Efficacy and safety of novel oral anticoagulants for the treatment of cancer-associated venous thromboembolism: protocol for an umbrella review of systematic reviews and meta-analyses

Yunqing Xia, Liang Tang, Yu Hu

ABSTRACT

Introduction Novel oral anticoagulants (NOACs) have been used in antithrombotic therapy in patients with cancer, and their efficacy and safety have been evaluated in several meta-analyses. Although a large body of findings has accumulated to support the benefit of NOACs for the treatment and prevention of cancer-associated thromboembolism, there is no convincing evidence because of inconsistent results across studies and questionable data quality. Its efficacy and safety remain controversial, especially with regard to the risk of bleeding.

Methods and analysis We will search PubMed, Embase and Web of science, Cochrane Library on 19 April 2022 (searches will be updated until complete) to identify systematic reviews, meta-analyses and pooled analyses of the efficacy and safety of NOACs for the treatment of cancer-associated venous thromboembolism. The quality of eligible systematic evaluations will be measured by a Measurement Tool to Assess Systematic Reviews. For each outcome, if a random effects model is not used, we will extract the data and estimate a 95% CI using the random effects model approach. For each random effects estimate, a 95% prediction interval is calculated. Heterogeneity between studies will be quantified using the I² metric. In addition, if an assessment contains at least three articles, we will reanalyse the assessment using Egger's asymmetry test to detect and visualise possible publication bias in the articles.

Ethics and dissemination No formal ethical approval is required since we will use publicly available data. We will disseminate the findings of the umbrella review through publication in a peer-reviewed journal and conference presentations.

PROSPERO registration number CRD42022342053.

BACKGROUND

Venous thromboembolism (VTE), which mainly includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is the second leading cause of death in oncology patients, after malignant disease itself. According to the survey statistics, the risk of venous embolism in oncology patients is at least 4–7 times higher than in non-oncology patients and accounts for about 20% of all venous thromboembolic diseases. In addition, cancer-associated venous thromboembolism (CAT) may lead to a series of consequences such as delayed treatment of patient’s primary oncological disease, longer hospitalisation cycles, reduced quality of life and increased healthcare costs. Therefore, it is crucial to choose the appropriate treatment option for oncology patients who develop VTE. Anticoagulants have long been an important cornerstone in the treatment of thrombosis. Heparin and vitamin K antagonists were considered to be the only available anticoagulants for most of the 20th century. Advances in structure-based drug design and high-throughput screening have accelerated the development of novel oral anticoagulants (NOACs) for specific targets. Currently, oral anticoagulants used in clinical treatment of thrombosis (apixaban, rivaroxaban, edoxaban,
dabigatran, etc) can inhibit factor Xa, or thrombin, or reduce the plasma concentration of precursor factor X and prothrombin, thereby achieving antithrombotic effects.7 The convenience of novel oral anticoagulation without routine anticoagulation monitoring and fixed dose administration significantly improves the management of thrombophilia compared with vitamin K antagonists or heparin.8 Although a large body of findings has accumulated to support the benefit of NOACs for the treatment and prevention of cancer-associated thromboembolism, there is no convincing evidence because of inconsistent results across studies and questionable data quality. Its efficacy and safety remain controversial, especially with regard to the risk of bleeding. To present, there is no comprehensive review of systematic evaluation and meta-analysis of NOACs in the treatment of cancer-associated thromboembolism. There is an urgent need to systematically evaluate the benefits and potential risks of direct oral anticoagulants in the treatment of cancer-associated thromboembolism. Therefore, we will use a rigorous approach to summarise the currently known systematic evaluations and meta-analyses.

**OBJECTIVE**

The umbrella review aims to provide comprehensive and evaluative evidence for healthcare decision makers such as patients, physicians and policy-makers.9 This umbrella review aims to examine the following questions:

- Whether NOACs are more effective than low-molecular heparin or vitamin K inhibitors for antithrombotic therapy in patients with cancer-associated thromboembolism.
- Whether NOACs are safer than low-molecular heparin or vitamin K inhibitors for antithrombotic therapy in patients with cancer-associated thromboembolism.

**METHOD**

We have registered this protocol within the PROSPERO (ID: CRD42022342053) database for systematic review

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**Table 1** Search strategy (through Embase)

<table>
<thead>
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<th>Search query</th>
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<tr>
<td>#1 'neoplasm'/exp</td>
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<tr>
<td>#2 'tumor-associated'</td>
<td>#26 'novel oral anticoagulant'</td>
</tr>
<tr>
<td>#3 'cancer-associated'</td>
<td>#27 'new oral anticoagulant'</td>
</tr>
<tr>
<td>#4 'neoplasm'</td>
<td>#28 'new oral anticoagulants'</td>
</tr>
<tr>
<td>#5 'tumor'</td>
<td>#29 'dabigatran'</td>
</tr>
<tr>
<td>#6 'tumors'</td>
<td>#30 'apixaban'</td>
</tr>
<tr>
<td>#7 'neoplasia'</td>
<td>#31 'rivaroxaban'</td>
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<td>#8 'cancer'</td>
<td>#32 'edoxaban'</td>
</tr>
<tr>
<td>#9 'cancers'</td>
<td>#33 'factor Xa inhibitor'</td>
</tr>
<tr>
<td>#10 'malignant neoplasm'</td>
<td>#34 'factor Xa inhibitors'</td>
</tr>
<tr>
<td>#11 'malignant neoplasms'</td>
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<tr>
<td>#12 'malignancy'</td>
<td>#36 'venous thromboembolism'/exp</td>
</tr>
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<td>#13 'malignancies'</td>
<td>#37 'thromboembolism'</td>
</tr>
<tr>
<td>#14 'neoplasm, malignant'</td>
<td>#38 'vte'</td>
</tr>
<tr>
<td>#15 'neoplasms, malignant'</td>
<td>#39 #36 OR #37 OR #38</td>
</tr>
<tr>
<td>#16 'benign neoplasms'</td>
<td>#40 'meta'</td>
</tr>
<tr>
<td>#17 'benign neoplasm'</td>
<td>#41 'meta-analysis'</td>
</tr>
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<td>#18 'neoplasms, benign'</td>
<td>#42 'meta-analyses'</td>
</tr>
<tr>
<td>#19 'neoplasm, benign'</td>
<td>#43 'systematic reviews'</td>
</tr>
<tr>
<td>#20 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19</td>
<td>#44 'systematic review'</td>
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<td>#21 'noac'</td>
<td>#45 'pooled analyses'</td>
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<tr>
<td>#22 'doac'</td>
<td>#46 #40 OR #41 OR #42 OR #43 OR #44 OR #45</td>
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<tr>
<td>#23 'noacs'</td>
<td>#47 #20 AND #35 AND #39 AND #46</td>
</tr>
<tr>
<td>#24 'doacs'</td>
<td></td>
</tr>
</tbody>
</table>
and meta-analyses. The protocol has been drafted and reported in accordance with the reporting guidelines provided in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols 2015 Statement.10

**Eligibility criteria**

**Participants**
A meta-analysis comparing treatment with NOACs to randomised controlled trials of low-molecular heparin, vitamin K inhibitors, or placebo in patients with acute symptomatic or episodic VTE, active cancer, or a recent history of cancer was eligible. Active cancer was defined as any cancer, including: (a) diagnosed within 6 months prior to study inclusion; (b) requiring treatment for cancer within 6 months prior to randomisation grouping; (c) recurrent metastasis. Any objectively confirmed symptomatic or episodic VTE was considered as an indication for venous thrombotic events.

**Interventions**
This umbrella review will consider systematic reviews and meta-analyses related to the use of NOACs in patients with cancer-associated thromboembolism, with the aim of assessing the efficacy and safety of NOACs. It will not be limited by dose, type of drug (apixaban, rivaroxaban, edoxaban, dabigatran, etc)

**Comparator**
This umbrella review will consider systematic reviews and meta-analyses comparing NOAC interventions with placebo, low-molecular heparin and vitamin K inhibitors.

**Outcomes of interest**
This umbrella review will consider systematic reviews and meta-analyses that include the following outcome measures:
1. Recurrent VTE.
2. Major bleeding.
3. Non-major clinical relevant bleeding.

**Types of studies**
Only quantitative systematic evaluations and meta-analyses with clear and comprehensive search strategies and critical assessments of risk of bias will be included in this review. Only systematic reviews and meta-analyses of randomised controlled trials published in English will be considered. Only systematic reviews of narrative abstracts will be excluded because we will not be able to base the analysis on narrative information.

**Search strategy and selection criteria**
We will search PubMed, Embase and Web of science, Cochrane Library on 19 April 2022 (searches will be updated until complete) to identify systematic reviews, meta-analysis and pooled analyses of efficacy and safety of NOACs for the treatment of CAT. The search was based on a combination of subject terms and free terms and was adapted to the characteristics of each database. The full search strategy will be shown in the online supplemental material. Table 1 provides Embase’s search strategy. We will use Endnote X9 to screen literatures. Two researchers will screen the titles and abstracts independently, then review the full text of selected articles and evaluate their eligibility. Any discrepancies will be resolved with discussion or the arbitration of the third author.

**Risk-of-bias assessment**
The quality of eligible systematic evaluations will be measured by A Measurement Tool to Assess Systematic Reviews (AMSTAR), which is the most frequently mentioned tool for evaluating the quality of systematic evaluations.12 13 AMSTAR consists of 11 items with excellent content validity and is used to measure the methodological quality of systematic evaluations. It has great consistency, reliability and structural validity and is convenient to use when evaluating the quality of published systematic evaluations.14 15 We will assess the feasibility of published systematic evaluations in the efficacy and safety of NOACs therapy. We classify the credibility of the evidence as: convincing evidence, suggestive evidence and weak evidence.16 17 The feasibility of the available evidence will be assessed using the following criteria: (1)

<table>
<thead>
<tr>
<th>Table 2 Khorana Score</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary location of the tumour:</td>
<td></td>
</tr>
<tr>
<td>Gastric or pancreatic cancer</td>
<td>2</td>
</tr>
<tr>
<td>Lung, kidney, lymphoma, myeloma and kidney cancer</td>
<td>1</td>
</tr>
<tr>
<td>Platelet count≥350×10^9/L</td>
<td>1</td>
</tr>
<tr>
<td>Haemoglobin concentration&lt;100g/L or use of erythropoietic agents</td>
<td>1</td>
</tr>
<tr>
<td>Leucocyte count≥11×10^9/L</td>
<td>1</td>
</tr>
<tr>
<td>Body mass index&gt;35kg/m^2</td>
<td>1</td>
</tr>
<tr>
<td>Patients with a total score=0 are at low risk of venous thromboembolism (VTE), patients with a total score=1 or 2 are at moderate risk of VTE and patients with a total score=3 or more are at high risk of VTE.</td>
<td></td>
</tr>
</tbody>
</table>

5. All-cause mortality.
   a. Recurrent VTE: symptomatic or episodic DVT of the upper or lower extremity; symptomatic or episodic PE involving a segmental or more proximal pulmonary artery, or fatal PE.
   b. Major bleeding: according to the ISTH (International Society of Thrombosis and Hemostasis) criteria as overt bleeding associated with a drop in haemoglobin of ≥20g/L or transfusion of ≥2 units of blood, or that occurred in a critical site or contributed to death.11
   c. Non-major clinically relevant bleeding: bleeding due to hospitalisation for bleeding, medical or surgical treatment, unplanned visits or changes in physician-directed antithrombotic therapy.
p<0.05 in a fixed effects model or p<0.01 in a random effects model; (2) a total sample size>1000; (3) low or moderate between-study heterogeneity (I²<50%); (4) 95% prediction interval (PI) that excludes the null value; and (5) no evidence of small-study effects and excess significance bias. The convincing evidence of effectiveness should meet all five criteria. Suggestive evidence should meet criteria 1–4, and other evidence is marked as weak evidence.

Data extraction
One reviewer extracted the study characteristic from the included articles:
1. Basic information of the study: such as author, year, country, journal, purpose, background, registration number, etc.
2. Study details: inclusion and exclusion criteria, number of included literatures, type of included studies, number of experimental and control groups, description of interventions in the experimental group, description of treatments in the control group.
3. Quality assessment tools.
4. Information on the results: analytical methods, assessment results, pooled effect (RR, OR, 95% CI, significant, heterogeneity).

Data analysis
For each study’s results, if a random effects model was not used in the original study, we will extract the original data and estimate 95% CIs using a random effects model approach. For each random effects estimate, a 95% PI is calculated, indicating where the estimates should lie for future studies.18 Heterogeneity between studies will be quantified using the I² metric. I² ranges from 0% to 100%, with I²<25% being small heterogeneity; I² in the range of 25%–49% being moderate heterogeneity, I² in the range of 50%–74% being large heterogeneity and I²>75% being very large heterogeneity. In addition, if an assessment contains at least three articles, we will reanalyse the assessment using Egger’s asymmetry test to detect and visualise possible publication bias in the articles. R V.4.1.1 statistical software will be used.

To assess the effects of small studies and publication bias, we will first examine whether there is evidence of small-study effects in the included meta-analyses via funnel plots. ES in small studies is more widely dispersed at the bottom of the funnel plot, while the dispersion in large studies is narrower at the top. When there is no small-study effect is present, the funnel plot is asymmetric, with small studies more dispersed on the bottom side. Contour funnel plots will be drawn to determine this.19 The number and significance levels of significant findings in small-scale studies will be set at 0.1, 0.05 and 0.01, respectively.20

Patient and Public Involvement
No patient involved.

DISCUSSION
To our knowledge, this umbrella review is the first comprehensive assessment of the efficacy and safety of NOACs currently being used in oncology patients through a quantitative approach. The results of this review provide patients, physicians and clinical investigators with information on the viability of current evidence and research directions for future studies.

When should antithrombotic prophylaxis be administered to patients with cancer?
The risk of CAT is multifactorial and no single risk factor or biomarker is a good predictor of risk. To better identify patients who merit primary prevention, a number of clinical predictive scores have been created, including the Khorana Score21 (see table 2), the Caprini Score22 and the Protecht Score23 (Khorana Score plus use of platinum-based therapy, use of gemcitabine) and the Vienna Score23 (Khorana Score plus soluble P-selectin, D-dimer) and others. The Khorana Score is currently the most commonly used recommendation in national and international guidelines, and anticoagulants should be given to patients with a moderate or high risk of Khorana Score.

Ethics and dissemination
We will use publicly available data from systematic reviews and meta-analyses; therefore, formal ethical approval is not required. We will disseminate the results of the review through publications in peer-reviewed journals and presentations at conferences.

Contributors This study was conceived by YX, L-VT and YH. YX and L-VT developed the eligibility criteria, search strategy, assessment of methodological quality and data extraction plan with guidance from YH. YX wrote the manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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