Digestive Endoscopy 2015; **27**: 649–656 doi: 10.1111/den.12498

Review

Recent clinical management of antithrombotic agents for gastrointestinal endoscopy after revision of guidelines in Japan

Satoshi Ono,[1] Mitsuhiro Fujishiro,[1,2] Yuichi Ikeda,[3] Issei Komuro[3] and Kazuhiko Koike[1]

Departments of [1]Gastroenterology, [2]Endoscopy and Endoscopic Surgery and [3]Cardiology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

In 2012, the Japan Gastroenterological Endoscopy Society (JGES) revised guidelines for the management of gastrointestinal endoscopy for patients using antithrombotic agents. The conventional guidelines emphasized reducing the bleeding risk that accompanies gastrointestinal endoscopy, but the present guidelines prioritize reduction of thromboembolism risk during discontinuation of antithrombotic agents, which is consistent with Western guidelines. When the advantages outweigh the disadvantages, the guidelines permit endoscopic biopsy and high-bleeding-risk procedures without discontinuation of selected antithrombotic agents. These guidelines created a paradigm shift that has slowly, but surely, changed clinical daily practice in Japan. As a result, endoscopic biopsy without discontinuation of antithrombotic agents has been widely accepted, although solid evidence for its support is still lacking. Additionally, feasibility of high-bleeding-risk procedures without discontinuation of selected antithrombotic agents is also controversial because evidence newly acquired after publication of the present guidelines is low in evidence level. Consequently, clinical studies with a high evidence level, including randomized controlled studies, are mandatory to establish reliable upcoming guidelines. At the same time, under the present guidelines, the accomplishment of such studies in Japan is expected.

Key words: antithrombotic agent, bleeding, endoscopy, guidelines, thromboembolism

MANAGEMENT OF ANTITHROMBOTIC AGENTS DURING THE PERI-ENDOSCOPIC PERIOD

THE MANAGEMENT OF antithrombotic agents during the peri-endoscopic period is a major concern for endoscopists and physicians because of the risks of bleeding and thromboembolism. The common management of antithrombotic agents prior to 2005 in Japan was a long discontinuation period that was sufficient to wash out the effects of antithrombotic agents before endoscopy.[1] This management procedure was the maximum precaution against bleeding risks that accompany endoscopic procedures. However, this management also exposed patients to the risk of thromboembolism.[2] Bleeding and thromboembolism are not equivalent complications based on clinical outcomes. The occurrence of a thromboembolic event may produce irreversible and miserable outcomes. The revised guidelines in 2005 slightly emphasized a reduction of thromboembolism risk compared to the previous guidelines, but the discontinuation of antithrombotic agents before endoscopic biopsy was recommended.[3] The number of patients who suffer thromboembolic events during the discontinuation of antithrombotic agents is not negligible. Therefore, there is an increasing need to revise and establish solid guidelines for the management of antithrombotic agents during the peri-endoscopic period.[4]

Based on clinical outcomes in 2010, Sung *et al*. demonstrated that bleeding is an acceptable complication compared to thromboembolism.[5] Their randomized controlled trial evaluated the re-bleeding rate and mortality rate of patients with peptic ulcer bleeding as a result of low-dose acetylsalicylic acid (ASA). Patients were allocated to two groups with or without ASA discontinuation. ASA discontinuation decreased the re-bleeding rate, but it also increased the mortality rate as a result of thromboembolism, including cardiovascular events. This result strongly affected the mindset of endoscopists, who have a vital concern for this problem.

Corresponding: Satoshi Ono, Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, 113-8655, Tokyo, Japan. Email: satoshi-tky@umin.ac.jp
Received 18 December 2014; accepted 25 May 2015.

2012 REVISED GUIDELINES

GUIDELINES BY THE Japan Gastroenterological Endoscopy Society (JGES) were updated in 2012 because of the limitations of the previous guidelines.[6] The 2012 revisions are based on concepts that put more emphasis on reducing thromboembolism risk (Table 1). Two points represent the characteristics of these guidelines. The first point relates to carrying out endoscopic biopsy and low-bleeding-risk procedures without the discontinuation of all types of antithrombotic agent. The second point relates to carrying out high-bleeding-risk procedures without the discontinuation of ASA and cilostazol (Fig. 1). Cilostazol was added as a recommended choice because of its short-effect duration and outcomes in clinical trials in Japan.[7] Initially, this opposite policy confused physicians because of the fear of bleeding. However, the new guidelines are slowly being accepted.

Endoscopic biopsy is the most common procedure in the clinical daily practice of gastrointestinal endoscopy. All patients have the possibility of undergoing endoscopic biopsy, and endoscopists must make a difficult decision in the management of antithrombotic agents by considering the various characteristics of these patients. The present JGES guidelines allow patients to undergo gastrointestinal endoscopic biopsy without discontinuation of antithrombotic agents if necessary. The present guidelines are most important to avoid careless discontinuation of antithrombotic agents which may be followed by occasional thromboembolic events. However, the present JGES guidelines do not necessarily recommend discontinuation, but only permit endoscopy without the discontinuation of antithrombotic agents for cases in which the pros outweigh the cons. Therefore, an evaluation of the necessity for endoscopic biopsy of lesions should be carried out carefully, and the use of other endoscopic modalities, including chromoendoscopy, magnifying endoscopy, and image-enhanced endoscopy, should be considered prior to biopsy.[8–10]

Additionally, endoscopic biopsy should be done under circumstances where hemostasis can be maintained safely and surely. Endoscopists must remember that the antithrombotic agent itself is a risk factor for gastrointestinal bleeding, especially for patients taking multiple antithrombotic agents.[11]

NEWLY ACQUIRED EVIDENCE AFTER PUBLICATION OF THE PRESENT GUIDELINES

RESULTS OF SEVERAL clinical trials were published after issue of the present guidelines. We searched PubMed and the Japanese Medical Abstract Society (JAMAS http://search.jamas.or.jp/) for studies published between January 2012 and March 2015 using the keywords 'endoscopy', and 'anti-coagulant', 'anti-platelet' or 'anti-thrombotic' to review new evidence after publication of the 2012 guidelines. Among articles found in PubMed and JAMAS, we selected all 11 original articles on clinical trials concerning continuation of antithrombotic agents during peri-endoscopic periods shown in Table 2. Among the 11 articles, nine articles were from Japan.

We previously reported the feasibility of endoscopic biopsy without discontinuation of antithrombotic agents. The present article investigated endoscopic bleeding time after 101 biopsies and revealed that hemostasis after endoscopic biopsy can be confirmed within approximately 2 min in patients without discontinuation of antithrombotic agents regardless of the use of anticoagulants or multiple antithrombotic agents.[12] Recently, Fujita *et al.* reported the current management of antithrombotic agents 1 year after publication of the new guidelines. In their report, 206 patients underwent endoscopic biopsy without discontinuation of antithrombotic agents, and no major bleeding complications were experienced. They also validated that endoscopic biopsy without discontinuation of warfarin is acceptable as long as international normalized ratio (INR) is within therapeutic ranges in Japan.[14] Ara *et al.* also reported the safety of endoscopic biopsy without discontinuation of antithrombotic agents. In their prospective study, 286 patients underwent endoscopic biopsy without discontinuation

Table 1 Management of antithrombotic agents during the peri-endoscopic period in various guidelines

	Endoscopic biopsy	Low-bleeding-risk procedures	High-bleeding-risk procedures
JGES before 2005	Discontinuation as long as possible.		
JGES 2005	Discontinuation of ASA, ticlopidine, and combination of both for 3, 5, and 7 days, respectively. Discontinuation of warfarin for 3–4 days.		
JCS 2009	Discontinuation of ASA, ticlopidine, and combination of both for 3, 5, and 7 days, respectively.		Discontinuation of ASA, ticlopidine, and cilostazol for 7, 10–14, and 3 days, respectively.
ASGE 2009	Continuation		Continuation in part
JGES 2012	Continuation		Continuation in part

ASA, acetylsalicylic acid; ASGE, American Society for Gastrointestinal Endoscopy; JCS, Japanese Circulation Society; JGES, Japan Gastrointestinal Endoscopy Society.

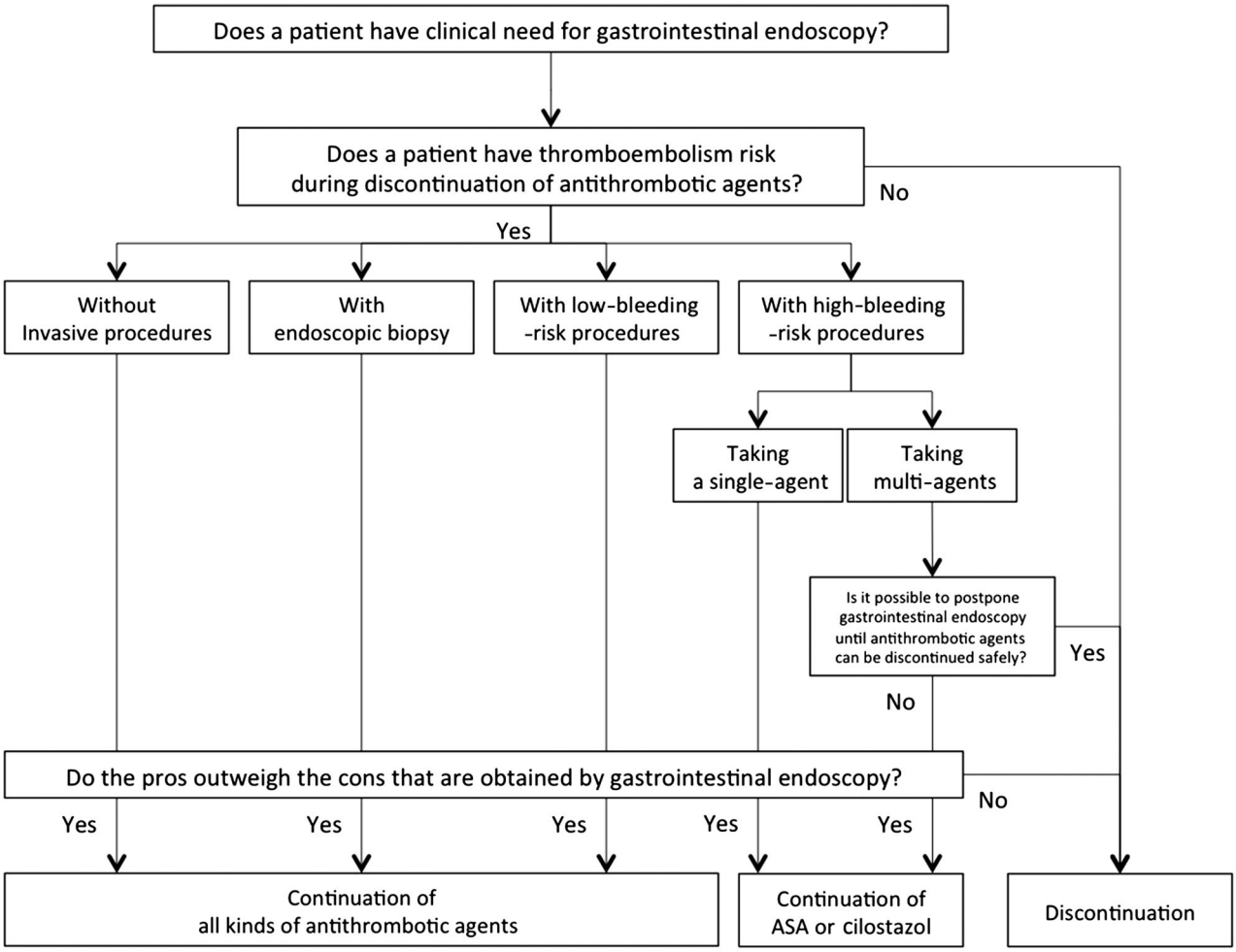

Figure 1 Flow chart of the management of antithrombotic agents during the peri-endoscopic period in the new Japan Gastroenterological Endoscopy Society (JGES) guidelines.

of antithrombotic agents and only one case of bleeding was noted. The evaluated bleeding rate was 0.35%, which was not significantly higher than for other patients.[15] Western guidelines already permit endoscopic biopsy or low-bleeding-risk procedures, and these data suggest that endoscopic biopsy without discontinuation of antithrombotic agents is also acceptable in Japan although the study sample was not large enough to draw solid evidence.[23,24] Therefore, precautionary measures, such as the use of thin-type biopsy forceps, are recommended to prevent bleeding after biopsy, as reported by Ishikawa *et al.*[13]

The present JGES guidelines also permit high-bleeding-risk procedures without discontinuation of ASA and cilostazol, as mentioned earlier. The guidelines include polypectomy, endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), endoscopic sphincterotomy (EST), papillectomy, endoscopic ultrasound–fine-needle aspiration (EUS-FNA), variceal treatment, and endoscopic dilatation as high-bleeding-risk procedures, although the safety of each procedure without discontinuation of ASA and cilostazol was not validated sufficiently. These procedures are all permitted based on the concept that bleeding is acceptable compared to thromboembolism during discontinuation, but this concept is not supported by solid evidence.

Several observational studies on the management of antithrombotic agents during gastric ESD were available, although most data were inconclusive because of the retrospective study design and restricted sample size. Whether antithrombotic agents are a risk factor for postoperative bleeding after gastric ESD is controversial. In 2012, Cho *et al*. reported that continuous ASA use increased the risk of postoperative bleeding after gastric ESD, but, in their retrospective studies, Lim *et al.*

Table 2 Newly published original articles concerning endoscopic procedures on continuation of antithrombotic agents

	Procedure	Year	Authors	Antithrombotic agent	Design	Patients	Sessions	Suggestion	Evidence level†
Biopsy	Upper and lower GI	2012	Ono *et al.*[12]	ASA, TD, AC etc.	Prospective observational study	60	112	Biopsy on antithrombotic agents can be acceptable if done carefully using thin-type biopsy forceps.	V
	Upper GI	2013	Ishikawa *et al.*[13]	ASA, TD, AC etc.	Prospective observational study	65	No data	Bleeding risk of gastric biopsy using ultra-thin biopsy forceps on antithrombotic agents seems to be low.	IVa
	Upper GI	2015	Fujita *et al.*[14]	ASA, TD, AC etc.	Retrospective observational study	206	No data	Non-cessation of antithrombotic agents before biopsy using ultra-thin biopsy seems to be safe and acceptable.	V
	Upper GI	2015	Ara *et al.*[15]	ASA, TD, AC etc.	Prospective observational study	286	No data	Non-cessation of antithrombotic agents before biopsy seems to be safe.	IVa
High-bleeding-risk procedures	Colonic polypectomy	2012	Manocha *et al.*[16]	ASA/NSAIDs	Retrospective observational study	502	1267	Cessation of ASA or NSAIDs before colonoscopy/polypectomy may not be necessary.	V
	Colonic polypectomy	2013	Feagins *et al.*[17]	Clopidogrel	Prospective interventional study	219	865	For patients who are at high risk for thromboembolic events with thienopyridine cessation and for whom colonoscopy cannot be delayed reasonably, continuation of thienopyridine during colonoscopy can be acceptable.	III
	EST	2014	Tomoda *et al.*[18]	ASA, CLZ	Retrospective observational study	29	29	EST on ASA or CLZ alone can be acceptable.	V
	Gastric ESD	2014	Sanomura *et al.*[19]	ASA	Retrospective observational study	25	28	Continued use of ASA does not increase the risk of bleeding during or after gastric ESD and may decrease the risk of ischemic events.	V
	Gastric ESD	2014	Matsumura *et al.*[20]	ASA, AC etc.	Retrospective observational study	21	No data	Continued ASA is not a risk factor for postoperative bleeding.	V

(Continues)

Table 2 (Continued)

	Procedure	Year	Authors	Antithrombotic agent	Design	Patients	Sessions	Suggestion	Evidence level[†]
	Gastric ESD	2015	Ono *et al.*([21])	ASA, TD	Prospective observational study	19	23	Multiple antithrombotic agents including thienopyridine derivatives increase delayed bleeding rate.	IVa
	Colonic ESD	2015	Ninomiya *et al.*[22]	ASA	Retrospective observational study	28	31	Continued ASA increased the risk of bleeding after colonic ESD compared with non-use of antithrombotic agents although no significant difference was seen between ASA-continued and ASA-interrupted groups.	V

[†] Evidence level: III, non-randomized controlled trial; IVa, cohort study; V, descriptive study.

AC, anticoagulant; ASA, aspirin; CLZ, cilostazol; ESD, endoscopic submucosal dissection; EST, endoscopic sphincterotomy; GI, gastrointestinal; NSAID, non-steroid anti-inflammatory drug; TD, thienopyridine derivatives.

reported that ASA did not increase this risk.[25,26] There are no reports of the feasibility of gastric ESD without discontinuation of antithrombotic agents from Japan where ESD was born and developed. We speculate that one reason for the lack of reports is the difficulty in carrying out clinical trials on this problem under the previous guidelines. However, recent reports from Japan provide evidence to solve this problem. Sanomura *et al.* reported a retrospective cohort study of gastric ESD without ASA discontinuation and revealed a postoperative bleeding rate of 4.8%, which is equivalent to the approximately 5% overall postoperative bleeding rate reported previously.[19] Their result proposed that gastric ESD during the continuation of ASA is acceptable.

However, Koh *et al.* noted that antithrombotic agents may be a risk factor for delayed postoperative bleeding after gastric ESD.[27] Tounou and Morita reported that the postoperative bleeding rate of gastric ESD was higher in patients taking multiple agents than patients taking ASA alone.[28] Hayashi *et al.* reported that the use of thienopyridine derivatives produced a strong tendency to cause postoperative bleeding after gastric ESD.[29] A multicenter prospective study (STRAP trial: Safe TReatment on Anti-Platelets) that we conducted also revealed that thienopyridine derivatives may be a risk factor for postoperative bleeding.[21] In the STRAP trial, all six patients with postoperative bleeding out of the 23 gastric ESD patients were taking thienopyridine derivatives. However, all postoperative bleeding after gastric ESD in this study occurred in patients taking multiple antithrombotic agents after resumption of thienopyridine derivatives. Patients taking multiple agents predominantly include patients receiving dual antiplatelet therapy (DAPT), which is a combination of ASA and thienopyridine derivatives. Therefore, the management of patients taking thienopyridine derivatives is a top-priority issue for the prevention of delayed postoperative bleeding.

Risk of bleeding for other high-bleeding-risk endoscopic procedures with continuation of antithrombotic agents has also been reported. Ninomiya *et al.* reported the clinical feasibility of colonic ESD without discontinuation of low-dose aspirin.[22] Their data revealed that use of ASA increased the postoperative bleeding risk, although there were no significant differences between the ASA-continued group and the ASA-interrupted group. Tomoda *et al.* evaluated the feasibility of EST without discontinuation of ASA or cilostazol[18] and compared intraoperative and postoperative bleeding rates between the following three groups: 29 patients without discontinuation, 45 patients with discontinuation, and 238 patients taking no antithrombotic agents. They revealed no significant differences in intraoperative and postoperative bleeding rates between these three groups and suggested that EST without discontinuation of ASA or cilostazol is acceptable.

FUTURE PERSPECTIVES

AS MENTIONED EARLIER, the present guidelines lack solid evidence to support the feasibility of endoscopic procedures without discontinuation of antithrombotic agents. The newly acquired evidence contains no clinical study with a high evidence level including a randomized controlled study, as shown in Table 2. All the authors of these articles also commented that restricted sample size, retrospective study design, or single-center study design were limitations of their studies. Therefore, large clinical trials are mandatory to raise the statements in the present guidelines to reliable ones. At the same time, the development of new prevention strategies for bleeding after endoscopic procedures in patients taking antithrombotic agents is required. Concerning prevention of bleeding, proton pump inhibitors or protective agents are already reported to be an easy and effective method, although their efficacy is limited in the upper gastrointestinal (GI) tract.[30] The effectiveness of shielding postoperative ulcers with polyglycolic acid (PGA) sheets after ESD was reported recently.[31] Tsuji *et al*. reported the efficacy of PGA sheets in the prevention of delayed perforation and postoperative bleeding in colonic ESD.[32] These novel attempts may provide answers that allow high-bleeding-risk procedures to be carried out in patients taking antithrombotic agents.

Another approach to this problem is the development of other less invasive modalities that can replace endoscopic biopsy, which is the most common invasive procedure in the clinical daily practice of gastrointestinal endoscopy. The combination of image-enhanced endoscopy and magnifying endoscopy is an established modality to narrow the differential diagnosis of suspicious lesions, although a final diagnosis still requires histopathological assessment of specimens obtained using endoscopic biopsy.[33] Endocytoscopy and confocal microscopy may provide future alternatives, but these modalities are not common.[34,35] Future modalities may minimize the number of unnecessary endoscopic biopsies.

Emerging antithrombotic agents are also unsolved problems in the revised guidelines. The previous guidelines were revised because of the lack of recommendations for emerging antithrombotic agents. The present JGES guidelines include recommendations for anticoagulants, but novel oral anticoagulants (NOAC) except for dabigatran are not mentioned. Therefore, the present JGES guidelines will require revision in the near future when physicians prescribe many NOAC, such as rivaroxaban, and apixaban. However, there is a paucity of outcome data concerning peri-endoscopic management of these NOAC. Consequently, at the present time, we have no choice but to refer expert opinions as do the US and Canadian guidelines. For instance, Desai *et al*. proposes peri-endoscopic management for patients taking NOAC considering half-life or drug eliminations as shown in Table 3.[36] This management also lacks solid evidence to support it. Therefore, further accumulation of evidence concerning management of NOAC is mandatory.

In contrast, NOAC may solve some problems at the same time. NOAC are characterized as direct inhibitors of the coagulation system. Therefore, the effect duration is shorter than warfarin, which is an indirect inhibitor of the coagulation system. Warfarin is thought to require a heparin bridge before endoscopic treatment because of its gradual diminishing effect, although postoperative bleeding rates that accompany heparin bridges are high. Heparin bridge in colonic polypectomy raises bleeding rates to approximately 20%.[37] Therefore, short-acting anticoagulants without a heparin bridge may be a solution for the prevention of postoperative bleeding in patients taking anticoagulants. Undoubtedly, evaluations of the appropriate timing for endoscopic procedures in patients taking NOAC are mandatory.

Future guidelines should be revised in accordance with changes in the daily clinical practice in other fields. The present JGES guidelines permit high-bleeding-risk procedures without ASA discontinuation. This procedure appears reasonable under present circumstances because many patients use ASA alone. For example, ASA is the most commonly continued treatment for cardiovascular disease after discontinuation of thienopyridine derivatives following DAPT. However, recommendations in this field may also be revised depending on the situation because thienopyridine derivatives more effectively prevent the re-occlusion of coronary stents.[38] The most common antiplatelet agent that is continued after reduction of DAPT in the near future might be thienopyridine derivatives,

Table 3 Peri-endoscopic management of patients taking NOAC before elective endoscopy

Procedure	Management
Low-bleeding-risk procedures including biopsy	Continue or withdraw the morning dose. Ideally, procedures should be carried out when drug is at trough level.
High-bleeding-risk procedures	Withdraw for 2–3 half-lives (24–48 h) for patients with normal drug elimination. For patients with impaired elimination, adjusted and longer withdrawal period should be considered.

NOAC, novel oral anticoagulants.

not ASA. In contrast, few reports validate the feasibility of high-bleeding-risk procedures without discontinuation of thienopyridine derivatives. Therefore, close coordination between endoscopists and physicians in other fields is mandatory. Guidelines will be and should be revised fluidly for physicians to provide the most suitable medical care based on current evidence.

CONCLUSION

THE CLINICAL DAILY practice of gastrointestinal endoscopy in Japan is surely changing after revision of the previous JGES guidelines. This change will promote further accumulation of evidence for the management of antithrombotic agent during the peri-endoscopic period in Japan. Meanwhile, accumulation of solid data through well-designed clinical studies is important for all Japanese endoscopists to make the guidelines more reliable because endoscopy was born and continues to develop in Japan.

CONFLICTS OF INTEREST

M.F RECEIVED LECTURE fees from Eisai, Co. Ltd. I.K. received lecture fees or commercial research funding from Takeda Pharmaceutical Co. Ltd/Nippon Boehringer Ingelheim Co. Ltd, MSD K.K., Astellas Pharma Inc., Dainippon Sumitomo Pharma Co. Ltd, DAIICHI SANKYO Co. Ltd, Genzyme Japan K.K. and Mitsubishi Tanabe Pharma Corp.

REFERENCES

1 Ido K, Togashi K, Yamamoto H, Satoh K. How antiplatelets and anti-coagulants should be managed in endoscopic treatment. *Gastroenterol. Endosc.* 2004; **46**: 2079–85 [in Japanese with English abstract].
2 Fujishiro M, Oda I, Yamamoto Y *et al.* Multi-center survey regarding the management of anticoagulation and antiplatelet therapy for endoscopic procedures in Japan. *J. Gastroenterol. Hepatol.* 2009; **24**: 214–18.
3 Ogoshi K, Kaneko E, Tada M *et al.* The management of anticoagulation and antiplatelet therapy for endoscopic procedures. *Gastroenterol. Endosc.* 2005; **47**: 2691–5.
4 Ono S, Fujishiro M, Kanzaki H *et al.* Conflicting clinical environment about the management of antithrombotic agents during the periendoscopic period in Japan. *J. Gastroenterol. Hepatol.* 2011; **26**: 1434–40.
5 Sung JJ, Lau JY, Ching JY *et al.* Continuation of low-dose aspirin therapy in peptic ulcer bleeding: a randomized trial. *Ann. Intern. Med.* 2010; **152**: 1–9.
6 Fujimoto K, Fujishiro M, Kato M *et al.* Guidelines for gastroenterological endoscopy in patients undergoing antithrombotic treatment. *Dig. Endosc.* 2014; **26**: 1–14.
7 Mabe K, Hirayama M, Kato M. Withdrawal of anti-coagulants and antiplatelet agents during endoscopy. *Gastroenterol. Endosc.* 2010; **52**: 2976–84.
8 Muto M, Minashi K, Yano T *et al.* Early detection of superficial squamous cell carcinoma in the head and neck region and esophagus by narrow band imaging: a multicenter randomized controlled trial. *J. Clin. Oncol.* 2010; **28**: 1566–72.
9 Kodashima S, Fujishiro M. Novel image-enhanced endoscopy with i-scan technology. *World J. Gastroenterol.* 2010; **16**: 1043–9.
10 Yoshizawa M, Osawa H, Yamamoto H *et al.* Diagnosis of elevated-type early gastric cancers by the optimal band imaging system. *Gastrointest. Endosc.* 2009; **69**: 19–28.
11 Hallas J, Dall M, Andries A *et al.* Use of single and combined antithrombotic therapy and risk of serious upper gastrointestinal bleeding: population based case–control study. *BMJ* 2006; **333**: 726.
12 Ono S, Fujishiro M, Kodashima S *et al.* Evaluation of safety of endoscopic biopsy without cessation of antithrombotic agents in Japan. *J. Gastroenterol.* 2012; **47**: 770–4.
13 Ishikawa S, Inaba T, Mizukawa S *et al.* Clinical study on performing upper gastrointestinal biopsy with small cup biopsy forceps in patients receiving antiplatelet agents. *Gastroenterol. Endosc.* 2013; **55**: 3357–67.
14 Fujita M, Shiotani A, Murao T *et al.* Safety of gastrointestinal endoscopic biopsy in patients taking antithrombotics. *Dig. Endosc.* 2015; **27**: 25–29.
15 Ara N, Iijima K, Maejima R *et al.* Prospective analysis of risk for bleeding after endoscopic biopsy without cessation of antithrombotics in Japan. *Dig. Endosc.* 2015; **27**: 458–64.
16 Manocha D, Singh M, Mehta N, Murthy UK. Bleeding risk after invasive procedures in aspirin/NSAID users: polypectomy study in veterans. *Am. J. Med.* 2012; **125**: 1222–7.
17 Feagins LA, Iqbal R, Harford WV *et al.* Low rate of postpolypectomy bleeding among patients who continue thienopyridine therapy during colonoscopy. *Clin. Gastroenterol. Hepatol.* 2013; **11**: 1325–32.
18 Tomoda T, Ueki T, Saito S *et al.* The safety of endoscopic sphincterotomy in patients receiving antiplatelet therapy. *Gastroenterol. Endosc.* 2014; **56**: 2150–5.
19 Sanomura Y, Oka S, Tanaka S *et al.* Continued use of low-dose aspirin does not increase the risk of bleeding during or after endoscopic submucosal dissection for early gastric cancer. *Gastric Cancer* 2014; **17**: 489–96.
20 Matsumura T, Arai M, Maruoka D *et al.* Risk factors for early and delayed post-operative bleeding after endoscopic submucosal dissection of gastric neoplasms, including patients with continued use of antithrombotic agents. *BMC Gastroenterol.* 2014; **14**: 172.
21 Ono S, Fujishiro M, Yoshida N *et al.* Thienopyridine derivatives as risk factors for bleeding following high risk endoscopic treatments: Safe Treatment on Antiplatelets (STRAP) study. *Endoscopy* 2015, DOI: 10.1055/s-0034-1391354

22 Ninomiya Y, Oka S, Tanaka S *et al*. Risk of bleeding after endoscopic submucosal dissection for colorectal tumors in patients with continued use of low-dose aspirin. *J. Gastroenterol.* 2015, DOI: 10.1007/s00535-015-1053-4
23 Anderson MA, Ben-Menachem T, Gan SI *et al*. Management of antithrombotic agents for endoscopic procedures. *Gastrointest. Endosc.* 2009; **70**: 1060–70.
24 Boustiere C, Veitch A, Vanbiervliet G *et al*. Endoscopy and antiplatelet agents. European Society of Gastrointestinal Endoscopy (ESGE) Guidelines. *Endoscopy* 2011; **43**: 445–61.
25 Cho SJ, Choi IJ, Kim CG *et al*. Aspirin use and bleeding risk after endoscopic submucosal dissection in patients with gastric neoplasms. *Endoscopy* 2012; **44**: 114–21.
26 Lim JH, Kim SG, Kim JW *et al*. Do antiplatelets increase the risk of bleeding after endoscopic submucosal dissection of gastric neoplasms? *Gastrointest. Endosc.* 2012; **75**: 719–27.
27 Koh R, Hirasawa K, Yahara S *et al*. Antithrombotic drugs are risk factors for delayed postoperative bleeding after endoscopic submucosal dissection for gastric neoplasms. *Gastrointest. Endosc.* 2013; **78**: 476–83.
28 Tounou S, Morita Y. Gastric and duodenal endoscopic submucosal dissection in patients on aspirin therapy has increased risk of hemorrhage but is feasible. *Gastroenterol. Endosc.* 2011; **53**: 3326–35.
29 Hayashi T, Doyama H, Takemura K *et al*. Evaluation of the risk and timing of bleeding after gastric endoscopic submucosal dissection with different antithrombotic therapies. *Gastroenterol. Endosc.* 2013; **55**: 1806–11.
30 Takeuchi T, Ota K, Harada S *et al*. The postoperative bleeding rate and its risk factors in patients on antithrombotic therapy who undergo gastric endoscopic submucosal dissection. *BMC Gastroenterol.* 2013; **13**: 136.
31 Takimoto K, Toyonaga T, Matsuyama K. Endoscopic tissue shielding to prevent delayed perforation associated with endoscopic submucosal dissection for duodenal neoplasms. *Endoscopy* 2012; **44** (Suppl 2 UCTN): E414–15.
32 Tsuji Y, Ohata K, Gunji T *et al*. Endoscopic tissue shielding method with polyglycolic acid sheets and fibrin glue to cover wounds after colorectal endoscopic submucosal dissection (with video). *Gastrointest. Endosc.* 2014; **79**: 151–5.
33 Nakayoshi T, Tajiri H, Matsuda K, Kaise M, Ikegami M, Sasaki H. Magnifying endoscopy combined with narrow band imaging system for early gastric cancer: correlation of vascular pattern with histopathology (including video). *Endoscopy* 2004; **36**: 1080–4.
34 Kaise M, Ohkura Y, Iizuka T *et al*. Endocytoscopy is a promising modality with high diagnostic accuracy for gastric cancer. *Endoscopy* 2014; **46**: 827–32.
35 Neumann H, Kiesslich R, Wallace MB, Neurath MF. Confocal laser endomicroscopy: technical advances and clinical applications. *Gastroenterology* 2010; **139**: 388–92.
36 Desai J, Granger CB, Weitz JI, Aisenberg J. Novel oral anticoagulants in gastroenterology practice. *Gastrointest. Endosc.* 2013; **78**: 227–39.
37 Inoue T, Nishida T, Maekawa A *et al*. Clinical features of post-polypectomy bleeding associated with heparin bridge therapy. *Dig. Endosc.* 2014; **26**: 243–9.
38 Rubboli A, Milandri M, Castelvetri C, Cosmi B. Meta-analysis of trials comparing oral anticoagulation and aspirin versus dual antiplatelet therapy after coronary stenting. Clues for the management of patients with an indication for long-term anticoagulation undergoing coronary stenting. *Cardiology* 2005; **104**: 101–6.