Dear editors and reviewers,

Thank you very much for reviewing our article and offering your edits. We have addressed the recommendations with changes in the text marked through “track changes” and detail our responses in the below point-by-point summary. We have now also added revisions in response to Reviewer 3, which were unfortunately not accessed prior to the last revision due to email logistics. Apologies for the confusion.

Thank you again for considering our revised manuscript.

Reviewer #1: I would like to thank the authors for their important work. Notes on the manuscript are highlighted

Title: could the authors add BIVAD?

We had originally done an analysis that included patients with BIVADs but ultimately decided to exclude these patients as it was a small number and the devices were also removed within a short time. All of the analyses are on patients with an LVAD and the text has been updated to remove the reference to BIVAD implantation.

[grouped from separate comments] **Why not present data in Hazards ratio or Risk ratio?, Instead of odds ratio. The authors mentioned:" VAD implantation until death," >>so why Kaplan Meier curve was not done, along with survival analysis? It is recommended to add a figure representing the survival or time to surgery in the cohort studied.**

Since our primary outcome was the presence of rebleeding (at any time point), multivariate logistic regression was utilized in order to account for cumulative incidence. Our intention was to look at the presence of rebleeding, not necessarily focus on the time to rebleed.

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

Thank you for the suggestion; this reference has been added to the discussion.

If you included BIVAD what is the percentage of patients? And why not mentioned in the title/abstract? "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.

Patients with BIVAD were not included and the text is updated to reflect this.

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?

Thank you for bringing our attention to the lack of definition. We have defined in these terms in the Methods as follows: “overt indicated bloody output from the GI tract (ie hematemesis, hematochezia,

melena, coffee-ground emesis), and occult indicated no bloody output visualized but the presence of a hemoglobin drop with no other known etiology."

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.

Thank you very much for this suggestion. We have added that exclusion from iatrogenic bleeding specifically refers to scenarios when the bleeding was from prior endoscopic procedures.

"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

We appreciate the point and thoughtful discussion. In this scenario, the intention was to compare those with intervention versus those without. Interestingly, another reviewer suggested highlighting the power calculation. Out of respect and consideration for both comments, we have decided to maintain the text as is, so to not overly emphasize or underemphasize its value in this study.

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. 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.

We appreciate the suggestions and role of medical management. While we did not assess the role of PPI or octreotide in the days prior to procedure, we have included text in the methods our institutional protocol for acid suppression therapy, as well as octreotide which is not routinely given unless variceal bleeding is suspected. Our primary goal was to look at the benefit of endoscopic therapy on bleeding during subsequent outpatient or inpatient encounters, rather than the benefit of endoscopic therapy during a hospitalization, and institutional protocols dictate medical management across hospitalizations.

Could you replace "expired">> with "died"

We made this edit.

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.

We agree this proposal deserves further study and evaluation and have now indicated such in the text. We also added another reference that suggests a role of early VCE for source localization in GIB.

The recommendation of the authors could be modified to >> prohibit "secondary diagnostic" endoscopic procedures, not primary (as diagnosis is important in the first episode).

We have clarified how the VCE may be useful especially when prior endoscopy evaluation has been performed.

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?

This is an interesting thought. Since many of the angiodysplasias arise in the presence of an LVAD, it is unclear if there would be benefit to performing VCE prior to implantation. Since our data did not directly address this, we have refrained from posing this recommendation, but agree that it warrants further study.

It would be better if the type of analysis is mentioned at the table title (eg logistic regression, spearman correlation, etc).

The tables include a combination of paired t test, Wilcoxon rank-sum test, Fisher's exact test, based on the nature of the data being continuous or categorical. This has been added to the table.

Reviewer #2: 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:

Title: I would suggest replacing "review" by "study", as it was a study and not a review.

We appreciate the suggestion and have updated the title accordingly.

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.

We appreciate the suggestion. Another reviewer suggested removing the power calculation. Out of respect for both comments, we have decided to maintain the text as is, so to not over emphasize or underemphasize its value in this study.

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. Sources of bleeding could be inserted, as written above, as well as risk factors for recurrent GIB.

We adjusted the aims as suggested. We opted to keep the results section of the abstract as written given limitations due to journal specifications.

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.

The journal had requested all removal of identifying information, but we would be happy to detail the place of study if/when the manuscript is accepted and if allowed. We had excluded patients with BiVADs in analysis and have updated the text to accurately reflect this. We have fixed the text to "aims" as noted.

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.

Thank you for this recommendation. Although we do not start with the primary aim, we think that this organizational structure allows for the most logical lead into the primary aim.

[grouped from separate comments] **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). 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?**

We corrected "overt causes" to "overt GIB." The "other overt causes" are now detailed in the results section.

Please rephrase "Three patients expired during active GIB".

The word expired has been replaced by "died."

Table 1 – please insert after "sex" – Male.

This has been added.

From Table 1, it would be important to mention in the main text - the significant difference of LVAD exposure (days) (IQR).

This difference is now mentioned in the main text.

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".

The repeat text has been removed. The body of the text describes the "non-specific oozing" with a little more clarification.

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.

The table text now explains how one encounter had two lesions. The word "deep" was also added as appropriately suggested.

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.

The table is accurate in that there were 97 encounters with no subsequent GIB and 141 encounters with subsequent GIB. Thank you for helping us realize that the patient characteristics did not belong in this table. The patient characteristics have been removed and the text has been updated.

Discussion paragraph is scientifically well addressed, including the limitations of the study. Reference about Welden et al is 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.

Thank you for bringing to our attention. The reference has been added.

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.

This is now all attached and available for review within the submission.

Reviewer #3:

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.

CT scans are readily available but not part of the guidelines at our institution for obscure GI bleeding. We have clarified in the main text now that "radiologic studies like CT are performed at the discretion of the cardiology team."

2. The authors should also evaluate factors associated with rebleeding, based on general condition, underlying cardiac disease, and cardiac function.

We appreciate the suggestion. Based on the data available, we represented cardiac factors of type of LVAD, LVAD purpose and LVAD exposure in days, but acknowledge the limitation and have now added this to the discussion.

Minor 1. Please describe possible causal relationship between LVADs and GI bleeding in Introduction section.

We have added a reference and brief explanation in the introduction.

2. (P8L19) Please describe other overt causes in more detail.

This is now added per above.

3. (P8L20) Please add the range of hemoglobin level.

We have added the IQR.

4. (P10L7) Why was the total number of encounters which the source was identified in not 9 but 10?

Thank you for this astute observation. There was a typo in that angioectasias were in 8 encounters and not 7 (totaling to the 10 listed). This has been corrected in the text.

5. (P15L8-9) The authors should correct this sentence as "no significant difference" doesn't necessarily mean "same as".

This has been corrected as suggested.

6. I recommend the authors also investigate the association between rebleeding and proton pump inhibitor administration for prevention of upper GI bleeding.

We tried to address per the comments above.

7. (Table 2) The authors should show the data of "culprit lesion", followed by those of "type of intervention".

This is a good idea and was attempted in response to this suggestion. We found that the resulting table was a bit hard to read, especially if it included both raw numbers and percentages, especially since the sum of percentages is greater than 100% due to some procedures involving multiple interventions. We

hope the readers find that the current table adequately shows the frequency of the different culprit lesions and the types of intervention.

8. Please use flowcharts for overviewing the flow of the patients.

For our cohort, there were no patients with missing data or loss to follow up but we detail how 120 patients were followed for less than 1 year due to death, device explantation, or heart transplantation. While we agree with the utility of a flowchart, we do not think it adds clarity int his particular manuscript, but are willing to reassess if there is a particular aspect that the reviewer thinks would be helpful to put in to a flowchart.

RE-REVIEW

Author:
unfortunately faced a few logistical hurdles in this resubmission: I could not find a way to attach the "track changes" version of the manuscript (I put it as a supplemental file but then it seemed to be removed), and I could not download the DCI form from the website. Would you be able to send me the correct form? I can resubmit prior to any other review so to not delay the process further.

Reviewer:
Thank you for your e-mail. I perfectly understand that the authors did not receive some messages. Since January 2021, I never received any message from the BPG to review a manuscript (therefore I look almost everyday on f6publishing.com to see if there is a manuscript for me to review). Moreover, I did not receive the acknowledgement message that I performed a review. I reviewed many papers, but there was no message from the BPG. Something must have happened. Maybe I am not anymore on the list. I contacted the Help Desk with this problem, but it was not solved. Therefore, I understand the problem of the authors. Thank you for sending the whole manuscript with corrections. I see that the authors agreed with some recommended changes, but not with all. Even though, I consider that their opinion has to be respected too and I agree with this version. I did only some minor changes of the English language (in the attached file). Best wishes and kind regards

Author:
Thank you so much for your understanding, and also for your detailed review. I accepted your edits and have attached the corrected, clean version. Thanks again!