Response to Reviewer Comments

We thank the reviewers for the valuable feedback that has helped us revise and improve our manuscript.

Reviewer #1:

The authors should clearly define what is meant by LGI Bleeding (and UGIB and small bowel bleeding) at the very outset. A mention should be made as to how the paradigm has shifted to identification of three (small bowel bleeding) distinctive patterns instead of the earlier recognition of two patterns of bleeding. See Small bowel bleeding: a comprehensive review. Gastroenterol Rep (Oxf). 2014 Nov;2(4):262-75.

Response: We agree and have added the following sentence to the Introduction section.

"Traditionally, gastrointestinal bleeding (GIB) was classified into upper gastrointestinal bleeding (UGIB) and lower gastrointestinal bleeding (LGIB). LGIB was defined as bleeding from the lesion distal to the ligament of Treitz, including the small and large bowels. In the last decade, the availability of advanced diagnostic innovations such as capsule endoscopy and balloon-assisted enteroscopy has led to better understanding of the etiological profile of small bowel bleeding. Thus, some recent reports adopted three categories of GIB: upper-, mid-, and lower GIB[1]."

1. Gunjan D, Sharma V, Rana SS, Bhasin DK . Small bowel bleeding: a comprehensive review. Gastroenterol Rep (Oxf) 2014; 2: 262-275 [PMID: 24874805 DOI:10.1093/gastro/gou025 [doi]]

How does systolic blood pressure aid in discriminating UGIB and LGIB? Please clarify with details as the line ". A blood urea nitrogen/creatinine (BUN/Cr) ratio > 30 (likelihood ratio, 7.5)[15], nasogastric aspirate/lavage with blood or coffee grounds (likelihood ratio, 9.6)[15], and systolic blood pressure (odds ratio [OR], 0.725/5 mmHg increase)[16] are useful to distinguish UGIB. Upper endoscopy is recommended if the likelihood of UGIB is high" does not clarify the direction of association

Response: As suggested, we have described in detail how to discriminate UGIB and LGIB as follows.

"A blood urea nitrogen/creatinine (BUN/Cr) ratio > 30 (likelihood ratio, 7.5) and nasogastric aspirate/lavage with blood or coffee grounds (likelihood ratio, 9.6) are the features of UGIB[15], being useful to distinguish UGIB from LGIB. In addition, in a report of patients with hematochezia, the systolic blood pressure was significantly lower in UGIB than in LGIB (mean pressure, 114 mmHg vs. 133 mmHg) [16]. If the likelihood of UGIB is high based on these factors, upper endoscopy is recommended."

15. Srygley FD, Gerardo CJ, Tran T, Fisher DA . Does this patient have a severe upper gastrointestinal bleed?. JAMA 2012; 307: 1072-1079 [PMID: 22416103 DOI:10.1001/jama.2012.253 [doi]]

16. Sittichanbuncha Y, Senasu S, Thongkrau T, Keeratikasikorn C, Sawanyawisuth K . How to differentiate sites of gastrointestinal bleeding in patients with hematochezia by using clinical factors?. Gastroenterol Res Pract 2013; 2013: 265076 [PMID: 24348531 DOI:10.1155/2013/265076 [doi]]

There is a distinct divide amongst the cause of LGIB in the West and the tropical

countries and this should be alluded to. Diverticular bleeding is much less common a cause in tropical countries while infectiouc colitis like amebic and enteric fever are more common.

Response: As Reviewer 1 recommends, we have added the difference of disease distribution between the Western and tropical countries to the *Risk stratification* section as follows.

"The causes of acute LGIB **in the Western countries** are as follows[17]: diverticular bleeding (30–65%), ischemic colitis (5–20%), hemorrhoids (5–20%), colorectal polyps/neoplasms (2–15%), angioectasia (5–10%), post-polypectomy bleeding (2–7%), inflammatory bowel disease (3–5%), infectious colitis (2–5%), rectal ulcer (0–5%), colorectal varices (0–3%), radiation proctitis (0–2%), drug-induced colitis (0–2%), and Dieulafoy's lesion (rare). **On the other hand, in the tropical countries, colorectal polyps/neoplasms (29–53%) and colitis (23–38%) are the common causes, and diverticular bleeding is less common (4–19%)[16,18].**"

16. Sittichanbuncha Y, Senasu S, Thongkrau T, Keeratikasikorn C, Sawanyawisuth K . How to differentiate sites of gastrointestinal bleeding in patients with hematochezia by using clinical factors?. Gastroenterol Res Pract 2013; 2013: 265076 [PMID: 24348531 DOI:10.1155/2013/265076 [doi]]

17. Gralnek IM, Neeman Z, Strate LL . Acute Lower Gastrointestinal Bleeding. N Engl J Med 2017; 376: 1054-1063 [PMID: 28296600 DOI:10.1056/NEJMcp1603455 [doi]]

18. Morkar DN, Hazare S. Spectrum of the causes of lower gastrointestinal bleeding in geriatric patients in tertiary care hospital. J Sci Soc 2017**; 44**: 148-151

[DOI:10.4103/jss.JSS_17_16]

The issue of anticoagulants and antiplatelet use and LGIB is extremely important and it would be better if the authors provide a flow-chart or a table for assessment of anticoagulation and when to stop, when to reverse (and how) anticoagulation.

Response: Thank you for this valuable comment. We have added a flow-chart for the management of medication as Figure 1.

Figure 1. Recommendation for the management of medication based on current studies.

NSAIDs, nonsteroidal anti-inflammatory drug; DOAC, direct-acting oral anticoagulant; PT-INR, prothrombin time-international normalized ratio.

a. During the first 30 days following coronary stenting and during the first 90 days following acute coronary syndrome.

b. The influence of short-term discontinuation has not been determined.

c. Aspirin should be continued.

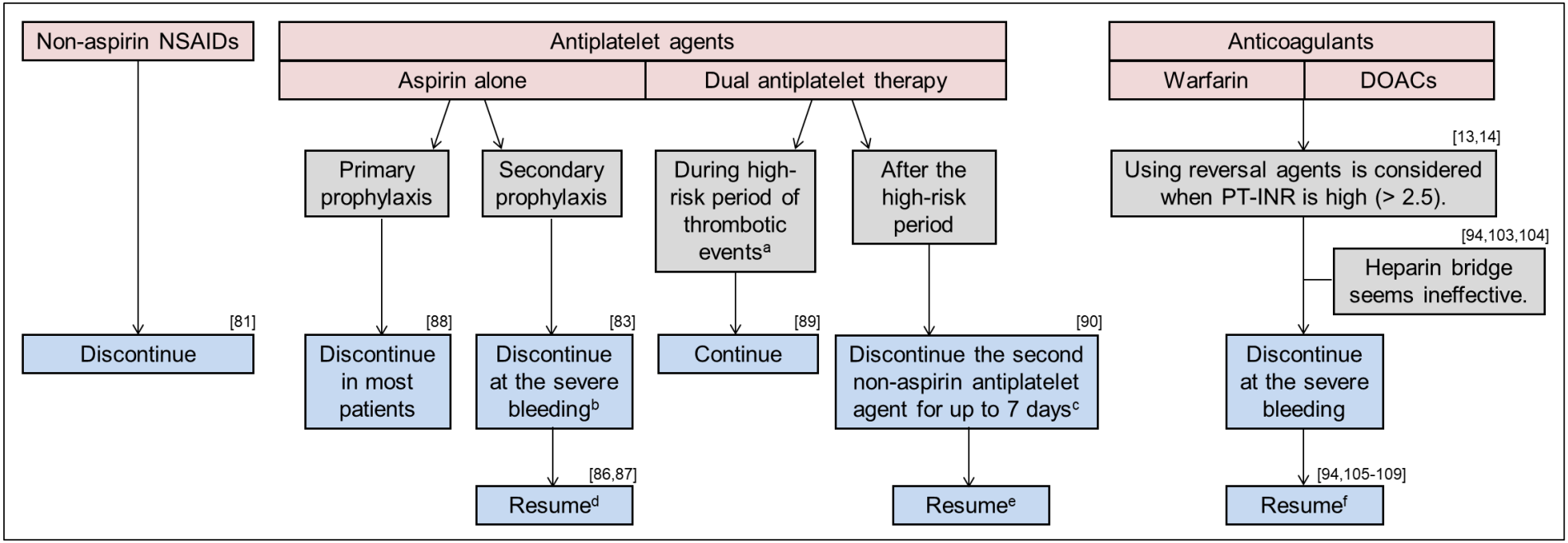
d. Resumption reduces cardiovascular events but may increase rebleeding.

e. The influence of long-term discontinuation has not been determined.

f. Changing to apixaban, or reducing the dose of dabigatran to 110 mg b.i.d may reduce rebleeding in GIB patients taking warfarin, dabigatran (150 mg b.i.d) or rivaroxaban.

[reference numbers]

For the details, see the main body text.


Non-aspirin NSAIDs
Antiplatelet agents
Aspirin alone
Dual antiplatelet therapy
Anticoagulants
Warfarin
DOACs
Primary prophylaxis
Secondary prophylaxis
During high-risk period of thrombotic events[a]
After the high-risk period
[13,14]
Using reversal agents is considered when PT-INR is high (> 2.5).
[94,103,104]
Heparin bridge seems ineffective.
[81]
Discontinue
[88]
Discontinue in most patients
[83]
Discontinue at the severe bleeding[b]
[89]
Continue
[90]
Discontinue the second non-aspirin antiplatelet agent for up to 7 days[c]
Discontinue at the severe bleeding
[86,87]
Resume[d]
Resume[e]
[94,105-109]
Resume[f]

In Table 3 it is better to exclude data from meta-analysis and provide only data from original comparative studies

Response: We agree that it would become simple if the data of meta-analyses were excluded from Table 3. However, we still believe that it is significant to include the data of meta-analyses in Table 3. It is because sample sizes, outcomes, and results varied between RCTs and meta-analyses, and the Table is better than sentences to describe the variation. Therefore, we would like to leave Table 3 in the current form.

Reviewer #2: The mini review titled "Initial management for acute lower gastrointestinal bleeding" from Aoki T and Coworkers is a valuable and exhaustive contribution in the field. This practical review focusses on the initial assessment of LGIB patients, together with risk stratification, initial management, diagnosis and treatment, and medication management. Controversial issues are also debated. I think that the paper worth to be published after a reference revision because ref. 8 and 11 are duplicated.

Response: As Reviewer 2 comments, we have revised the reference section.