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Direct oral anticoagulants for cancer-associated venous thromboembolism: a systematic review and meta-analysis

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Abstract:
Direct oral anticoagulants (DOACs) are an emerging treatment option for cancer patients with acute venous thromboembolism (VTE), but studies have reported inconsistent results. This systematic review and meta-analysis compared the efficacy and safety of DOACs and low-molecular-weight heparins (LMWH) in these patients. MEDLINE, Embase, CENTRAL, and conference proceedings were searched to identify relevant randomized controlled trials. Additional data were obtained from the original authors to homogenize definitions for all study outcomes. The primary efficacy and safety outcomes were recurrent VTE and major bleeding, respectively. Other outcomes included the composite of recurrent VTE and major bleeding, clinically relevant non-major bleeding (CRNMB), and all-cause mortality. Summary relative risks (RR) were calculated in a random effects meta-analysis. In the primary analysis comprising 2,607 patients, the risk of recurrent VTE was non-significantly lower with DOACs than with LMWH (RR 0.68; 95% CI, 0.39 to 1.17). Conversely, the risks of major bleeding (RR 1.36; 95% CI, 0.55 to 3.35) and CRNMB (RR 1.63, 95%, 0.73 to 3.64) were non-significantly higher. The risk of the composite of recurrent VTE or major bleeding was non-significantly lower with DOACs than with LMWH (RR 0.86; 95% CI, 0.60 to 1.23). Mortality was comparable in both groups (RR 0.96; 95% CI, 0.68 to 1.36). Findings were consistent during the on-treatment period and in those with incidental VTE. In conclusion, DOACs are an effective treatment option for cancer patients with acute VTE, although caution is needed in patients at high risk of bleeding.

Conflict of interest: COI declared - see note

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Running head

Direct oral anticoagulants in cancer patients

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Key points:

- The composite of recurrent VTE and major bleeding was non-significantly lower for DOACs than LMWH.
- DOACs should be used with caution in patients at high risk for bleeding.

Abstract

Direct oral anticoagulants (DOACs) are an emerging treatment option for cancer patients with acute venous thromboembolism (VTE), but studies have reported inconsistent results. This systematic review and meta-analysis compared the efficacy and safety of DOACs and low-molecular-weight heparins (LMWH) in these patients. MEDLINE, Embase, CENTRAL, and conference proceedings were searched to identify relevant randomized controlled trials. Additional data were obtained from the original authors to homogenize definitions for all study outcomes. The primary efficacy and safety outcomes were recurrent VTE and major bleeding, respectively. Other outcomes included the composite of recurrent VTE and major bleeding, clinically relevant non-major bleeding (CRNMB), and all-cause mortality. Summary relative risks (RR) were calculated in a random effects meta-analysis. In the primary analysis comprising 2,607 patients, the risk of recurrent VTE was non-significantly lower with DOACs than with LMWH (RR 0.68; 95% CI, 0.39 to 1.17). Conversely, the risks of major bleeding (RR 1.36; 95% CI, 0.55 to 3.35) and CRNMB (RR 1.63, 95%, 0.73 to 3.64) were non-significantly higher. The risk of the composite of recurrent VTE or major bleeding was non-significantly lower with DOACs than with LMWH (RR 0.86; 95% CI, 0.60 to 1.23). Mortality was comparable in both groups (RR 0.96; 95% CI, 0.68 to 1.36). Findings were consistent during the on-treatment period and in those with incidental VTE. In conclusion, DOACs are an effective treatment option for cancer patients with acute VTE, although caution is needed in patients at high risk of bleeding.

Introduction

Venous thromboembolism (VTE) is a common complication in patients with cancer. Its management in cancer patients is challenging because the risks of bleeding events and recurrent VTE during anticoagulant treatment are high.[1] Until recently, subcutaneous low-molecular-weight heparin (LMWH) was the mainstay of treatment for cancer-associated VTE, because of the lower risk of recurrent VTE compared with vitamin K antagonists.[2,3] However, LMWH is relatively expensive and the subcutaneous route of administration is often considered burdensome by patients, possibly leading to poor adherence.[4–6]

Direct oral anticoagulants (DOACs) include apixaban, edoxaban, and rivaroxaban, which inhibit factor Xa, and dabigatran, which inhibits thrombin. These drugs are easy to use as they can be administered orally in fixed doses without routine monitoring. Based on their favorable safety profile compared to vitamin K antagonists, DOACs have been established as the recommended treatment for VTE in the general population.[7]

Recently, several randomized controlled trials have compared DOACs with LMWH for treatment of VTE in patients with cancer associated VTE.[8–11] Some of these trials showed that DOACs, compared to LMWH, were associated with a higher risk of bleeding,[8,9] while others did not.[10,11] These conflicting results could reflect differences in patient characteristics across the studies (i.e. index VTE and type and stage of cancer), heterogeneity in the definition of study outcomes, or variability in follow-up period analyses (i.e. complete follow-up period vs. on-treatment period). In addition, most studies were designed as non-inferiority studies and therefore had limited precision in evaluating the efficacy or safety of DOACs relative to LMWH. Hence, questions remain about the overall benefit-risk ratio of DOACs vs. LMWH for VTE treatment in cancer patients.

In this systematic review and meta-analysis, we evaluated the efficacy and safety of DOACs versus LMWH for treatment of VTE in cancer patients. In addition, by collecting additional outcome data for the individual studies, this report extends current knowledge by 1) aggregating all current evidence using a uniform study outcome definition, 2) reporting a summary on-treatment analysis, 3) providing a subgroup analysis of patients with incidental VTE, and 4) performing an analysis of net clinical benefit by evaluating the composite outcome of first recurrent VTE and major bleeding.

Methods

This study was registered (Open Science Framework (OSF): https://osf.io/vn9aq). The study report was prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance (Supplementary Table 1).[12]

Search strategy and data collection

A systematic literature search was performed on March 29th, 2020 in MEDLINE, Embase, and the Cochrane central register of controlled trials to identify randomized controlled trials that compared any DOAC with any low-molecular-weight heparin (LMWH) for the treatment of VTE in cancer patients by combining terms for VTE, deep vein thrombosis (DVT), pulmonary embolism (PE), cancer, and DOACs. No restrictions for year of publication or language were applied. The search strategy is shown in Supplementary Table 2. Additionally, a manual search was performed to identify relevant abstracts presented at the most recent conferences of the American Society of Hematology, the International Society on Thrombosis and Haemostasis (ISTH), European Society of Cardiology, and American College of Cardiology. All included studies were approved by their local Institutional Review Board

Two reviewers (F.I.M and F.T.M.B.) independently screened titles, abstracts, and subsequently full texts for potentially eligible articles. Both reviewers independently assessed risk of bias using the Cochrane tool of bias assessment in randomized controlled trials version 2.0.[13] Bias was assessed in the domains of randomization process, deviations from intended intervention, missing outcome data, measurement of outcome, and selection of the reported results. Data on study characteristics and outcomes were extracted using a standardized form. Discrepancies were resolved by consensus or contact with a third author (N.v.E).

Inclusion criteria and outcomes

Randomized controlled trials that compared a therapeutic dose of a DOAC with a therapeutic dose of LMWH (either full-dose or full-dose followed by reduced dose) in patients with acute symptomatic or incidental VTE and active cancer or a recent history of cancer were eligible. Active cancer was defined as any cancer other than non-melanoma skin cancer that i) was diagnosed in the 6 months prior to

study inclusion, ii) required cancer treatment in the 6 months before randomization, iii) was recurrent or metastatic, or iv) was a hematologic malignancy not in complete remission. A recent history of cancer was defined as a cancer diagnosis in the 2 years prior to inclusion and not fulfilling the criteria for active cancer. Any objectively confirmed symptomatic or incidental VTE was allowed as an index venous thromboembolic event, except superficial vein thrombosis.

The primary efficacy outcome was recurrent VTE, defined as symptomatic or incidental new DVT of the upper or lower extremities, symptomatic or incidental PE involving segmental or more proximal pulmonary arteries, or fatal PE including unexplained death for which PE could not be ruled out. Splanchnic vein thrombosis, cerebral vein thrombosis, and arterial thromboembolic events were not part of the primary efficacy outcome.

The primary safety outcome was major bleeding, defined using the ISTH criteria as overt bleeding associated with a drop in hemoglobin of 2 g per deciliter or more or transfusion of 2 or more units of blood, or that occurred in a critical site or contributed to death.[14] Other safety outcomes were all-cause mortality, fatal recurrent VTE, fatal major bleeding, and clinically relevant non-major bleeding, which was defined using the ISTH criteria as overt bleeding not meeting the criteria for major bleeding but associated with the need for medical intervention, contact with a physician, interruption of the assigned treatment, discomfort, or impairment of activities of daily living.[14] The definitions of fatal PE and major bleeding used in the original studies were accepted. The composite outcome of first recurrent VTE or major bleeding was also evaluated as a measure of net clinical benefit.

We intended to evaluate all outcomes during a maximum of 6 months of follow-up in the intention-to-treat or modified intention-to-treat population which included all patients who were randomized and received at least one dose of the assigned study drug. Recurrent VTE and major bleeding events were also evaluated during the on-treatment period (while taking the assigned study drug or up to 3 days after discontinuation) in the per-protocol population as defined in the individual studies. If the per-protocol population was not specified, the (modified) intention-to-treat population was used for the on-treatment analysis. The certainty of evidence was graded according to the GRADE guidelines, and presented in a summary of findings table with GRADEpro GDT software.[12]

Statistical analysis

The primary effect measure was the relative risk for DOACs compared with LMWH for all study outcomes. The secondary effect measure was the absolute risk reduction for DOACs relative to LMWH. Since relative risks are generally more consistent across studies than absolute risks,[15] the anticipated absolute risk reduction was calculated by applying the summary estimate of the relative risk to the observed baseline risk in the LMWH groups, as is generally recommended.[15,16]

Logit transformation and inverse variance weighting was used to calculate summary estimates using a Knapp-Hartung random-effects model, which is generally preferred in a meta-analysis of few studies.[17,18] Forest plots were constructed for all back-transformed outcome measures with corresponding 95% confidence intervals. Between-study heterogeneity was assessed by calculating tau-squared (τ^2) and I-squared (I^2) using restricted maximum likelihood estimations.

The primary analysis was restricted to studies that included patients with acute, symptomatic or incidentally detected lower-extremity DVT involving the popliteal, femoral, or iliac veins or the inferior vena cava, acute symptomatic PE, incidentally detected PE involving segmental or more proximal pulmonary arteries as the index event. A secondary analysis included results from studies that had enrolled patients with any type of VTE index event.

A subgroup analysis was performed for patients whose index event was incidental VTE, which was defined as VTE events detected on radiologic imaging scans performed for reasons other than suspected VTE. Of the incidental VTE in the Hokusai VTE Cancer Study, only those confirmed by blinded adjudication were included.[19]

Publication bias was explored by visual inspection of the funnel plots. No formal tests for publication bias were performed, because they lack statistical power when few studies are included. Since there were differences across studies in outcome definitions, reporting of on-treatment analyses, reporting of the composite outcome, and reporting of the subgroups gastrointestinal cancer and incidental index VTE, additional data were requested from the corresponding authors.

Analyses were performed with R computing software, version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria, www.r-project.org), using the *meta* package version 4.9-2.

Data sharing statement

For original data, please contact f.i.mulder@amsterdamumc.nl.

Results

The electronic database and manual searches for conference abstracts yielded 545 unique articles and one abstract, of which 215 were duplicates and 318 were excluded after screening of title and abstract. After full-text assessment, another nine studies were excluded because the study was either a duplicate (n=3), not a randomized trial (n=2), included a different population (n=3), or did not evaluate a DOAC (n=1) (Supplementary Figure 1). Inter-observer agreement for study selection was 97% (Cohen's kappa 0.72).

Four randomized controlled trials were included in the meta-analysis, which had enrolled a total of 2,894 cancer patients with acute VTE.[8–11] Study characteristics are specified in Table 1. In all studies, the proportion of patients with active cancer was 97% or higher. The included studies evaluated either apixaban 5 mg twice daily (ADAM-VTE and Caravaggio),[10,11] edoxaban 60 mg once daily (Hokusai VTE Cancer),[8] or rivaroxaban 20 mg once daily (SELECT-D).[9] The patients in the control groups in all studies received subcutaneous dalteparin (200 IU per kilogram for the first 30 days, followed by 150 IU per kilogram thereafter). One study included upper extremity and splanchnic DVT as index events,[10] while the others limited inclusion to patients with proximal DVT or PE. All studies allowed inclusion of patients with incidental VTE. Two studies followed patients for 6 months[10,11] and two for 12 months.[8,9]

Additional unpublished data were obtained for three studies to homogenize definitions and results,[8–10] including the study outcome recurrent VTE without splanchnic or cerebral vein thrombosis,[9,10] major gastrointestinal bleeding,[8] outcomes for patients with incidental VTE,[9] bleeding events during the on-treatment period according to our definition of a bleeding up until 3 days after study drug discontinuation,[8–10] bleeding events in the overall study period,[10] and the net clinical benefit outcome as determined by the composite of first recurrent VTE or major bleeding.[9,10]

Risk of Bias assessment

Using the Cochrane tool of bias assessment in randomized controlled trials version 2.0, none of the studies was judged to be at high risk of bias for one of the bias domains. Despite the open-label study design, all studies were considered to be at low risk of bias in the domain 'measurement of the

outcome' because outcomes were centrally adjudicated by committees blinded to treatment allocation. One study was assessed as having 'some concerns' in the bias domain of missing data, because 5% of patients were lost to follow-up.[10] The results of the risk of bias assessment are presented in Figure 1. Visual inspection of the funnel plot did not indicate evidence of publication bias (Supplementary Figure 2).

Primary analysis

In the three studies that restricted enrollment to patients with proximal DVT or PE (N=2,607),[8,9,11] the risk of recurrent VTE was non-significantly lower in the DOAC group than in the LMWH group (RR 0.68; 95% CI, 0.39 to 1.17; I^2 0%; moderate quality evidence). With a baseline risk of recurrent VTE of 8.3% in LMWH users, the absolute risk reduction with DOACs was -2.7% (95% CI, -5.1 to 1.4). Conversely, the risk of major bleeding was non-significantly higher in the DOAC group than in the LMWH group during the follow-up period (RR 1.36; 95% CI, 0.55 to 3.35; I^2 15%; moderate quality evidence). With a baseline risk of major bleeding of 3.5% in LMWH users, the absolute risk increase with DOACs was 1.3% (95% CI, -1.6 to 8.3). Net clinical benefit – composite of first recurrent VTE or major bleeding was non-significantly lower in the DOAC than in the LMWH group (RR 0.86; 95% CI, 0.60 to 1.23; I^2 0%; moderate quality evidence), with an absolute risk reduction with DOACs of -1.6% (95% CI,-4.4 to 2.6). The risk of clinically relevant non-major bleeding was also non-significantly higher in the DOAC group than in the LMWH group (RR 1.63, 95% CI, 0.73 to 3.64; I^2 49%; moderate quality evidence). Based on a baseline risk of clinically relevant non-major bleeding of 6.5% in LMWH users, the absolute risk increase with DOAC was 4.1% (95% CI, -1.8 to 17.2). All-cause mortality was comparable in both treatment groups (RR 0.96; 95% CI, 0.68 to 1.36; I^2 30%; moderate quality of evidence). Figure 2 shows the forest plots of the relative risk of these study outcomes in both treatment groups. The risk of fatal VTE was non-significantly higher in the DOAC group than in the LMWH group (RR 1.25; 95% CI, 0.26 to 5.94; Supplementary Figure 3). Conversely, the risk of fatal bleeding was non-significantly lower in the DOAC group than in the LMWH group (RR 0.37; 95% CI, 0.03 to 3.91; Supplementary Figure 3). The summary of findings, including absolute risk reduction and quality of evidence according to the GRADE criteria, are presented in Table 2.

During the on-treatment period, the risk of recurrent VTE was significantly lower in the DOAC group compared to the LMWH group (RR 0.60; 95% CI, 0.38 to 0.95; I^2 0%; high quality evidence). The risk of major bleeding and clinically relevant non-major bleeding was not materially different than in the total observation period. Relative risks of recurrent VTE, major bleeding, and clinically relevant non-major bleeding during the on-treatment period are shown in Table 2 and Supplementary Figure 4.

Subgroup with incidental VTE

The primary analysis in patients with incidental VTE as their index event was based on data from 774 cancer patients enrolled in three trials.[8,9,11] Among patients with incidental VTE, the risk of recurrent VTE was non-significantly lower in the DOAC group than in the LMWH group (RR 0.54; 95% CI, 0.26 to 1.11; I^2 0%; moderate quality evidence). With a baseline risk of recurrence in the LMWH group of 6.4%, the absolute risk reduction with a DOAC was -2.9 (95% CI, -4.7 to 0.7). The risk of major bleeding was non-significantly higher in patients with incidental VTE receiving DOACs than in those given LMWH (relative risk 1.29%; 95% CI, 0.74 to 2.28; I^2 0%; moderate quality evidence). With a baseline risk of major bleeding in the LMWH group of 4.6%, the absolute risk increase with DOACs was 1.3 (95% CI, -1.2 to 5.9). There was no evidence of interaction between type of index VTE (symptomatic vs incidental VTE) and treatment for the study outcomes recurrent VTE (P=0.1677) or major bleeding (p=0.5225). The summary of findings for this subgroup in the primary analysis is shown in Table 3, and the corresponding forest plot of the relative risk in Supplementary Figure 5.

Secondary analysis

The secondary analysis, was based on data from 2,894 cancer patients with any acute VTE index event, from four trials.[8–11] Overall, results were comparable to that of the primary analysis. The risk of recurrent VTE was non-significantly lower in the DOAC groups (RR 0.66; 95% CI, 0.39 to 1.13; I^2 26%; moderate quality of evidence), while the risks of major bleeding (RR 1.32 95% CI, 0.70 to 2.47; I^2 1%; moderate quality of evidence) and clinically relevant non-major bleeding (RR 1.60; 95% CI, 0.99 to 2.60; I^2 29%; moderate quality of evidence) were non-significantly higher. The risk of the composite of first recurrent VTE or major bleeding was non-significantly lower in the DOAC group than in the LMWH

group (RR 0.84; 95% CI, 0.63 to 1.34; I^2 38%; moderate quality of evidence). All-cause mortality risk was similar in both groups (RR 0.99; 95% CI, 0.74 to 1.32; I^2 37%; moderate quality of evidence) (Supplementary Figure 6; Supplementary Table 3). No fatal events were reported in the ADAM-VTE trial.

In the on-treatment period, the risk of recurrent VTE was significantly lower in the DOAC group (RR 0.59; 95% CI, 0.35 to 0.99; I^2 5%, high quality evidence), while the risk of major bleeding was non-significantly higher (RR 1.35; 95% CI, 0.54 to 3.37; I^2 36%, moderate quality evidence). The risk of clinically relevant non-major bleeding in this period was significantly higher in DOAC recipients (RR 1.83, 95% CI, 1.06 to 3.14; I^2 18%; high quality evidence) (Supplementary Figure 7; Supplementary Table 3). The ADAM-VTE trial did not report incidental index events, therefore this subgroup could not be evaluated in the secondary analysis.

Discussion

In this systematic review and meta-analysis, data from four randomized controlled trials that compared DOACs with LMWH for cancer-associated VTE were aggregated. The main finding is that, compared with LMWH, DOACs were associated with a 32% lower risk of recurrent VTE and a 36% higher risk of major bleeding, although both these effects were not statistically significant. The net clinical benefit, defined as the composite of recurrent VTE and major bleeding, was non-significantly lower in the DOAC group. Results did not change materially when only considering events during treatment with the study drug.

The results of this meta-analysis support DOACs as an acceptable treatment option for cancer associated VTE, thereby strengthening current guidelines.[20–22] Results in patients with incidentally detected VTE, a group that is rapidly expanding because of the widespread use of high-resolution CT-scanning for staging and follow-up of cancer patients, were consistent with those in patients with symptomatic events.

Compared with LMWH, the reported risk of major bleeding and clinically relevant-non major bleeding was non-significantly higher with DOACs than with LMWH, suggesting that DOACs should be avoided in patients at high risk of bleeding. One such group includes patients with gastrointestinal

cancer, as the majority of major bleeding events occurred in the gastrointestinal tract, in 36 of 62 events (58%). An increased risk of major bleeding in patients with gastrointestinal cancer was observed in the Hokusai VTE Cancer and SELECT-D studies,[9,23,24] but not in the ADAM-VTE study.[10] Despite these observations, the incidence of major bleeding in this patient group was not reported in the later Caravaggio study.[11] However, the overall major bleeding risk was not increased in the apixaban recipients despite that one third (33%) of patients had gastrointestinal cancer. It is unclear whether these conflicting results between studies relate to the pharmacodynamics of the particular DOAC (apixaban vs. others). Although head-to-head comparisons between DOACs in the setting of atrial fibrillation or VTE are lacking, observational studies suggest that some DOACs may be associated with a lower risk of gastrointestinal bleeding than others.[25–27] Another potential explanation could be the enrolment of fewer gastrointestinal cancer patients at high risk for bleeding in Caravaggio and ADAM-VTE studies, which were conducted after publication of the Hokusai VTE Cancer and SELECT-D study results.

Overall, there were only few fatal VTE and major bleeding events in the studies (range, 0 to 0.6%) resulting in relatively wide confidence intervals around the summary estimates. The risk of fatal VTE in each study may have been underestimated as adjudication of fatal VTE is often difficult in the cancer population when detailed information on death is not available.[28] Case fatality rates for VTE were 6.8% in the DOAC group and 3.4% in the LMWH group, while case fatality rates for major bleeding were 1.6% and 10.4% in these groups, respectively. The apparent higher case fatality rate with LMWH could reflect a more severe course of bleeding than with DOACs, which was reported previously.[24]

The majority of patients in the trials received systemic cancer therapy. Plasma concentrations of DOACs can be altered by drugs that inhibit or induce P-glycoprotein or cytochrome P450 3A4, including several chemotherapeutic agents, tyrosine kinase inhibitors, tamoxifen, and immune-modulating agents such as dexamethasone.[29] Unfortunately, we were not able to evaluate such potential interactions as data on this subgroup of patients was not available. More research is needed to better understand the pharmacokinetics of DOACs when given concurrently with cancer drugs.

All trials in this meta-analysis had included a broad spectrum of cancer patients and the proportion of patients with metastatic disease was consistently and substantial, ranging from 53% to

65%. Nonetheless, important differences between the four individual trials included in this meta-analysis should be noted. The risk of major bleeding in the Hokusai VTE Cancer, SELECT-D, and Caravaggio study ranged from 4% to 6% in the DOAC group, and from 3% to 4% in the LMWH group. In ADAM-VTE, which was not included in the primary analysis, there were no bleeding events in the DOAC group and only 2 in the LMWH group (1.4%). Possible explanations include differences in case-mix as reflected by the substantially lower mortality risk in ADAM-VTE or because patients with upper-extremity DVT and splanchnic vein thrombosis were enrolled in ADAM-VTE but not in the other studies. The secondary analysis, however, which included the ADAM-VTE study, did not yield materially different results.

Strengths of this systematic review and meta-analysis include the availability of additional data from three studies, which allowed us to homogenize study outcomes, evaluate additional outcomes, and perform subgroup analyses for patients with incidental VTE. Between-study heterogeneity in the analyses was generally low and most of the included studies were considered to be at low risk of bias in all the bias domains. The study population comprised 2,894 cancer patients, of which the majority received cancer treatment and had metastatic disease, making the study groups representative of clinical practice. Since only four studies were included in this study, we used the Knapp-Hartung method to combine results, which less likely leads to artificially small confidence intervals.[17] Therefore, our estimates of uncertainty, as reflected by the confidence intervals, may be more conservative than with other methods. However, the more commonly used DerSominian-Laird method for random effects results in false-positive findings in up to 15% of pooled results when fewer than five studies are included.[30]

Several limitations need to be acknowledged. Lack of detailed descriptions of patient characteristics precluded evaluation of several other important subgroups of patients, such as those with gastrointestinal cancer, urogenital cancer or hematological cancer. Precision in the individual trials and in this systematic review was limited for evaluating effects in the subgroup of patients with incidental VTE. Therefore, findings in this subgroup need to be interpreted with caution. All included studies were performed with an open-label design, since subcutaneous placebo injections were considered inappropriate. The risk of bias in outcome assessment was considered low because there was central adjudication of study outcomes with blinding of allocated treatment in all included trials.

The present findings show that DOACs are an effective treatment option, and safe for most cancer patients with acute VTE. DOACs should be used with caution in patients at high risk for bleeding. Choosing the optimal anticoagulant drug for cancer-associated VTE should be based on a careful balance of the risks of recurrent VTE and bleeding, the consideration of potential drug-drug interactions, and patient preference.

Authorship

Contribution: all authors made a substantial contribution to the concept and design of the study, interpreted the data, and reviewed the manuscript; F.I.M. and F.T.M.B. performed the data extraction, analyses, and wrote the first draft; All authors critically revised the paper for important intellectual content, approved the final version, and agree with the submission.

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Figure legends

Figure 1. Risk of bias asssement.

Figure 2. Forest plots of summary relative risks between direct oral anticoagulants and low-molecular-weight heparin groups.

Figure 2 legend: Results are based on the primary analysis, which included three studies that used pulmonary embolism or proximal deep-vein thrombosis as index event. For Caravaggio, bleeding events during the on-treatment period were used.

Table 1. Baseline characteristics and 6-month study outcomes of included randomized trials.

			Baseline characteristics							Study outcomes			
Study name	Year	Treatment allocation*	Male (%)	Age years (mean/ median with SD/IQR)	Index event PE ± DVT (%)	Incidental VTE (%)	Prior VTE (%)	Metastatic disease (%)	Gastro-intestinal cancer (%)	Recurrent VTE (%)†	Major bleeding (%)	Clinically relevant non-major bleeding (%)	All-cause mortality (%)
Hokusai VTE Cancer	2018	Edoxaban N=522‡	277 (53.1)	64±11	328 (62.8)	167 (32.0)	49 (9.4)	274 (52.5)	165 (31.6)	34 (6.5)	29 (5.6)	64 (12.3)	140 (26.8)
		Dalteparin N=524	263 (50.2)	63±12	329 (62.8)	173 (33.0)	63 (12.0)	280 (53.4)	140 (26.7)	46 (8.8)	17 (3.2)	43 (8.2)	127 (24.2)
Select-D	2018	Rivaroxaban N=203	116 (57.1)	67 (22-87)	150 (73.9)	108 (53.2)	NR	118 (58.1)	94 (46.3)	7 (3.4)	11 (5.4)	25 (12.3)	48 (23.6)
		Dalteparin N=203	98 (48.3)	67 (34-87)	145 (71.4)	105 (51.7)	NR	118 (58.1)	86 (42.4)	17 (8.4)	6 (3.0)	7 (3.5)	56 (27.6)
ADAM-VTE§	2019	Apixaban N=150	72 (48.0)	64±11	81 (54.0)	NR	8 (5.3)	96 (64.0)	48 (32.0)	0 (0)	0 (0)	9 (6.2)	23 (15.9)
		Dalteparin N=150	73 (48.7)	64±11	75 (50.0)	NR	12 (8.0)	97 (64.7)	57 (38.0)	5 (3.5)	2 (1.4)	7 (4.9)	15 (10.6)
Caravaggio	2020	Apixaban N=576	292 (50.7)	67±11	304 (52.8)	116 (20.1)	45 (7.8)	389 (67.5) ¶	188 (32.6)	32 (5.6)	22 (3.8)	52 (9.0)	135 (23.4)
		Dalteparin N=579	276 (47.7)	67±11	334 (57.7)	114 (19.7)	61 (10.5)	396 (68.4) ¶	187 (32.3)	46 (7.9)	23 (4.0)	35 (6.0)	153 (26.4)

* Number of patients in (modified) intention to treat analysis.

† excluding splanchnic vein thrombosis and cerebral thrombosis.

‡ 122 (23.4%) of patients receiving edoxaban met the criteria of dose reduction to 30mg edoxaban OD.

§ In the ADAM-VTE trial, baseline characteristics were presented for all 300 randomized patients, the analysis was performed in the mITT population (n=145 in the rivaroxaban group, n=142 in the dalteparin group)

¶ Also included patients with recurrent locally advanced cancer.

Abbreviations: IQR, interquartile range; NR, not reported; SD, standard deviation

Table 2. Summary of findings for DOACs versus LMWH for the treatment of cancer associated thrombosis.

Outcomes	Number of participants (studies)	Certainty of the evidence (GRADE)	Relative risk (95% CI)	Observed risk with LMWH	Anticipated absolute effects	
					Risk with DOACs	Absolute risk difference
Recurrent VTE	2607 (3 RCTs)	⊕⊕⊕◯ *MODERATE* due to imprecision[a]	**0.68** (0.39 to 1.17)	8.3%	5.6%	-2.7% (-5.1 to 1.4%)
Major bleeding	2607 (3 RCTs)	⊕⊕⊕◯ *MODERATE* due to imprecision[a]	**1.36** (0.55 to 3.35)	3.5%	4.8%	1.3% (-1.6 to 8.3%)
Composite outcome of first recurrent VTE and major bleeding	2607 (3 RCTs)	⊕⊕⊕◯ *MODERATE* due to imprecision[a]	**0.86** (0.60 to 1.23)	11.1%	9.5%	-1.6% (-4.4 to 2.6%)
Clinically relevant non-major bleeding	2607 (3 RCTs)	⊕⊕⊕◯ *MODERATE* due to imprecision[a]	**1.63** (0.73 to 3.64)	6.5%	10.6%	4.1% (-1.8 to 17.2%)
All-cause mortality	2607 (3 RCTs)	⊕⊕⊕◯ *MODERATE* due to imprecision[a]	**0.96** (0.68 to 1.36)	25.7%	24.7%	-1.0% (-8.2 to 9.3%)
On-treatment analyses:						
Recurrent VTE (on-treatment)	2440 (3 RCTs)	⊕⊕⊕⊕ HIGH	**0.60** (0.38 to 0.95)	8.1%	4.9%	-3.2% (-5.0 to -0.4%)
Major bleeding (on-treatment)	2440 (3 RCTs)	⊕⊕⊕◯ *MODERATE* due to imprecision[a]	**1.43** (0.46 to 4.45)	3.2%	4.6%	1.4%(-1.7 to 11.0%)
Clinically relevant non-major bleedin (on-treatment)	2440 (3 RCTs)	⊕⊕⊕◯ *MODERATE* due to imprecision[a]	**1.93** (0.70 to 5.31)	4.6%	8.9%	4.3% (-1.4 to 19.7%)

Outcomes	Number of participants (studies)	Certainty of the evidence (GRADE)	Relative risk (95% CI)	Observed risk with LMWH	Anticipated absolute effects	
					Risk with DOACs	Absolute risk difference

*__The risk in the DOAC group__ (and its 95% confidence interval) is based on the observed risk in the LMWH group and the **relative effect** of the intervention (and its 95% CI).
[a] Graded down for imprecision due to a broad 95% CI intervals with a possible positive and negative effect of DOAC vs. LMWH.

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Table 3. Summary of findings for DOACs versus LMWH for the treatment of cancer associated thrombosis in patients with incidental VTE.

Outcomes	Number of participants (studies)	Certainty of the evidence (GRADE)	Relative risk (95% CI)	Observed risk with LMWH	Anticipated absolute effects	
					Risk with DOACs	Absolute risk difference
Recurrent VTE	774 (3 RCTs)	⊕⊕⊕◯ *MODERATE* due to imprecision[a]	**0.54** (0.26 to 1.11)	6.4%	3.5%	-2.9% (-4.7 to 0.7%)
Major bleeding	774 (3 RCTs)	⊕⊕⊕◯ *MODERATE* due to imprecision[a]	**1.29** (0.74 to 2.28)	4.6%	5.9%	1.3% (-1.2 to 5.9%)

*__The risk in the DOAC group__ (and its 95% confidence interval) is based on the observed risk in the LMWH group and the **relative effect** of the intervention (and its 95% CI).
[a] Graded down for imprecision due to a broad 95% CI intervals with a possible positive and negative effect of DOAC vs. LMWH.

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Figure 1.

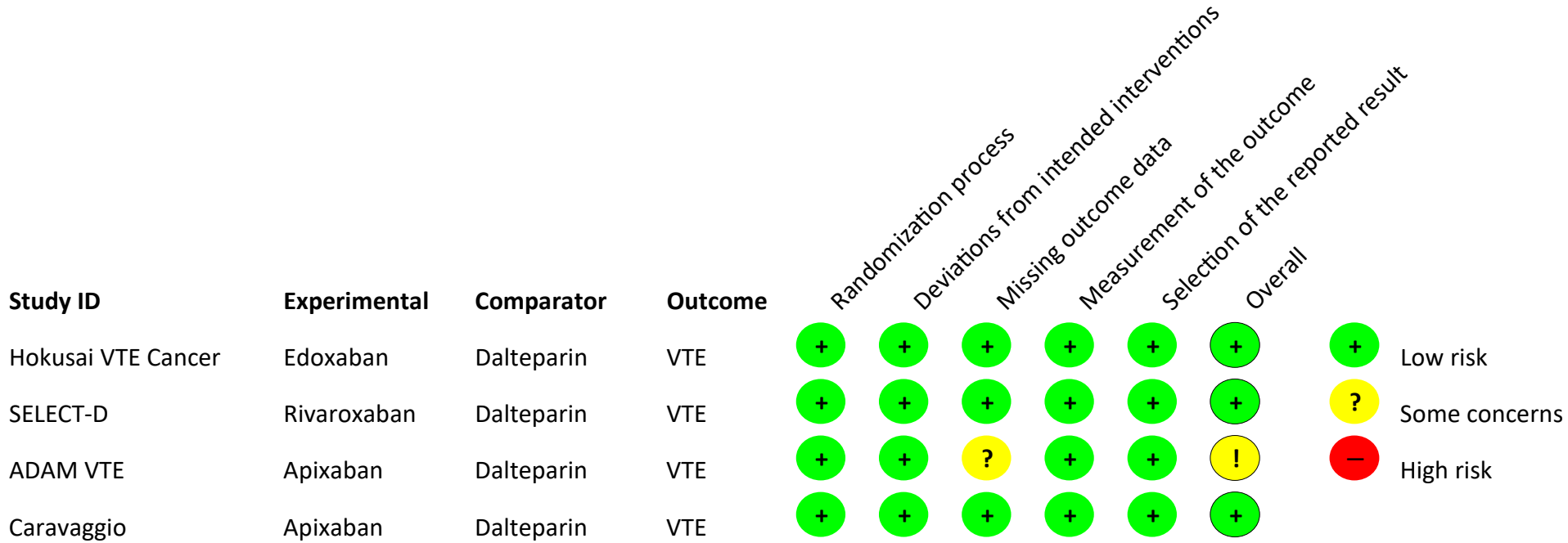
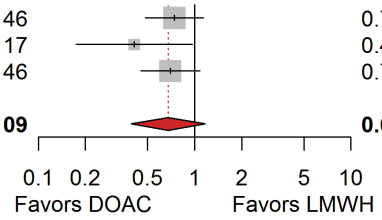


Figure 2.

Recurrent VTE

Study	DOAC agent	DOAC Patients	DOAC Event	LMWH Patients	LMWH Event	RR	95%-CI	Weight
Hokusai VTE Cancer	edoxaban	522	34	524	46	0.74	[0.48; 1.14]	45.4%
SELECT-D	rivaroxaban	203	7	203	17	0.41	[0.17; 0.97]	11.2%
Caravaggio	apixaban	576	32	579	46	0.70	[0.45; 1.08]	43.4%
Random effects model		**1301**	**73**	**1306**	**109**	**0.68**	**[0.39; 1.17]**	**100.0%**

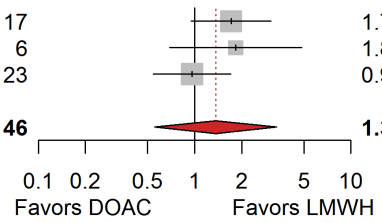
Heterogeneity: I^2 = 0%, τ^2 < 0.0001, p = 0.48



Major bleeding

Study	DOAC agent	DOAC Patients	DOAC Event	LMWH Patients	LMWH Event	RR	95%-CI	Weight
Hokusai VTE Cancer	edoxaban	522	29	524	17	1.71	[0.95; 3.08]	40.3%
SELECT-D	rivaroxaban	203	11	203	6	1.83	[0.69; 4.86]	18.0%
Caravaggio	apixaban	576	22	579	23	0.96	[0.54; 1.71]	41.7%
Random effects model		**1301**	**62**	**1306**	**46**	**1.36**	**[0.55; 3.35]**	**100.0%**

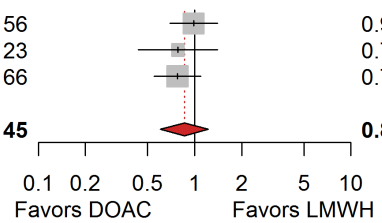
Heterogeneity: I^2 = 15%, τ^2 = 0.0379, p = 0.31



Composite of first major bleeding or recurrent VTE

Study	DOAC agent	DOAC Patients	DOAC Event	LMWH Patients	LMWH Event	RR	95%-CI	Weight
Hokusai VTE Cancer	edoxaban	522	55	524	56	0.99	[0.69; 1.40]	41.8%
SELECT-D	rivaroxaban	203	18	203	23	0.78	[0.44; 1.41]	15.1%
Caravaggio	apixaban	576	51	579	66	0.78	[0.55; 1.10]	43.1%
Random effects model		**1301**	**124**	**1306**	**145**	**0.86**	**[0.60; 1.23]**	**100.0%**

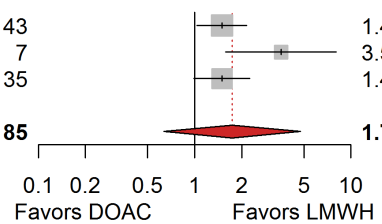
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.60



Clinically relevant non-major bleeding

Study	DOAC agent	DOAC Patients	DOAC Event	LMWH Patients	LMWH Event	RR	95%-CI	Weight
Hokusai VTE Cancer	edoxaban	522	64	524	43	1.49	[1.04; 2.16]	43.2%
SELECT-D	rivaroxaban	203	25	203	7	3.57	[1.58; 8.07]	17.5%
Caravaggio	apixaban	576	52	579	35	1.49	[0.99; 2.26]	39.3%
Random effects model		**1301**	**141**	**1306**	**85**	**1.74**	**[0.64; 4.77]**	**100.0%**

Heterogeneity: I^2 = 49%, τ^2 = 0.0589, p = 0.14



All-cause mortality

Study	DOAC agent	DOAC Patients	DOAC Event	LMWH Patients	LMWH Event	RR	95%-CI	Weight
Hokusai VTE Cancer	edoxaban	522	140	524	127	1.11	[0.90; 1.36]	39.2%
SELECT-D	rivaroxaban	203	48	203	56	0.86	[0.61; 1.20]	20.1%
Caravaggio	apixaban	576	135	579	153	0.89	[0.73; 1.08]	40.7%
Random effects model		**1301**	**323**	**1306**	**336**	**0.96**	**[0.68; 1.36]**	**100.0%**

Heterogeneity: I^2 = 30%, τ^2 = 0.0074, p = 0.24