Dear Editors and Reviewers,

Thank you for taking the time to review our manuscript. We appreciate your insightful comments and are grateful for the opportunity to improve our work. Our point-by-point response is provided below.

Comments to the Editor

We attempted to adhere to all of the formatting requirements for the manuscript as outlined in the instructions that were provided. However, we created Figure 1 using a separate software (not Microsoft PowerPoint), and thus parts of the figure are not editable. Please let us know if this will be sufficient. If an editable format is required, we can readily provide access to the software used (available online) along with the figure file so that changes can be made.

Comments to Reviewer 1

1. You have to precise in the section materials and methods, the definition of large volume of epinephrine.

    Response: We have added the following sentence: "Epinephrine volume was categorized as follows: small (up to 5 mL), moderate (more than 5 mL but less than 10 mL), or large (10 mL or more)."

    We would like to specifically note that we did not specify 20 mL as the upper limit for the large-volume group in the above statement because we did not have this information prior to data collection. In our results, it became evident that 20 mL was the maximum volume used in our cohort.

2. The number of patients who received large volumes (only 18) is very small to be able to draw conclusions.

    Response: Yes, we agree that the number of patients who received large-volume injections is rather small. This was included as a limitation in our discussion on two separate occasions:

"The majority of the patients in our cohort also received epinephrine injections of 1 to 5 mL, which is markedly less than the average volume (6 to 21 mL) reported in prior prospective combination therapy studies that included Forrest class Ia, Ib, and IIa ulcers."

"Only 18 patients received 10 or more mL of epinephrine, and the maximum volume used was 20 mL (one individual). Therefore, the impact of volumes greater than 10-20 mL in patients treated with combination therapy remains unclear."

3. Other important factors were not studied as: duodenal ulcer location and vitamin K overdose.

Response: We have additional information relating to anticoagulation and ulcer location available as follows: 6 patients on warfarin had supratherapeutic INR values > 3 (range 3.5 to 6.4). Because this was uncommon, we did not specifically discuss this in the manuscript aside from denoting which patients received anticoagulation. In terms of ulcer location: 8 were in the gastric cardia, 7 in the gastric fundus, 23 in the gastric body, 1 (1%) in the gastric incisura, 15 in the gastric antrum, 57 in the first portion of the duodenum, 20 in the second portion of the duodenum, and 1 in the third portion of the duodenum.

We have modified the results section to better characterize the endoscopic findings as follows: "Endoscopy occurred at a mean time of 29 hours (standard deviation 29 hours, range 1-199 hours). Ulcers were present in the following locations: 8 (6%) in the gastric cardia, 7 (5%) in the gastric fundus, 23 (17%) in the gastric body, 1 (1%) in the gastric incisura, 15 (11%) in the gastric antrum, 57 (43%) in the first portion of the duodenum, 20 (15%) in the second portion of the duodenum, and 1 (1%) in the third portion of the duodenum. Ulcer size ranged from 2 to 50 mm, and actively bleeding ulcers (Forrest class Ia or Ib) were encountered in 45% of cases. The mean volume of epinephrine was 5.5 mL (standard deviation 3 mL, range 1-20 mL), and 18 patients (14%) received 10 or more mL. There was no association between the volume used and ulcer location (P = 0.50), ulcer size (P = 0.15), or Forrest classification (P = 0.92)."

4. In the section discussion: In the last line you mean table 4 not 3.

Response: Yes, we apologize for the mistake; it has now been corrected. The last sentence now reads as follows: "Of the previously-cited prospective combination therapy studies that reported epinephrine volume, 10 of 11

reported rebleeding rates between 4% and 10% with no clear relationship to epinephrine volume (Table 4)."

5. In the conclusion: you cannot conclude about the effect of epinephrine volume on the prognosis in the case of monotherapy (it is not the aim of this study).

Response: Yes, it is true that this is not the aim of this study. However, in general, it is appropriate to include an overview of the relevant literature and how our study fits within the overall body of evidence in the discussion and conclusion sections of a manuscript. Because multiple prospective studies have illustrated that the use of large volumes of epinephrine is beneficial when monotherapy is used, we believe that is reasonable to make this statement:

"Therefore, providers should not be reluctant to use large volumes if deemed necessary, and in cases where ulcer location or size pose therapeutic challenges or when additional modalities cannot be utilized, it is conceivable that this strategy may still be beneficial. However, large volumes of epinephrine will likely not overcome patient factors that are not readily modifiable and predispose to further bleeding."

The statement is carefully worded to suggest that providers should not simply disregard epinephrine as a modality. We believe that it is important to mention this in light of our study findings. Ultimately, we want to highlight that, although the results of this study were negative, epinephrine still plays an important role in the endoscopic management of gastrointestinal bleeding, especially in situations where the use of other modalities may be limited. This helps contextualize our findings for clinicians.

6. It would be better if you modify the title: Impact of epinephrine volume on peptic ulcer recurrent bleeding in the combination therapy era.

Response: Thank you for the suggestion. Because further bleeding is the defined endpoint that we used (further bleeding = ongoing bleeding + rebleeding), it may be best to keep the phrase "further bleeding" in the title for the purposes of maintaining accuracy. Additionally, our title includes the phrase "high-risk." We believe that this is important because it highlights the fact that we specifically studied ulcers that warrant endoscopic treatment as suggested by society guidelines.

Comments to Reviewer 2

General: In this study, the authors investigated the impact of epinephrine volume in bleeding peptic ulcers patients treated with combination endoscopic therapy, such as endoscopic thermal therapy and/or clipping. Authors showed that there was no association between epinephrine volume and all primary and secondary outcomes in multivariable analyses.

1. Technics of endoscope may be influenced factor for re-bleeding. Where to inject the drug is important.

Response: The practice in our institution is to inject epinephrine in the ulcer margin, typically in 2-4 spots. This information is not always readily provided in our endoscopy reports, largely because most providers apply the same technique.

2. Please add information of H. pylori infection in Table 1.

Response: We agree that H. pylori infection is an important risk factor for peptic ulcer disease. However, we re-queried our dataset, and the H. pylori status of the majority of patients is unclear. A limited number of patients did have testing during their bleeding episode (and while on proton pump inhibitor therapy), but testing in this context is impacted by reduced sensitivity. Others had a history of infection that was treated, but their status at the time of their bleeding was unclear. Because of these factors, we believe that reporting H. pylori infection in Table 1 would be misleading due to a lack of accuracy. We would like to specifically note that, in our institution, providers often avoid performing biopsies at the time of index endoscopy if high-risk/bleeding ulcers are encountered.

3. Rebleeding may depend on location of peptic ulcer, such as lower area of stomach.

Response: We agree that the specific ulcer location may impact the risk for further bleeding. As mentioned in our response to Reviewer 1 (comment #3), we collected this information but refrained from using it for statistical analysis because the sample size limitations would introduce additional variability. Rather, we simply compared gastric versus duodenal ulcers (see Tables 1 and 2). However, we have added the following information to our results section: "Ulcers were present in the following locations: 8 (6%) in the gastric cardia, 7 (5%) in the gastric fundus, 23 (17%) in the gastric body, 1 (1%) in the gastric incisura, 15 (11%) in the gastric antrum, 57 (43%) in the first portion of the

duodenum, 20 (15%) in the second portion of the duodenum, and 1 (1%) in the third portion of the duodenum."

Of note, prior studies suggest that duodenal ulcers, in general, pose a higher risk for rebleeding, perhaps because they are typically more challenging to treat from a technical perspective (less accessible, higher risk for complications).

4. How many cases are on dialysis?

Response: 22 patients received dialysis. This information has been added to Table 1 under the "Medical History" section.

5. Please add numbers in the table 2.

Response: We are not sure which numbers are being referred to in the comment. In regards to comment 4 (above), we have included the data pertaining to dialysis use in Table 1 (baseline characteristics). We also included the breakdown of ulcer location in the text as outlined above (including this in Table 1 would potentially result in excess clutter in the table). In regards to the other covariates listed in the univariable and multivariable models in Table 2, the specific patient numbers that correspond to those are available in Table 1. It would be redundant to list those again in Table 2.

6. I general, antithrombotic drug is a risk factor for re-bleeding. Why did authors fail to show significant difference in this study?

Response: For the purposes of our analysis, we used a combined covariate of antiplatelet agents, anticoagulants, and non-steroidal anti-inflammatory drugs. The majority of patients in our study had advanced comorbidities and used one or more of these agents (70%). Furthermore, our cohort was influenced by a large number of patients with underlying critical illness (i.e. patients in the intensive care unit with shock and organ dysfunction). In light of the size and composition of our cohort, detecting a difference in outcomes in relation to the use of these agents would be challenging. If our cohort was larger and generally less critically ill, we believe that traditional covariates such as antiplatelet agents, anticoagulants, and non-steroidal anti-inflammatory drugs would have been more closely associated with the risk for further bleeding.

7. What is the difference between 7 days and 30 days?

Response: These are follow-up times that have been traditionally used in major gastrointestinal bleeding studies. The outcome of 30 days is much more

common. However, because epinephrine typically has a transient hemostatic effect (i.e. theoretically much more short-lived than other modalities), we also included a shorter follow-up time (7 days) to determine if its impact was on further bleeding varied based on the duration of follow-up. Our 7- and 30-day models were very similar, and the only factors associated with further bleeding in those models were hypotension requiring pressors and elevated creatinine values.

8. Is it necessary to change the measures depending on the difference?

Response: As outlined above, we believe that it was necessary to study both time points for the reasons mentioned, but the models were ultimately very similar. This supports our conclusion that, for our cohort, outcomes were mainly driven by patient factors (i.e. degree of underlying illness) rather than endoscopic factors.

9. The use of epinephrine as a first-line treatment may not be popular in the world. Recently, Clipping or coagulation may be selected as a first-line treatment.

Response: Yes, we agree that epinephrine monotherapy has become less popular since studies have demonstrated the combination therapy provides more durable results. However, epinephrine continues to be an important component of combination therapy as most providers opt to inject epinephrine around an ulcer margin prior to clip placement or thermal therapy. Finally, as mentioned in our discussion/conclusions, we believe that epinephrine monotherapy is still useful in places were additional modalities may not be unavailable or if endoscopic factors limit the use of additional therapies.

10. Authors need to clarify the position of epinephrine treatment.

Response: Our study had important limitations, namely that the majority of patients received less than 10 mL of epinephrine. However, taken together with the body of work that is available from combination therapy studies (Table 4), it is less likely that larger volumes of epinephrine are routinely necessary in patients who also receive clipping or thermal therapy. In such cases, smaller volumes less than 10 mL are likely sufficient. Regardless, we believe that epinephrine still maintains an important role in the treatment of bleeding peptic ulcers, and there are situations in which larger volumes of epinephrine may be helpful. The following excerpts from our discussion and conclusion highlight our position:

"Our study suggests that larger volumes of epinephrine up to a range of 10 to 20 mL for Forrest class Ia, Ib, and IIa PUD are unlikely to be associated with improved UGIB outcomes in the combination therapy era. In the context of improvements in standard medical therapy, including widespread PPI use, and the incorporation of additional endoscopic modalities such as thermal therapy and clipping, further bleeding due to therapeutic failure has become less common, and the relative impact of epinephrine volume is likely limited in most cases."

"Because of its availability, safety, and efficacy, epinephrine will continue to maintain an important role in the management of UGIB from PUD. However, in light of the other medical and endoscopic therapies that have emerged over the past 20 years, there is likely a limited role for the use of increased volumes of epinephrine for patients who require endoscopic therapy for high-risk PUD. Endoscopists should decide on the appropriate volume on a case-by-case basis depending on a combination of technical factors, including the magnitude of active bleeding encountered and ulcer location and size."

11. Injection of epinephrine at higher epinephrine may exacerbate ulcers. How about in this study?

Response: Our multivariable analyses did not show that patients who received larger volumes had a higher risk for further bleeding or any other outcome that we measured. Furthermore, prior monotherapy studies did not demonstrate any significant risk associated with large volumes of epinephrine. However, it is challenging to make a definitive statement about this question since it was not necessarily the premise of our study. Ultimately, we agree with Reviewer 2 – there is a possibility that, in some cases, larger volumes/more aggressive injection practices could theoretically predispose to further bleeding.