Response to Reviewer Comments

We thank the reviewers for their valuable feedback. We have revised the manuscript in accordance with the comments received and explain our revisions below.

Comments from the Reviewers

Reviewer Comments

Reviewer #1: <Comments to Author>

This paper confirmed the validity of the endoscopy guidelines for patients taking warfarin or direct oral anticoagulants (DOAC). It got the conclusion that PPB risk was similar between patients taking warfarin and DOAC. Thromboemolism was observed in warfarin users only. The guideline recommendations for HPB should be re-considered.

Response:

Thank you for your review of our manuscript. We also think that the guidelines statement should be re-considered.

Reviewer #2: <Comments to Author>

This paper is interesting, clinicallly useful, and well prepared. It deserves the publication in this journal. Some revisions should be addressed**.**

1) ISTH major and minor bleeding definitions should be employed. Further comparison should be performed.

Response:

As suggested, we have employed major bleeding defined according to the International Society on Thrombosis and Haemostasis (ISTH) bleeding scale as (1) fatal bleeding, and/or (2) symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or (3) bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells[1]. After re-evaluation, there were only 2 patients with major bleeding, both of whom were warfarin users and received HPB. Because of this limited sample, we described the details of patients without comparing major and minor bleeding. We have added to these points to the Method and Results sections, as indicated below, and newly cited the ISTH bleeding scale.

Method section:

"Major bleeding was defined according to the International Society on Thrombosis and Haemostasis (ISTH) bleeding scale as (1) fatal bleeding, and/or (2) symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or (3) bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells[1]."

Results section:
"There were 32 patients with PPB and only 2 patients with major bleeding, both of whom were warfarin users and received HPB."

2) The authors described the date and cause of death as the clinical outcomes. They are important. However, the results did not report any information regarding the mortality.

Response:
Information regarding mortality appears on page 12, line 2 as follows:

"No mortality events were noted in either group."

3) The authors analyzed the patients undergoing colonoscopic polypectomy. I want to know whether your conclusions are suitable for the patients undergoing gastroscopic polypectomy. Please add some discussion.

Response:
Thank you for this interesting question. Given that a recent population-based study reported a higher proportion of gastric polypectomy/EMR-related bleeding in warfarin users than in DOAC users ($p = 0.06$)[2], post-procedure bleeding may differ between gastric polypectomy and colon polypectomy. We have added this to the Discussion section, with an appropriate citation, as follows:

"In agreement with this, a recent population-based study reported PPB in 14% of DOAC users and 16.9% of warfarin users ($p = 0.324$)[2]. However, post-polypectomy-related bleeding differ according to site of the bleed in the upper or lower GI tract, because upper GI polypectomy-related bleeding was higher in warfarin users than in DOAC users ($p = 0.06$)[2]."

4) The interval between polypectomy and PPB is important. Please add them. Did the authors divide early and late PPB?

Response:
Thank you for pointing this out. We defined late PPB as bleeding occurring more than 24 h after polypectomy[3] and classified PPB into late and early PPB. There were 4 patients with early PPB and 28 with late PPB: 9 cases at day 2, 9 cases at day 3, 6 cases at day 4, 1 case at day 5, 2 cases at day 6, and 1 case at day 8. Patients with early PPB were all warfarin users. We have added to these points to the Method and Results sections as follows.

Method section:
"In addition, we defined late PPB as bleeding occurring more than 24 h after polypectomy and all other cases as early PPB[3]."

Results section:
"Four patients had early PPB (bleeding within 24 h) and 28 with late PPB: 9 cases at day 2, 9 at day 3, 6 at day 4, 1 at day 5, 2 at day 6, and 1 at day 8. The 4 patients with early PPB were all warfarin users."

5) PSM analysis methods and results are a bit obscure. Please clarify them.

Response:
We have added to the description about propensity score matching method in the Method section as follows.

"In multivariate analysis, we developed multivariate models adjusting for propensity score for each strategy. Although there are four different propensity score methods—matching, stratification, inverse probability treatment weighting, and covariates adjustment[4,5]—we used propensity score as a covariate rather than perform a regression adjustment with all of the covariates (traditional covariate adjustment[6]), because many covariates were associated with a small number of bleeding outcomes in this study and we did not want to lose the observations of patients as typically occurs in matching. Propensity score as a covariate method allows for a large number of baseline variables to be included in the regression model, which are not adequately adjusted for

when there are insufficient numbers of outcomes[4,5]. To estimate the propensity score, we employed a logistic regression model including potentially clinically important variables. Some of these were shown to differ ($P < 0.10$) between groups."

Reviewer #3: <Comments to Author>
An interesting study that found that anticoagulant (AC) users were at higher risk of post-polypectomy bleeding (PPB) than controls. Second, PPB risk was similar between warfarin users and direct oral anticoagulant (DOAC) users, whereas thromboembolism risk was observed only in warfarin users. Third, PPB risk was not significantly different between rivaroxaban, dabigatran, and apixaban users. Fourth, the strategy of discontinuing AC with heparin bridgeas recommended in the endoscopy guidelines showed a higher bleeding rate than continuing AC alone and had one thrombotic event, thus indicating that heparin bridge increased bleeding and may not prevent thromboembolism.

Response:
Thank you for your review of our manuscript.

Reviewer #4: <Comments to Author>
I have review this vary interesting single-center study focused on the risk of delayed bleeding or thrombosis in patients on treatment with anticoagulants than require endoscopic resection. The authors have shown than the risk of delayed bleeding is comparable between DOAC and warfarin. The most interesting data is regarding heparin bridge therapy and the risk of bleeding. I have understood, and I would like the authors clarify this item, than risk of bleeding with HPB occurs with intravenous heparin, because the authors have no data with subcutaneous heparin.

Response:
Thank you for your comments. In Japan, intravenous unfractionated heparin is administered during the periendoscopic period in all institutions, whereas in Western countries subcutaneous unfractionated heparin is often administered. Robertson *et al*[7] reported a similar incidence of major bleeding between patients treated with subcutaneous unfractionated heparin and those treated with intravenous unfractionated heparin (OR 0.91). Furthermore, Hirsh *et al*[8] reported that optimal APTT levels were achieved at 24 h after heparin administration in only 37% of patients receiving subcutaneous heparin, compared with 71% receiving intravenous heparin. We added

this information as a limitation to the Discussion section as follows.

“Third, we have no data on subcutaneous heparin because intravenous heparin is used in Japan. However, a previous study reported a similar incidence of major bleeding between patients treated with subcutaneous unfractionated heparin and those treated with intravenous unfractionated heparin (OR 0.91).”

Other crucial decision is when should we reintroduce the anticoagulants after the resection?

Response:
Anticoagulants were resumed as soon as possible upon confirming the absence of hematochezia after polypectomy, in accordance with guidelines of the Japan Gastroenterological Endoscopy Society[9]. We added this information and the citation to the Method section.

REFERENCES

1. Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis . Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005**; 3**: 692-694 [PMID: 15842354 DOI:JTH1204 [pii]]

2. Nagata N, Yasunaga H, Matsui H, Fushimi K, Watanabe K, Akiyama J, Uemura N, Niikura R . Therapeutic endoscopy-related GI bleeding and thromboembolic events in patients using warfarin or direct oral anticoagulants: results from a large nationwide database analysis. *Gut* 2017 [PMID: 28874418 DOI:gutjnl-2017-313999 [pii]]

3. Park SK, Seo JY, Lee MG, Yang HJ, Jung YS, Choi KY, Kim H, Kim HO, Jung KU, Chun HK, Park DI . Prospective analysis of delayed colorectal post-polypectomy bleeding. *Surg Endosc* 2018 [PMID: 29344790 DOI:10.1007/s00464-018-6048-9 [doi]]

4. Austin PC . An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate Behav Res* 2011**; 46**: 399-424 [PMID: 21818162 DOI:10.1080/00273171.2011.568786 [doi]]

5. Kurth T, Walker AM, Glynn RJ, Chan KA, Gaziano JM, Berger K, Robins JM . Results of multivariable logistic regression, propensity matching, propensity adjustment, and propensity-based weighting under conditions of nonuniform effect. *Am J Epidemiol* 2006**; 163**: 262-270 [PMID: 16371515 DOI:kwj047 [pii]]

6. Elze MC, Gregson J, Baber U, Williamson E, Sartori S, Mehran R, Nichols M, Stone GW, Pocock SJ . Comparison of Propensity Score Methods and Covariate Adjustment: Evaluation in 4 Cardiovascular Studies. *J Am Coll Cardiol* 2017**; 69**: 345-357 [PMID: 28104076 DOI:S0735-1097(16)37036-X [pii]]

7. Robertson L, Strachan J . Subcutaneous unfractionated heparin for the initial treatment of venous thromboembolism. *Cochrane Database Syst Rev* 2017**; 2**: CD006771 [PMID: 28195640 DOI:10.1002/14651858.CD006771.pub3 [doi]]

8. Hirsh J, Warkentin TE, Shaughnessy SG, Anand SS, Halperin JL, Raschke R, Granger C, Ohman EM, Dalen JE . Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. *Chest* 2001**; 119**: 64S-94S [PMID: 11157643 DOI:S0012-3692(15)60781-4 [pii]]

9. Fujimoto K, Fujishiro M, Kato M, Higuchi K, Iwakiri R, Sakamoto C, Uchiyama S, Kashiwagi A, Ogawa H, Murakami K, Mine T, Yoshino J, Kinoshita Y, Ichinose M, Matsui T, Japan Gastroenterological Endoscopy Society . Guidelines for gastroenterological endoscopy in patients undergoing antithrombotic treatment. *Dig Endosc* 2014**; 26**: 1-14 [PMID: 24215155 DOI:10.1111/den.12183 [doi]]