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Review Article

Direct Oral Anticoagulants for Treatment of Venous Thromboembolism Associated with Cancer: A Systematic Review and Meta-Analysis

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ABSTRACT

There is uncertainty about the choice of anticoagulation therapy in patients with malignancy and venous thromboembolism (VTE). While low-molecular weight heparin (LMWH) remains the current standard, direct oral anticoagulants (DOACs) have emerged as an appealing alternative option. The primary objective of this analysis was to compare the efficacy and safety of DOACs versus LMWH in patients with malignancy and VTE. The secondary objective was to compare the safety and efficacy of the different DOACs. An online search of PubMed, EMBASE, the Cochrane Library and ClinicalTrials.gov from inception until April 2020 was conducted. Four RCTs encompassing 2,907 patients, (50.5% men and mean age of 65.7 \pm 10.5) were selected. At a mean follow up of 12 months, moderate certainty evidence showed no differences between DOAC and LMWH in VTE recurrence (HR, 0.54 [CI 0.23 to 1.28], I² = 56%, p=0.23), in major bleeding (HR, 1.38 [CI 0.45 to 4.22], I² = 33%, p=0.21) or clinically relevant non-major bleeding (CRNMB) (HR, 1.77 [CI 0.49 to 6.40], I² = 73.9%, p=0.087). There was no difference between the DOACs when compared to each other. In conclusion, DOACs are an acceptable alternative to LMWHs for the treatment of VTE in patients with malignancy.

Introduction

Patients with cancer are at higher risk of developing venous thromboembolism (VTE) compared to patients without cancer [1, 2]. Furthermore, those with cancer have a particularly high risk of VTE recurrence (up to 20%) despite appropriate anticoagulation [1]. Despite the use of direct oral anticoagulants (DOACs) as the mainstay of therapy

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for VTE in patients without malignancy, their use in the treatment of VTE associated with malignancy remains uncertain. Several large randomized controlled trials (RCTs) have proven the superiority of low-molecular weight heparin (LMWH) compared to warfarin for the treatment of cancer-associated VTE. These data have led to LMWH use as the standard of care for the management of cancer associated VTE even in the post-DOAC era [3, 4].

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As the field is evolving, current data on the use of DOACs for VTE in cancer patients are growing. Few RCTs studying the efficacy and safety of edoxaban (Hokusai VTE Cancer trial), apixaban (SELECT-D and Caravaggio trials) and rivaroxaban (ADAM VTE trial) exist; in all four of these trials, the comparator group was dalteparin, an LMWH [5-8]. Given this relative paucity of data to date, we performed a systematic review and meta-analysis to assess the efficacy and safety of DOACs compared to LMWH, and DOACs to each other, for the treatment of malignancy-associated VTE.

Methods

This meta-analysis was conducted following the Cochrane Collaboration guidelines and reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) (Appendix Table 5). The protocol, although not registered, was submitted to PROSPERO on 3rd April 2020.

I Data Sources and Searches

The literature search was performed without language restriction using electronic databases of Cochrane Central Register of Controlled Trials (Issue 4 of 12, April 2020), MEDLINE (OVID), MEDLINE (PubMed) and ClinicalTrials.gov from inception to 3rd April 2020. The search strategy included broad search terms like "new oral anticoagulant", "NOAC", "DOAC", "venous thromboembolism", "clot", "thrombosis" "cancer", "malignancy", "enoxaparin", "LMWH" and "heparin". The details of the search strategy are presented in the online appendix (Appendix Table 1).

II Study Selection

The pre-specified inclusion criteria were: 1) RCTs comparing DOAC vs. LMWH in patients with diagnoses of cancer and venous thromboembolism. 2) RCTs reporting the recurrence of VTE and bleeding outcomes were of interest. There were no limitations on the sample size or follow-up duration of RCTs. We excluded observational studies, registries, and post hoc analyses of RCTs. After removing the duplicates and following the selection criteria, we screened the remaining articles at the title and abstract level and then at the full-text level. The whole process of study search and selection was performed independently by two investigators (MS and SF). Any conflicts were resolved by discussion, mutual consensus, referring to the original study or opinion of the third investigator (MO).

III Data Extraction and Quality Assessment

Two investigators (MS and SF) independently abstracted the data using pre-specified data collection forms. Discrepancies were resolved by consensus after discussion with a third investigator (MO). We extracted hazard ratios (HRs) and corresponding confidence intervals (CI) for studies reporting HRs for inclusion in the analysis. Two investigators (MS and MO) independently appraised the potential risks of bias of the RCTs using the Cochrane Risk of Bias Tool at the study level as well as at the outcome level (Appendix Figure 1). The GRADE summary of findings table was developed using GRADEpro (Link). It provides a summary of findings for each of the included studies and the quality of evidence rating for each of the three outcomes (Appendix Table 2).

IV Data Synthesis and Analysis

The primary efficacy endpoints were recurrence of VTE, incidental new deep venous thrombosis (DVT) and pulmonary embolism (PE), including segmental or more proximal pulmonary arteries, fatal PE or unexplained death for which PE could not be ruled out as the cause. The secondary safety endpoints were major bleeding and clinically relevant non-major bleeding (CRNMB). Major bleeding was defined as overt bleeding associated with a decrease in the hemoglobin level of at least two grams per deciliter, bleeding requiring a transfusion of at least two units of blood, bleeding occurring at a critical site (intracranial, retroperitoneal etc.), or contributing to death. CRNMB was defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, and unscheduled contact with the health care team, or temporary anticoagulant cessation (Appendix Table 4).

For statistical analysis, estimates were pooled using an inverse-variance random-effects model. The Paule-Mandel (PM) method was used for the estimation of $\tau 2$. We applied Hartung-Knapp/Sidik-Jonkman (HKSJ) or modified HKSJ (in case $\tau 2=$ 0) small-sample adjustments considering the number of studies was less than 10 [9]. We reported effect sizes as HRs with 95% CIs. We used I² statistics to measure the extent of unexplained heterogeneity: I² greater than 50% was considered a high degree of between-study heterogeneity [10]. We did not examine publication bias due to the small number of studies (<10). Additionally, subgroup analysis could not be performed as only two studies (Caravaggio and Hokusai) had performed it.

To further compare the efficacy and safety among different DOACs, we performed additional analyses using a Bayesian approach with a random-effects model [11, 12]. Analyses were performed using the Markov Chain Monte Carlo method, with 5000 adaptation iterations followed by 100,000 iterations of 10 chains [11]. Outcomes were reported as HRs, with 95% credible intervals (CrIs). Consistency models were generated using a Poisson likelihood [13]. Non-informative vague priors were used for all parameters. The 95% CIs or CrIs that did not cross 1 were considered statistically significant. We used "Admetan" commands from Stata, 15 and GeMTC package on R Software, version 3.4.1 (R Foundation for Statistical Computing) for all analysis.

Results

I Search Results

260 articles were retrieved after removal of duplicates, of which 242 were considered irrelevant based on title and abstract screening. A total of 18 articles were reviewed in full text for eligibility. We further excluded 14 articles based on the *a* priori study selection criteria. Ultimately, 4 RCTs, including 2,907 patients, were selected for analysis (Figure 1).



Figure 1: Flow chart for the systematic review and meta-analysis as per the Preferred Reporting System for Systematic Review and Meta-analysis (PRISMA).



Figure 2: Forest plots comparing VTE recurrence, Major Bleeding and CRNMB between DOAC and LMWH.

DOAC: direct oral anticoagulant; DVT: deep vein thrombosis; LMWH: low-molecular-weight heparin; CRNMB: Clinically relevant non-major bleeding; VTE: venous thromboembolism; SCC: squamous-cell carcinoma skin.

Apixaban	0.276 (0.031, 2.447)	0.400 (0.009, 18.158)	0.622 (0.014, 26.714)
	Dalteparin	1.431 (0.067, 31.633)	2.253 (0.103, 48.424)
		Edoxaban	1.577 (0.020, 123.470)
VTE Recurrence			Rivaroxaban
Apixaban	1.545 (0.340, 16.281)	2.630 (0.219, 76.394)	2.980 (0.212, 86.730)
	Dalteparin	1.728 (0.194, 15.597)	1.898 (0.183, 18.662)
		Edoxaban	1.096 (0.043, 24.720)
Major Bleeding			Rivaroxaban
Apixaban	0.761 (0.286, 2.264)	1.000 (0.186, 6.027)	2.839 (0.472, 19.342)
	Dalteparin	1.324 (0.321, 5.246)	3.724 (0.821, 17.848)
		Edoxaban	2.824 (0.361, 23.194)
<u>CRNMB</u>			Rivaroxaban

Figure 3: League Tables showing the results of the network meta-analysis.

CRNMB: Clinically relevant non-major bleeding; VTE: venous thromboembolism.

League or Consistency Table showing the results of the network meta-analyses comparing the three outcomes amongst all the drugs, including hazard ratios (HR) and 95% credible intervals. HR <1 means the top left treatment is better for the respective adverse outcome. Comparisons between treatments should be read left-to-right (i.e. apixaban vs dalteparin). Each cell gives the effect of the column-defining intervention relative to the row-defining intervention. If the CI includes 1, results are not statistically significant. For VTE recurrence, all DOACs lower events of VTE recurrence compared to dalteparin. For VTE recurrence amongst DOACs, apixaban < edoxaban, apixaban < rivaroxaban, apixaban < rivaroxaban. Note how all the results are not statistically significant.



Figure 4: Forest Plots showing the network meta-analysis of the three outcomes and each drug compared amongst each other including hazard ratios (HR) and 95% confidence intervals (CI).

CRNMB: Clinically relevant non-major bleeding; VTE: venous thromboembolism.

II Study and Participant Characteristics

Baseline characteristics of the included trials are shown in (Appendix Table 3). Briefly, the mean age of the patients was 65.7 ± 10.5 years, and 50.45% were men.

III Risk of Bias Assessment

All trials had an open-label design, subjecting to treatment or reporting bias. The risk of bias summary is shown in (Appendix Figure 1).

IV Primary Efficacy Outcome

At a mean follow up of 12 months, moderate certainty evidence showed no differences between DOAC and LMWH in VTE recurrence (HR, 0.54 [CI 0.23 to 1.28], $I^2 = 56\%$, p=0.23) (Figure 2).

V Secondary Safety Outcomes

Moderate certainty evidence showed no difference between DOAC and LMWH in major bleeding (HR, 1.38 [CI 0.45 to 4.22], $I^2 = 33\%$, p=0.21) or CRNMB (HR, 1.77 [CI 0.49 to 6.40], $I^2 = 73.9\%$, p=0.087) (Figure 2, Appendix Tables 6 & 7).

VI Bayesian Network Analysis

There was no difference between any of the DOACs (apixaban, rivaroxaban and edoxaban) and LMWH in terms of VTE recurrence, major bleeding or CRNMB. Moreover, there was no difference among each of the DOACs when compared with each other (Figures 3 & 4, Appendix Figures 2-4).

Discussion

In the current systematic review and meta-analysis, including 2,907 patients from 4 RCTs comparing DOACs to LMWH in the treatment of cancer associated VTE, there are several important observations. First, there was moderate certainty evidence suggesting that DOACs are as effective as LMWH in the prevention of recurrent VTE. Second, there was moderate certainty evidence supporting DOACs safety compared to LMWH in patients with cancer. Finally, we could not prove an overwhelming benefit of any one specific DOAC over another on network meta-analysis.

Over the past decade, DOACs have transformed the therapeutic landscape for the treatment of VTE, but an extension to malignancy associated VTE has not been fully implemented. Even though the current standard care to date has favored LMWH for cancer associated VTE, the results of our analysis suggest that DOACs are a reasonable alternative. These results suggest that DOAC therapy is as effective and safe as LMWH. Practically, LMWH therapy has several significant drawbacks, including the need for repeated subcutaneous injections, lack of a complete antidote, need for serum drug level monitoring in significant renal dysfunction, dose reductions in thrombocytopenia, risk of developing heparin-induced thrombocytopenia, and cost. On the other hand, DOACs are orally administered at fixed dosing regimens that do not require laboratory monitoring, have effective antidotes, and do not have associated heparin-induced thrombocytopenia risk [14, 15]. However, cost, as well as difficulties of use in significant renal dysfunction and thrombocytopenia, are shared shortcomings of either approach. Nonetheless, the totality of data to date and practical considerations make DOACs an attractive option for the treatment of VTE in cancer patients.

All four RCTs included in this analysis enrolled patients with active cancer who had acute symptomatic or incidental VTE (DVT or PE) [5-8]. Patients were assigned to receive either subcutaneous dalteparin or oral DOAC (apixaban, edoxaban or rivaroxaban), in standard fixed doses and regimens. Primary outcomes were based either on efficacy, determined by the recurrence of VTE, or on safety, determined by major bleeding or CRNMB. The SELECT-D and Caravaggio trials used VTE recurrence as the primary outcome; the ADAM-VTE trial used bleeding as the primary outcome, and the Hokusai-VTE trial used both VTE recurrence and bleeding events as the co-primary outcomes.

The patient population differed in these trials, secondary to the inclusion of a wide range of malignancies at different stages, exclusion of certain cancers (Appendix Table 3) and different functional status of patients. This contributed to significant variance in the results, as evident by large CIs and high I². Between DOAC and LMWH, VTE recurrence has a HR of 0.54 [CI 0.23 to 1.28], I² = 56%, p=0.2, major bleeding has a HR of 1.38 [CI 0.45 to 4.22], I² = 33%, p=0.2 and CRNMB has a HR of 1.77 [CI 0.49 to 6.40], $I^2 = 73.9\%$, p=0.09, none of which are clinically significant differences. The Caravaggio trial had fewer patients with upper gastrointestinal (GI) cancers and excluded patients with primary brain and hematologic cancers, which account for the lower rates of major and clinically non-major bleeding rates in comparison with other trials. In addition, the subgroup analysis performed by the Caravaggio trial showed a significant interaction between age groups and treatment for VTE. The ADAM VTE trial reported no major bleeding events and lower overall mortality (13.2%), but this may have been due in part to the smaller sample size (n=300) and patient selection (included patients with upper extremity VTE). The Hokusai-VTE trial investigated edoxaban, although patients had received an initial week of LMWH therapy, which complicates interpretation.

Currently, there is no data showing the superiority of one DOAC over another due to a lack of prospective head-to-head comparisons. The purpose of conducting a Bayesian network meta-analysis was to compare different DOACs across trials. This network analysis did not reveal any statistically significant difference in the efficacy and safety of different DOACs. However, these results are not conclusive, and RCTs comparing DOACs head-to-head are warranted.

This study has several limitations that need to be acknowledged. First, a heterozygous patient population existed across the included trials. Second, all the included trials had open-label designs with the consequent risk of bias. Third, there was a limited number of available RCTs for analysis, and only apixaban was studied in more than one trial. Fourth, there is limited information on drug interactions between DOACs and chemotherapeutic agents, which adds another layer of uncertainty in terms of individualized efficacy and safety profiles. Fifth, the included high-risk patient population had a high mortality rate causing a significant loss to follow up and may represent a reverse

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survivorship bias. However, to avoid bias, most RCTs conducted an intention-to-treat analysis. Sixth, the efficacy of DOACs in patients on newer cancer therapies such as checkpoint inhibitors is also unknown, as only a minority of patients in these trials had received the novel, emerging agent. Finally, the number of subjects enrolled in certain trials like ADAM-VTE was small. However, the trial was designed as a superiority trial with 80% power to detect a difference in major bleeding as the primary outcome.

The aim of this analysis was to find a difference in efficacy and safety between DOACs and LMWH in the treatment of cancer associated VTE. Pooled analysis has been conducted before, but our analysis has a few unique attributes [16-19]. This study included the new RCT, Caravaggio trial, which was recently published after the prior meta-analysis, hence, allowing for an updated review and analysis of the current evidence. It also includes RCTs only, to provide the highest level of evidence with the least amount of bias, albeit at the cost of limiting overall sample size and widening of the CIs. Some of the prior meta-analysis documented clinically significant differences in outcomes, but this updated analysis does not reveal a clinically significant difference in VTE recurrence or bleeding between DOACs and LMWH. We also just compared DOACs to LMVH and excluded trials that included comparison of DOACS to Coumadin. Additionally, we included trials that were analyzing the treatment of VTE and not just prophylaxis of it. Furthermore, we enhanced our analysis by performing a network analysis to compare the efficacy and safety among different DOACs.

With the available evidence, this study showed no difference between the two classes of anticoagulants. Clinically, this provides an alternative and less cumbersome option for cancer patients for the treatment of VTE. Shared decision-making between the patients and care providers should be used to choose an agent that is best for the patient. Each trial included in this analysis had a unique patient population. Even though most trials excluded basal cell and squamous cell carcinoma of the skin, potentially limiting the applicability of this study to such malignancies, the ADAM-VTE trial did not exclude any specific malignancies, including brain metastasis. The Hokusai trial performed a subgroup analysis with GI cancer patients, which showed a higher risk of bleeding with edoxaban compared to dalteparin. However, the recently published Caravaggio trial showed a similar major bleeding risk in the apixaban and dalteparin groups (3.8% and 4%; p=0.6), including major GI bleeds (11 vs. 10 events). This expands the proportion of patients who are eligible for treatments with DOACs, including patients with GI cancers. In conclusion, DOACs can be considered an alternative anticoagulant option to LMWH for the treatment of VTE in patients with cancer, given the comparable rates of VTE recurrence and bleeding events.

Disclosure

None.

Conflicts of Interest

None.

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