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MINIREVIEWS

Clinical problems with antithrombotic therapy for endoscopic submucosal dissection for gastric neoplasms

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Abstract

Endoscopic submucosal dissection (ESD) is minimally invasive and thus has become a widely accepted treatment for gastric neoplasms, particularly for patients with comorbidities. Antithrombotic agents are used to prevent thrombotic events in patients with comorbidities such as cardio-cerebrovascular diseases and atrial fibrillation. With appropriate cessation, antithrombotic therapy does not increase delayed bleeding in low thrombosis-risk patients. However, high thrombosis-risk patients are often treated with combination therapy with antithrombotic agents and occasionally require the continuation of antithrombotic agents or heparin bridge therapy (HBT) in the perioperative period. Dual antiplatelet therapy (DAPT), a representative combination therapy, is frequently used after placement of drug-eluting stents and has a high risk of delayed bleeding. In patients receiving DAPT, gastric ESD may be postponed until DAPT is no longer required. HBT is often required for patients treated with anticoagulants and has an extremely high bleeding risk. The continuous use of warfarin or direct oral anticoagulants may be possible alternatives. Here, we show that some antithrombotic therapies in high thrombosis-risk patients increase delayed bleeding after gastric ESD, whereas most antithrombotic therapies do not. The management of high thrombosis-risk patients is crucial for improved

outcomes.

Key words: Antithrombotic therapy; Endoscopic submucosal dissection; Heparin bridge therapy; Dual antiplatelet therapy; Delayed bleeding

Core tip: It is unclear if antithrombotic therapy increases delayed bleeding after endoscopic submucosal dissection (ESD) of gastric neoplasms. With appropriate cessation, antithrombotic therapy does not increase delayed bleeding in low thrombosis-risk patients. However, high thrombosis-risk patients are often treated with combination therapy with antithrombotic agents, such as dual antiplatelet therapy (DAPT), and occasionally require the continuation of antithrombotic agents or heparin bridge therapy (HBT) in the perioperative period. Both patients with DAPT and HBT have a high risk of delayed bleeding. The management of these antithrombotic therapies is important in the perioperative period of ESD.

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INTRODUCTION

Endoscopic resection of early gastric cancer (EGC) has been developed and applied to many patients since the establishment of criteria for node-negative cancers[1] and the advancement of endoscopic submucosal dissection (ESD)[2,3]. In multicenter studies, we have reported that ESD is a feasible method for the treatment of EGC[4] and that the long-term outcome of gastric ESD is satisfactory[5]. A risk of metachronous gastric cancer exists following ESD or endoscopic mucosal resection, even when the procedure is curative[6,7]. The cumulative 3-year risk is 5.9%[7]. However, we also demonstrated that nearly all secondary cancers after ESD (97%) were treatable by repeated ESD following scheduled endoscopic surveillance[5]. Consequently, ESD can preserve the entire stomach and improve patient post-operative quality of life. Therefore, ESD has become a more acceptable treatment option for EGC than gastrectomy, particularly for patients with comorbidities[8].

Delayed bleeding is one of the major complications of gastric ESD, and the delayed bleeding rate is 3.1%-6.5%[4,9,10]. In most cases, delayed bleeding is treated successfully by endoscopic hemostasis; however, some patients require transfusion or surgery, and these situations can be fatal[11]. The reported risk factors for delayed bleeding include larger lesions[10], lesions with ulceration[10,12], and longer procedure time[1,13]. The risk is highest for lesions in the middle and lower third[9]. Electronic coagulation of vessels in the ulcer bed after ESD was reported to decrease delayed bleeding[9]. In our analysis, half of delayed bleeding occurred the day of ESD or the next day, and the remainder occurred within 2 wk, with the exception of 1 case that occurred 22 d after ESD[14]. It has been argued that second-look endoscopy after ESD prevents delayed bleeding. However, Goto *et al*[15] showed that second-look endoscopy did not decrease delayed bleeding in a retrospective analysis. A prospective randomized control study also denied a preventive effect of second-look endoscopy for delayed bleeding[16].

Antithrombotic therapy, including antiplatelet agents and anticoagulants, is increasingly used worldwide to prevent cerebro-cardiovascular events[17,18]. These prophylactic agents reduce the risks of thromboembolic events but simultaneously increase the risk of bleeding complications. Most patients with EGC are elderly, and these patients commonly exhibit several comorbidities that require medical treatment, particularly antithrombotic therapy. Risks for delayed bleeding after ESD in patients with antithrombotic therapy depend on the type of endoscopic treatment and the use of antithrombotic therapy.

In this review, we discuss the problems of antithrombotic therapy associated with delayed bleeding after gastric ESD. This review is not a systematic review because of the limited evidence and the variety of patients with various comorbidities receiving many types of antithrombotic agents. However, we searched the entire MEDLINE database to identify the literature on antithrombotic therapy and gastric ESD and included as many studies as possible.

EFFECT OF ANTIPLATELET AGENTS ON GASTRIC ESD

Antiplatelet agents are used to prevent platelet aggregation for prophylaxis of secondary cerebro-cardioembolic events after the occurrence of stroke or ischemic heart disease[19]. Antiplatelet agents include thienopyridines, protease-activated receptor-1 inhibitors, glycoprotein IIb/IIIa receptor inhibitors, aspirin and non-steroidal anti-inflammatory drugs. When patients exhibit a low risk of thrombosis, antithrombotic agents can be discontinued. Antithrombotic therapy with appropriate cessation is not considered to increase delayed bleeding rates[14,20]. In some high thrombosis-risk patients, it is difficult to discontinue antithrombotic therapy during the perioperative period of ESD. Administration of these antithrombotic agents in combination further complicates the management of these agents. In these patients, the continuous use of minimum antithrombotic agents during ESD is an option.

The recent guidelines of the American Society for Gastrointestinal Endoscopy (ASGE) in 2016[21] and

the Japan Gastroenterological Endoscopy Society in 2014[22] recommend the continuous use of aspirin during endoscopic procedures in high thrombosis-risk patients, even if the procedures carry a high risk of bleeding. For gastric ESD, a multivariate analysis[23-25] found that the continuous use of aspirin did not increase delayed bleeding, supporting the application of this treatment; however, the delayed bleeding rate was slightly increased (3.6%-21.1%)[23-26]. Moreover, the delayed bleeding rate was considerably higher in patients receiving dual antiplatelet therapy (DAPT) with continuous aspirin and cessation of thienopyridines (35.5%) than in patients who did not receive antithrombotic medications[25].

For patients with coronary artery stents, DAPT with aspirin plus thienopyridines is recommended for 30 d after placement of a bare metal stent and for one year after placement of a drug-eluting stent (DES)[27]. Cessation of these agents within the period resulted in a high risk of stent thrombosis[28]. Thus, according to the consensus statement from the American College of Cardiology Foundation and the American College of Gastroenterology, it is recommended to defer elective endoscopic procedures up to 12 mo from the time of DES placement and perform endoscopic procedures 5 to 7 d after thienopyridine cessation[29]. In addition, aspirin should be continued throughout the perioperative period, and thienopyridine should be resumed once hemostasis is achieved[29]. The timing of ESD for EGC should be decided based on the balance of cancer progression and bleeding risk. EGC often remains in the early stage for a period[30]. Thus, ESD can be delayed in patients with DES placement, provided that the EGC lesion is still considered resectable after the completion of required DAPT.

The management of patients with DAPT for ESD is difficult. A delayed bleeding rate as high as 35.5%[25] was reported when ESD was performed with continuous aspirin and cessation of thienopyridines following the guidelines[21,22,29]. Moreover, patients receiving DAPT for ESD face thrombotic risk from the cessation of thienopyridines, and this thrombotic risk can be increased if delayed bleeding occurs[11,14]. However, it is sometimes necessary to perform ESD in patients with DAPT with continuous aspirin and cessation of thienopyridines who have a risk of delayed bleeding and thrombosis. Care must be taken to identify the initial symptoms of delayed bleeding and thrombotic events. There is insufficient evidence for methods to minimize both bleeding risk and thrombotic risk during DAPT, and we have no data on cases of continuous administration of both aspirin and thienopyridines or cessation of aspirin and continuous thienopyridines.

EFFECTS OF ANTICOAGULANTS ON GASTRIC ESD

Anticoagulants prevent thrombotic events in patients with conditions such as arterial fibrillation (AF) and deep vein thrombosis by interfering with the native clotting cascade. Anticoagulants include oral warfarin, direct oral anticoagulants (DOACs: Dabigatran, rivaroxaban, apixaban, and edoxaban), and heparin derivatives.

The risk of thromboembolism associated with withdrawal of anticoagulants varies considerably. AF is the most common reason for the use of anticoagulant therapy, and the risk of thrombotic events is approximately 1% when anticoagulation is interrupted for 4 to 7 d[31,32]. Thrombotic events can cause serious complications and can be fatal. Thus, all patients on anticoagulant therapy are recommended to be treated as having a high risk of thrombosis[22]. Thus, for the cessation of anticoagulants, heparin bridge therapy (HBT) is required to prevent thrombotic events during the perioperative period[33-35]. However, ESD with HBT carries an extremely high risk of delayed bleeding, with a delayed bleeding rate of 23.8%-37.5% as we previously reported[14,36-38].

DOACs are administered without the need to monitor their effects due to their rapid action and effectiveness in preventing cerebrovascular events[39-42]. Before endoscopic procedures, 1 to 3 d of cessation is recommended in patients without renal dysfunction according to the ASGE guideline[21] based on the half-lives of the agents (8-15 h)[39-42]. According to the British Society of Gastroenterology and ESGE guidelines, at least 2 d of cessation is recommended before endoscopic procedures[43]. By contrast, warfarin requires 5 d of cessation to cancel the effect[44], and HBT is required during this period. After the procedure, DOACs should be re-administered without heparin because DOACs achieve their maximum effect shortly (1-4 h) after re-administration, in contrast to warfarin[39-42,45]. Thus, shorter perioperative periods of controlling anticoagulant effects can be applied for DOACs compared with warfarin.

Unfortunately, no study has examined the effect of DOACs on endoscopic procedures except our following conference paper. For gastric ESD for patients, we observed a delayed bleeding rate of 16.7% (3/18) in patients using DOACs, which did not differ significantly from the delayed bleeding rate of 23.5% (4/17) observed in patients using warfarin during the same period[46]. However, the hospitalization period was significantly shorter in patients on DOACs compared with those on warfarin (8 d *vs* 14 d: $P < 0.01$) because the period of HBT was shorter[46]. Further investigations are needed to understand the effect of DOACs on endoscopic procedures.

In high thrombosis-risk patients with comorbidities, combination use of antiplatelet agents and anticoagulants is occasionally required, which also increases delayed bleeding[14].

TIMING OF DELAYED BLEEDING

Koh *et al*[47] reported that antithrombotic therapy was a risk factor for late bleeding [later than post-operative

Table 1 Multivariate analysis of risk factors for delayed bleeding: Antithrombotic therapy and patient and lesion characteristics

Ref.	No. of patients	Risk factor identified by multivariate analysis	OR (95%CI)	Risk factors identified by univariate analysis
Furuhata *et al*[36]	1781	HBT Multiple antithrombotic agents Lower third location Operation time longer than 100 min	10.04 (4.35-23.16) 5.44 (2.00-14.79) 2.17 (1.32-3.58) 2.00 (1.25-3.20)	HBT, multiple antithrombotic agents, tumor size greater than 20 mm, lower third location, UL+ tumors, operation time longer than 100 min, and cardiovascular disease
Matsumura *et al*[37]	413	CKD undergoing hemodialysis HBT Lesion size greater than 40 mm	33.86 (4.72-242.74) 5.77 (1.67-19.96) 3.70 (1.09-12.52)	HBT, tumor size over 40 mm, CKD undergoing hemodialysis

HBT: Heparin bridge therapy; CKD: Chronic kidney disease.

day (POD) 5]. Tounou *et al*[25] reported late bleeding (later than POD 8) was significantly more frequent in cases with DAPT but not cases with single aspirin therapy. In cases with HBT, the timing of delayed bleeding was later than in cases without HBT (POD 3.8 ± 4.1 *vs* POD 8.0 ± 5.7, $P < 0.05$)[14]. In cases without HBT, half of delayed bleeding cases occurred on POD 0 and 1; however, in cases with HBT, only 10% of the cases occurred on POD 0 and 1[14].

IS HBT FEASIBLE FOR GASTRIC ESD?

A recent, randomized control study compared discontinued anticoagulant use with or without HBT in 1884 surgical cases and revealed that HBT did not reduce perioperative arterial thromboembolism but significantly increased major bleeding complications[48]. A meta-analysis of studies of elective invasive procedures or surgeries revealed that warfarin-treated patients receiving bridge therapy with low-molecular-weight heparin appear to be at an increased risk of both overall and major bleeding and exhibited a similar risk of thromboembolic events as non-bridged patients[49].

Another randomized control study involving 681 cases of pacemaker or defibrillator surgery revealed that bleeding complications occurred less frequently in patients with continuous warfarin use than in patients in whom warfarin was discontinued with HBT[50]. Additional meta-analyses supported these results[51].

Considering these findings together, continuous use of warfarin throughout the perioperative period is a better choice than HBT because continuous use of warfarin likely does not increase bleeding complications and exhibits the same risk for thrombosis. None of them are originated of the outcome of endoscopic procedures nor gastric ESD, these results will change our treatment. Tounou *et al*[52] reported a case of gastric ESD safely performed with continuous use of warfarin; however, further investigation is needed, such as a randomized study comparing gastric ESD with continuous ESD and with HBT.

For patients requiring HBT, continuous use of warfarin and switching warfarin to DOACs are candidate new strategies, although data to support their use are lacking.

ANALYSIS OF BLEEDING RISK IN ANTITHROMBOTIC THERAPY BY COMPARING PATIENT AND LESION CHARACTERISTICS

High thrombosis-risk patients are often at a high risk of delayed bleeding under antithrombotic therapy with multiple agents, particularly patients with HBT and accompanying comorbidities. The antithrombotic therapies, patient comorbidities and EGC characteristics with the highest risks for delayed bleeding remain unclear.

Furuhata *et al*[36] conducted a multivariate analysis of these factors and identified HBT (OR = 10.04), multiple antithrombotic agents (OR = 5.44), the lower third of the stomach (OR = 2.17), and an operation time longer than 100 min (OR = 2.00) as independent risk factors. Matsumura *et al*[37] identified chronic kidney disease (CKD) undergoing hemodialysis (OR = 33.86), HBT (OR = 5.77) and a lesion size greater than 40 mm (OR = 3.70) as risk factors (Table 1).

We performed a bleeding risk analysis in 1563 consecutive patients with 1671 gastric neoplasms treated by ESD[53] as an extended analysis of our previous study[11] (unpublished data). This study included 283 (18%) patients receiving antithrombotic agents who all discontinued the agents before ESD. The delayed bleeding rates were similar between patients receiving no antithrombotic therapy and those who discontinued antithrombotic agents without HBT (5.6% *vs* 4.9%); however, the delayed bleeding rate was significantly higher (21.9%) in patients with HBT ($P < 0.01$). Moreover, the delayed bleeding rate increased in proportion to the number of discontinued drugs (two drugs: 15.6%, $P < 0.01$; three drugs: 27.3%, $P < 0.05$). Patients on warfarin or ticlopidine had a significant risk of delayed bleeding compared with patients receiving no antithrombotic agent. In a univariate analysis of tumor and patient factors, tumor size greater than 30 mm, tumor in the middle third of the stomach, tumor with ulceration, patients with CKD and male gender were identified as risk factors for delayed bleeding.

Multivariate analysis showed that HBT (OR = 6.14), lesion in the middle third of the stomach (OR = 2.21),

ulceration in tumor (OR = 1.97) and tumor size greater than 30 mm (OR = 1.75) were significant, independent risk factors for delayed bleeding. HBT (OR = 16.43) and CKD (OR = 6.34) were identified as significant risk factors for blood transfusions by multivariate analysis.

The results of these studies show that HBT is the most significant independent factor for delayed bleeding compared with other factors involving patient and lesion characteristics.

THROMBOTIC EVENTS

Few studies of the relationship between thrombotic events and endoscopic procedures have been conducted, and incidence rates of thrombotic events related to gastric ESD of 0%-4.2% have been reported[14,20,23,54]. We observed one patient who developed a thrombotic event[14]. This patient received HBT during the peri-operative period and exhibited delayed bleeding on POD 10. After successful endoscopic hemostasis, we restarted heparin, and his activated partial thromboplastin time was sufficiently prolonged on POD 11. However, a cerebral infarction developed on POD 13. This case suggests that delayed bleeding can lead to thrombotic events by reducing intravascular volume and causing hypercoagulability after bleeding. Numata *et al*[11] also reported a case of femoral artery infarction consequent to delayed bleeding after gastric ESD that led to death. These findings suggest that the prevention of delayed bleeding is important for preventing thrombotic events in patients at a high risk for thromboembolism.

CONCLUSION

Most antithrombotic therapies do not increase the risk of delayed bleeding during gastric ESD; however, patients receiving multiple antithrombotic agents, including DAPT, and patients on anticoagulants requiring HBT have a high risk for delayed bleeding. These high thrombosis-risk patients with accompanying comorbidities may have a high risk of delayed bleeding under strong antithrombotic therapy.

To prevent the exposure of these patients to a serious risk of acute ischemic events, new strategies should be developed to replace HBT and to address DAPT. Well-designed prospective and comparative clinical studies are needed to obtain further evidence regarding the management of antithrombotic therapy.

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REFERENCES

1 **Gotoda T**, Yanagisawa A, Sasako M, Ono H, Nakanishi Y, Shimoda T, Kato Y. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. *Gastric Cancer* 2000; **3**: 219-225 [PMID: 11984739 DOI: 10.1007/PL00011720]

2 **Yamamoto H**, Kawata H, Sunada K, Satoh K, Kaneko Y, Ido K, Sugano K. Success rate of curative endoscopic mucosal resection with circumferential mucosal incision assisted by submucosal injection of sodium hyaluronate. *Gastrointest Endosc* 2002; **56**: 507-512 [PMID: 12297765 DOI: 10.1067/mge.2002.128108]

3 **Oyama T**, Tomori A, Hotta K, Morita S, Kominato K, Tanaka M, Miyata Y. Endoscopic submucosal dissection of early esophageal cancer. *Clin Gastroenterol Hepatol* 2005; **3**: S67-S70 [PMID: 16013002 DOI: 10.1016/S1542-3565(05)00291-0]

4 **Akasaka T**, Nishida T, Tsutsui S, Michida T, Yamada T, Ogiyama H, Kitamura S, Ichiba M, Komori M, Nishiyama O, Nakanishi F, Zushi S, Nishihara A, Iijima H, Tsujii M, Hayashi N. Short-term outcomes of endoscopic submucosal dissection (ESD) for early gastric neoplasm: multicenter survey by osaka university ESD study group. *Dig Endosc* 2011; **23**: 73-77 [PMID: 21198921 DOI: 10.1111/j.1443-1661.2010.01062.x]

5 **Kato M**, Nishida T, Yamamoto K, Hayashi S, Kitamura S, Yabuta T, Yoshio T, Nakamura T, Komori M, Kawai N, Nishihara A, Nakanishi F, Nakahara M, Ogiyama H, Kinoshita K, Yamada T, Iijima H, Tsujii M, Takehara T. Scheduled endoscopic surveillance controls secondary cancer after curative endoscopic resection for early gastric cancer: a multicentre retrospective cohort study by Osaka University ESD study group. *Gut* 2013; **62**: 1425-1432 [PMID: 22914298 DOI: 10.1136/gutjnl-2011-301647]

6 **Nasu J**, Doi T, Endo H, Nishina T, Hirasaki S, Hyodo I. Characteristics of metachronous multiple early gastric cancers after endoscopic mucosal resection. *Endoscopy* 2005; **37**: 990-993 [PMID: 16189772 DOI: 10.1055/s-2005-870198]

7 **Nakajima T**, Oda I, Gotoda T, Hamanaka H, Eguchi T, Yokoi C, Saito D. Metachronous gastric cancers after endoscopic resection: how effective is annual endoscopic surveillance? *Gastric Cancer* 2006; **9**: 93-98 [PMID: 16767364 DOI: 10.1007/s10120-006-0372-9]

8 **Nishida T**, Kato M, Yoshio T, Akasaka T, Yoshioka T, Michida T, Yamamoto M, Hayashi S, Hayashi Y, Tsujii M, Takehara T. Endoscopic submucosal dissection in early gastric cancer in elderly patients and comorbid conditions. *World J Gastrointest Endosc* 2015; **7**: 524-531 [PMID: 25992191 DOI: 10.4253/wjge.v7.i5.524]

9 **Takizawa K**, Oda I, Gotoda T, Yokoi C, Matsuda T, Saito Y, Saito D, Ono H. Routine coagulation of visible vessels may prevent delayed bleeding after endoscopic submucosal dissection--an analysis of risk factors. *Endoscopy* 2008; **40**: 179-183 [PMID: 18322872 DOI: 10.1055/s-2007-995530]

10 **Okada K**, Yamamoto Y, Kasuga A, Omae M, Kubota M, Hirasawa T, Ishiyama A, Chino A, Tsuchida T, Fujisaki J, Nakajima A, Hoshino E, Igarashi M. Risk factors for delayed bleeding after endoscopic submucosal dissection for gastric neoplasm. *Surg Endosc* 2011; **25**: 98-107 [PMID: 20549245 DOI: 10.1007/s00464-010-1137-4]

11 **Numata N**, Oka S, Tanaka S, Higashiyama M, Sanomura Y, Yoshida S, Arihiro K, Chayama K. Clinical outcomes of endoscopic submucosal dissection for early gastric cancer in patients with chronic kidney disease. *J Gastroenterol Hepatol* 2013; **28**: 1632-1637 [PMID: 23808356 DOI: 10.1111/jgh.12320]

12 **Mukai S**, Cho S, Kotachi T, Shimizu A, Matuura G, Nonaka M, Hamada T, Hirata K, Nakanishi T. Analysis of delayed bleeding after endoscopic submucosal dissection for gastric epithelial neoplasms. *Gastroenterol Res Pract* 2012; **2012**: 875323 [PMID: 22536221 DOI: 10.1155/2012/875323]

13 **Toyokawa T**, Inaba T, Omote S, Okamoto A, Miyasaka R, Watanabe K, Izumikawa K, Horii J, Fujita I, Ishikawa S, Morikawa T, Murakami T, Tomoda J. Risk factors for perforation and delayed bleeding associated with endoscopic submucosal dissection for

early gastric neoplasms: analysis of 1123 lesions. *J Gastroenterol Hepatol* 2012; **27**: 907-912 [PMID: 22142449 DOI: 10.1111/j.1440-1746.2011.07039.x]

14 **Yoshio T**, Nishida T, Kawai N, Yuguchi K, Yamada T, Yabuta T, Komori M, Yamaguchi S, Kitamura S, Iijima H, Tsutsui S, Michida T, Mita E, Tsujii M, Takehara T. Gastric ESD under Heparin Replacement at High-Risk Patients of Thromboembolism Is Technically Feasible but Has a High Risk of Delayed Bleeding: Osaka University ESD Study Group. *Gastroenterol Res Pract* 2013; **2013**: 365830 [PMID: 23843783 DOI: 10.1155/2013/365830]

15 **Goto O**, Fujishiro M, Kodashima S, Ono S, Niimi K, Hirano K, Yamamichi N, Koike K. A second-look endoscopy after endoscopic submucosal dissection for gastric epithelial neoplasm may be unnecessary: a retrospective analysis of postendoscopic submucosal dissection bleeding. *Gastrointest Endosc* 2010; **71**: 241-248 [PMID: 19922919 DOI: 10.1016/j.gie.2009.08.030]

16 **Mochizuki S**, Uedo N, Oda I, Kaneko K, Yamamoto Y, Yamashina T, Suzuki H, Kodashima S, Yano T, Yamamichi N, Goto O, Shimamoto T, Fujishiro M, Koike K. Scheduled second-look endoscopy is not recommended after endoscopic submucosal dissection for gastric neoplasms (the SAFE trial): a multicentre prospective randomised controlled non-inferiority trial. *Gut* 2015; **64**: 397-405 [PMID: 25301853 DOI: 10.1136/gutjnl-2014-307552]

17 **Lansberg MG**, O'Donnell MJ, Khatri P, Lang ES, Nguyen-Huynh MN, Schwartz NE, Sonnenberg FA, Schulman S, Vandvik PO, Spencer FA, Alonso-Coello P, Guyatt GH, Akl EA. Antithrombotic and thrombolytic therapy for ischemic stroke: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; **141**: e601S-e636S [PMID: 22315273 DOI: 10.1378/chest.11-2302]

18 **Levine GN**, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, Chambers CE, Ellis SG, Guyton RA, Hollenberg SM, Khot UN, Lange RA, Mauri L, Mehran R, Moussa ID, Mukherjee D, Nallamothu BK, Ting HH. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol* 2011; **58**: e44-122 [PMID: 22070834 DOI: 10.1016/j.jacc.2011.08.007]

19 **D'Agostino RB**, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 2008; **117**: 743-753 [PMID: 18212285 DOI: 10.1161/CIRCULATIONAHA.107.699579]

20 **Ono S**, Fujishiro M, Niimi K, Goto O, Kodashima S, Yamamichi N, Omata M. Technical feasibility of endoscopic submucosal dissection for early gastric cancer in patients taking anti-coagulants or anti-platelet agents. *Dig Liver Dis* 2009; **41**: 725-728 [PMID: 19230799 DOI: 10.1016/j.dld.2009.01.007]

21 **Acosta RD**, Abraham NS, Chandrasekhara V, Chathadi KV, Early DS, Eloubeidi MA, Evans JA, Faulx AL, Fisher DA, Fonkalsrud L, Hwang JH, Khashab MA, Lightdale JR, Muthusamy VR, Pasha SF, Saltzman JR, Shaukat A, Shergill AK, Wang A, Cash BD, DeWitt JM. The management of antithrombotic agents for patients undergoing GI endoscopy. *Gastrointest Endosc* 2016; **83**: 3-16 [PMID: 26621548 DOI: 10.1016/j.gie.2015.09.035]

22 **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. Guidelines for gastroenterological endoscopy in patients undergoing antithrombotic treatment. *Dig Endosc* 2014; **26**: 1-14 [PMID: 24215155 DOI: 10.1111/den.12183]

23 **Lim JH**, Kim SG, Kim JW, Choi YJ, Kwon J, Kim JY, Lee YB, Choi J, Im JP, Kim JS, Jung HC, Song IS. Do antiplatelets increase the risk of bleeding after endoscopic submucosal dissection of gastric neoplasms? *Gastrointest Endosc* 2012; **75**: 719-727 [PMID: 22317881 DOI: 10.1016/j.gie.2011.11.034]

24 **Cho SJ**, Choi IJ, Kim CG, Lee JY, Nam BH, Kwak MH, Kim HJ, Ryu KW, Lee JH, Kim YW. Aspirin use and bleeding risk after endoscopic submucosal dissection in patients with gastric neoplasms. *Endoscopy* 2012; **44**: 114-121 [PMID: 22271021 DOI: 10.1055/s-0031-1291459]

25 **Tounou S**, Morita Y, Hosono T. Continuous aspirin use does not increase post-endoscopic dissection bleeding risk for gastric neoplasms in patients on antiplatelet therapy. *Endosc Int Open* 2015; **3**: E31-E38 [PMID: 26134769 DOI: 10.1055/s-0034-1390764]

26 **Sanomura Y**, Oka S, Tanaka S, Numata N, Higashiyama M, Kanao H, Yoshida S, Ueno Y, Chayama K. 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**: 489-496 [PMID: 24142107 DOI: 10.1007/s10120-013-0305-3]

27 **Grines CL**, Bonow RO, Casey DE, Gardner TJ, Lockhart PB, Moliterno DJ, O'Gara P, Whitlow P. Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents: a science advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians. *Circulation* 2007; **115**: 813-818 [PMID: 17224480 DOI: 10.1161/CIRCULATIONAHA.106.180944]

28 **Eisenberg MJ**, Richard PR, Libersan D, Filion KB. Safety of short-term discontinuation of antiplatelet therapy in patients with drug-eluting stents. *Circulation* 2009; **119**: 1634-1642 [PMID: 19289638 DOI: 10.1161/CIRCULATIONAHA.108.813667]

29 **Becker RC**, Scheiman J, Dauerman HL, Spencer F, Rao S, Sabatine M, Johnson DA, Chan F, Abraham NS, Quigley EM. Management of platelet-directed pharmacotherapy in patients with atherosclerotic coronary artery disease undergoing elective endoscopic gastrointestinal procedures. *Am J Gastroenterol* 2009; **104**: 2903-2917 [PMID: 19935784 DOI: 10.1038/ajg.2009.667]

30 **Tsukuma H**, Oshima A, Narahara H, Morii T. Natural history of early gastric cancer: a non-concurrent, long term, follow up study. *Gut* 2000; **47**: 618-621 [PMID: 11034575 DOI: 10.1136/gut.47.5.618]

31 **Garcia DA**, Regan S, Henault LE, Upadhyay A, Baker J, Othman M, Hylek EM. Risk of thromboembolism with short-term interruption of warfarin therapy. *Arch Intern Med* 2008; **168**: 63-69 [PMID: 18195197 DOI: 10.1001/archinternmed.2007.23]

32 **Blacker DJ**, Wijdicks EF, McClelland RL. Stroke risk in anticoagulated patients with atrial fibrillation undergoing endoscopy. *Neurology* 2003; **61**: 964-968 [PMID: 14557569 DOI: 10.1212/01.WNL.0000086817.54076.EB]

33 **Kearon C**, Hirsh J. Management of anticoagulation before and after elective surgery. *N Engl J Med* 1997; **336**: 1506-1511 [PMID: 9154771 DOI: 10.1056/NEJM199705223362107]

34 **Hirsh J**, Fuster V, Ansell J, Halperin JL. American Heart Association/American College of Cardiology Foundation guide to warfarin therapy. *J Am Coll Cardiol* 2003; **41**: 1633-1652 [PMID: 12742309 DOI: 10.1016/S0735-1097(03)00416-9]

35 **Hirsh J**, Anand SS, Halperin JL, Fuster V. Guide to anticoagulant therapy: Heparin : a statement for healthcare professionals from the American Heart Association. *Circulation* 2001; **103**: 2994-3018 [PMID: 11413093 DOI: 10.1161/01.CIR.103.24.2994]

36 **Furuhata T**, Kaise M, Hoteya S, Iizuka T, Yamada A, Nomura K, Kuribayashi Y, Kikuchi D, Matsui A, Ogawa O, Yamashta S, Mitani T. Postoperative bleeding after gastric endoscopic submucosal dissection in patients receiving antithrombotic therapy. *Gastric Cancer* 2016 Jan 11; Epub ahead of print [PMID: 26754296 DOI: 10.1007/s10120-015-0588-7]

37 **Matsumura T**, Arai M, Maruoka D, Okimoto K, Minemura S, Ishigami H, Saito K, Nakagawa T, Katsuno T, Yokosuka O. 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 [PMID: 25280756 DOI: 10.1186/1471-230X-14-172]

38 **Matsumoto M**, Mabe K, Tsuda M, Ono M, Omori S, Takahashi M, Yoshida T, Ono S, Nakagawa M, Nakagawa S, Shimizu Y, Kudo T, Sakamoto N, Kato M. Multicenter study on hemorrhagic risk of

heparin bridging therapy for periendoscopic thromboprophylaxis. *BMC Gastroenterol* 2015; **15**: 89 [PMID: 26215103 DOI: 10.1186/s12876-015-0315-1]

39 **Connolly SJ**, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; **361**: 1139-1151 [PMID: 19717844 DOI: 10.1056/NEJMoa0905561]

40 **Patel MR**, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011; **365**: 883-891 [PMID: 21830957 DOI: 10.1056/NEJMoa1009638]

41 **Granger CB**, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011; **365**: 981-992 [PMID: 21870978 DOI: 10.1056/NEJMoa1107039]

42 **Giugliano RP**, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Špinar J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, Mercuri M, Antman EM. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013; **369**: 2093-2104 [PMID: 24251359 DOI: 10.1056/NEJMoa1310907]

43 **Veitch AM**, Vanbiervliet G, Gershlick AH, Boustiere C, Baglin TP, Smith LA, Radaelli F, Knight E, Gralnek IM, Hassan C, Dumonceau JM. Endoscopy in patients on antiplatelet or anticoagulant therapy, including direct oral anticoagulants: British Society of Gastroenterology (BSG) and European Society of Gastrointestinal Endoscopy (ESGE) guidelines. *Endoscopy* 2016; **48**: 385-402 [PMID: 26890676 DOI: 10.1055/s-0042-102652]

44 **Schulman S**, Elbazi R, Zondag M, O'Donnell M. Clinical factors influencing normalization of prothrombin time after stopping warfarin: a retrospective cohort study. *Thromb J* 2008; **6**: 15 [PMID: 18925967 DOI: 10.1186/1477-9560-6-15]

45 **Vanassche T**, Hirsh J, Eikelboom JW, Ginsberg JS. Organ-specific bleeding patterns of anticoagulant therapy: lessons from clinical trials. *Thromb Haemost* 2014; **112**: 918-923 [PMID: 25187203 DOI: 10.1160/TH14-04-0346]

46 **Tomida H**, Yoshio T, Ninomiya T, Michitaka K, Fujisaki J, Igarashi M. The effects of anticoagulants on the clinical outcome of endoscopic submucosal dissection. *J Gastroenterol Hepatol* 2015; **30**: 303

47 **Koh R**, Hirasawa K, Yahara S, Oka H, Sugimori K, Morimoto M, Numata K, Kokawa A, Sasaki T, Nozawa A, Taguri M, Morita S, Maeda S, Tanaka K. Antithrombotic drugs are risk factors for delayed postoperative bleeding after endoscopic submucosal dissection for gastric neoplasms. *Gastrointest Endosc* 2013; **78**: 476-483 [PMID: 23622974 DOI: 10.1016/j.gie.2013.03.008]

48 **Douketis JD**, Spyropoulos AC, Kaatz S, Becker RC, Caprini JA, Dunn AS, Garcia DA, Jacobson A, Jaffer AK, Kong DF, Schulman S, Turpie AG, Hasselblad V, Ortel TL. Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation. *N Engl J Med* 2015; **373**: 823-833 [PMID: 26095867 DOI: 10.1056/NEJMoa1501035]

49 **Siegal D**, Yudin J, Kaatz S, Douketis JD, Lim W, Spyropoulos AC. Periprocedural heparin bridging in patients receiving vitamin K antagonists: systematic review and meta-analysis of bleeding and thromboembolic rates. *Circulation* 2012; **126**: 1630-1639 [PMID: 22912386 DOI: 10.1161/CIRCULATIONAHA.112.105221]

50 **Birnie DH**, Healey JS, Wells GA, Verma A, Tang AS, Krahn AD, Simpson CS, Ayala-Paredes F, Coutu B, Leiria TL, Essebag V. Pacemaker or defibrillator surgery without interruption of anticoagulation. *N Engl J Med* 2013; **368**: 2084-2093 [PMID: 23659733 DOI: 10.1056/NEJMoa1302946]

51 **Ghanbari H**, Phard WS, Al-Ameri H, Latchamsetty R, Jongnarngsin K, Crawford T, Good E, Chugh A, Oral H, Bogun F, Morady F, Pelosi F. Meta-analysis of safety and efficacy of uninterrupted warfarin compared to heparin-based bridging therapy during implantation of cardiac rhythm devices. *Am J Cardiol* 2012; **110**: 1482-1488 [PMID: 22906894 DOI: 10.1016/j.amjcard.2012.06.057]

52 **Tounou S**, Morita Y, Hosono T, Harada H, Hayasaka K, Katsuyama Y, Suehiro S, Nagano S, Shimizu T. Endoscopic submucosal dissection for early gastric cancer without interruption of warfarin and aspirin. *Endosc Int Open* 2015; **3**: E307-E310 [PMID: 26357675 DOI: 10.1055/s-0034-1392018]

53 **Yoshio T**, Nishida T, Kawai N, Yuguchi K, Yamada T, Kitamura S, Komori M, Michida T, Iijima H, Tsujii M, Takehara T. Sa1564 heparin replacement was the most significant risk of delayed bleeding in gastric ESD by multivariate analysis of anti-thrombotic therapy, comorbidities and characteristics of tumors: a multicenter study by Osaka University ESD Study Group. *Gastrointest Endosc* 2013; **77**: AB252 [DOI: 10.1016/j.gie.2013.03.615]

54 **Takeuchi T**, Ota K, Harada S, Edogawa S, Kojima Y, Tokioka S, Umegaki E, Higuchi K. The postoperative bleeding rate and its risk factors in patients on antithrombotic therapy who undergo gastric endoscopic submucosal dissection. *BMC Gastroenterol* 2013; **13**: 136 [PMID: 24010587 DOI: 10.1186/1471-230X-13-136]

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