16 January, 2017

Dear Prof Ma,

Manuscript Number: 31891

Title: Gastrointestinal bleeding in patients on novel oral anticoagulants: Risk, Prevention and Management.

Thank you for your letter concerning the revision of our manuscript. The manuscript has been revised according to the reviewers' comments. The changes have been highlighted in the manuscript for your reference. The followings are the point-by-point responses to the reviewers' comments.

We hope that the reviewers and editors will find this revised version acceptable for publication in the World Journal of Gastroenterology.

Yours sincerely,

Wai K. Leung

Editor's comments

1. Don't need blank space between reference number and the before words. Please check throughout.

We thank you for your comments. Changes have been made.

2. Concerning the language of the manuscript, we have asked for advice from our colleague who is a native English speaker.

Reviewers' Comments to Author

Reviewer no: 3633577

In this new class of oral anti-coagulants. This reviewer has concerns as listed below. Major manuscript, authors summarized current understandings regarding gastrointestinal bleeding in patients who administered concerns

1. Authors used "NOAC (Novel Oral Anti-Coagulants)" for anti-coagulants discussed in this review. However, this terminology has been argued recently and use of "DOAC" is recommended in literatures below. Barnes et al. J Thromb Haemost (JTH), 2015, 13, 1154-1156; Husted et al. JTH 2015, 13, 2130-2132; Barnes et al, JTH, 2015, 13, 2132-2133. This issue should be included and discussed in the present manuscript.

We thank you for your comments. Due to the controversial nomenclature of this class of drug, a new section has been added to address this issue with the suggested references added on page 5 lines 17-26.

2. Many review papers regarding gastrointestinal bleeding associated with anti-coagulant treatment have already been published (For example, Curr Opinion Gastroenterol, 2016, 32, 474-480). This reviewer suggests that authors expand Introduction section by adding statement regarding what is already argued about this topic in the previous reviews and what is newly added by this paper. This would be helpful for readers and significantly improves manuscript.

We thank you for your comments. The focus of our review has been added on page 5 lines 12 to 15.

Minor issues

1. Page 2 line 11, "lose" should be "dose"?

We thank you for your comments. Changes have been made on page 3 line 13

2. Page 4, line 21, “[Cl]” shoud be “[CrCl]”?

Changes have been made on page 6 line 11

3. Page 6 line 2, full name of NSAIDs should be given in the text.

Changes have been made on page 7 lines 19 and 20

4. Page 11, line 19, “creatinine clearance” should be “CrCl”.

Changes have been made on page 13 line 16

Reviewer no: 3650239

The authors' manuscript discusses the risk of GI bleeding in patients taking NOACs, and it also discusses strategies to prevent and treat such bleeding. This is highly topical and of great clinical interest at present.

1. In the abstract, you mention that NOACs are associated with an increased risk of bleeding. When discussing NOACs, we typically compare them to warfarin. This is because these patients generally have a good indication for anticoagulation, and withholding anticoagulation puts them at risk for serious adverse outcomes. As a class, NOACs generally have a lower risk for bleeding than warfarin. Additionally, it is obvious that NOACs have a higher bleeding risk than nothing at all (or placebo), and there are no anticoagulants or antiplatelet agents on the market that do not have an on-target effect of increasing bleeding risk. Therefore, this statement needs to be changed. I would also emphasize throughout the manuscript whether any increased risk is compared to warfarin or no therapy at all (which you do nicely in the conclusion). Additionally, the clear message should be that these patients have a very strong indication for anticoagulation in order to prevent serious outcomes. NOACs are becoming the standard of care and are generally safer than warfarin. Therefore, our goal as physicians should be to figure out how to safely administer them to patients and how to identify the small population of patients who truly should not use them.

We thank you for your comments. Changes have been made on page 3 lines 6 to 7 and line 10. In describing the risk of GIB of NOACs, in the RCT section, we have specified it the comparison is standard care (LMWH, vit K antagonist, antiplatelet therapy or placebo) according to that meta-analysis (Page 8 lines 16 to 17); for the section on observational studies, we have specified that it is ‘compared with warfarin’ (page 10 line 14).

We have emphasize the importance of preventing NOAC-associated bleeding by making the statement that 'prevention of GIB relies on first reviewing the indications of NOACs …' on page 13 line 12. We have newly added a sentence 'Reviewing the indications of NOAC and prescribing a particular NOAC on an individual basis is therefore of utmost importance' *in the conclusion section to highlight this important point on page 16 lines 14 to 16*

2. The dosing for these agents is quite complicated, especially since some require parenteral anticoagulation first and others can be initiated following several days of a "loading dose." It might be nice to include this either in Table 1 or in the text of the article.

We thank you for your comments. An additional table (Table 2) has been added on page 25 and 26 to summarize the dosing of various NOACs.

3. The pathogenesis of GI bleeding in the setting of anticoagulation is an interest topic. You briefly mention that they may inhibit GI mucosal healing, but I think it would be nice to expand this discussion.

Thank your for this comment. The statement came from the article by Desai et al, but no further explanation was provided in the article. We have searched for relevant literature on this but no further data were available.

4. The HAS-BLED tool performs well. However, clinically, it is not terribly useful because many of the factors that increase risk of thromboembolism also increase the risk of bleeding. Since you do not also include a table of the CHADS-Vasc score, this limitation should be acknowledged somewhere in the manuscript.

We have addressed this limitation on page 12 lines 18 to 21.

5. You mention that some have advocated for screening colonoscopies prior to NOAC initiation. This is not recommended in the ACC/AHA or CHEST guidelines, and it would almost certainly not be reimbursed by many insurers. You need to acknowledge that it is not standard of care.

We have addressed this on page 14 lines 3 to 6.

Reviewer no: 3633629

The present review is well written and complete: it does provide an interesting overview on NOAC-associated gastrointestinal (GI) bleeding.

1. MAJOR COMMENTS - 'Specific management of patients taking NOACs who present with overt GIB involves cessation of the drug, reversing anticoagulation, dialysis and endoscopic management' (page 12): this statement is not completely correct. Only patients with major bleeding events should receive a reversal agent.

We thank you for your comments. We have add the phrase ‘ non-major GIB’, and removed ‘reversing anticoagulation’ on page 14 line 10 to 11

2. Furthermore, several statements contained in this paragraph are imprecise. Please, refer to i.e. 10.1160/TH16-05-0363 for details. - Data from interventional trials indicate that the risk of thromboembolism after PCC administration is comparable to that following FFP use (10.1111/acem.12911.), while PCC administered to healthy volunteers are associated with no thromboembolic events (10.1111/bjh.13821). In absolute numbers, the recent trials on specific NOAC antidotes showed much higher rates of thromboembolic complications (approx. 18%) than what observed in PCC studies (approx 8% at 90 dd, approx 2NOAC% at 7 dd from PCC infusion). - Please, implement the iconografic material.

We thank you for your comments. The comparison of thromboembolic risks between PCCs and plasma has been included on page 15 lines 1 to 4; the risks of thromboembolism of the specific antidotes have been included on page 15 lines 22 to 25.

3. A central figure summarizing the main factors involved in the pathogenesis of NOAC-associated GI bleeding would be greatly appreciated by the readers.

We thank you for your comments. A table has been added on page 29 to explain the main factors involved in the pathogenesis

MINOR COMMENTS

4. - Consider mentioning the different dosage approval of many NOACs between North America and Europe (i.e. the availability in Europe, but not in the US, of the reduced-dose rivaroxaban 15 mg qd for VTE treatment, as well as the different cutoffs for renal function contraindicating its prescription [eGRF 30 vs 15 ml/min]). Since no reviews focused on this aspect, it would be of interest for a potential reader to see what the differences are between North America, Europe, and Asia in terms of eligibility for single-NOAC treatments for each indication.

We thank you for your comments. We have added a new table on Pages 25 and 26 to deliver this important information

5. - Would GI bleeding have an impact on occult cancer diagnosis? Consider mentioning i.e. DOI: 10.3109/07853890.2014.952327.

We thank you for your comments. We have included this message on page 14 lines 5 to 6.

6. - I would reformulate the last sentence of the introduction as follows ′there is still concern on the risk of gastrointestinal bleeding′, since multiple meta-analyses and phase IV studies have confirmed the favourable safety profile of NOACs.

*We thank you for your comments. We have rephrased this sentence as '*Although the NOACs have been shown to have favorable safety profile from multiple meta-analyses and phase IV studies, the risk of bleeding, particularly gastrointestinal bleeding (GIB), is still a concern in high-risk patients' *on page 5 lines 9 to 11.*