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Peer Review File

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Reviewer A

This is a well-written review addressing an important topic that is known to be considered high-priority by patients. Congratulations to the authors. I had only minor suggestions (below):

Abstract:

Comment 1: Line 55: suggest change to: "with limited numbers of patients with GI malignancies"

Reply: Yes we have added these changes.

Please see the line 70 in the revised manuscript.

Comment 2: Line 58: suggest change to: "..to evaluate the impact of the above-mentioned factors in the efficacy of DOACS..."

Reply: Yes we have added these changes.

Please see the line 73 in the revised manuscript.

Comment 3: Line 60: suggest change to : "Until more evidence is availalbe, LMWH are a more reasonable choice in selected subgroups..."

Reply: Yes we have added these changes.

Please see the line 75-76 in the revised manuscript.

Introduction:

Comment 4: Line 74: suggest change to ".. in increased risk of bleeding, therefore several international guidelines and review..."

Reply: Yes we have added these changes.

Please see the line 88-90 in the revised manuscript.

Comment 5: Line 81: suggest change to: ".. Patients with CAT in the setting of GI malignancy represent a special..."

Reply: Yes we have added these changes.

Please see the line 97 in the revised manuscript.

Methods:

Comment 6: Suggest including the detailed search string (perhaps as a supplemental file)

Reply: Yes we have added these changes.

Please see the line 109 to 114 in the revised manuscript.

We have added the supplementary file also.

Comment 7: Discussion: consider change to "results"

Hokusai VTE Cancer (include cancer, as the Hokusai VTE trial was a different RCT). Please standardize the data included in each trial summary. It is useful therefore to include the numbers of patients enrolled (as you have done for the Caravaggio trial).

Reply: Yes we have added these changes.

Please see the line 137 for change in the title of Hokusai VTE trial. In all four RCTs we have standardized the format with Table 1 reporting the inclusion/exclusion criteria's and outcome definition.

We have added a separate table 2 to explain the subtypes of all GI malignancies and number included in each of the four RCTs. This table also describes the data on resection of primary tumour provided in each trial or not.

Comment 8: SELECT-D trial: again, include total numbers of patients enrolled. Suggest include a short paragraph outlining any limitations for the SELECT-D and ADAM trial

Reply: Yes we have added these changes.

The total number of patients enrolled in SELECT-D trial were added in line 162-163.

The limitation of SELECT-D for example limited number of upper GI cancer patients and exclusion of patient after interim analysis is already in the text. The limitation of ADAM-VTE trial added in line 206-209

Comment 9: Line 229: "Apixaban needs to be avoided with strong dual CYP3A4/p-glycoprotein inducers but can be used at a reduced dose with dual Cyp 3A4/p-glycoprotein inhibitors: include an explanatory paragraph and references (eg for relevant guidelines).

Reply: We have added the reference for these line. Please see line 299, for Ref No 18.

O'Connell C, Escalante CP, Goldhaber SZ, McBane R, Connors JM, Raskob GE. Treatment of Cancer-Associated Venous Thromboembolism with Low-Molecular-Weight Heparin or Direct Oral Anticoagulants: Patient Selection, Controversies, and Caveats. The oncologist. 2021;26(1):e8-e16.

Comment 10: Line 232-235: the list is confusing, as it suggests that the cancer-specific P-gp inhibitors (including tyrosine kinase inhibitors) and immunomodulating agents should somehow be handled differently. Consider re-wording.
Reply: We have reworded these lines and the new lines are from line 300-305.

Reviewer B

The article addresses a very hot topic in this fields that I enjoyed reading. These are my comments after reading the text:

Comment 1: Title. May be the title should contain something about "bleeding risk in gastrointestinal cancers.....", which is the main concern in this review.
Reply: Please accept our apology we have not changed the title largely as this article also addresses the impact on DOACs efficacy and safety from drug-drug interaction and alteration in anatomy.

Comment 2: In the introduction, the objectives of the article could be stated clearer and earlier. Namely, the lack of detailed data on bleeding risk in gastrointestinal cancers treated with DOACs.
Reply: Yes please the line 88-91 informs about the lack of data about GI malignancies

Comment 3: Methods. There is no list of searching terms. There could be a list of the selected trials. If the review is made with the intention of helping clinicians, maybe other study designs other than RCTs should be included. Single-arm or observational studies could also provide useful information about safety profile, and is often more representative of the patient cohort the clinician will meet in their everyday work. Guidelines of ISTH and ASH could also have been reviewed.
Reply: We have included the search string and figure 1 and supplementary material provide the search strategies. We have included references for ISTH and ASH guidelines.

There is a comprehensive review on four large observational studies included as per the reviewer suggestions. There is a section on real world data from line 351- 383.

Comment 4: Line 113. Which RCTs? These are others studies than the ones included when you search for RCTs comparing DOACs to LMWH as stated in line 93?
Reply: We have only reviewed major RCTs done specifically for CAT, and have not included studies done for comparison of DOACs and LMWH where the population was not limited to CAT.

Comment 5: Discussion. It would be easier to digest the information given of the different trials if you could but the numbers into a table. For example numbers of the specific gastrointestinal cancer with major bleeding in each study in 1 line ect. The information given about the four trials is a bit heterogeneous and could be a bit more schematic, this would make it easier to compare and more easily spot differences between the studies. I see you have a table at the end comparing the trials. This could contain more specific information, and you could then reduce the text in the discussion.
Reply: Yes, we have made these changes.

We have added a separate table 2 to explain the subtypes of all GI malignancies and number included in each of the four RCTs. This table also describes the data on resection of primary tumour provided in each trial or not.

We removed the heterogeneity in the reported information for all four trials.
The written information on all trial follow a sequence :

1. Information on number of patient in text
2. Information on outcome in text
3. Inclusion and exclusion criteria in table 1
4. Types of GI cancer recruited in each study in table 2

Comment 6: In line 220 you state that CARRAVAGGIO had have very small number of upper gastrointestinal cancers, here a table with numbers of all upper gastrointestinal cancers in all the trials would be very interesting to see, and easy for the eye to quickly compare.
In line 240, you could also mention guidelines of ISTH and ASH for recommendations on gastrointestinal cancers.

Reply: As per the reviewer comment : Table 2 gives information on numbers of upper GI cancer included in CARAVAGGIO study.
The line 240 changes have been made and are now in line 315-319.

Comment 7: Line 247-271, this is a very interesting part of the article and could be elaborated more at the expense of the extensive description of the four trials earlier in the discussion.
Reply: We have made changes and elaborated the information on drug-drug interactions with new references from line 307-310 in the revised manuscript.

Comment 8: Table 1. Information about major bleeding and CRNMB for specific GI malignancies in the CARRAVAGGIO trial are now published here https://www.thieme-connect.com/products/ejournals/pdf/10.1055/s-0040-1720975.pdf.
Reply: Yes we have added this reference and information from this reference in the following lines (238-259).