

PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 64311

Title: Does endoscopic intervention prevent subsequent GI bleeding in patients with left ventricular assist devices? A retrospective study

Reviewer's code: 03478404

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Associate Professor

Reviewer's Country/Territory: Romania

Author's Country/Territory: United States

Manuscript submission date: 2021-02-14

Reviewer chosen by: Jia-Ping Yan

Reviewer accepted review: 2021-02-16 07:41

Reviewer performed review: 2021-02-17 17:30

Review time: 1 Day and 9 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

In this manuscript, the authors showed, after an in-deep analysis of 295 patients with LVAD and 238 hospital encounters, that a high proportion of gastrointestinal bleeding stopped without endoscopic therapy and that endoscopic intervention did not prevent subsequent bleeding. Even given the retrospective nature of the study, the overall findings appear very useful for practice and they prompt for prospective studies on this topic. The manuscript is written in an elegant manner, easily to be followed. The overall structure is respected and paragraphs are written in detail. There is a plethora of results in this manuscript, which should be emphasized. Comments/suggestions: 1. Title: I would suggest replacing “review” by “study”, as it was a study and not a review.

2. Since this is the first study (powered enough) to evaluate whether endoscopic intervention reduces the risk for subsequent GIB or not, it should be mentioned both in the Abstract and Core tip, to emphasize the importance and impact of the research. 3. Abstract: Please remove “using multivariate logistic regression” from “Aims” and add it to Methods. Also, the authors could include here all secondary aims of the study (i.e. – “describe GIB presentations and sources identified, and determine risk factors for recurrent GIB”), as they included the frequency of GIB (and this is also a secondary aim). Results could also include ALL the corresponding findings, which are of interest. I would suggest correcting “other overt causes (21.4%)”, when describing “presentation of GIB”, as this is not about causes, but about type of bleeding (besides mentioned melena and occult bleeding). Sources of bleeding could be inserted, as written above, as well as risk factors for recurrent GIB. 4. Materials and Methods: Study population – please mention the place where the study was performed (not only “at our large academic institution”); please state clearly that 319 patients were found with LVADs (or with other VAD too). Please describe BIVAD, before using the abbreviation. Instead of writing

“type of LVAD implantation”, the authors should mention “type of device implantation” (as there were also BiVAD and other types of interventions etc). In “Independent (exposure) and dependent (outcome) variables” – please write “For the secondary aims...”, as they were three. 5. Results start with the “Frequency of GIB in patients with LVADs” paragraph. Although this has perfect logic, this is not the primary aim. Please rephrase and re-arrange according to the Aims. Please mention in detail what you mean by “other overt causes (21.4%)” - page 8 (this should not be about causes, but type of bleeding) - how many with hematemesis, hematochezia etc? Please rephrase “Three patients expired during active GIB”. Table 1 – please insert after “sex” – Male. From Table 1, it would be important to mention in the main text - the significant difference of LVAD exposure (days) (IQR). The source of bleeding was detected in only 54.6% encounters, which is pretty low, given that “the median number of endoscopic procedures done per encounter was 2” and maximum 8, but the authors nicely addressed this issue in Discussion. Table 2 : Please delete « Sum of percentages is greater than 100% as some procedures involved multiple interventions. », as it is repeated twice. Also, please describe here more about “non-specific oozing” and “others”. Please also double check: in the main text is written: “An endoscopic intervention was performed in 34.8% (71/204) of encounters”, while Table 2 contains 72 lesions (if too lesions in 1 encounter, please mention). With endoscopic procedures, it is clear. Also, please correct the following: “Of 22 cases of recurrent bleeding when the prior GIB source was deep small bowel, the current source was also in the small bowel in 18; the other 4 encounters sourced the bleed in the duodenum.” since duodenum is also small bowel; please insert “deep” before small bowel above. Table 3 has to be corrected – “Had a subsequent GIB” = 97, and not the other way around. Otherwise, both columns are wrong. Please revise the entire Table. 6. Discussion paragraph is scientifically well addressed, including the limitations of the study. Reference about Welden et al is



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missing – page 14 – please insert: “Welden CV, Truss W, McGwin G, Weber F, Peter S. Clinical Predictors for Repeat Hospitalizations in Left Ventricular Assist Device (LVAD) Patients With Gastrointestinal Bleeding. *Gastroenterology Res.* 2018 ;11(2):100-105. doi: 10.14740/gr972w. PMID: 29707076. 7. Minor revision of the English language is required (grammar [verb use, concordance], syntax and punctuation - missing commas etc). 8. There are no « Conflict-of-Interest Disclosure Form » and « Copyright License Agreement ». Contribution of the Authors is not written. There are no ORCID numbers of the other authors, except for the Corresponding Author. Please insert. 9. The manuscript is not written according to the requested format of the WJG, including references. Please correct. 10. STROBE statement was not checked (page number not inserted), just added as a file.

PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 64311

Title: Does endoscopic intervention prevent subsequent GI bleeding in patients with left ventricular assist devices? A retrospective study

Reviewer's code: 03486791

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: China

Author's Country/Territory: United States

Manuscript submission date: 2021-02-14

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-02-18 09:55

Reviewer performed review: 2021-02-18 12:29

Review time: 2 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

This is an interesting topic.

PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 64311

Title: Does endoscopic intervention prevent subsequent GI bleeding in patients with left ventricular assist devices? A retrospective study

Reviewer's code: 05382551

Position: Editorial Board

Academic degree: PhD

Professional title: Associate Professor

Reviewer's Country/Territory: Spain

Author's Country/Territory: United States

Manuscript submission date: 2021-02-14

Reviewer chosen by: Jia-Ping Yan

Reviewer accepted review: 2021-02-18 09:41

Reviewer performed review: 2021-02-18 22:39

Review time: 12 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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SPECIFIC COMMENTS TO AUTHORS

The authors present a study on the association between endoscopic intervention and subsequent gastrointestinal bleeding using multivariate logistic regression. The article is well written and structured. The subject described is within the scope of the journal. His reading is fluent. The results presented constitute an important advance in the study area.

PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 64311

Title: Does endoscopic intervention prevent subsequent GI bleeding in patients with left ventricular assist devices? A retrospective study

Reviewer's code: 05230210

Position: Editorial Board

Academic degree: MD

Professional title: Associate Professor

Reviewer's Country/Territory: Egypt

Author's Country/Territory: United States

Manuscript submission date: 2021-02-14

Reviewer chosen by: Jia-Ping Yan

Reviewer accepted review: 2021-02-16 08:50

Reviewer performed review: 2021-02-21 09:05

Review time: 5 Days

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input checked="" type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input type="checkbox"/> Anonymous <input checked="" type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

I would like to thank the authors for their important work. Notes on the manuscript are highlighted

- Title: could the authors add BIVAD?
- Abstract: why not present data in Hazards ratio or Risk ratio?, Instead of odds ratio.
- Introduction: References for bleeding with LVAD could add the following: Baumann Kreuziger LM. Management of anticoagulation and antiplatelet therapy in patients with left ventricular assist devices. J Thromb Thrombolysis. 2015 Apr;39(3):337-44. doi: 10.1007/s11239-014-1162-6. PMID: 25549823
- Study population: 1- If you included BIVAD what is the percentage of patients? And why not mentioned in the title/abstract?

2- "We excluded patients with temporary devices implanted (CentriMag, Thor BIVAD, Total Artificial Heart), leaving a total of 295 patients.">> so why not mention this in the abstract, that your included patients were permanently using the LVD.

3- The authors mentioned: "VAD implantation until death," >>so why Kaplan Meier curve was not done, along with survival analysis?

4- The authors stated that: "We classified the GIB presentation as overt versus occult". >>Could the authors clarify if they did tests for occult bleeding, or other lab assessment, and how they dealt with the issue that most tests will get false positive with anti-platelets as aspirin?

5- the authors state "All encounters with procedures for non-bleeding related indications or iatrogenic bleeding were excluded from analysis." >>>Could the authors explore on that part?, as most of the GIB in LVAD is related to the anti-coagulation, and anti-platelet medications the patients receive as a protective measure from thrombosis.

6- "power calculation:" this is a post hoc power calculation, and in my humble opinion this calculation carry a little value and better omitted, since this is a retrospective study and there is a debate about the usefulness in this case. Added to this; it is mainly used for comparison between two independent groups, and this is a one group cohort (LVAD patients) there is no control

group. Reference: Zhang Y, Hedo R, Rivera A, et al. Post hoc power analysis: is it an informative and meaningful analysis?. *General Psychiatry* 2019;32:e100069. doi: 10.1136/gpsych-2019-100069 • Results: 1- there is no mention of octreotide or PPI use, as a control measure especially for patients who had delay in their endoscopic procedure for up to five days, and if these medical treatments ameliorated their condition or not. Also, no relation is mentioned between the type of medical intervention received and the time of stopping of bleeding? ref: Molina TL, Krisl JC, Donahue KR, Varnado S. Gastrointestinal Bleeding in Left Ventricular Assist Device: Octreotide and Other Treatment Modalities. *ASAIO J.* 2018 Jul/Aug;64(4):433-439. doi: 10.1097/MAT.0000000000000758. PMID: 29406356. 2-could you replace "expired">> with "died" • Discussion: 1- Why no medical measures was discussed as preventive measure for subsequent episodes? eg. mucosal coating medications as local measures to stop bleeding (sucralfate, antacids), PPI and H2 blockers, octreotide, etc. 2- the authors recommend " we propose that the VCE be performed urgently in the acute setting while awaiting normalization of the INR, and possible endoscopy.">> but could this be of benefit , if the patient is bleeding, which could mask the visualization of the lesion by digested or coagulated blood that attaches to the lens, best scenario will be 50% yield? and also cost effectiveness, please discuss. ref: Nadler M, Eliakim R. The role of capsule endoscopy in acute gastrointestinal bleeding. *Therap Adv Gastroenterol.* 2014 Mar;7(2):87-92. doi: 10.1177/1756283X13504727. PMID: 24587821; PMCID: PMC3903085.

3- The recommendation of the authors could be modified to >> prohibit "secondary diagnostic" endoscopic procedures, not primary (as diagnosis is important in the first episode). 4- Another recommendation that the authors could discuss, if most of the lesions are angiodysplasia, would a baseline capsule endoscopy before or synchronously with the LVAD insertion be of prognostic benefit for those patients? • Tables and figures: 1. It would be better if the type of analysis is mentioned at the table title (eg

logistic regression, spearman correlation, etc). 2. It is recommended to add a figure representing the survival or time to surgery in the cohort studied.

PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 64311

Title: Does endoscopic intervention prevent subsequent GI bleeding in patients with left ventricular assist devices? A retrospective study

Reviewer's code: 05194798

Position: Editorial Board

Academic degree: MD

Professional title: Director

Reviewer's Country/Territory: Japan

Author's Country/Territory: United States

Manuscript submission date: 2021-02-14

Reviewer chosen by: Jia-Ping Yan

Reviewer accepted review: 2021-02-16 07:26

Reviewer performed review: 2021-02-22 07:30

Review time: 6 Days

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

This manuscript is a retrospective cohort study that evaluated an association between endoscopic intervention and subsequent gastrointestinal bleeding (GIB) in patients with left ventricular assist devices (LVAD) using multivariate logistic regression. The authors found that GIB resolved on its own by discharge in 70% of all 235 encounters, while recurrent GIB occurred in the majority of patients. Furthermore, the authors showed that endoscopic interventions did not significantly decrease the odds of subsequent GIB in patients with LVAD. This study was conducted well, and the methods are appropriate. The topic of this study was unique and interesting, and the results will be of interest to clinicians in the field. However, the following major and minor issues require clarification: Major 1. In some guidelines for obscure GI bleeding, a high-resolution contrast-enhanced CT scan is recommended as the first step in the diagnosis of a patient to detect abnormalities in the intramural and extramural structures as well as extra-intestinal lesions. The authors should include the indication and the data of CT scan, and discuss the availability of CT scan as well. 2. The authors should also evaluate factors associated with rebleeding, based on general condition, underlying cardiac disease, and cardiac function. Minor 1. Please describe possible causal relationship between LVADs and GI bleeding in Introduction section. 2. (P8L19) Please describe other overt causes in more detail. 3. (P8L20) Please add the range of hemoglobin level. 4. (P10L7) Why was the total number of encounters which the source was identified in not 9 but 10? 5. (P15L8-9) The authors should correct this sentence as “no significant difference” doesn’t necessarily mean “same as”. 6. I recommend the authors also investigate the association between rebleeding and proton pump inhibitor administration for prevention of upper GI bleeding. 7. (Table 2) The authors should show the data of “culprit lesion”, followed by those of “type of intervention”. 8.



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Please use flowcharts for overviewing the flow of the patients.

RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 64311

Title: Does endoscopic intervention prevent subsequent GI bleeding in patients with left ventricular assist devices? A retrospective study

Reviewer's code: 05194798

Position: Editorial Board

Academic degree: MD

Professional title: Director

Reviewer's Country/Territory: Japan

Author's Country/Territory: United States

Manuscript submission date: 2021-02-14

Reviewer chosen by: Man Liu

Reviewer accepted review: 2021-04-21 20:40

Reviewer performed review: 2021-04-22 10:38

Review time: 13 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS



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My review comments has not been reflected to the revised manuscript.

RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 64311

Title: Does endoscopic intervention prevent subsequent GI bleeding in patients with left ventricular assist devices? A retrospective study

Reviewer's code: 03478404

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Associate Professor

Reviewer's Country/Territory: Romania

Author's Country/Territory: United States

Manuscript submission date: 2021-02-14

Reviewer chosen by: Man Liu

Reviewer accepted review: 2021-04-21 16:53

Reviewer performed review: 2021-04-22 17:45

Review time: 1 Day

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS



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I attentively and carefully read the “Answering Reviewers” file. The authors chose to agree with only some of the suggestions. Many suggested changes were not performed. In any case, they wrote “We have addressed the recommendations with changes in the text marked through “track changes””. However, there is no modified text with “Track Changes” provided. They said they modified the Tables, but there is no Table to review. Disclosures and Conflict of Interest form – still not in the appropriate form. STROBE statement: page number still not inserted, just mentioned “completed”.