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PEER-REVIEW REPORT

Name of journal: World Journal of Clinical Cases

Manuscript NO: 41072

Title: Impact of an acute hemodynamic response-guided protocol for primary prophylaxis of variceal bleeding

Reviewer's code: 03024207

Reviewer's country: China

Science editor: Ruo-Yu Ma

Date sent for review: 2018-07-23

Date reviewed: 2018-08-01

Review time: 9 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	[ ] Accept (High priority)	Peer-Review:
[ ] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] Accept (General priority)	[Y] Anonymous
[Y] Grade C: Good	[ ] Grade C: A great deal of language polishing	[Y] Minor revision	[ ] Onymous
[ ] Grade D: Fair	[ ] Grade D: Rejection	[ ] Major revision	Peer-reviewer's expertise on the topic of the manuscript:
[ ] Grade E: Do not publish		[ ] Rejection	[Y] Advanced
			[ ] General
			[ ] No expertise
			Conflicts-of-Interest:
			[ ] Yes
			[Y] No

SPECIFIC COMMENTS TO AUTHORS

Recommendation: minor revisions. The manuscript entitled "Impact of an acute hemodynamic response-guided protocol for primary prophylaxis of variceal bleeding" by Fortea et al describes that an acute hemodynamic response-guided protocol in which

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acute responders received traditional non-selective betablockers (NSBB) and acute non-responders received carvedilol. This is an interesting study, in which they demonstrated that the acute hemodynamic response-guided protocol improves the clinical outcome of non-responders for primary prophylaxis of variceal bleeding in real clinical practice. The manuscript is also well written. However, there are still some important issues should be considered and addressed. 1.The authors concluded "carvedilol improved the long-term outcome of acute non-responders, presumably by its greater effects on reducing portal pressure, and should be the preferred choice over NSBB for primary prophylaxis of variceal bleeding when hemodynamic testing is not available". However, it seems carvedilol's greater effects on reducing portal pressure haven't been fully validated in the results. Furthermore, could this study claim that carvedilol should be the preferred choice? 2.Paragraph 2 in "Introduction" "the role of the acute hemodynamic response to guide therapy has never been assessed in the setting of primary prophylaxis of variceal bleeding". In fact, ref.6 was just about this. 3.Hemodynamic measurements:"a Swan-Ganz catheter into the pulmonary artery under fluoroscopic guidance". Is this needed in HVPG measurement? 4.In the result chronic hemodynamic response: "...had a second hemodynamic study performed after 26.3 (12.8) and 28.0 (18.8)[] weeks, respectively" What does 26.3(12.8) mean?

INITIAL REVIEW OF THE MANUSCRIPT

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PEER-REVIEW REPORT

Name of journal: World Journal of Clinical Cases

Manuscript NO: 41072

Title: Impact of an acute hemodynamic response-guided protocol for primary prophylaxis of variceal bleeding

Reviewer's code: 02920064

Reviewer's country: Japan

Science editor: Ruo-Yu Ma

Date sent for review: 2018-08-14

Date reviewed: 2018-08-17

Review time: 3 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	[ ] Accept (High priority)	Peer-Review:
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] Accept (General priority)	[Y] Anonymous
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Minor revision	[ ] Onymous
[Y] Grade D: Fair	[ ] Grade D: Rejection	[Y] Major revision	Peer-reviewer's expertise on the topic of the manuscript:
[ ] Grade E: Do not publish		[ ] Rejection	[Y] Advanced
			[ ] General
			[ ] No expertise
			Conflicts-of-Interest:
			[ ] Yes
			[Y] No

SPECIFIC COMMENTS TO AUTHORS

Comment to the authors This paper was written about the non-inferiority of carvedilol to NSBB. I can agree the importance of this paper, but this manuscript has serious point to be revised. For the demonstration of non-inferiority trial (or study), the

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setting of required sample size is very important. If the sample size is too small, any comparison between two groups does not have significant difference. Therefore, I am worried about if the rightness of your sample size was guaranteed. [Major points] 1. The setting of required sample size is very important. Please mention the way to lead the size. If the sample size is too small, any comparison between two groups does not have significant difference. As a trial, I have calculated the required sample size by using the 2-years decompensation rate result (13.7 % and 20%, Figure 3A)(the setting as alfa-error of 0.05, power of 0.8), and the results was 938 patients. If the 2-years further decompensations (26.1% and 50.0%, Figure 3B) was set, the required size was 144 patients. 2. Control group without takin any drug (neither NSBB nor carvedilol) is necessary for the comparison of NSBB or carvedilol group. Please add this control group. 3. The authors mentioned (p14, lines 10), "The 2-year actuarial probability of variceal bleeding was 2.0% and 16.3%; this complication occurred in 2 patients in the traditional NSBB group and in 3 patients in the Carvedilol group (p=0.078)." This result is very important. Please add in the table 3. I think NSBB is more useful for preventing variceal bleeding from this result, even if the p value was 0.078. Please consider about this result in the discussion. If more patients were enrolled, there may be significant difference. 4. In the last sentence of Introduction section, the authors mentioned the aim of this study, but it is different from the description of primary endpoint. Please revise this sentence. 5. In the abstract, there is the word as 'non-responders received carvedilol.' This word is very confusing for WJG readers, because we can not find the target of non-responders. This word may cause misunderstanding as 'non-responder to carvedilol.' I think that some sentences describing non-responder in Core tip should be moved to abstract section. 6. In result part of the abstract, the result of primary endpoint should be described at first. The sentence (p4, lines 11), "No clinical, laboratory, endoscopic or hemodynamic parameter predicted the acute hemodynamic response." is not so

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important for your manuscript. 7. The limitation should be described more in detailed.

INITIAL REVIEW OF THE MANUSCRIPT

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PEER-REVIEW REPORT

Name of journal: World Journal of Clinical Cases

Manuscript NO: 41072

Title: Impact of an acute hemodynamic response-guided protocol for primary prophylaxis of variceal bleeding

Reviewer's code: 00182114

Reviewer's country: Japan

Science editor: Ruo-Yu Ma

Date sent for review: 2018-08-14

Date reviewed: 2018-08-21

Review time: 7 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection	Peer-Review: [Y] Anonymous [ ] Onymous Peer-reviewer's expertise on the topic of the manuscript: [ ] Advanced [Y] General [ ] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

According to auther's paper ,Carvedilol leads to a significantly greater decrease in HVPG than propranolol. Using carvedilol for primary prophylaxis a substantial proportion of nonresponders to propranolol can achieve a haemodynamic response,

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which is associated with improved outcome with regard to prevention of variceal bleeding, hepatic decompensation and death. Carvedilol is effective in a substantial proportion of patients who did not achieve a haemodynamic response to propranolol I ask some questions to author. 1.I think Carvedilol prevent the frequency of variceal bleeding due to decrease in HVPG. Please tell me the etiology why Carvedilol prevent hepatic decompensation. 2. Carvedilol may cause arterial hypotension and worsen renal function potentially compromising its beneficial effect in the long term. Please comment renal function in Carvedilol. 3.I think Higher doses of carvedilol (>12.5 mg/day) may not further decrease portal pressure, while increasing the risk of arterial hypotension and bradycardia. Therefore, comment about higher dose of carvedilol.

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