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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
ESPS manuscript NO: 31891
Title: Gastrointestinal bleeding in patients on novel oral anticoagulants: Risk, prevention and management
Reviewer's code: 03633629
Reviewer's country: Netherlands
Science editor: Jing Yu
Date sent for review: 2016-12-14 10:53
Date reviewed: 2016-12-16 00:35

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[Y] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[Y] Minor revision
[ ] Grade E: Poor		[Y] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

The present review is well written and complete: it does provide an interesting overview on NOAC-associated gastrointestinal (GI) bleeding. 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. 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 2% at 7 dd from PCC infusion). - Please, implement the iconografic material. A central figures summarizing the main factors involved in the

pathogenesis of NOAC-associated GI bleeding would be greatly appreciated by the readers. MINOR COMMENTS - 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. - Would GI bleeding have an impact on occult cancer diagnosis? Consider mentioning i.e. DOI: 10.3109/07853890.2014.952327. - 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.

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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[Y] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[Y] Minor revision
[ ] Grade E: Poor		[Y] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

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. 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. 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. 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. 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.

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ESPS PEER-REVIEW REPORT

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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	Google Search:	[ ] Accept
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		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

In this manuscript, authors summarized current understandings regarding gastrointestinal bleeding in patients who administered new class of oral anti-coagulants. This reviewer has concerns as listed below. Major 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. 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. Minor issues 1. Page 2 line 11, "lose" should be "dose"? 2. Page 4, line 21, "[Cl]" shoud be "[CrCl]"? 3. Page 6 line 2, full name of NSAIDs should be given in the text. 4. Page 11,

line 19, “creatinine clearance” should be “CrCl”.