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# Efficacy and Safety of Direct Oral Anticoagulants for Risk of Cancer-Associated Venous Thromboembolism

**Jie Zeng, MSc[1,2], Xuhui Zhang, MD[3], Gregory Y. H. Lip, MD[4,5], Xiaochen Shu, MD[6], Lehana Thabane, PhD[7,8], Junzhang Tian, MD[1], and Guowei Li, PhD, MSc, MBBS[1,7,8]**

**Abstract**

Efficacy and safety of direct oral anticoagulants (DOACs) for preventing primary and recurrent venous thromboembolism (VTE) in patients with cancer remain unclear. In this study, we conducted a systematic review to summarize the most up-to-date evidence from randomized controlled trials (RCTs). Our primary outcomes included the benefit outcome (VTE) and safety outcome (major bleeding). A random-effects model was used to pool the relative risks (RRs) for data syntheses. The Grading of Recommendations Assessment, Development and Evaluation tool was used to evaluate the quality of the entire body of evidence across studies. We included 11 RCTs with a total of 3741 patients with cancer for analyses. The DOACs were significantly related with a reduced risk of VTE when compared with non-DOACs: RR = 0.77, 95% confidence interval [CI]: 0.61-0.99, $P = .04$. Nonsignificant trend towards a higher risk of major bleeding was found in DOACs: RR = 1.28 95% CI: 0.81-2.02, $P = .29$. The quality of the entire body of evidence was graded as moderate for risk of VTE, and low for risk of major bleeding. To summarize, DOACs were found to have a favorable effect on risk of VTE but a nonsignificant higher risk of major bleeding compared with non-DOACs in patients with cancer. The safety effect of DOACs in patients with cancer requires further evaluation in adequately powered and designed studies.

**Keywords**

direct oral anticoagulant, venous thromboembolism, major bleeding, vitamin K antagonist, low molecular weight heparin

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## Background

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), occurs in up to 15% of patients with cancer during the course of their disease.[1,2] Venous thromboembolism is found to be the second leading cause of death after malignancy itself.[3] Compared with those without cancer, the risk of recurrent VTE is at least 2 fold higher in patients with cancer.[4] Although anticoagulant therapy is recommended to prevent VTE, the increased risk of anticoagulant-induced bleeding is however of significant concern in patients with cancer.

The use of low molecular weight heparin (LMWH) for at least 6 months is currently the standard treatment for acute VTE in patients with cancer, due to its better effect on preventing VTE and similar bleeding profile when compared with vitamin K antagonists (VKAs).[5,6] Given that LMWH is administrated subcutaneously, VKAs are an acceptable alternative for long-

[1] Center for Clinical Epidemiology and Methodology (CCEM), Guangdong Second Provincial General Hospital, Guangzhou, China
[2] School of Public Health, Southern Medical University, Guangzhou, China
[3] Department of Oncology No.2, Guangdong Second Provincial General Hospital, Guangzhou, China
[4] Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, UK
[5] Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark
[6] Department of Epidemiology, School of Public Health, Soochow University, Suzhou, China
[7] Department of Health Research Methods, Evidence, and Impact (HEI), McMaster University, Hamilton, ON, Canada
[8] St. Joseph's Healthcare Hamilton, Hamilton, ON, Canada

**Corresponding Author:**
Guowei Li, Center for Clinical Epidemiology and Methodology (CCEM), Guangdong Second Provincial General Hospital, 466 Newport Middle Road, Haizhu District, Guangzhou 510317, Guangdong Province, China.; Department of Health Research Methods, Evidence, and Impact (HEI), McMaster University, 1280 Main St West, Hamilton, ON, Canada L8S 4L8.
Email: lig28@mcmaster.ca

term prophylaxis due to patients' preference or the unavailability of LMWH.[5] Recently the direct oral anticoagulants (DOACs) have been used to prevent VTE in patients with cancer with a promising benefit–harm profile reported. Meta-analyses based on findings from randomized controlled trials (RCTs) have reported conflicting results, as follows: (1) DOACs had superior efficacy and safety over VKAs, though nonsignificantly, and (2) DOACs are equally effective and safe when compared with LMWH.[7-9] Nevertheless, some studies also reported a lower risk of VTE and an increased risk of bleeding in DOACs than in VKAs or LMWH,[10,11] while others indicated reduction in risk of major bleeding in DOACs.[12,13]

Given the inconsistent findings in the literature, and especially given more contemporary RCTs published, we aimed to systematically summarize the most up-to-date evidence from RCTs to assess the efficacy and safety of DOACs compared with conventional therapy (VKAs and LMWH) for preventing primary and recurrent cancer-associated VTE. Results of this systematic review and meta-analysis may help clarify the benefit–harm profile of DOACs in patients with cancer.

## Methods

We conducted this study by following the recommendations from the Cochrane Handbook of Systematic Reviews[14] and reported results based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline.[15] We registered our study in the Prospective Register of Ongoing Systematic Reviews (identifier: CRD42018109053)

### Search Strategy

We searched the following electronic databases to identify eligible RCTs: MEDLINE, CINAHL and EMBASE from inception to October 28th, 2018. We used descriptors including synonyms for trial, VTE or bleeding, and DOACs in the search (detailed terms for search were presented in Supplemental Table 1). Reference lists of included studies and other review or editorial articles were also searched for relevant reports. No language restriction was used. We also searched the annual meeting abstracts up to October 2018 for relevant unpublished and ongoing studies from the American Society of Hematology and American Society of Clinical Oncology.

### Study Eligibility Criteria

In this systematic review, we focused on patients with cancer (ie, with history of cancer or with active cancer) who used DOACs, VKAs or LMWH for preventing primary or recurrent VTE. Phase III RCTs comparing the efficacy and safety of DOACs with VKAs or LMWH for prevention or treatment of cancer-associated VTE were included. The DOACs we assessed included direct thrombin inhibitor (dabigatran) and factor Xa inhibitors (apixaban, rivaroxaban, and edoxaban).

### Outcomes

Primary outcomes included the benefit outcome (VTE) and safety outcome (major bleeding). Secondary outcome included clinically relevant nonmajor bleeding and all-cause mortality. All the outcome measurements collected were defined as from the individual included studies.

### Data Extraction

Two reviewers (J.Z. and X.Z.) independently screened and chose potential eligible studies, with the agreement measured by the κ statistics.[16] Disagreement was resolved by discussion between the 2 reviewers, and if no consensus could be reached, a third reviewer (G.L.) was involved to make a final decision. The 2 reviewers used data extraction forms to extract data independently. Data collected included study design, characteristics of patients, details on interventions and follow-ups, outcome measures, and treatment effect estimates.

### Quality Assessment of Individual Included Study

We used the Risk of Bias assessment tool from the Cochrane Collaboration to evaluate the quality of individual included study, where the tool included domains of *sequence generation*, *allocation concealment*, *blinding*, *incomplete outcome data*, *selective outcome reporting and other issues.*[14] Studies were rated as low-risk-of-bias if low risks were found in all the domains, while studies were classified as high-risk-of-bias if high risks were found in one or more domains.

### Statistical Analyses

We used the random-effects model to pool the relative risks (RRs) from the RCTs for data syntheses. Some studies may report data on hazard ratios (HRs), rather than RRs, then we calculated the crude RRs from the contingency tables for these studies. Results were presented as the pooled RRs with 95% confidence intervals (CIs).

We used the $I^2$ statistic to evaluate the heterogeneity, with an $I^2 > 50\%$ or $P$ value $<.1$ considered as indicating significant heterogeneity. To account for potential heterogeneity, we performed 5 a priori subgroup analyses by: (1) different comparators (ie, comparing DOACs with VKAs, and comparing DOACs with LMWH); (2) different follow-up time (ie, $\leq 6$ months vs $> 6$ months); (3) disease status (ie, active cancer vs history of cancer); (4) different VTE profiles (DVT vs PE); and (5) different purposes of VTE prevention (primary prevention vs recurrent VTE prevention). We used the test by Borenstein *et al* to assess whether the subgroup differences were significant,[17] and used the Altman and Bland method to explore whether subgroup results significantly differed from the main findings.[18] Two predefined sensitivity analyses were conducted by: (1) excluding high-risk-of-bias studies; and (2) excluding trials that provided subgroup analysis data on patients with cancer (ie, excluding those RCTs that

randomized heterogeneous populations, rather than patients with cancer only).

### Publication Bias Assessment

Funnel plots were drawn to detect the potential publication bias, using visual inspection for signs of asymmetry, Egger regression test, and Begg rank correlation test.[14]

### Quality Assessment for the Entire Body of Evidence Across Studies

We used the Grading of Recommendations Assessment, Development and Evaluation tool to evaluate the quality of the entire body of evidence across studies for primary outcomes.[19] The quality of the entire body of evidence across studies can be categorized as high, moderate, low, or very low. While synthesized evidence from RCTs is originally rated as high, several reasons can downgrade the quality including *limitations in study design, imprecision of study results, unexplained heterogeneity or inconsistency of results, indirectness of evidence, and probability of publication bias.*[19] Two independent investigators (J.Z. and X.Z.) conducted the quality assessment first; a group discussion was subsequently performed to reach a consensus on the quality rating for the entire body of evidence in this systematic review.

## Results

There was a total of 3027 records included for screening. After removing duplicates and screening titles and/or abstracts, we evaluated 79 full-text articles for further eligibility judgment ($\kappa = 0.85$, 95% CI: 0.79-0.91). We included 11 eligible RCTs[20-30] for quantitative syntheses (Supplemental Figure 1 shows the study selection process).

Study and patient characteristics are summarized in Table 1. The included trials were published form year 2009 to 2018, with 7 comparing DOACs with VKAs [20,21,23-26,30] and the other 4 comparing DOACs with LMWH.[22,27-29] Two RCTs were conducted to prevent primary VTE,[28,29] while the other 9 were for prevention of recurrent VTE. A total of 3741 patients (1897 in DOACs, 1844 non-DOACs) with cancer were included for analyses. The mean age varied from 54 to 71 years. Follow-up periods ranged from 3 to 36 months. Regarding study quality assessment, the domains of included trials were rated as high in general. However, some studies were graded as high-risk-of-bias due to lack of blinding of participants and personnel[22-24,27] (Supplemental Figure 2). Information on patients with cancer was from subgroup data in the majority (9/11, 82%) of included trials, while only 2 trials specifically randomized all the patients with cancer.[22,27] We extracted such subgroup data from their *post-hoc* publications for RE-COVER I and II studies,[31] EINSTEIN DVT and PE studies,[32] MAGELLAN and ADOPT studies,[33] Hokusai-VTE study,[34] and AMPLIFY study.[35] Subgroup data for RE-MEDY study were retrieved from both the main report[20] and communications with the authors.

Figure 1 shows the synthesized treatment effect estimate comparing DOACs with non-DOACs for risk of VTE in patients with cancer. The DOACs were found to be significantly related with reduced risk of VTE: RR = 0.77, 95% CI: 0.61-0.99, $P = .04$. No significant heterogeneity was observed. The risk of major bleeding in DOACs compared with non-DOACs in patients with cancer was reported in Figure 2. Nonsignificantly higher risk of major bleeding was found with DOACs, with a RR of 1.28 (95% CI: 0.81-2.02, $P = .29$). The heterogeneity was nonsignificant ($I^2 = 30\%$, $P = .19$). Regarding secondary outcomes, DOACs were nonsignificantly related with increased risk of clinically relevant nonmajor bleeding (RR = 1.13, 95% CI: 0.66-1.95) and all-cause mortality (RR = 1.02, 95% CI: 0.89-1.18; Supplemental Figures 3 and 4).

Table 2 displays results from subgroup and sensitivity analyses. Unlike the main analysis result, DOACs were nonsignificantly related with decreased risk of major bleeding when pooling studies that compared DOACs with VKAs (RR = 0.72, $P = .31$), and that focused on patients with history of cancer (RR = 0.57, $P = .17$). No significant subgroup effect or no significant difference between subgroup results and main findings was observed. Sensitivity analyses yielded similar RRs but wider 95% CIs to the main analyses. No evidence of publication bias was detected when comparing DOACs with non-DOACs in risk of VTE and major bleeding (Supplemental Figures 5 and 6), with all the $P$ values of >.05 from Egger and Begg tests. The quality of the entire body of evidence was graded as moderate for risk of VTE due to limitation in study design when the majority of data were from subgroup analyses, and graded as low for risk of major bleeding due to limitation in study design and imprecision of study results (Supplemental Table 2).

## Discussion

In this study, we summarized all the available evidence from RCTs to investigate efficacy and safety of DOACs compared with conventional therapy in patients with cancer. A favorable effect on risk of VTE was found in DOACs; however, the latter had a trend towards increased risk of major bleeding when compared with non-DOACs. Given the quality of the entire body of evidence, the choice of DOACs in patients with cancer for prevention and treatment of VTE still warrants further clinical research.

We assessed the comparative efficacy and safety between DOACs and non-DOACs (Figures 1 and 2) and tried to explore whether results were robust across subgroup and sensitivity analyses (Table 2). Similar to the main results, DOACs were related with lower risk of VTE when compared with either VKAs or LMWH. The DOACs seemed to have a favorable benefit–harm profile than VKAs, which was consistent with previous studies.[7,13,36] Nevertheless, DOACs were found to significantly increase risk of major bleeding when compared with LMWH. This finding was consistent when pooling all the

**Table 1.** Description of Study and Patient Characteristics of Included Studies.

| | Population Characteristics | | | | | | | | Outcome Measure | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Study Name (Year) | Number of Randomized Patients | Study Arm | Sample Size for Each Arm (% for males) | Age, years | Patients With Cancer | Time in Therapeutic Range | Creatinine Clearance <50 mL/min | Intervention/Control (Dosage, Administration, Duration) | Efficacy | Safety | Follow-Up Period (Months) |
| RE-COVER I (2009) | 2539 | DOAC | 1273 (58) | 56 | 5% | NA | 5.0% | Dabigatran (150 mg orally twice daily) | Primary end point of venous thromboembolism or related death | Major bleeding event or clinically relevant bleeding | 12 |
| | | VKA | 1266 (59) | 54 | 4.5% | 60.0% | 4.5% | Warfarin (dose-adjusted) | | | |
| EINSTEIN-DVT (2010) | 3449 | DOAC | 1731 (57) | 56 | 6.8% | NA | 6.9% | Rivaroxaban (15 mg twice daily for 3 weeks, then 20 mg daily) | Symptomatic recurrent VTE | Clinically relevant bleeding | 12 |
| | | VKA | 1718 (56) | 56 | 5.2% | 57.7% | 7.5% | Warfarin or acenocoumarol for long-term use | | | |
| EINSTEIN-PE (2012) | 4832 | DOAC | 2419 (54) | 58 | 4.7% | NA | 8.8% | Rivaroxaban (15 mg twice daily for 3 week, then 20 mg daily) | Symptomatic recurrent VTE | Clinically relevant bleeding | 7 |
| | | VKA | 2413 (52) | 58 | 4.5% | 62.7% | 8.0% | Warfarin or acenocoumarol for long-term use | | | |
| RE-MEDY (2013) | 2856 | DOAC | 1430 (61) | 55 | 4.2% | NA | NA | Dabigatran, 150 mg orally twice daily | Recurrent Symptomatic VTE or VTE mortality | Major bleeding event or clinically relevant bleeding | 36 |
| | | VKA | 1426 (61) | 54 | 4.1% | 65.3% | NA | Warfarin | | | |
| AMPLIFY (2013) | 5395 | DOAC | 2691 (58) | 57 | 2.5% | NA | 6.5% | Apixaban (10 mg, twice daily for 7 days, then 5 mg twice daily) | Recurrent symptomatic VTE or VTE mortality | Major bleeding | 6 |
| | | VKA | 2704 (59) | 57 | 2.8% | NA | 6.1% | Warfarin for long-term use | | | |
| Hokusai-VTE (2013) | 8240 | DOAC | 4118 (57) | 56 | 9.2% | NA | 6.5% | Edoxaban (60 mg daily) | Symptomatic recurrent VTE | Clinically relevant bleeding | 12 |
| | | VKA | 4122 (57) | 56 | 9.5% | 63.5% | 6.6% | Warfarin | | | |
| RE-COVER II (2014) | 2568 | DOAC | 1280 (61) | 55 | 3.9% | NA | NA | Dabigatran (150 mg twice daily) | Venous thromboembolism or related death | Major bleeding | 6 |
| | | VKA | 1288 (60) | 55 | 3.9% | 56.9% | NA | Warfarin | | | |

*(continued)*

**Table 1.** (continued)

| | Population Characteristics | | | | | | | | Outcome Measure | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Study Name (Year) | Number of Randomized Patients | Study Arm | Sample Size for Each Arm (% for males) | Age, years | Patients With Cancer | Time in Therapeutic Range | Creatinine Clearance <50 mL/min | Intervention/Control (Dosage, Administration, Duration) | Efficacy | Safety | Follow-Up Period (Months) |
| MAGELLAN (2013) | 8101 | DOAC | 4050 (56) | 71 | 7.3% | NA | 21.5% | Rivaroxaban (10 mg once daily) | Composite of asymptomatic proximal or symptomatic VTE | Composite of major or clinically relevant nonmajor bleeding | 3 |
| | | LMWH | 4051 (53) | 71 | 7.3% | NA | 21.5% | Enoxaparin (subcutaneously 40 mg once daily) | | | |
| ADOPT (2014) | 6528 | DOAC | 3255 (50) | 67 | 50% | NA | NA | Apixaban (2.5 mg twice daily) | Thirty-day composite of death related to VTE, PE, symptomatic DVT, or asymptomatic proximal-leg DVT | Major bleeding event or clinically relevant bleeding | 3 |
| | | LMWH | 3273 (48) | 67 | 48.2% | NA | NA | Enoxaparin (subcutaneously 40 mg once daily) | | | |
| Hokusai VTE Cancer (2017) | 1046 | DOAC | 522 (53) | 64 | 100% | NA | 7.3% (30-50 mL/min) | Edoxaban (60 mg once daily) | Symptomatic recurrent VTE | Major bleeding | 9 |
| | | LMWH | 524 (50) | 64 | 100% | NA | 6.5% (30-50 mL/min) | Dalteparin | | | |
| SELECT-D (2018) | 406 | DOAC | 203 (57) | 67 | 100% | NA | NA | Rivaroxaban (15 mg twice daily for 3 weeks, then 20 mg once daily) | Symptomatic recurrent VTE | Major bleeding and clinically relevant nonmajor bleeding | 24 |
| | | LMWH | 203 (48) | 67 | 100% | NA | NA | Dalteparin (200 IU/kg daily during month 1, then 150 IU/kg daily for months 2-6) | | | |

Abbreviations: ADOPT, Apixaban Dosing to Optimize Protection from Thrombosis; AMPLIFY, Investigators in the Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy; DOACs, direct oral anticoagulants; DVT, deep-vein thrombosis; LMWH, low-molecular-weight heparin; NA, not available; PE, pulmonary embolism; SELECT-D, Selected Cancer Patients at Risk of Recurrence of Venous Thromboembolism; VKAs, vitamin K antagonists; VTE, venous thromboembolism.

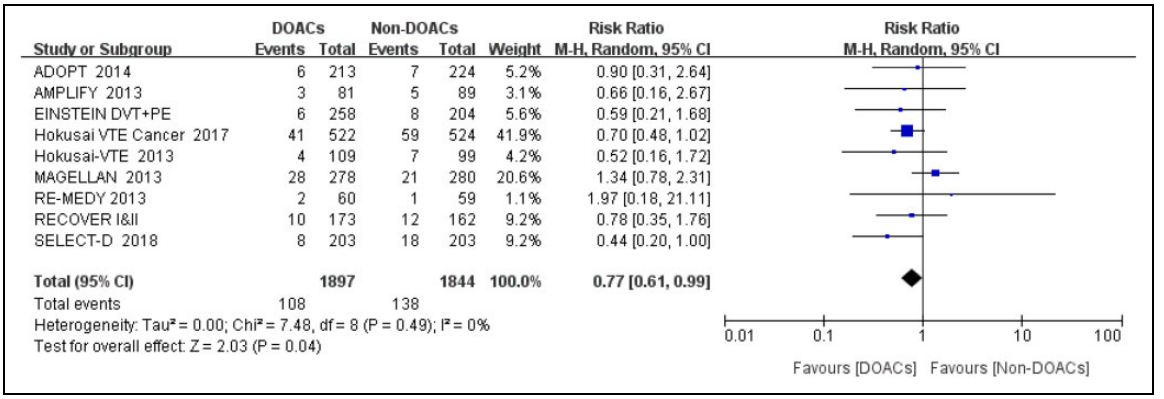


**Figure 1.** The forest pthe lot of the risk of VTE in patients with cancer.

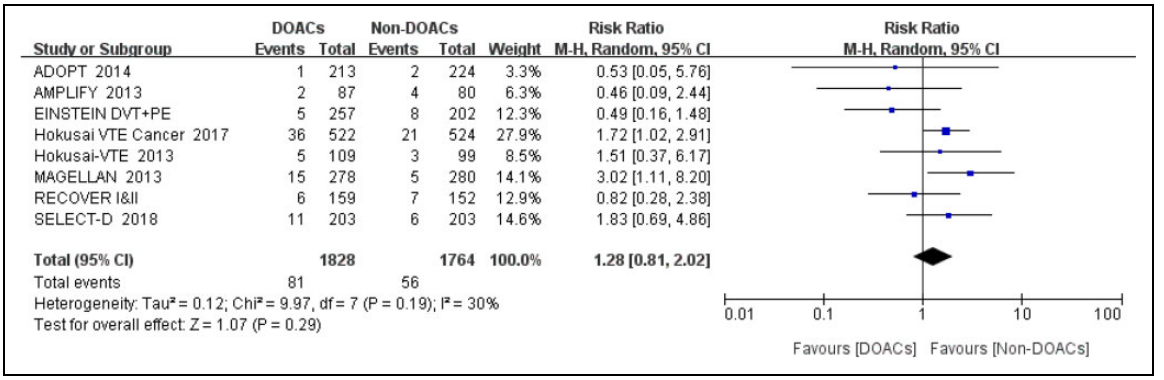


**Figure 2.** The forest plot of the risk of major bleeding in patients with cancer.

**Table 2.** Result of Subgroup and Sensitivity Analyses for Comparison between DOACs and non-DOACs.

| | VTE | | Major Bleeding | |
|---|---|---|---|---|
| Analysis | Number of Studies/Patients | Pooled RR (95% CI), *P* Value | Number of Studies/Patients | Pooled RR (95% CI), *P* Value |
| Subgroup analysis | | | | |
| Different non-DOACs | | | | |
| DOACs vs VKAs | 7/1294 | 0.69 (0.42, 1.15), .16 | 6/1145 | 0.72 (0.39, 1.35), .31 |
| DOACs vs LMWH | 4/2447 | 0.80 (0.51, 1.26), .34 | 4/2447 | 1.85 (1.22, 2.80), .003 |
| Follow-up time | | | | |
| ≤6 months | 3/1165 | 1.16 (0.73, 1.83), .53 | 3/1162 | 1.12 (0.28, 4.55), .87 |
| >6 months | 8/2576 | 0.66 (0.49, 0.88), .005 | 7/2430 | 1.26 (0.78, 2.03), .34 |
| Type of cancer | | | | |
| Active cancer | 8/2941 | 0.63 (0.49, 0.81), <.001 | 8/2746 | 1.07 (0.60, 1.92), .82 |
| History of cancer | 4/1594 | 0.50 (0.23, 1.07), .07 | 4/1601 | 0.57 (0.25, 1.28), .17 |
| Different VTE profile | | | | |
| DVT | 2/1452 | 0.53 (0.32, 0.87), .01[b] | 0/0 | -[a] |
| PE | 2/1452 | 0.79 (0.40, 1.55), .49[b] | 0/0 | -[a] |
| VTE prevention | | | | |
| Primary prevention | 2/995 | 0.82 (0.50, 1.32), .39[b] | 2/995 | 2.32 (0.96, 5.59), .06[b] |
| Recurrent VTE prevention | 9/2746 | 0.66 (0.49, 0.88), .004 | 8/2597 | 1.16 (0.72, 1.88), .54 |
| Sensitivity analysis | | | | |
| Including low-risk-of-bias studies only | 4/662 | 0.74 (0.39, 1.42), .37 | 3/519 | 1.03 (0.44, 2.40), .95 |
| Excluding trials that only provided subgroup analysis data | 2/1452 | 0.61 (0.42, 0.89), .01[b] | 2/1452 | 1.75 (1.10, 2.77), .02[b] |

Abbreviations: CI, confidence interval; DOACs, direct oral anticoagulants; DVT, deep-vein thrombosis; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; RR, relative risk; VKAs, vitamin K antagonists; VTE, venous thromboembolism.

[a]No meta-analysis conducted due to insufficient studies or data available.

[b]Fixed-effects model used due to only two studies included for analyses.

available data (RR = 1.85, $P = .003$) or when using data from trials[22,27] that specifically randomized all the patients with cancer (RR = 1.75, $P = .02$; Table 2). The difference in bleeding risk between DOACs and LMWH may be due to different drug interaction in patients with cancer who were commonly taking anticancer agents and other co-medications. Since LMWH was administrated subcutaneously, its plasmatic concentration and pharmacokinetics may be less influenced by drug interaction than DOACs that were orally consumed. Chemotherapy-related vomiting, different cancer severity and stages, and different outcome definitions/measures, may also interpret the difference in risk of major bleeding. Moreover, individual DOACs (dabigatran, apixaban, rivaroxaban, and edoxaban) may yield different benefits and safety effects. For example, in a head-to-head comparison between 3 individual DOACs (dabigatran, apixaban, and rivaroxaban) for stroke prevention in atrial fibrillation based on evidence from observational studies, apixaban was associated with the most favorable safety profile (risk of major bleeding).[37] Unfortunately, the small number of included studies precluded us from further exploring the difference in risk of major bleeding between DOACs and LMWH (Table 1).

The purpose of this review was to show a general picture regarding the effect of DOACs in patients with cancer in clinical practice. We tried to explore all sources of heterogeneity and test whether the heterogeneity was significant. Some results were different between subgroups; however all the subgroup effects were not significant (Table 2). Moreover, the overall pooled analyses did not find significant heterogeneity (Figures 1 and 2). Therefore we synthesized all the data to provide a simple and straightforward summary with extreme caution for result interpretation and clinical implication.

Our study included 11 RCTs and a total of 3741 patients with cancer for analyses, which is the largest population size based on the latest available evidence. Brunetti *et al* reported that after pooling data on 1952 patients with cancer from 9 RCTs, DOACs produced a favorable effect on both risk of VTE (odds ratio [OR] = 0.79, $P = .96$) and major bleeding (OR = 0.96, $P = .10$) compared with non-DOACs. However it only used all the subgroup data and did not include the 2 trials that randomized all patients with cancer.[22,27] Data from subgroup analyses in trials, especially for those from *post-hoc* publications without a priori hypotheses, should be interpreted with caution due to their weak credibility.[38] Posch *et al* conducted a network meta-analysis of RCTs to compare DOACs with non-DOACs in patients with cancer.[9] They reported favorable benefit–harm profile in DOACs compared with VKAs based on the data from direct comparisons in 6 RCTs. However, when they performed an indirect network comparison by using data from DOACs versus VKAs and from LMWH versus VKAs, they found a higher risk of VTE (RR = 1.08) but lower risk of major bleeding (RR = 0.67) in DOACs compared with LMWH, which conflicted with our findings. Likewise, the evidence strength of indirect comparisons should be largely weakened; such evidence is usually used to generate hypothesis and to advocate direct comparative evidence for validation.[14,39] By contrast, another systematic review comparing DOACs with LMWH only included the 2 trials that randomized all patients with cancer.[10] It reported significantly higher risk of major bleeding than LMWH (RR = 1.74, $P = .03$), but lower risk of VTE (RR = 0.65, $P = .06$), which was similar to our results.

Our study has some strengths. We summarized all the evidence to systematically assess the comparative effect of DOACs and performed vigorous analyses to examine the robustness of findings in patients with cancer. A standardized and comprehensive procedure was conducted to obtain all the relevant and most updated research and extract the required information in duplicate with a good level of agreement. Data analyses and study quality assessment were carried out by following the guidelines and our prespecified protocol. There are some limitations in our study. First, the majority of the data were from those trials that provided subgroup analysis results, which thus impaired the evidence strength. For example, the imbalance between the patients with and without cancer may challenge the RCT-design, the small number of patients with cancer and VTE events prevented covariate adjustment, and the subgroup analyses were performed postrandomization and without a prespecified hypothesis. Therefore, the quality of the entire body of evidence was downgraded even though there was no significant difference between overall findings (Figures 1 and 2) and sensitivity analysis results that excluded trials that only provided subgroup analysis data (Table 2). Besides, the insufficient number of included studies and data may not provide adequate power to detect significant effect size with precision. Likewise, the data collected did not allow us to further explore subgroup difference stratified by sex, renal dysfunction, individual DOACs, cancer stages, different age categories, and different dosages of both DOACs and non-DOACs. In addition, information on the cancer status or staging may be inaccurate in some trials since these studies were not designed to the conducted subgroup analysis a priori. Furthermore, even though no significant subgroup effect was found in subgroup analyses, the nonsignificant heterogeneity in the populations (with different cancer status) and the clinical purposes (prevention or treatment of VTE) should be taken into careful consideration. Therefore the overall and subgroup findings from this study should be interpreted with caution, which should not lead to clinical decisions for individual patients in clinical practice before further high-quality evidence is available.

In conclusion, the DOACs were found to have a favorable effect on risk of VTE but a nonsignificantly higher risk of major bleeding compared with non-DOACs in patients with cancer. The safety effect of DOACs in patients with cancer, especially compared with LMWH, requires further evaluation in adequately powered and designed research studies.

## Authors' Note

Jie Zeng, Xuhui Zhang, Junzhang Tian and Guowei Li contributed equally to this work.

## Declaration of Conflicting Interests

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## ORCID iD

Guowei Li https://orcid.org/0000-0002-3472-8513

## Supplemental Material

Supplemental material for this article is available online.

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