Current Practices in the Management of Antithrombotic Therapy During the Periendoscopic Period for Patients With Cardiovascular Disease

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Summary

The management of antithrombotics during the periendoscopic period is traditionally represented as a double-edged sword for cardiologists and endoscopists. Appropriate administration prevents thromboembolic events, whereas excessive administration provokes bleeding events. Therefore, cardiologists and endoscopists must consider the risks of bleeding and thromboembolism in individual cases, before deciding whether to continue antithrombotic use. Several guidelines exist concerning antithrombotic management in Asian and Western countries. These guidelines generally classify procedural bleeding risk and thromboembolic risk into high risk and low risk groups and recommend that the two risks be weighed when managing a given patient. Moreover, they generally do not recommend interrupting antithrombotics during the periendoscopic period unless absolutely necessary; however, the details surrounding this point differ among the guidelines after several revisions. In this review, we describe the present state, problems, and future perspectives concerning the management of antithrombotics in patients with cardiovascular disease undergoing gastrointestinal endoscopy. (Int Heart J 2016; 57: 530-534)

Key words: Gastrointestinal endoscopy, Bleeding, Thromboembolism, Guideline

Currently, gastrointestinal endoscopy plays an important role in the management of digestive disease. High resolution images from esophagagogastroduodenoscopy and colonoscopy enable detailed observations of the gastrointestinal mucosa, with image enhancement technology providing even more information as an “optical biopsy” compared with those enabled by conventional endoscopy. Endoscopic ultrasound sonography (EUS) provides a wealth of information about the mucosa of the gastrointestinal tract and indirectly assists when obtaining specimens using fine needle aspiration (FNA). Combining endoscopy and fluoroscopy is now mandatory in diagnosing biliary or pancreatic ductal disorders. Additionally, various endoscopic procedures, including biopsy and therapeutic procedures, can be performed through the endoscopes. However, these procedures are relatively invasive and are accompanied by varying risks of bleeding. For example, postoperative bleeding is reported to occur in 5–10% of patients undergoing endoscopic submucosal dissection (ESD), which can lead to life-threatening events. Therefore, the prevention of postoperative bleeding remains a major problem for endoscopists today.

Antithrombotic medicine is indispensable in daily clinical practice, especially in cardiovascular medicine. As the use of antithrombotics becomes more widely accepted for the primary and secondary preventions of cardiovascular and cerebrovascular events, the population of patients receiving antithrombotics will also increase. Dual antiplatelet therapy (DAPT) is accepted as a standard treatment after the implantation of drug eluting stents (DESs) in coronary arteries, whereas anticoagulant therapy is an established component in the prevention of thrombotic stroke in patients with atrial fibrillation. However, antithrombotics act as a double-edged sword that can prevent thromboembolic complications while provoking bleeding complications simultaneously. Gastrointestinal bleeding is one of the more well-known complications caused by antithrombotics. Furthermore, combining several antithrombotic agents significantly increases the risk of bleeding to a greater degree than does the use of a single agent. Because of its different risks and benefits, the management of patients receiving antithrombotics during the periendoscopic period has been a major concern for both cardiologists and endoscopists. However, their standpoints conflict, with the former placing greater emphasis on the risk of thromboembolism and the latter on the risk of bleeding.

The attitudes of endoscopists have gradually been changing over time. In 2011, Sung, et al conducted a randomized...
controlled study of patients with bleeding peptic ulcers who were receiving low-dose aspirin and reported that although the continuation of aspirin increased the rebleeding rate, it also decreased all-cause mortality rates. Thus, this important study demonstrated that antithrombotic discontinuation does not necessarily improve prognosis and has had a great impact on the endoscopy community. Key guidelines have since been revised based upon this idea.

In this review, we describe the recent advances in the use of antithrombotics in the clinical management of patients with cardiovascular disease undergoing gastrointestinal endoscopy.

Guidelines for Antithrombotic Management During the Periendoscopic Period

To minimize the risk of bleeding, longer cessation periods are preferred before endoscopy although they increase thromboembolic risks. Various guidelines concerning this dilemma have been issued worldwide. The American Society of Gastrointestinal Endoscopy (ASGE) guidelines published in 1998 were the first to propose the management of antithrombotics during the periendoscopic period. These guidelines emphasized the need to consider both the risk of bleeding associated with the endoscopic intervention and the risk of thromboembolic events associated with interrupted antithrombotic treatment. This practice continues today, though the estimates of the associated risks have fluctuated, with guideline revisions following accordingly.

In the revised ASGE guidelines issued in 2005, the risks of gastrointestinal endoscopy were categorized by the attendant bleeding risk of the endoscopic procedure and the attendant thromboembolic risk of the patient comorbidities requiring antithrombotic therapy. The guiding principle of these guidelines was that, considering the pros and cons, continued antithrombotic treatment could be acceptable for procedures with low risks of bleeding in patients at high risk of thromboembolism. However, the estimates of these risks were controversial because of the lack of sufficient evidence. The Japan Gastroenterological Endoscopy Society (JGES) issued guidelines in 2005 that continued to recommend the cessation of antithrombotics before endoscopic biopsy, despite the ASGE guidelines recommending continuation in that setting. Despite a lack of empirical evidence, this discrepancy between guidelines was based on presumed racial differences, with Asians known to have a higher bleeding risk and lower thromboembolic risk compared with that in whites. Since then, it has been demonstrated that thromboembolic events in Asians lead to severe clinical outcomes comparable to bleeding-related events in endoscopic procedures among whites. Thus, in 2012, the JGES guidelines were revised to emphasize the risk of thromboembolism over bleeding, thereby resolving the discrepancy between the JGES and ASGE guidelines.

The latest guidelines from various societies are summarized in Figure. As shown, differences in the details of the guidelines still prevail. A major reason for this is the lack of sufficient evidence based on clinical trials to establish reliable guidelines.

Biopsy and Low Bleeding Risk Procedures

Biopsy is a common procedure for assessing gastrointestinal disease and is generally categorized by the existing guidelines as having a low risk of bleeding. Biopsy is included in a category with balloon-assisted endoscopy, marking, stenting in the gastrointestinal tract and pancreatic-biliary duct, and endoscopic papillary balloon dilatation, as shown in Figure. The rate of bleeding accompanying these procedures is often too low to estimate accurately; thus, the rate underlying these procedures without discounting antithrombotics has not been evaluated.

We previously evaluated endoscopic bleeding time as a surrogate marker of bleeding after biopsy in patients receiving antithrombotics. Endoscopic bleeding time was defined as the time from biopsy to the confirmation of hemostasis after repetitive water flushes every 30 seconds. In the study, hemostasis after endoscopic biopsy using thin forceps was confirmed within approximately 2 minutes in most patients receiving antithrombotics. The number of antithrombotics received and the administration of warfarin did not affect the endoscopic bleeding time significantly. Furthermore, several reports have been...
published concerning the clinical feasibility of endoscopic biopsy without antithrombotic discontinuation, particularly in Japan where the use of endoscopic biopsy without antithrombotic discontinuation was only recently permitted.\textsuperscript{17,18}

Although there is no solid evidence concerning the safety of other procedures with low bleeding risk without antithrombotic discontinuation, it is thought that their risk is not significantly higher than that of endoscopic biopsy. As long as procedures are performed carefully, they can be assumed to be safe to perform without antithrombotic discontinuation, as recommended by many guidelines.

**Polyectomy, Endoscopic Mucosal Resection, and Endoscopic Submucosal Dissection**

Mucosal resection procedures, including polypectomy, endoscopic mucosal resection, and ESD, are categorized as procedures with high risks of bleeding. Although there have been discrepancies between the Western and JGES guidelines, current guidelines generally recommend antithrombotic discontinuation and the continuation of certain antithrombotic agents during the periendoscopic period considering the risk and severity of a possible thromboembolic event. However, there is not enough data of sufficient quality (high evidence level) to support this concept.

Among the procedures associated with a high bleeding risk, ESD is one of the most investigated concerning antithrombotic management. In retrospective studies in 2012, Cho, et al reported that aspirin administration induced postoperative bleeding after gastric ESD, whereas the report of Lim, et al contradicted this finding.\textsuperscript{19,20} Thus, the safety of gastric ESD without aspirin discontinuation was controversial. In 2014, Samotoura, et al studied the safety of gastric ESD without aspirin discontinuation in a single-center retrospective study.\textsuperscript{21} They concluded that aspirin continuation did not increase the risk of postoperative bleeding after gastric ESD. To further this research, we conducted a multicenter prospective study in 2015 to evaluate the safety of gastric ESD without aspirin discontinuation. In our study, gastric ESD while continuing aspirin alone was feasible and safe, but gastric ESD treatment combined with aspirin and a thienopyridine derivative increased the risk of postoperative bleeding after resuming the latter.\textsuperscript{22} In contrast, it was reported that a single dose of clopidogrel, a thienopyridine derivative, did not increase the risk of postoperative bleeding after colonic polypectomy.\textsuperscript{23} Because their use is expected to increase in cardiology, further investigation regarding their effect on gastric ESD is required.

**Endoscopy in Biliary-PANCREATIC SYSTEM AND INTERVENTIONS**

Endoscopic retrograde cholangiopancreatography (ERCP) without endoscopic sphincterotomy (EST) is categorized as a low bleeding risk procedure in the JGES, ASGE, and European Society of Gastrointestinal Endoscopy (ESGE) guidelines. This is because postoperative bleeding after ERCP is reported to be related to EST. As such, antithrombotic continuation is permitted for ERCP without EST in contrast to ERCP with EST, which is categorized as having a high risk of bleeding. Post-procedural bleeding after EST is reported to be approximately 6% higher than the rate for endoscopic papillary balloon dilatation (EBPD).\textsuperscript{24}

For ERCP with EST, all 3 guidelines permit aspirin continuation, but the feasibility of EST with aspirin continuation is still debated because only a few studies have investigated the matter, and among them, the results have varied. Hussain, et al evaluated the safety of EST with aspirin continuation in a case-control study and concluded that antiplatelet agents do not increase the risk of postoperative bleeding after EST.\textsuperscript{25} Conversely, Hui, et al evaluated the safety of EST with aspirin continuation in a retrospective study.\textsuperscript{26} They concluded that aspirin continuation increased the risk of postoperative bleeding even when there was a discontinuation period of one week before EST. Recently, Hamada, et al analyzed a large number of EST and EPBD cases from a nationwide administrative database in Japan and concluded that both procedures could be safely performed in patients receiving antiplatelet agents, although post-procedural bleeding risk might be increased in patients receiving anticoagulants.\textsuperscript{27} Taken together, the guidelines indicate that continuation of aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) can be acceptable when performing ERCP with EST or EPBD but the continuation of anticoagulants should be avoided.

**Endoscopic Ultrasonography and Interventions**

In the JGES, ASGE, and ESGE guidelines, EUS without FNA is categorized as a procedure with a low risk of bleeding. Thus, it is acceptable to continue antithrombotics for EUS as long as FNA is not performed in conjunction. In contrast, all 3 major guidelines state that EUS with FNA is associated with a high risk of bleeding. Aspirin continuation leading up to the procedures is permissible, but discontinuation of thienopyridine derivatives and anticoagulants is recommended. Kien-Fong, et al evaluated the safety of EUS with FNA in patients receiving aspirin, NSAI\textregistered{}Ds, or low molecular weight heparin (LMWH). In their prospective, controlled study, they found bleeding rates of 0%, 33.3%, and 3.7% in patients receiving aspirin/NSAI\textregistered{}Ds, LMWH, and no agent, respectively.\textsuperscript{28} Although EUS with FNA is acceptable while taking aspirin, further data is needed to ensure its safety.

**Percutaneous Endoscopic Gastrostomy**

In the guidelines prepared by endoscopic societies, percutaneous endoscopic gastrostomy is categorized as a procedure with a high risk of bleeding. The bleeding risk is associated not with the endoscopic procedures themselves but with the manual procedures necessary to penetrate the abdominal and gastric walls. Bleeding complications are reported in 2.5% of such cases. However, the use of antithrombotics as a risk factor of postoperative bleeding is controversial, with Ruthmann, et al reporting it as a risk factor and Richter, et al reporting the contrary.\textsuperscript{29,30}

**Anticoagulants, Novel Oral Anticoagulants, and Heparinization**

Because patients receiving anticoagulants are, by their diagnoses, at a high risk of thromboembolic events, many guidelines recommend avoiding careless withdrawal of anticoagulants during the periendoscopic period. Anticoagulants are categorized as either warfarins or novel oral anticoagulants
(NOACs; eg, dabigatran, apixaban, rivaroxaban, or edoxaban); the former are indirect inhibitors, whereas the latter are direct inhibitors of the coagulation system. Because of the difference in the mechanisms of action, patients receiving warfarin require longer time for the recovery of the coagulation system compared with those receiving NOACs. Therefore, transient heparinization (heparin bridge) has become a common practice for patients receiving warfarin. However, it has been reported that the heparin bridge does not prevent thromboembolic events effectively, despite increasing the postoperative bleeding. Recently, Douketis, et al reported the clinical outcomes of perioperative heparin bridging in patients with atrial fibrillation. They concluded that this approach may increase the risk of major bleeding, but it does not decrease the risk of thromboembolism perioperatively. Additionally, heparin bridging for patients receiving NOACs is controversial because of its short duration. Taking these studies into perspective, we cannot conclusively evaluate the matter without further evidence.

Future Perspective

The management of antithrombotics periendoscopically should not be decided by endoscopists in isolation. This is because the thromboembolic risks associated with comorbidities should be evaluated by the physicians who prescribed the antithrombotics. Therefore, upcoming guidelines should also consider the latest evidence in other fields. For example, continuation periods for antithrombotics are still controversial after DES implantation in coronary arteries, with many clinical trials having addressed the topic. A meta-analysis of these data indicated that a longer DAPT period increased the bleeding risk but did not decrease the stent thrombosis risk compared with those of a shorter DAPT period. Depending on the results of these clinical trials, future guidelines may recommend postponing endoscopic procedures until there is a step down from DAPT to single antiplatelet therapy. Additionally, single antiplatelet therapy after DAPT is controversial because thienopyridine derivatives are reported to be more effective in preventing stent thrombosis compared with aspirin. Moreover, the use of biodegradable stents in coronary arteries may bring about a massive change in the use of antithrombotics. To ensure that upcoming guidelines are comprehensive, it will be necessary to be able to respond flexibly to upcoming trends in the treatment of cardiovascular disease.

Conclusion: Taken together, the guidelines concerning the management of antithrombotics during the periendoscopic period are gradually being unified. There is a clear move toward antithrombotic discontinuation only if absolutely necessary and only after careful consideration; however, discrepancies among the guidelines remain, which is largely because of insufficient evidence. Future guidelines should be adapted for daily clinical practice of incorporating novel endoscopic procedures and agents. Finally, we recommend that all guidelines should be unified based on sufficient solid evidence.

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References


