Journal of Clinical Question

Decision Letter (JCQ-2025-0020)

From: [redacted]
To:
CC:
BCC:

Subject: Journal of Clinical Question - Decision on Manuscript ID JCQ-2025-0020

Body: 14-Jul-2025

Dear Dr Koitabashi,

Manuscript ID JCQ-2025-0020 entitled "The Efficacy of Different Treatment Strategies of Direct Oral Anticoagulants in Cancer-Associated Thrombosis: A Systematic Review and Network Meta-Analysis" which you submitted to the Journal of Clinical Question, has been reviewed. The comments of the reviewer(s) are included at the bottom of this letter.

The reviewer(s) have recommended publication, but also suggest some revisions to your manuscript. Therefore, I invite you to respond to the reviewer(s)' comments and revise your manuscript.

To submit your revised manuscript, follow the below steps.
1. Access to https://mc.manuscriptcentral.com/jcq and log into the site.
2. Click "Author" at the top left of the screen at "Home" page.
3. Click "Manuscripts with Decisions" on Author Dashboard page.
4. Click "create a revision" on the manuscript you are going to revise.
5. The system creates your revision manuscript form. Provide your comments about the revised points at the response field, fill in on each field step by step as same as you did for the original submission, and submit your revised manuscript.
IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.
Your manuscript number has been appended to denote a revision.

You will be unable to make your revisions on the originally submitted version of the manuscript. Instead, revise your manuscript using a word processing program and save it on your computer. Please also highlight the changes to your manuscript within the document by using the track changes mode in MS Word or by using bold or colored text.

Once the revised manuscript is prepared, you can upload it and submit it through your Author Center.

When submitting your revised manuscript, you will be able to respond to the comments made by the reviewer(s) in the space provided. You can use this space to document any changes you make to the original manuscript. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the reviewer(s).

IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

Because we are trying to facilitate timely publication of manuscripts submitted to the Journal of Clinical Question, your revised manuscript should be uploaded as soon as possible. If it is not possible for you to submit your revision in a reasonable amount of time, we may have to consider your paper as a new submission.

Once again, thank you for submitting your manuscript to the Journal of Clinical Question and I look forward to receiving your revision.

Sincerely,
Richard Isaacs
Editor in Chief,
Journal of Clinical Question

[Editor's Comments]
Associate Editor
Comments to the Author:
(There are no comments.)

[Reviewer(s)' Comments]
Reviewer: 1

Comments to the Author
Summary
We performed a systematic review and network meta-analysis (NMA) to compare the efficacy and safety of different DOAC regimens for CAT. The meta-analysis consists of 15 RCTs of 8,468 patients and compares different durations and dosing regimens of DOACs with standard therapies such as dalteparin and VKAs. The principal results indicate that reduced-dose long-term DOAC therapy achieves a satisfactory balance between efficacy and safety, particularly in preventing recurrent VTE, without increasing the risk of significant bleeding. It is safe for dalteparin to be continued in those with a high bleeding risk.

2. Major Comments
Strengths:
Timeliness and clinical relevance: CAT is a significant issue in oncology, and not only the evidence of DOACs, but also their role, is rapidly changing.
Advanced methodology used: Frequentist NMA is the appropriate choice, and the reporting is by PRISMA-NMA guidelines.
Dynamic overview of evidence: 15 high-quality RCTs, robust for subgroup and SUCRA analysis.
Assessment of risk of bias and GRADE assessment: adds transparency and enhances the credibility of conclusions.
Concerns:
1. Variation in DOACs and Dose:
The authors pooled outcomes across various DOACs (apixaban, rivaroxaban, edoxaban, and dabigatran) without conducting sub-analyses of the individual DOAC agents. This could potentially undermine clinically significant alterations, considering variations in pharmacodynamic effects and bleeding patterns, particularly in GI malignancies.
2. Patient-Level Data Missing for Key Variables:
Significant covariates such as cancer site (GI vs. non-GI), renal function, thrombocytopenia, and use of concomitant chemotherapy were not considered. These factors may have a significant impact on both the risk of VTE recurrence and bleeding.
3. Assumption of Trial Equivalence in the Short Term:
It may be inappropriate to pool 3-month regimens with longer treatment durations, given the differences in risk profiles. The justification for the classification of the duration (for example, as “intermediate” after 6 months and “long” after 12 months), should be guided by supporting documentation.
4. No Sensitivity Analysis for Open-Label Bias:
As we considered most of the studies to be open-label, which was a high risk in the GRADE rating, this could further strengthen the robustness by performing a sensitivity analysis with the exclusion of open-label trials (e.g., ADAM VTE, SELECT-D).
5. Clinical Implications Need Clarification:
The results highlight the effectiveness and safety of reduced-dose long-term DOACs; however, the authors will need to clarify how clinicians should weigh the risk of bleeding, particularly in cancers involving mucosa.

3. Minor Comments
The three-letter acronym R12mDOAC and the others (e.g., 3mDOAC, 6mDOAC) should be better defined both here and in the legends of each figure for the sake of clarity.
A few typos and layout errors to correct (including spaces, line breaks, and missing articles).
Expand “Ethical Statement” to explain the exemption from IRB instead of only “waived.”
Include the O SF T registration ID number within the abstract or under the methods section.

Reviewer: 2

Comments to the Author
This manuscript presents a timely and relevant network meta-analysis comparing different DOACs in patients with cancer-associated thrombosis (CAT). The study addresses an important clinical gap and offers practical insights for treatment decisions.

The methodology is generally sound, and the findings are of interest. Notably, your work complements the recent meta-analysis by Mousavi et al. (Am J Cardiol, 2025; DOI: [10.1016/j.amjcard.2025.06.022]), which compared DOACs with LMWH in CAT. While their analysis focused on the DOAC vs. LMWH comparison, your study adds value by exploring head-to-head comparisons among DOACs—an area with limited evidence to date.

I have a few suggestions to improve the clarity and robustness of the manuscript:

Justify the assumption of transitivity and address the potential for clinical heterogeneity across included trials.

The limitations section should be expanded to acknowledge variability in cancer types, risk of bias across studies, and differences in outcome definitions.

Some conclusions could be phrased more cautiously, especially where the credible intervals overlap or statistical significance is not reached.

Minor language and grammar revisions are needed for improved fluency and clarity.

Date Sent: 14-Jul-2025

Print Close Window

Journal of Clinical Question

Author's Response to Decision Letter for (JCQ-2025-0020)

The Efficacy of Different Treatment Strategies of Direct Oral Anticoagulants in Cancer-Associated Thrombosis: A Systematic Review and Network Meta-Analysis

Response Letter

Dear Reviewers,
We sincerely thank the reviewers for their careful evaluation and insightful comments on our manuscript. We have carefully addressed each of the points raised and made corresponding revisions to the manuscript where applicable. Below, we provide a detailed point-by-point response.

Reviewer: 1
Major Comments1: The authors pooled outcomes across various DOACs (apixaban, rivaroxaban, edoxaban, and dabigatran) without conducting sub-analyses of the individual DOAC agents. This could potentially undermine clinically significant alterations, considering variations in pharmacodynamic effects and bleeding patterns, particularly in GI malignancies.
Response: We appreciate the reviewer's important observation. We acknowledge the pharmacological differences across individual DOACs and the potential implications on safety and efficacy, particularly in patients with gastrointestinal cancers. Unfortunately, due to the limitations in data availability, especially in subgroup reporting across included trials, we were unable to conduct agent-specific sub-analyses. We have now explicitly acknowledged this as a limitation in the discussion section as follows "First, our study was limited by the inability to perform agent-specific analyses of individual DOACs due to insufficient data in the included trials."

Major Comment 2: Significant covariates such as cancer site (GI vs. non-GI), renal function, thrombocytopenia, and use of concomitant chemotherapy were not considered. These factors may have a significant impact on both the risk of VTE recurrence and bleeding.
Response: We agree that these covariates are critical in determining both thrombotic and bleeding risks. However, as our meta-analysis relied on aggregate trial-level data, patient-level information on variables such as renal function, platelet counts, chemotherapy status was not consistently reported across studies. We idenitfied data from several studies specified with GI. We have added the contents in the manuscript as follows "Subgroup analyses were performed for patients with gastrointestinal cancer. The network graph illustrating major bleeding outcomes is presented in Figure S13. Regarding the risk of major bleeding, direct comparisons indicated that a reduced dose of DOAC therapy administered for 12 months was associated with the lowest risk (OR 0.50; 95% CI: 0.16–1.60), followed by treatment durations of 18 months (OR 0.72; 95% CI: 0.11–4.85), 3 months (OR 0.74; 95% CI: 0.22–2.53), 12 months (OR 0.94; 95% CI: 0.38–2.32), and 6 months (OR 1.00; 95% CI: 0.48–2.21), as shown in Figure S14. These results were supported by the network meta-analysis, which found no statistically significant differences among the treatment strategies (Table S4). Safety rankings for major bleeding based on 1,000 simulations are shown in Figure S15, reflecting the same order observed in the direct comparisons."

Major Comment 3: It may be inappropriate to pool 3-month regimens with longer treatment durations, given the differences in risk profiles. The justification for the classification of the duration (for example, as "intermediate" after 6 months and "long" after 12 months), should be guided by supporting documentation.
Response: Thank you for pointing this out. We have now defined the duration categories as follows: short-term (3 months), intermediate-term (6 months), long-term (12–18 months), and reduced-dose long-term regimens (defined as a maintenance phase with approximately half the standard dose administered for at least 12 months). The manuscript has been revised accordingly to reflect these definitions.

Major Comment 4: As we considered most of the studies to be open-label, which was a high risk in the GRADE rating, this could further strengthen the robustness by performing a sensitivity analysis with the exclusion of open-label trials (e.g., ADAM VTE, SELECT-D).
Response: We thank the reviewer for this valuable suggestion. As most of the studies used dalteparin in the control groups, the remaining data were insufficient to conduct a subgroup meta-analysis. We have added the following content to the limitations section: "Second, most of the trials had open-label designs, which may have introduced potential biases in outcome assessment, despite the use of objective endpoints."

Major Comment 5: The results highlight the effectiveness and safety of reduced-dose long-term DOACs; however, the authors will need to clarify how clinicians should weigh the risk of bleeding, particularly in cancers involving mucosa.
Response: We appreciate this valuable comment and have revised the discussion accordingly to address this concern. Most studies defined major bleeding using standard criteria, including: 1.a decrease in hemoglobin of >=2 g/dL; 2.transfusion of >=2 units of packed red blood cells; 3.bleeding in critical sites (intracranial, intraspinal, intraocular [within the corpus of the eye], pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal); 4. fatal bleeding; 5. bleeding requiring surgical intervention.
However, such major bleeding events are relatively uncommon in routine clinical practice. Although our subgroup analysis comparing different DOAC strategies in patients with gastrointestinal cancers showed no significant differences, it remains difficult to conclude that DOACs are completely safe in scenarios involving minor but recurrent mucosal bleeding. Therefore, careful patient selection, close monitoring, and regular follow-up are essential when considering long-term reduced-dose DOACs in this population. We added contents as follows "Although an increased risk of major bleeding was not observed in patients with gastrointestinal cancers, clinicians should carefully weigh the benefits of reduced-dose long-term DOACs against the potential bleeding risks, particularly in cancers involving mucosal surfaces, where such risks may be higher. An individualized assessment considering tumor location, bleeding history, and overall risk profile is essential to guide the selection and dosing of anticoagulants."

Minor Comment1: The three-letter acronym R12mDOAC and the others (e.g., 3mDOAC, 6mDOAC) should be better defined both here and in the legends of each figure for the sake of clarity.
Response: Thank you for this suggestion. We have revised the text and all figure legends to ensure that all acronyms (e.g., 3mDOAC, 6mDOAC, R12mDOAC) are clearly defined at first use and consistently throughout the manuscript and figures.

Minor Comment 2: A few typos and layout errors to correct (including spaces, line breaks, and missing articles). Expand "Ethical Statement" to explain the exemption from IRB instead of only "waived." Include the OSF registration ID number within the abstract or under the methods section.
Response: We have carefully reviewed and corrected all identified typographical and formatting errors. We have modified the ethical sataement as "Institutional Review Board approval was waived due to the nature of this study as a meta-analysis of previously published data." We also included thue OSF registiation ID number as follows "This review was registered with the Open Science Framework (Registration ID number: m74sx)."

Reviewer: 2
Comment 1: Justify the assumption of transitivity and address the potential for clinical heterogeneity across included trials.
Thank you for this important methodological comment. We included randomized controlled trials comparing DOACs with other treatments, ensuring that the enrolled patients had similar clinical backgrounds and that the studies reported consistent outcome measures. This approach was taken to support the assumption of transitivity. Additionally, we have added the following statement to the Limitations section to acknowledge potential clinical heterogeneity: "Third, heterogeneity in patient populations, including variations in cancer types, stages, and concurrent therapies, could have influenced the results, although NMA methods attempt to account for such variability."

Comment 2: The limitations section should be expanded to acknowledge variability in cancer types, risk of bias across studies, and differences in outcome definitions.
Response: We agree with the reviewer's suggestion and have now expanded the limitations section to as follows "Although a subgroup analysis in patients with gastrointestinal cancers showed no increased risk of major bleeding, there were insufficient data to support similar analyses for other specific cancer types in terms of effectiveness and safety."

Comment 3: Some conclusions could be phrased more cautiously, especially where the credible intervals overlap or statistical significance is not reached.
Response: We appreciate this feedback and have revised several parts of the conclusion to adopt a more cautious tone, especially in instances where the certainty of evidence is low or credible intervals overlap. These edits aim to avoid overstating the findings.

Comment 4: Minor language and grammar revisions are needed for improved fluency and clarity.
Response: We have revised the manuscript for grammar, style, and clarity. The manuscript was also reviewed by a native English speaker to improve fluency and readability.

We are grateful to the reviewers and editors for their constructive feedback, which has significantly improved the quality and clarity of our manuscript. We believe the revised version addresses all concerns and presents a more rigorous and clinically relevant analysis. We hope the revised manuscript will meet your expectations and are happy to respond to any additional questions.

Sincerely,
Bilal Farooqi
Department of Medicine, Mercer University School of Medicine, Macon, Georgia, USA.
Email: bilal.farooqi@wmchealth.org

1. Response Letter.pdf PDF

Print Close Window