding events, which was found to be similar between the two groups. All studies enrolled patients with symptomatic or incidental VTE, including deep venous thrombosis and/or pulmonary embolism. Treatment with DOACs as secondary prophylaxis lasted between 6-12 months, with a duration of follow-up of up to two years in some studies. The enrolled patient population in all studies included adults with active cancer of different types, and with differing functional statuses.

It is important to mention that all included studies utilized different DOACs, as well as different dosing schedules (edoxaban 60 mg once daily for 6-12 months [7], rivaroxaban 15 mg twice daily for 3 weeks and then 20 mg once daily for 6 months [8], apixaban 10 mg twice daily for 1 week and then 5 mg twice daily for 6 months [9, 10]). One trial (CANVAS) allowed for the use of any DOAC, with dosing according to the treatment choice. The available evidence cannot provide support for a particular DOAC to be used as an alternative to LMWH in cancer patients.

Similar comparisons have been previously made regarding the use of DOACs in patients with cancer and atrial fibrillation. In that context, Mariani et al. reported a higher efficacy and safety of DOACs in comparison to warfarin for reducing the risk of systemic embolism and ischemic stroke. The risk of bleeding was lower with DOAC and there was also a reduced rate of gastrointestinal and intracranial bleeding events [16]. Of note, DOAC dosing and mechanism of action are different for the prevention of thrombosis in patients with atrial fibrillation, which may be an explanation behind the heterogeneous results.

CONCLUSION

Our results suggest that DOACs are non-inferior to LMWH for the treatment and prevention of VTE in patients with cancer, and therefore, they may be a reasonable treatment option for this group of patients. The use of oral DOACs for the secondary prevention of VTE in patients with cancer is feasible and more practical than the use of parenteral medications. Likewise, DOACs have similar efficacy and safety to low molecular weight heparin with the advantages of less frequent monitoring. Available data, including this meta-analysis, are sufficient to recommend DOACs as first-line therapy in eligible patients with cancer and VTE, as well as for prevention in patients at high risk of VTE occurrence.

LIST OF ABBREVIATIONS

ASCO	=	American Society of Clinical Oncology
ASH	=	American Society of Hematology
CIs	=	Confidence Intervals
DOACs	=	Direct Oral Anticoagulants
DVT	=	Deep Vein Thrombosis
LMWH	=	Low Molecular Weight Heparin
NETs	=	Neutrophil Extracellular Traps
PAI-1	=	Plasminogen Activator Inhibitor-1
PE	=	Pulmonary Embolism
PRISMA	=	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	=	Randomized Controlled Trials
RRs	=	Risk Ratios
VTE	=	Venous Thromboembolic Events

STANDARDS OF REPORTING

PRISMA guidelines and methodology were followed. PRISMA checklist is available on the publisher's website.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The data and supportive information are available within the article.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

SUPPLEMENTARY MATERIAL

PRISMA checklist is available as supplementary material on the publisher's website along with the published article.

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