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

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## Abstract

**Background** International guidelines have endorsed the use of edoxaban or rivaroxaban as an alternative to low-molecular-weight heparin (LMWH) for the treatment of acute venous thromboembolism (VTE) in cancer patients. Recently, a large randomized controlled trial of apixaban versus dalteparin in patients with cancer was completed. We performed an updated meta-analysis to assess the efficacy and safety of direct oral anticoagulants (DOACs) versus LMWH in patients with cancer-associated VTE.

**Methods** MEDLINE, EMBASE, and CENTRAL (Cochrane Controlled Trials Registry) were systematically searched up to March 30, 2020 for randomized controlled trials comparing DOACs versus LMWH for the treatment of VTE in patients with cancer. The two coprimary outcomes were recurrent VTE and major bleeding at 6 months. Data were pooled by the Mantel–Haenszel method and compared by relative risk ratios (RRs) and 95% confidence intervals (CIs).

**Results** Four randomized controlled studies (2,894 patients) comparing apixaban, edoxaban, or rivaroxaban with dalteparin were included in the meta-analysis. Recurrent VTE occurred in 75 of 1,446 patients (5.2%) treated with oral factor Xa inhibitors and in 119 of 1,448 patients (8.2%) treated with LMWH (RR 0.62; 95% CI 0.43–0.91; $I^2$, 30%). Major bleeding occurred in 62 (4.3%) and 48 (3.3%) patients receiving oral factor Xa inhibitors or LMWH, respectively (RR 1.31; 95% CI 0.83–2.08; $I^2$, 23%).

**Conclusion** In patients with cancer-associated VTE, oral factor Xa inhibitors reduced the risk of recurrent VTE without a significantly higher likelihood of major bleeding at 6 months compared with LMWH.

**Keywords**
- direct oral anticoagulants
- oral factor Xa inhibitors
- cancer
- dalteparin
- meta-analysis
- venous thromboembolism

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## Introduction

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a frequent cause of morbidity and mortality in patients with cancer and is associated with a high economic burden.[1,2] The therapeutic management of VTE in cancer patients is challenging because of the increased risk for thromboembolic recurrences and anticoagulant-associated bleedings.[3,4] Several risk factors related to cancer, anticancer treatment, and patient features contribute to both the thrombotic and bleeding risk in these patients.[5] For more than a decade, low-molecular-weight heparin (LMWH) has been the gold standard for the treatment of cancer-associated VTE. In the general population, direct oral anticoagulants (DOACs), including apixaban, dabigatran, edoxaban, and rivaroxaban, have emerged as the preferred treatment strategy for the treatment of acute VTE.[6] Beyond their favorable efficacy and safety profile, these agents have the advantage of a predictable effect, the ease of administration, and no need for laboratory monitoring. Recent randomized controlled trials (RCTs) have assessed the efficacy and safety of edoxaban and rivaroxaban in comparison with dalteparin for the treatment of VTE in cancer patients.[7,8] Based on the results of these studies, international guidelines have suggested the use of edoxaban and rivaroxaban for the treatment of cancer-associated VTE in selected patients.[6,9–12] More recently, apixaban was compared with dalteparin in a pilot safety study in 287 cancer patients.[13] Finally, the results of the Caravaggio study on the efficacy and safety of apixaban in the treatment of VTE in cancer patients were recently published.[14]

We performed an updated meta-analysis of RCTs to assess the efficacy and safety of DOACs compared with LMWH for the treatment of cancer-associated VTE.

## Methods

This systematic review and meta-analysis was conducted in accordance with the "Cochrane Handbook for Systematic Review of Interventions" and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[15,16] The study protocol was registered in PROSPERO (CRD42020175589).

### Search Strategy

We performed an unrestricted search in MEDLINE and CENTRAL (Cochrane Controlled Trials Registry) and EMBASE from inception to March 30, 2020. Additional studies were identified by hand searching bibliographies of the review articles and retrieved articles. Search terms included: "Cancer" OR "Tumor" OR "Neoplasms" AND "Anticoagulants" OR "Factor Xa Inhibitors" OR "Heparinoids" OR "Dabigatran" OR "Rivaroxaban" OR "Edoxaban" OR "Apixaban" OR "Heparin, Low-Molecular-Weight" AND "Venous Thromboembolism" OR "Pulmonary Embolism" OR "Venous Thrombosis" AND "Randomized Controlled Trial" OR "Controlled Clinical Trial." The research strategy is reported in the ►**Supplementary Material** (available in the online version).

Two authors (M.G. and C.B.) independently performed the literature search using an unblinded standardized approach. Study selection was initially performed by review of title and candidate abstracts were then reviewed. Disagreements between reviewers were resolved through revision by senior authors and by discussion.

### Study Selection

Studies were considered potentially eligible for this meta-analysis if they met the following predefined criteria: (1) were RCTs, (2) included only adult cancer patients with acute VTE, (3) compared DOACs with LMWH, and (4) reported on objectively confirmed VTE recurrences and bleedings in each treatment group. For duplicate publications, only the most recent one was considered. To assess agreement between reviewers for study selection, we used the kappa statistic, which measures agreement beyond chance.[17]

### Study Outcomes

Two coprimary outcomes were identified for the meta-analysis: recurrent VTE and major bleeding at 6 months. Study outcomes were considered according to the definition used in the individual studies (►**Table 1**). Secondary efficacy outcomes were recurrent PE, recurrent DVT, and fatal PE. Secondary safety outcomes were clinically relevant nonmajor bleeding (CRNMB), clinically relevant bleeding (CRB) (the composite of major bleeding and CRNMB), and fatal bleeding. All-cause death was also reported.

### Data Extraction

For each study, the following data were independently extracted by two authors: (1) general data (study design, year of publication), (2) characteristics of trials participants (number, mean age, gender, number of patients with active cancer, metastatic cancer, solid or hematological disease at presentation), (3) type of intervention (type of anticoagulant, dose, duration, and frequency), and (4) type of outcome measure and number of patients with study outcomes in each treatment arm.

### Risk of Bias in Individual Studies

To explore the validity of eligible randomized trials, two reviewers (M.G. and C.B.) independently determined the appropriate generation of random allocation sequence, allocation concealment, blinding of patients and personnel, blinding of outcomes assessment, incomplete outcome data, selective reporting, and other bias. Risk of bias was defined as high, medium, or low. We resolved disagreements by opinion of senior authors or by discussion. The risk of bias and strength of evidence were assessed by using the Cochrane Collaboration's tool and the GRADE system, respectively.[15,18]

### Statistical Analysis

The statistical analyses, forest plots, and publication bias analyses were produced with Review Manager release 5.3 (The Cochrane Collaboration, Oxford, United Kingdom) and the influence analysis with R software. Meta-analyses were performed by using the Mantel–Haenszel with a random effects model to estimate pooled effect sizes. Relative risk ratios (RRs) were reported with 95%

**Table 1** Description of the included studies according to the PICO criteria

| Source | Study design | No. of patients | Participants | Intervention | Comparator | Treatment duration | Primary outcome |
|---|---|---|---|---|---|---|---|
| Raskob et al, 2018[7] | Randomized, open-label, noninferiority trial with blinded central outcome adjudication | 1,046 | Patients with active cancer or cancer diagnosed within 2 y before study inclusion | Therapeutic-dose of LMWH for at least 5 d, followed by edoxaban 60 or 30 mg[a] once daily | Dalteparin at 200 IU/kg daily for 1 mo, followed by 150 IU/kg daily | 6 up to 12 mo | Composite of recurrent VTE (symptomatic and incidental DVT or PE and fatal PE) and major bleeding defined according to the ISTH criteria |
| Young et al, 2018[8] | Randomized, open-label, pilot trial with blinded central outcome adjudication | 406 | Patients with active cancer | Rivaroxaban 15 mg twice daily for 3 wk, followed by 20 mg once daily | Dalteparin 200 IU/kg daily for 1 month, followed by 150 IU/kg daily | 6 mo | Recurrent VTE which included proximal DVT, PE (symptomatic, incidental or fatal), other sites of thrombosis (e.g., subclavian vein, hepatic vein, and inferior caval vein) |
| McBane et al, 2020[13] | Randomized, open-label, superiority trial with blinded central outcome adjudication | 287 | Patients with active cancer | Apixaban 10 mg twice daily for 7 d, followed by 5 mg twice daily | Dalteparin 200 IU/kg daily for 1 mo, followed by 150 IU/kg daily | 6 mo | Major bleeding defined according to the ISTH criteria |
| Agnelli et al, 2020[14] | Randomized, open-label, noninferiority trial with blinded central outcome adjudication | 1,155 | Patients with active cancer or cancer diagnosed within 2 years before study inclusion | Apixaban 10 mg twice daily for 7 d, followed by 5 mg twice daily | Dalteparin 200 IU/kg daily for 1 month, followed by 150 IU/kg daily | 6 mo | Primary efficacy outcome: Recurrent VTE which included proximal DVT of lower limbs (symptomatic or incidental), symptomatic DVT of upper limbs and PE (symptomatic, incidental or fatal)<br>Primary safety outcome: Major bleeding defined according to the ISTH criteria + bleeding requiring surgical intervention |

Abbreviations: DVT, deep vein thrombosis; ISTH, International Society of Thrombosis and Haemostasis; LMWH, low molecular weight heparin; PE, pulmonary embolism; PICO, Patient, Intervention, Comparison, Outcome; VTE, venous thromboembolism.

[a]According to study dose reduction criteria.

confidence intervals (CIs). Cochran's test and the $I^2$ test were used to assess between-study heterogeneity.[19–21] Statistically significant heterogeneity was considered present at $p < 0.10$ and $I^2 > 50\%$. Forest plots were created for each outcome. Publication bias was assessed visually by the use of funnel plots.

The case fatality rate of recurrent VTE and major bleeding was also calculated. Case fatality rate was expressed as a percentage, computed from the number of fatal events divided by the number of fatal plus nonfatal events.

Prespecified subgroup analyses were performed according to features of study outcome: major bleeding in specific sites such as gastrointestinal, genitourinary, and intracranial; or according to the characteristics of trials participants at randomization: (1) initial clinical presentation (only DVT or PE ± DVT); (2) symptomatic and incidental VTE; (3) active cancer; (4) metastatic or locally advanced cancer; (5) solid cancer and hematological malignancy; (6) Eastern Cooperative Oncology Group (ECOG) performance status of two or more; (7) age of 65 years or lower; (8) study outcomes in the overall study treatment period; (9) use of apixaban; and (10) single drug approach. Data of the HOKUSAI VTE Cancer Study refer to the 12-month study period in case of unavailability of 6-month data.

## Results

The literature search provided a total of 1,282 citations (March 30, 2020). After adjusting for duplicates, 1,046 articles remained. Of these, 1,013 were excluded because they did not meet the inclusion criteria as described. After a full review of the remaining articles, four RCTs enrolling 2,894 cancer patients with acute VTE were included in the meta-analysis.[7,8,13,14] The flow diagram of literature search is shown in ►**Fig. 1**. The agreement between reviewers for initial study selection was good (kappa statistic 0.87).

Of the included studies, three were designed to assess noninferiority[7,8,14] and one was a safety trial designed to

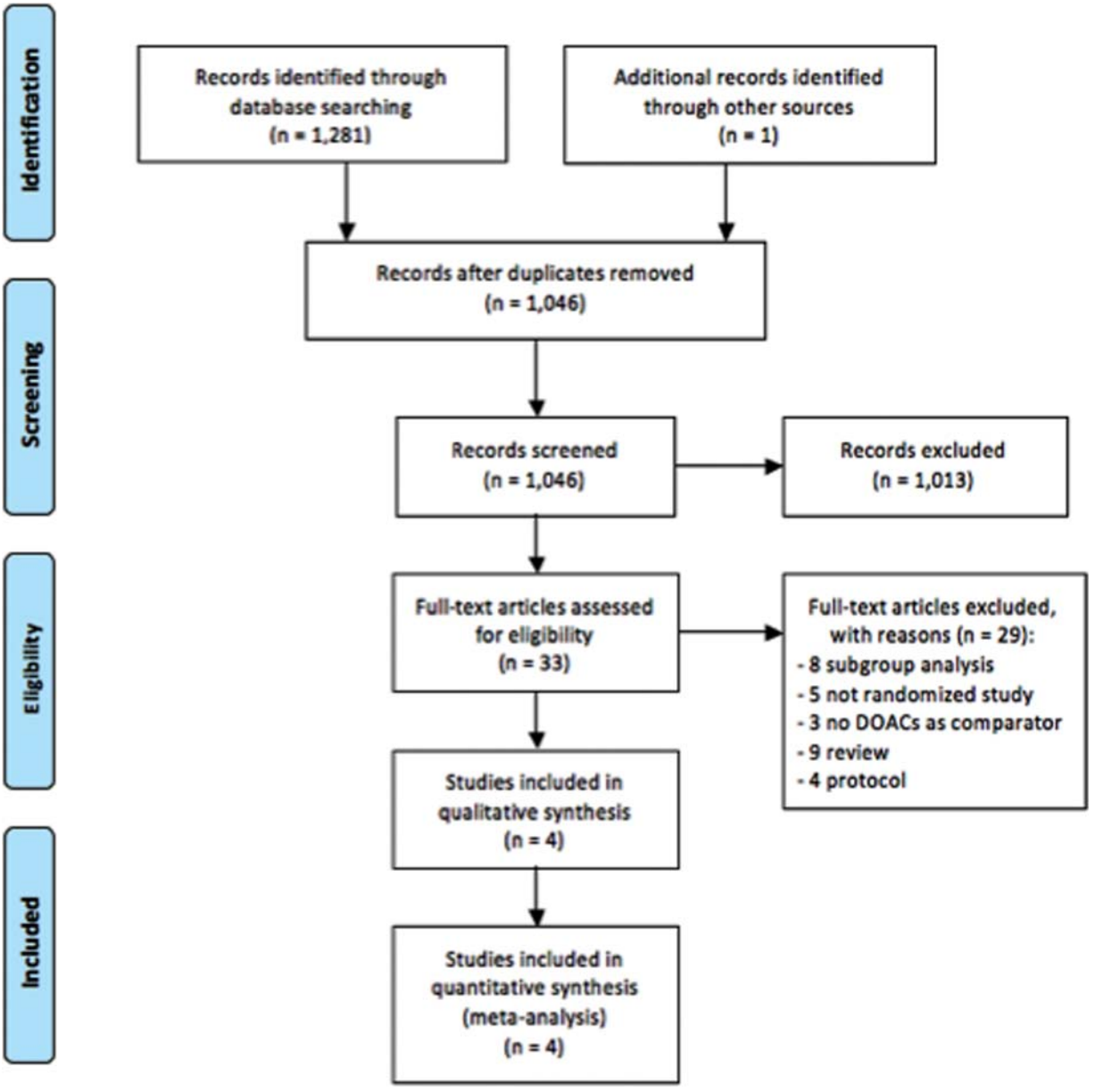


**Fig. 1** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

assess superiority.[13] The duration of study treatment was 6 months in three studies[8,13,14] and 12 months in one.[7] For the purpose of this meta-analysis, the results of HOKUSAI Cancer Study at 6 months were considered. Patients received apixaban in two studies,[13,14] and edoxaban[7] and rivaroxaban[8] in one study each. As dabigatran was not used in any study, the wording DOACs refer to apixaban, edoxaban, or rivaroxaban. Dalteparin was the comparator in all four studies, therefore the wording LMWH refers to dalteparin. The primary outcome differed among the trials. ►**Table 1** shows the main characteristics of the studies according to the Patient, Intervention, Comparison, Outcome criteria. Study cohorts varied from 287 to 1,170 patients (►**Table 2**). Two studies included patients with both active cancer and history of cancer (cancer not fulfilling the criteria for active cancer but diagnosed within 2 years from randomization).[7,14] Mean age varied from 64 to 67 years, and similar proportions of women and men were included in the studies. More than half of included patients had locally advanced or metastatic cancer and about a quarter had an ECOG score of two or more (►**Table 2**).

Three of the included trials had an overall low risk of bias, with the exception of performance bias due to the absence of blinding of participants and personnel.[7,13,14] The SELECT-D trial had a high risk of bias for selection and detection bias.[8] The risk of bias is reported in ►**Supplementary Fig. S1** (available in the online version).

## Recurrent VTE and Major Bleeding

Data on 6-month recurrent VTE and major bleeding were reported for all the trials (►**Table 3**, ►**Fig. 2**).

Recurrent VTE occurred in 75 of 1,446 patients (5.2%) treated with DOACs and in 119 of 1,448 patients (8.2%) treated with dalteparin. DOACs were associated with a significant reduction in VTE recurrence (RR 0.62; 95% CI 0.43–0.91; $I^2$, 30%).

Major bleeding occurred in 62 of 1,446 patients (4.3%) treated with DOACs and in 48 of the 1,448 patients (3.3%) treated with LMWH (RR 1.31; 95% CI 0.83–2.08; $I^2$, 23%).

Funnel plot inspection showed no evidence of publication bias (►**Supplementary Fig. S2**, available in the online version). The certainty in evidence according to the GRADE system was high for recurrent VTE and moderate for major bleeding. Influence analysis for recurrent VTE and for major bleeding is reported in ►**Supplementary Fig. S3** (available in the online version).

## Secondary Outcomes

Overall, 46 of 1,446 DOAC-treated patients (3.2%) and 66 of 1,448 LMWH-treated patients (4.6%) had recurrent PE (RR 0.71; 95% CI 0.49–1.03; $I^2$, 0%). A total of 32 of 1,446 DOAC-treated patients (2.2%) and 55 of 1,448 LMWH-treated patients (3.8%) had recurrent DVT (RR 0.60; 95% CI 0.36–1.00; $I^2$, 16%) (►**Table 3**). Fatal PE occurred in 5 of 1,446 patients treated with DOACs and in 4 of 1,448 patients treated with LMWH (RR 1.25, 95% CI 0.34–4.67, $I^2$, 0%). Case fatality rate of recurrent VTE was 6.7% (5 out of 75 events) in the DOACs arm and 3.4% (4 out of 119 events) in the LMWH arm (RR 2.12, 95% CI 0.53–8.47, $I^2$, 0%).

CRNMB occurred in 150 of 1,446 patients treated with DOACs and in 92 of 1,448 patients treated with LMWH (10.4%

**Table 2** Main clinical features of the included studies

| Source | | Mean age (y) | Male sex | Active cancer | Metastatic cancer | ECOG status of 2 | Solid tumor | Hematological malignancy | Creatinine clearance 30–50 mL/min | Platelet count 50–100.000/mm$^3$ | Incidental PE at diagnosis | Anticoagulant dose reduction |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Raskob et al, 2018[7] | I | 64.3 | 53.1% | 98.3% | 52.5% | 23.6% | 89.1% | 10.7% | 7.3% | 6.1% | 32.0%[a] | Reduction if creatinine clearance 30–50 mL/min or body weight ≤60 kg or concomitant treatment with potent P-glycoprotein inhibitors |
| | C | 63.7 | 50.2% | 97.5% | 53.4% | 23.7% | 89.1% | 10.5% | 6.5% | 4.4% | 33.0%[a] | Temporary reduction if platelet count < 100,000/mm$^3$ |
| Young et al, 2018[8] | I | 67 | 57% | 100% | 58% | 26% | 96% | 2% | NR | NR | 53% | Reduction if creatinine clearance 30–50 mL/min and patient's risk for bleeding outweighs the risk for recurrent VTE |
| | C | 67 | 48% | 100% | 58% | 21% | 94% | 3% | NR | NR | 52% | Dose adjustment if platelet count < 100,000/mm$^3$ or significant renal failure |
| McBane et al, 2020[13] | I | 64.4 | 48.0% | 100% | 65.3% | 13.3% | 89.3% | 8.6% | 9.3% | 6.7% | NR | Reduction if concomitant treatment with strong CYP3A4 and/or P-glycoprotein inhibitors.<br>Temporary reduction if platelet count < 50,000/mm$^3$ |
| | C | 64.0 | 48.7% | 100% | 66.0% | 8.0% | 88.6% | 10.0% | 9.3% | 8.7% | NR | Dose adjustment if > 10% change in body weight; acute kidney injury (creatinine clearance 15–30 mL/min) or platelet count < 50,000/ mm$^3$ |
| Agnelli et al, 2020[14] | I | 67.2 | 50.7% | 97.0% | 67.5% | 18.9% | 94.3% | 5.7% | 8.9% | 3.6% | 20.1%[a] | None |
| | C | 67.2 | 47.7% | 97.6% | 68.4% | 22.8% | 91.0% | 9.0% | 10.5% | 3.8% | 19.7%[a] | Temporary reduction if platelet count < 100,000/mm$^3$ |

Abbreviations: C, comparator; DVT, deep vein thrombosis; ECOG, Eastern Cooperative Oncology Group; I, intervention; NR, not reported; PE, pulmonary embolism; VTE, venous thromboembolism.
[a]Incidental PE and DVT.

**Table 3** Primary and secondary study outcomes

| Outcomes | DOACs % (95% CI) | Dalteparin % (95% CI) | RR | 95% CI | $I^2$ |
|---|---|---|---|---|---|
| Recurrent VTE | 5.2% (4.2–6.5) | 8.2% (6.9- 9.8) | 0.62 | 0.43–0.91 | 30% |
| Major bleeding | 4.3% (3.4–5.5) | 3.3% (2.5–4.4) | 1.31 | 0.83–2.08 | 23% |
| Recurrent PE | 3.2% (2.4–4.2) | 4.6% (3.6–5.8) | 0.71 | 0.49–1.03 | 0% |
| Recurrent DVT | 2.2% (1.6–3.1) | 3.8% (2.9–4.9) | 0.60 | 0.36–1.00 | 16% |
| Fatal PE | 0.3% (0.2–0.8) | 0.3% (0.1–0.7) | 1.25 | 0.34–4.67 | 0% |
| CRNMB | 10.4% (8.912.1) | 6.4% (5.2–7.7) | 1.65 | 1.19–2.28 | 29% |
| CRB | 13.7% (12.0–15.6) | 9.3% (7.8–10.9) | 1.51 | 1.09–2.09 | 49% |
| Fatal bleeding[a] | 0.2% (0.07–0.6) | 0.3% (0.2–0.8) | 0.37 | 0.07–2.00 | 0% |
| All-cause death | 23.9% (21.8–26.2) | 24.2% (22.1–26.5) | 0.99 | 0.83–1.18 | 37% |

Abbreviations: CI, confidence interval; CRB, clinical relevant bleeding; CRNMB, clinically relevant nonmajor bleeding; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; PE, pulmonary embolism; RR, relative risk; VTE, venous thromboembolism.
[a]For HOKUSAI Cancer data at 12 months were considered.

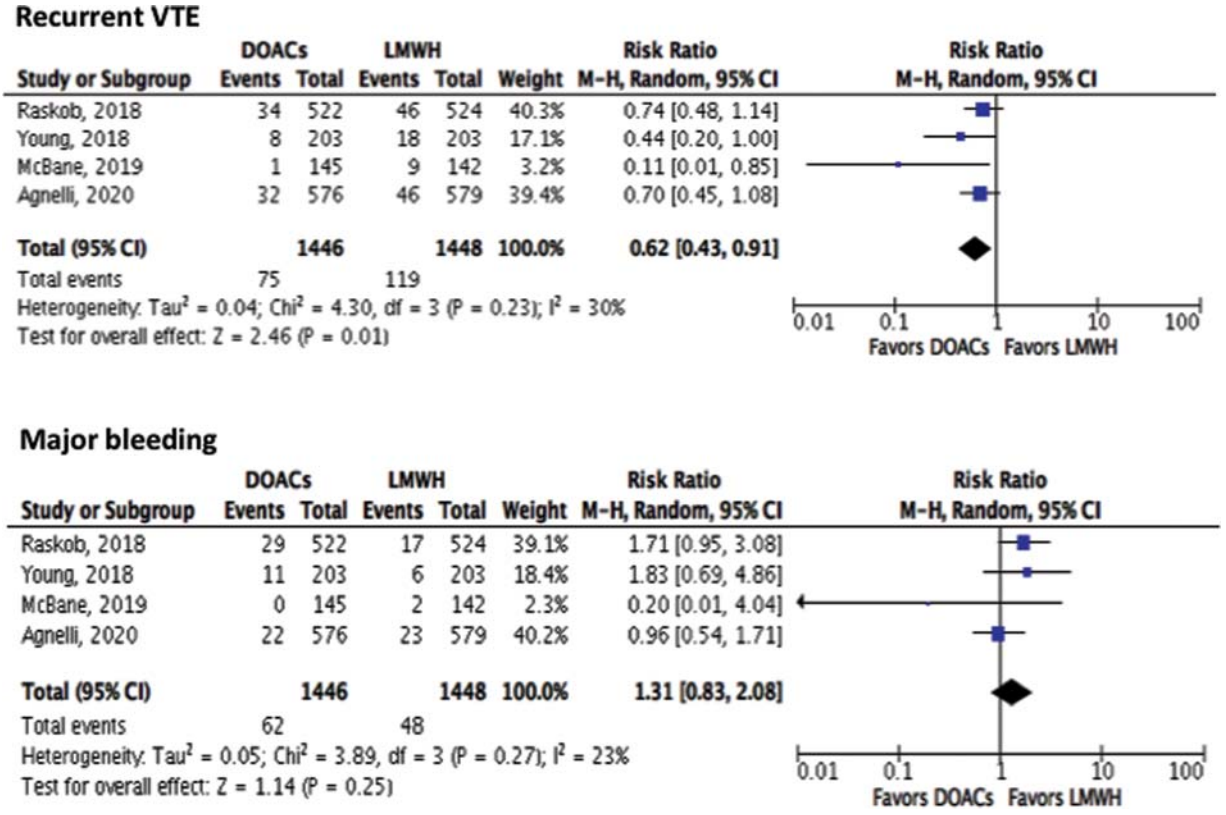


**Fig. 2** Forest plot of the main study outcomes comparing direct oral anticoagulants (DOACs) and low-molecular-weight heparin (LMWH).

vs. 6.4%; RR 1.65; 95% CI 1.19–2.28; $I^2$, 29%). Risk of CRB was also higher in patients treated with DOACs (RR 1.51; 95% CI 1.09–2.09, $I^2$, 49%). One of 1,446 DOAC-treated patients (0.2%) and 5 of 1,448 LMWH-treated patients (0.3%) had a fatal bleeding (RR 0.37, 95% CI 0.07–2.00, $I^2$, 0%). Case fatality rate of major bleeding was 1.6% (1 out of 62 events) in the DOACs arm and 10.4% (5 out of 48 events) in the LMWH arm (RR 0.21, 95% CI 0.04–1.12, $I^2$, 0%). All-cause death occurred in 346 of 1,446 (23.9%) DOACs-treated patients and in 351 of 1,448 (24.2%) LMWH-treated patients (RR 0.99, 95% CI 0.83–1.18, $I^2$, 37%) (►**Table 3**).

### Subgroup Analyses

Overall, 39 of 1,446patients (2.7%) treated with DOACs and 20 of 1,448 patients (1.4%) with LMWH had a gastrointestinal bleeding (RR 1.91, 95% CI 0.96–3.82, $I^2$, 35%) (►**Supplementary Fig. S3**, available in the online version). Major bleeding occurred at the genitourinary site in 10 of 1,446 DOACs patients (0.7%) and in 1 of 1,448 LMWH patients (0.01%) (RR 4.99, 95% CI 1.08–23.08, $I^2$, 0%). Two of 1,446 patients (0.1%) and 7 of 1,448 patients (0.5%) had intracranial hemorrhage in the DOACs and LMWH arm, respectively (RR 0.37, 95% CI 0.10–1.49, $I^2$, 0%).

**Table 4** Results of subgroup analyses on recurrent VTE and major bleeding for the comparison between DOACs and LMWH

| Patients' characteristics at presentation[a] | *N* studies; *N* patients | Recurrent VTE RR (95% CI, $I^2$%) | Major bleeding RR (95% CI, $I^2$%) |
|---|---|---|---|
| Active cancer | 4 studies; 2,841 patients | 0.61 (0.44–0.86, $I^2$ 23%) | 1.40 (0.87–2.27, $I^2$ 30) |
| Metastatic cancer | 2 studies; 1,388 patients | 0.78 (0.56–1.10, $I^2$ 0%) | 1.28 (0.82–2.02, $I^2$ 0) |
| Solid tumor | 2 studies; 2,000 patients | 0.68 (0.51–0.91, $I^2$ 0%) | 1.38[b] (0.86–2.20, $I^2$ 33) |
| Hematological malignancy | 2 studies; 196 patients | 0.81 (0.23–2.83, $I^2$ 0%) | 0.98 (0.21–4.66, $I^2$ not estimable) |
| Age < 65 y | 2 studies; 916 patients | 0.46 (0.18–1.18, $I^2$ 74%) | 0.97 (0.38–2.44, $I^2$ 54) |
| ECOG ≥2 | 2 studies; 488 patients | 0.70 (0.37–1.31, $I^2$ 0%) | 1.48 (0.63–3.46, $I^2$ 39) |
| Incidental PE or incidental DVT | 2 studies; 570 patients | 0.45 (0.23–0.89, $I^2$ 0%) | 1.57 (0.77–3.18, $I^2$ 12) |
| Symptomatic PE or DVT | 2 studies; 1,631 patients | 0.77 (0.56–1.06, $I^2$ 0%) | 1.20 (0.74–1.93, $I^2$ 0) |
| DVT only | 2 studies; 906 patients | 0.72 (0.49–1.05, $I^2$ 0%) | 1.08 (0.56–2.10, $I^2$ 0) |
| PE ± DVT | 2 studies; 1,295 patients | 0.67 (0.43–1.03, $I^2$ 0%) | 1.48 (0.85–2.56, $I^2$ 25) |
| Study outcome during overall treatment period | 4 studies; 2,894 patients | 0.62 (0.44–0.87; $I^2$ 26) | 1.33 (0.84–2.11, $I^2$ 27) |
| Single drug approach | 3 studies; 1,848 patients | 0.63 (0.48–0.84, $I^2$ 0%) | 1.31 (0.82–2.08, $I^2$ 34) |
| Use of apixaban | 2 studies; 1,442 patients | 0.36 (0.06–2.13, $I^2$ 68%) | 0.88 (0.49–1.57, $I^2$ 3) |

Abbreviations: CI, confidence interval; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; ECOG, Eastern Cooperative Oncology Group; LMWH, low molecular weight heparin; PE, pulmonary embolism; RR, relative risk; VTE, venous thromboembolism.
[a]All analyses include HOKUSAI Cancer results at 12 months.
[b]Three studies, 2,386 patients.

Subgroup analyses according to the initial clinical VTE presentation (only DVT or PE ± DVT; symptomatic or incidental) and characteristics of trials participants at randomization (active cancer, metastatic or locally advanced cancer, solid tumor, and hematological malignancy), ECOG of 2 or more, study outcomes in the overall study treatment period, use of apixaban, and single drug approach are reported in ►**Table 4**.

A reduction in recurrent VTE with DOACs compared with dalteparin was seen in active cancer, solid tumor, age < 65 years, and incidental PE or incidental DVT (►**Table 4**). When used according to the single drug approach, that is, with apixaban or rivaroxaban only, DOACs showed a significant 46% reduction in the risk of VTE recurrence with no increase in major bleeding compared with dalteparin.

## Discussion

This meta-analysis of RCTs for the treatment of acute VTE in cancer patients shows that, in comparison to the LMWH dalteparin, oral factor Xa inhibitors significantly reduced the risk of recurrent VTE and nonsignificantly increased the risk of major bleeding.

The superiority of DOACs over dalteparin for the prevention of recurrent VTE is reinforced by our meta-analysis in cancer patients. Of note, DOACs were already shown to be noninferior to initial LMWH followed by vitamin K antagonists in the general population of patients with VTE.[22] Reasons for superiority of DOACs compared with LMWH could be related to a better adherence to oral agents compared with parenteral agents and to the label-based regimen of dalteparin, consisting of a 25% dose reduction after the first month of treatment. The improvement in efficacy is a very relevant clinical finding for a fragile patient population at particular high risk for recurrent VTE. The finding of a reduced risk of recurrent VTE was consistent for both recurrent PE and DVT, although the definition of recurrent VTE differed slightly across the studies. Indeed, the Caravaggio study included symptomatic DVT of the upper limb as recurrent VTE and the ADAM-VTE study included unusual site VTEs (subclavian vein, hepatic vein, and inferior vena cava). The different definition of recurrent VTE may have led to differences in recurrence rates and potentially in efficacy results across studies. However, the low level of heterogeneity and the consistency of the efficacy results across studies observed in this meta-analysis strengthen the validity and generalizability of the efficacy of oral factor Xa inhibitors compared with dalteparin in the treatment of VTE in cancer patients.

Although the rate of major bleeding was numerically higher in the DOAC-treated patients, the 95% CI of the odds ratio for major bleeding included unity. Major bleeding was defined according to the International Society of Thrombosis and Haemostasis (ISTH) criteria in three studies. The European Medicines Agency definition was used in the Caravaggio study[23] and includes all the ISTH criteria for major bleeding and bleeding requiring surgical intervention. Rates of major bleeding in DOACs or dalteparin-treated patients differed across studies. Whether these differences in safety profiles should be seen as agent and regimen-specific is uncertain in absence of a direct comparison of the different DOACs and requires further assessment.[24] However, we found that the overall heterogeneity contribution for major bleeding was mainly related to the apixaban studies, the results of which may have influenced the overall rates of major bleeding. Interestingly and importantly, in our meta-analysis, the risk of intracranial hemorrhage as well as the case–fatality rate for major bleeding was lower—

although not statistically significant—in patients treated with DOACs compared with those treated with LMWH. This is consistent with the lower rate of intracranial hemorrhage in DOAC-treated patients compared with patients treated with vitamin K antagonists in noncancer-associated VTE.[25] In contrast, gastrointestinal and genitourinary major bleedings were more common in patients treated with oral factor Xa inhibitors than in those treated with dalteparin. The association between the site of bleeding and the site of cancer is still a matter of debate and whether a companion class effect exists remains to be defined. Indeed, while in the Hokusai VTE Cancer and in the SELECT-D studies, patients with gastrointestinal cancer had an increased risk of major bleeding with factor X inhibitors compared with dalteparin, data on apixaban are currently not yet available. However, the results of these subgroup analyses should be regarded with caution.

The higher risk of CRNMB and CRB observed with DOACs compared with dalteparin reflects the numerical increase already seen in the individual studies. In this specific case, the bleeding profile differs across individual agents as shown by the degree of heterogeneity.

All-cause mortality rates and fatal recurrent PE rates differed between patients treated with DOACs or LMWH. Despite the fact that the included trials were not aimed or powered to determine overall survival differences, the high risk of competing death due to advanced cancer likely overrules any potential survival benefit associated with a lower risk of recurrent VTE.

## Limitations and Strengths

Several limitations of our study should be considered. First, as an aggregated data meta-analysis, we could not assess the study outcomes in patients with different type of cancer or baseline characteristics. However, subgroup analyses were performed and showed consistent results with the primary study analysis, with the limits of potential underpowering. Second, results are limited to dalteparin alone, being the comparator in all studies. Also, according to previous studies, it is conceivable that the results obtained with dalteparin are representative of other LMWHs.[26] Third, all the studies were open-label trials to avoid the use of parenteral placebo for several months. However, in the studies considered in this analysis, all studies used a PROBE design with suspected study outcome events being centrally adjudicated by a committee blinded to assigned treatment. Moreover, the ethics of a double-blind trial in this setting is questionable. Lastly, the subgroup analyses included considerable smaller patient cohorts than the main analysis, causing wide CIs, and thus preventing strong conclusions.

Strengths of our meta-analysis in comparison to previous ones, include the inclusion of the Caravaggio study, thereby increasing generalizability and power of the individual analyses.[27–29] Our findings indicate that the evaluated oral factor Xa inhibitors may replace LMWH in the majority of patients with cancer-associated VTE. Moreover, state-of-the-art methodology was used according to current guidelines for performing meta-analyses.

## Conclusion

Patients with cancer-associated VTE who were treated with oral factor Xa inhibitors had a significant lower risk of recurrent VTE, without a significantly higher likelihood of major bleeding, than when treated with dalteparin. Gastrointestinal and genitourinary are the most common sites of major bleeding with factors Xa inhibitors. Therefore, the choice of anticoagulant agent for treatment of cancer-associated thrombosis in patients at high risk of gastrointestinal or genitourinary bleeding should be taken into account for the competing risks of recurrent VTE and major bleeding.

### What is known about this topic?

- The management of venous thromboembolism (VTE) in cancer patients is challenging because of the high risk for venous thromboembolic recurrences and anticoagulant-associated bleedings.
- Besides low molecular weight heparin (LMWH), current guidelines suggest the use of oral edoxaban or rivaroxaban for the treatment of acute VTE in cancer, with an exception for patients with gastrointestinal cancer or at high bleeding risk.
- The results of the Caravaggio study in the treatment of VTE in cancer patients demonstrated noninferiority of apixaban compared with dalteparin in prevention of venous thromboembolic recurrence, with no increase in major bleeding.

### What does this paper add?

- We performed an updated meta-analysis of randomized trials assessing the efficacy and safety of direct oral anticoagulants (DOACs) versus LMWH in patients with cancer-associated VTE.
- Our meta-analysis includes four randomized controlled studies comparing oral factor Xa inhibitors with dalteparin (2,894 patients). VTE recurrences were reduced in patients treated with factor Xa inhibitors compared with dalteparin (RR 0.62, 95% CI 0.43–0.91). Rates of major bleeding were not significantly different between the factor Xa inhibitors and dalteparin-treated patients (RR 1.31; 95% CI 0.83–2.08).

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Conflict of Interest
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