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**Assessment of delayed bleeding after endoscopic submucosal dissection of early-stage gastrointestinal tumors in patients receiving direct oral anticoagulants**

Sugimoto M *et al*. Post-ESD bleeding and DOACs

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**Abstract**

Delayed bleeding is a major and serious adverse event of endoscopic submucosal dissection (ESD) for early-stage gastrointestinal tumors. The rate of post-ESD bleeding for gastric cancer is higher (around 5%-8%) than that for esophagus, duodenum and colon cancer (around 2%-4%). Although investigations into the risk factors for post-ESD bleeding have identified several procedure-, lesion-, physician- and patient-related factors, use of antithrombotic drugs, especially anticoagulants [direct oral anticoagulants (DOACs) and warfarin], is thought to be the biggest risk factor for post-ESD bleeding. In fact, the post-ESD bleeding rate in patients receiving DOACs is 8.7%-20.8%, which is higher than that in patients not receiving anticoagulants. However, because clinical guidelines for management of ESD in patients receiving DOACs differ among countries, it is necessary for endoscopists to identify ways to prevent post-ESD delayed bleeding in clinical practice. Given that the pharmacokinetics (*e.g.*, plasma DOAC level at both trough and Tmax) and pharmacodynamics (*e.g.*, anti-factor Xa activity) of DOACs are related to risk of major bleeding, plasma DOAC level and anti-FXa activity may be useful parameters for monitoring the anti-coagulate effect and identifying DOAC patients at higher risk of post-ESD bleeding.

**Key Words:** Direct oral anticoagulants; Gastrointestinal tumors; Endoscopic submucosal dissection; Delayed bleeding; Adverse events; Anticoagulants

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**Core Tip:** Recent international clinical guidelines for early-stage gastrointestinal tumors recommend endoscopic submucosal dissection (ESD) as the first-line treatment. Direct oral anticoagulants (DOACs) are a major risk factor for post-ESD bleeding and the pharmacokinetics and pharmacodynamics of DOACs may be related to risk of post-ESD bleeding. Therefore, one way to monitor the anticoagulant effect of DOACs in clinical practice may be to develop a system that effectively measures anti–FXa activity and plasma concentration. In the future, it may be useful to stratify risk of post-ESD delayed bleeding based on a scoring system that includes pharmacological parameters of DOACs.

**INTRODUCTION**

Endoscopic resection, a minimally invasive endoscopic non-surgical treatment, is now accepted as first-line management for most cases of early-stage esophageal cancer, gastric cancer and colorectal cancer or adenoma around the world[1]. Endoscopic resection mainly includes endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). Indication for endoscopic resection for EMR and ESD is typically a local mucosal lesion with an extremely low risk of metastasis to lymph nodes (generally less than 1%), and lesions that can be resected *en-bloc*, irrespective of localization in the esophagus, stomach, duodenum or colon. Because ESD enables complete *en-bloc* resection and is associated with a lower recurrence rate than EMR[2,3], recent international clinical guidelines for early-stage gastrointestinal tumors recommend ESD as the first-line treatment over EMR and surgical resection[1,3-7]. To achieve good results and prognosis in ESD for early-stage gastrointestinal tumors, endoscopists and gastroenterologists require excellent skills and knowledge of the diagnosis, indications, actual procedures, and evaluation of curability, complications, long-term postoperative surveillance, and histopathology[3].

ESD often causes adverse events such as intra-operative and delayed bleeding from an artificial ulcer and perforation. The occurrence of such events has been linked to several procedure-, lesion-, physician- and patient-related factors[8-12]. Of the possible risk factors for post-ESD delayed bleeding, use of antithrombotic drugs, especially anticoagulants, is the biggest risk factor[13,14]. Although anticoagulants are mainly divided into warfarin and direct oral anticoagulants (DOACs), no parameters identified to date can be used to accurately monitor the anti-coagulate effect of DOACs in clinical practice or endoscopic/surgical procedures. Thus, it is important to clarify the association between post-ESD delayed bleeding for early-stage gastrointestinal tumors and DOACs, identify risk factors of post-ESD delayed bleeding in patients taking DOACs and methods to prevent bleeding in these patients.

Here, we review delayed bleeding after ESD for gastrointestinal tumors, risk factors for post-ESD bleeding, the pharmacological characteristics of DOACs, international clinical guidelines for endoscopic procedures in patients receiving DOACs, and post-ESD bleeding in patients receiving DOACs.

**DELAYED BLEEDING AFTER ESD FOR GASTROINTESTINAL TUMORS**

In Japan, upper and lower gastrointestinal tumors are detected in the early stages in many patients, mainly through the use of optimal screening methods, appropriate surveillance and the development of endoscopic diagnostic techniques for early detection and endoscopic equipment[15-17]. In general, evaluation of early-stage gastrointestinal tumors should be performed by expert endoscopists, using a high-definition endoscope by white-light imaging and advanced image-enhanced endoscopy[18]. The experience of the endoscopist may be related to the incidence of adverse events and effective prevention of procedure-related adverse events after ESD. Careful and appropriate coagulation for exposed blood vessels may reduce the gastrointestinal bleeding risk, especially in the stomach[7,19]. The rate of bleeding and its risk factors are known to differ among patients with esophagus, stomach, duodenum and colon cancer.

***Esophageal squamous cell carcinoma***

The recent development of high-vision endoscopes and techniques for endoscopic diagnosis, including narrow band imaging, has led to more frequent early detection of esophageal esophageal squamous cell carcinoma (SCC)[15,20]. Therefore, ESD is accepted as an effective procedure for detecting superficial esophageal SCC. In Japan, the Esophageal Cancer Practice Guidelines 2017 weakly recommends endoscopic resection as first-line treatment for preoperatively diagnosed cT1a-MM/T1b-SM1 non-circumferential SCC[6]. In 2014, a meta-analysis of 15 studies with 776 patients with ESD-treated SCC reported pooled estimates of complete resection and *en bloc* resection rates of 89.4% [95%CI 86.2%–91.9%] and 95.1% (92.6%–96.8%), respectively[21]. In addition, pooled estimates of adverse events such as post-ESD bleeding, perforation, and stenosis were 2.1% (95%CI 1.2%–3.8%), 5.0% (3.5%–7.2%), and 11.6% (8.2%–16.2%), respectively[21].

***Barrett's neoplasia and esophageal adenocarcinoma***

The incidence of esophageal adenocarcinoma (EAC) located in Barrett’s epithelium has been increasing, especially in Western countries, due to decreases in the *Helicobacter pylori (H. pylori)* infection rate and increases in reflux esophagitis[22]. The European Society of Gastrointestinal Endoscopy (ESGE) recommends using EMR for ≤ 20 mm visible lesions with low probability of submucosal invasion and for larger or multifocal benign dysplastic lesions. In Japan, ESD is strongly recommended over EMR for the radical treatment of superficial EAC with a low risk of metastasis[6]. A meta-analysis of 11 studies investigating the efficacy and safety of ESD for EAC (mean size: 27 mm) reported pooled estimates for *en bloc* resection and pooled R0 resection of 92.9% (95%CI 90.3%-95.2%) and 74.5% (66.3%-81.9%), respectively[23]. Incidence of recurrence after curative resection was 0.17% (95%CI 0%-0.3%) at a mean follow-up of 22.9 mo (17.5-28.3 mo)[23]. In adverse events, estimates for bleeding, perforation, and stricture were 1.7% (95%CI 0.6%-3.4%), 1.5% (0.4%-3.0%) and 11.6% (0.9%-29.6%), respectively. Thus, the rate of post-ESD delayed bleeding in both esophageal SCC and EAC may not be very high (1.7%-2.1%).

***Gastric cancer***

In the ESGE, gastric cancers that are ≤ 30 mm, submucosal (sm1), and well-differentiated, or ≤ 20 mm, intramucosal, and poorly differentiated, and without ulcerative findings for both sets of criteria can be considered for ESD, although the decision should be individualized[4]. ESD for gastric cancer is associated with high rates of *en bloc* and R0 resection (> 90%), curative resection (75%–80%), low local recurrence (< 5%) and acceptable rates of adverse events (post-ESD bleeding 5%–10% and perforation < 3%)[24,25]. A recent meta-analysis of 22 studies in Western countries reported estimates for *en bloc* resection and R0 resection of 96% (95%CI 93%-98%) and 84% (79%-89%), respectively[26]. Overall, adverse events occur in 9.5% of patients, including delayed bleeding (5.8%), perforation (3.4%), and stenosis (0.35%)[26]. The odds ratio (OR) indicates that there is no significant difference in risk of post-ESD bleeding between ESD and EMR (OR 1.26, 95%CI 0.88-1.80)[27]. Another meta-analysis of 74 articles by Libânio *et al*[28] reported post-ESD bleeding rates ranging from 0.6% to 26.9% and a pooled bleeding rate of 5.1% (95%CI 4.5%-5.7%), with significant heterogeneity across studies (I2: 84.46, *P* < 0.001). However, bleeding rates were not significantly different among different study designs (5.9% in randomized clinical trials, 6.1% in prospective studies, and 4.9% in retrospective studies). The elderly Japanese population aged ≥ 85 years has increased from 1.4 to 4.8 million over the last two decades[29] and our investigation of a cohort of 10,320 patients showed that the incidence of bleeding in elderly patients aged > 80 years was 5.7% (95%CI 4.6%-6.9%), which was significantly higher than in patients aged < 80 years (4.5%, 4.1%-5.0%)[30].

***Duodenum***

Because ESD for duodenal tumors is associated with high rates of post-ESD bleeding and perforation at both the early and late phases, the ESGE suggests reserving its use for selected cases and tumors in expert centers[4]. In particular, perforation rates are high, with an incidence > 10% in studies involving expert centers[31]. Further, distal location to the ampulla of Vater is a risk factor for delayed perforation[32]. A meta-analysis reported pooled rates of *en bloc* resection, need for surgical intervention, delayed bleeding, intraoperative and delayed perforation of 87%, 4%, 2%, 15% and 2%, respectively[33]. Meanwhile, a recent large retrospective Japanese study reported that the rate of post-ESD adverse events was significantly reduced in cases with complete closure of the mucosal defect compared to partial closure and no closure (1.7%, 25.0% and 15.6%, respectively, *P* < 0.01)[34].

***Colon***

In Japan, indications for ESD for colorectal tumors are lesions for which endoscopic *en bloc* resection is required, as follows: (1) Lesions for which *en bloc* resection with snare EMR is difficult to apply; (2) Mucosal tumors with submucosal fibrosis; (3) Sporadic localized tumors in conditions of chronic inflammation such as ulcerative colitis; and (4) Post-EMR local residual or recurrent early-stage cancers[5]. A recent systematic review of 109 studies on 19484 colorectal lesions resected by ESD reported rates of *en bloc* resection of 91%, R0 resection of 82.9%, and local recurrence of 2%. The study also reported a rate of post-ESD bleeding of 2.7% and perforation of 5.2%, and that 1.1% of all patients needed surgical treatment by severe adverse events[35].

Because the rate of post-ESD bleeding may be higher for gastric cancer (5%-8%) than that at other sites (around 2%-4%) due to direct exposure of artificial ulcers to gastric acid and bile, it is necessary for endoscopists to be aware of and develop countermeasures for gastric ESD.

**RISK FACTORS FOR POST-ESD GASTROINTESTINAL DELAYED BLEEDING**

Risk factors for post-ESD bleeding are expected to differ among patients with esophagus, stomach, duodenum and colon cancer. Post-ESD bleeding has been shown to be associated with procedure-related factors (*e.g.*, type of knife, coagulation machine and endoscope, and coagulation mode), lesion-related factors (*e.g.*, gastrointestinal organ, large lesion size, location, presence within the ulcerated lesion, scarring, and fibrosis), physician-related factors (*e.g.*, experience with ESD) and patient-related factors [hemodialysis, drugs (antiplatelet drugs, anticoagulants, steroids, and non-steroidal anti-inflammatory drugs), hemostasis ability, and platelet count] (Figure 1)[8-12].

Libânio *et al*[28] showed in a meta-analysis of 74 articles that male sex (OR 1.25), cardiopathy (OR 1.54), antithrombotic drugs (OR 1.63), cirrhosis (OR 1.76), chronic kidney disease (CKD) (OR 3.38), tumor size > 20 mm (OR 2.70), resected specimen size > 30 mm (OR 2.85), localization in the lesser curvature (OR 1.74), flat/depressed morphology (OR 1.43), carcinoma histology (OR 1.46), and ulceration (OR 1.64) were significant risk factors for post-ESD bleeding of gastric cancer, whereas age, hypertension, submucosal invasion, fibrosis, and location (upper, middle, or lower third of stomach) were not. In terms of procedural factors, procedure duration > 60 min (OR, 2.05) and use of histamine-2 receptor antagonists instead of proton pump inhibitors (PPIs) (OR, 2.13) were associated with post-ESD bleeding, whereas endoscopist experience was not. Recently, Hatta *et al*[36] conducted a nationwide multicenter retrospective study focusing on post-ESD bleeding for gastric cancer and used the data to develop a model that applies 10 factors [warfarin, DOAC, hemodialysis, P2Y12 receptor antagonist, aspirin, tumor size > 30 mm, tumor location in the lower third, presence of multiple tumors and interruption of each kind of antithrombotic agent] to predict post-ESD bleeding (BEST-J score). According to the BEST-J score, rates of bleeding in patients categorized as low-risk, intermediate-risk, high-risk, and very high-risk were 2.8%, 6.1%, 11.4%, and 29.7%, respectively[36]. A validation study of the BEST-J score showed that the area under the curve for the BEST-J score at multicenter trials was 0.713 (95%CI 0.625–0.802), which suggests that the BEST-J score may be useful for predicting post-ESD bleeding in not only expert centers but also general hospitals[37]. In addition, because the healing speed of post-ESD artificial ulcers is related to the post-ESD bleeding rate, factors that affect the healing speed of ulcers, namely *H. pylori* infection status, type of acid inhibitory drug (*e.g.*, PPIs and vonoprazan) and severity of gastric atrophy, may also be risk factors for post-ESD bleeding in gastric cancer[11,12,38]. In today’s aging society, the number of patients taking anti-platelet drugs and anticoagulants for the prevention of cardio- and cerebrovascular diseases has risen. That a multicenter study reported a high incidence of post-ESD bleeding in Japanese aged > 80 years, especially in patients receiving hemodialysis and taking warfarin[30], indicates that careful management of ESD is required to prevent bleeding in patients aged > 80 years compared to younger patients.

Major risk factors for post-ESD bleeding for colorectal tumors are generally larger tumor size, location in the rectum or cecum, long procedure time, number of tumors, and taking anti-thrombotic drugs. Recently, Li *et al*[39] reported that post-ESD bleeding for colorectal tumors is observed in 4.7% of patients, and that hypertension (OR 2.829, 95%CI 1.101-7.265) and using hot biopsy forceps for wound management (OR 2.873, 95%CI 1.013-8.147) remain significant risk factors for bleeding after multivariate analysis. In another study, Seo *et al*[40] developed a risk-scoring model to predict bleeding after colorectal ESD following identification of the tumor location in the rectosigmoid colon (OR 6.49; 95%CI 1.96-21.42), large tumor (> 30 mm) (2.10, 1.01-4.40), and use of antiplatelet agents except for aspirin alone (4.04, 1.44-11.30) as risk factors for bleeding[40]. When use of antiplatelet agents except for aspirin alone was scored as 1 point, tumor size > 30 mm as 1 point, and location in the rectosigmoid area as 2 points, the incidence of bleeding in low-risk (score 0-2) and high-risk groups (score 3-4) was 1.5% and 6.0%, respectively.

Thus, current evidence indicates that the use of antithrombotic drugs, especially anticoagulants (DOACs and warfarin) is the biggest risk factor for post-ESD bleeding[13,14].

**PHARMACOLOGICAL CHARACTERISTICS OF DOACS**

DOACs are currently the first-line drug for the pharmacological prevention of systemic embolism or stroke in atrial fibrillation patients. They are categorized into two main classes: Direct thrombin inhibitors (*i.e.*, dabigatran) and activated coagulation factor X (FXa) inhibitors (*i.e.*, apixaban, edoxaban, rivaroxaban, and betrixaban). Compared with anticoagulation with vitamin K antagonists (*i.e.*, warfarin) or low-molecular-weight heparins, DOACs are new agents that demonstrate superiority or noninferiority to prior standards of care in reducing the risk of thromboembolic complications and major and minor bleeding risk, have fewer monitoring requirements and less frequent follow-up need; and have more immediate drug onset and offset effects and fewer drug and food interactions[41-44]. However, an advantage of using vitamin K antagonist therapy is that a therapeutic international normalized ratio range of 2.0-3.0 has been established and is recommended to prevent embolic complications in non-valvular atrial fibrillation in the treatment of deep vein thrombosis and pulmonary embolism. In contrast, a disadvantage of DOACs is that their anticoagulant effects in patients are unclear because there are no Food and Drug Administration (FDA)-approved methods to measure correctly the anticoagulant effect of DOACs. Although qualitative coagulation assays (*e.g.*, thrombin time, activated partial thromboplastin time, and prothrombin time) can be selected as first-line tests, they do not accurately measure the anticoagulant effect of DOACs (Table 1). Quantitative measures for direct assessment of anticoagulant effects do exist, including anti–FXa activity, plasma drug concentration (standard method in preclinical/clinical research and the most accurate method), dilute thrombin time, and ecarin thrombin time[45,46]. In fact, plotting anti–FXa activity against plasma levels of apixaban and rivaroxaban has been confirmed to show a direct linear relationship for both compounds[47].

Pharmacokinetic characteristics such as oral bioavailability, plasma protein binding and relative involvement of renal and non-renal elimination differ substantially among DOACs (Table 2). Pharmacokinetics is influenced by the type of DOAC, dose, renal function, liver function, age, sex, body weight, drug metabolic enzyme gene polymorphisms and drug-drug interactions, but not ethnicity, geographic region, aspirin use, or clopidogrel use[48]. DOACs are relatively safe and effective in patients with moderate CKD [creatinine clearance (Ccr) 30–50 mL/min]. Rivaroxaban, dabigatran and edoxaban will require dose adjustment for renal impairment and patients with severe renal dysfunction (Ccr < 30 mL/min) are recommended to avoid their use[49]. Regulatory agencies such as the FDA and European Medicines Agency have provided guidelines for performing dose adjustments according to the DOAC dose based on Ccr and anticoagulant indications[50]. The International Society on Thrombosis and Hemostasis suggests that use of DOACs are safe in patients of body mass index ≤ 40 kg/m2 (body weight ≤ 120 kg) at standard doses but does not recommend them for patients of body weight > 120 kg[51]. Compared to warfarin, DOACs are more effective and safer in patients with low body weight (< 50 kg)[52].

DOACs are metabolized by either cytochrome P450 (CYP) metabolic enzymes in the liver or permeability glycoprotein transporters; thus, agents that induce or inhibit CYP metabolic enzymes or glycoprotein transporters can lead to major drug-drug interactions and place the patient at undue risk for adverse events. In fact, concomitant use of apixaban, rivaroxaban, or dabigatran with clarithromycin, a potent inhibitor of CYP3A4, and ATP-binding cassette multidrug transporters increases serum levels of DOACs by 20% to 100% and prolongs coagulation time[53,54]. The pharmacokinetics of DOACs also depend on genetic variations, such as *ABCB1* (ATP-binding cassette multidrug transporters, MDR1) (1236C > T, 2677G > T/A, and 3435C > T), *ABCG2* (421C > A), and *CYP3A5* polymorphisms (6986A > G)[55]. The plasma trough C/D ratio of apixaban is significantly higher in patients with the ABCG2 421A/A genotype and CYP3A5 6986 G allele carriers than in patients with the ABCG2 421C/C genotype and CYP3A5 6986 A/A genotype[55]. Given that CYP3A5 6986A > G and ABCG2 421C > A polymorphisms have allele frequencies of 65%-85%[56] and 29%-36%[57], respectively, in Asians, ABCB1, ABCG2, and CYP3A5 genotypes play pivotal roles in the interindividual variability of apixaban concentrations in Japanese patients.

Although the pharmacodynamic parameters of DOACs differ significantly among individuals and anticoagulant effects also vary widely among patients receiving DOACs, the lack of approved methods to monitor the anticoagulant effect of DOACs makes it unclear whether the effect is adequate in patients receiving DOAC. Compared with vitamin K antagonist therapy (therapeutic international normalized ratio range: 2.0-3.0), a disadvantage of DOACs is that the dosage of DOAC cannot be controlled according to anticoagulant effect. Therefore, the trough and time to reach maximum plasma concentration (Tmax) and anti-FXa activity of DOAC-metabolizing enzyme polymorphisms may be useful parameters for accurately monitoring the anti-coagulate effects of DOACs and selecting patients at higher risk of major bleeding. Developing a system that easily measures the anti–FXa activity and plasma level could be an important way to monitor the anticoagulant effect of DOACs in clinical practice.

**PHARMACOKINETICS OF DOACS AND MAJOR BLEEDING**

Clinical trials have investigated the efficacy of dabigatran (RE-LY trial[58]), apixaban (ARISTOTLE trial[41]), edoxaban (ENGAGE AF TIMI48 trial[59]) and rivaroxaban (ROCKET AF trial[60]) for the prevention of stroke and embolism. According to these trials, adverse events of major bleeding and gastrointestinal bleeding occur at rates of 3.11% and 1.51% for dabigatran 150 mg given twice daily (bid), 2.13% and 0.76% at apixaban 5 mg bid, 2.75% and 1.51% at edoxaban 60 mg given once daily (oid) and 3.6% and 3.2% at rivaroxaban 20 mg oid (Table 3), respectively.

Because the anti-coagulate effects of DOACs are linked to plasma levels of DOAC and anti-FXa activity at trough and Tmax[48,61,62], these pharmacokinetic and pharmacodynamic parameters are also expected to be related to risk of major bleeding, such as intracerebral and gastrointestinal bleeding. Using multiple logistic regression, Reilly *et al*[48] showed that major bleeding risk increased with dabigatran exposure (*P* < 0.0001), age (*P* < 0.0001), aspirin use (*P* < 0.0003), and diabetes (*P* = 0.018) as significant covariates. Further, patients with major bleeding had higher trough levels (55%) and post-dose levels (36%) than non-bleeding patients[48]. Reilly *et al*[48] also reported a median trough level of 116 ng/mL in 323 major bleeding patients compared with 75.3 ng/mL in 5899 no bleeding patients[48]. Additionally, a Cox regression analysis of time to first major bleeding with trough level, age, and CHADS2 score as covariates showed that, compared with the median trough level of 88 ng/mL, the rate of major bleeding doubled at a level of 210 ng/mL after adjustment for age and CHADS2 score. Moreover, Sakaguchi *et al*[63] showed that, in rivaroxaban-treated patients with major bleeding in Japan, major bleeding is independently predicted to be higher peak rivaroxaban levels and higher anti-FXa activity.Additionally, Sin *et al’s* prospective study[64] of rivaroxaban-treated patients with atrial fibrillation with differing severity of CKD (Stage 1–3) showed that trough levels of rivaroxaban were higher in those with bleeding (59.9 ± 35.6 ng/mL)than in those without (41.1 ± 29.2 ng/mL; *P* < 0.05). Therefore, although plasma level and anti–FXa activity may be useful parameters for selecting patients receiving DOACs at higher risk of major bleeding, there is no evidence that patients with higher plasma levels and anti–FXa activity have higher risk of post-ESD bleeding.

A retrospective analysis of 5041 patients demonstrated that concomitant dabigatran–PPI treatment is linked to a significant reduction in bleeding risk compared with dabigatran alone without a PPI[65]. Although dabigatran is an orally administered prodrug, it is rapidly absorbed and converted to its active form, dabigatran. Thus, a potential mechanism for PPI–dabigatran interaction may be reduced dabigatran absorption and availability, which is most probably mediated *via* the effects of PPI on gastric pH, given the poor solubility of dabigatran at pH > 4[66]. Therefore, interactions between PPIs and dabigatran may lead to decreases in dabigatran levels[67].

In terms of gastrointestinal bleeding, unlike warfarin, DOACs remain in the gastrointestinal tract without being absorbed into the blood. Therefore, DOACs may directly inhibit the hemostatic mechanism in the gastrointestinal tract, thereby aggravating bleeding[68].

**CLINICAL GUIDELINES: MANAGEMENT FOR PATIENTS TAKING DOACS IN ENDOSCOPIC PROCEDURES WITH HIGHER RISK FOR BLEEDING (ESD)**

During gastrointestinal endoscopy and endoscopic treatment of patients receiving antithrombotic therapy, it is necessary to balance the risk of major and minor bleeding with the risk of thromboembolism resulting from withdrawal of antithrombotic therapy. Therefore, it is important to determine a management strategy (with withdrawal or not) that is optimized for individual patients based on consultation between the endoscopist and physician prescribing the antithrombotic drugs. The risk of thromboembolism is closely related to the underlying disease requiring anticoagulants, and the absolute risk of thromboembolism increases by more than 1% when anticoagulants are withdrawn for more than 4 d[69].

In 2012 the Japan Gastroenterological Endoscopy Society published “Guidelines for gastroenterological endoscopy in patients undergoing antithrombotic treatment” concerning thromboembolism associated with antithrombotic therapy withdrawal and bleeding[70]. The guidelines were updated with a 2017 appendix on anticoagulants in 2017[71]. Although the 2012 version recommends replacing DOACs with heparin during ESD in patients with high risk for post-procedure bleeding as an adverse event, the 2017 version recommends that patients receiving DOACs should continue to take the DOAC orally until the day before ESD and discontinue it on the morning of ESD (Table 4)[71]. Because the anticoagulant effects last 36–48 h for rivaroxaban and edoxaban given oid and 24–36 h for apixaban given bid, and the disappearance of anti-FXa activity and anticoagulant effects increase the risk of thrombosis, DOACs may be resumed the morning after ESD (up to 36 and 48 h when given bid and oid). In addition, when performing ESD, patients receiving concomitant DOAC and antiplatelet agents should be handled with care depending on the individual’s condition and needs, while ESD can be performed on patients receiving antiplatelet monotherapy with aspirin or cilostazol[71].

In contrast to the Japanese guidelines, the updated guidelines by the British Society of Gastroenterology and ESGE suggest that patients receiving low-risk procedures for bleeding withdraw from the morning dose of DOAC on the morning of ESD, and recommend that the last dose of DOAC be taken 3 d before ESD for high-risk endoscopic procedures (strong recommendation and low-quality evidence) (Table 4)[72]. For patients receiving dabigatran with a Ccr 30–50 mL/min, this updated version recommends that the last dose be taken 5 d prior to the procedure (strong recommendation and low-quality evidence)[72].

The American Society for Gastrointestinal Endoscopy (ASGE) published a guideline on how to manage patients receiving antithrombotic agents for endoscopy in 2016[73]. This guideline suggests that patients undergoing low-risk procedures should continue taking DOACs (Table 4)[73] and that the resumption of DOACs after ESD be delayed until adequate hemostasis is ensured. If DOACs cannot be resumed within 12 to 24 h post-ESD, thromboprophylaxis should be considered to decrease thromboembolism risk in those with high risk for thromboembolism. However, this version of the ASGE guideline recommends that patients at high risk for thromboembolic events withdraw DOACs and receive bridge therapy to adequately manage patients taking DOACs when ESD is performed (Table 4).

In contrast, the Korean clinical practice guideline does not recommend withdrawal of DOACs before low-risk procedures (weak recommendation and low-quality evidence) but suggests withdrawing DOACs > 48 h before high-risk procedures (weak recommendation and low-quality evidence) (Table 4)[74]. The recommendation to withdraw DOACs > 48 h before ESD is based on the fact that the half-life of DOACs is about 12 h and predictions that DOAC levels and anti-FXa activity will be almost undetectable after 48 h[74].

The Asian Pacific Association of Gastroenterology and Asian Pacific Society for Digestive Endoscopy guidelines recommend withholding DOACs at least 48 h before the procedure in DOAC patients receiving gastrointestinal ESD (strong recommendation and low-quality evidence) and do not recommend bridging anticoagulation (strong recommendation and low-quality evidence) (Table 4)[75]. In addition, these guidelines provide recommendations related to the timing of DOAC discontinuation before high-risk procedures according to Ccr[76]. In these guidelines, EMR for large colon polyp (≥ 2 cm) and ESD procedures, which have a higher risk of gastrointestinal bleeding compared with other high-risk endoscopic procedures, are categorized as ultra-high-risk endoscopic procedures[74,75].

Thus, as summarized in Table 4, guidelines for the management of patients undergoing ESD for early-stage gastrointestinal tumors who receive DOACs differ by country. Although subtle differences in the management of DOACs with ESD are important in clinical practice, we consider that these differences are dependent on the year in which the guidelines were published, the different dosage of DOAC in each country, the different numbers of concomitant antithrombotic drugs, and differences in the rate of genetic variations (*e.g.*, CYP3A4/5, ABCG2, and ABCB1 polymorphism).

**GASTROINTESTINAL BLEEDING AFTER ESD IN PATIENTS RECEIVING DOACS**

Post-ESD bleeding in patients receiving DOACs remains an unpreventable adverse event. Although the combination of heparin-bridging therapy and discontinuation of DOACs is one approach used to prevent thrombosis[70,71], heparin-bridging therapy with discontinuation of any anticoagulants causes an increased risk of delayed bleeding after surgical treatment, interventional procedures and ESD (gastric ESD: 10.8%-61.5%)[77-80] and does not reduce the risk of perioperative arterial thromboembolism[77-79]. In fact, a meta-analysis focused on heparin-bridging therapy with discontinuation of any anticoagulants for ESD found an increased risk of post-ESD bleeding without any benefit for thrombosis[81]. Another meta-analysis reported an increase in thrombosis in patients receiving heparin-bridging therapy with discontinuation of anticoagulants compared with those who discontinued anticoagulation without heparin bridging[82]. In Japan, although the updated guideline recommends discontinuing DOACs on the morning of ESD, most studies conducted on ESD for patients receiving DOACs have been retrospective and enrolled small numbers of patients (Table 5).

However, one study examined a large national database including 16977 patients receiving anticoagulation therapy who underwent high-risk endoscopic procedures. It showed that although warfarin led to a significantly higher post-procedure bleeding rate than DOACs (12.0% *vs* 9.9%, *P* = 0.002), the post-procedure bleeding rate was not significantly different in either upper or lower gastrointestinal ESD between patients receiving DOACs and warfarin[83]. In sub-analyses of procedure types in propensity-matched patients, the gastrointestinal bleeding rate in the DOAC group was 39.6% in patients who received upper gastrointestinal ESD and 13.2% in those who received lower gastrointestinal ESD[83].

In a recent retrospective Japanese study of 261 patients with early-stage gastric cancer receiving DOACs, post-ESD bleeding occurred in 14% of patients, which is comparable to that in patients receiving warfarin (18%)[84]. Multivariate analysis demonstrated that age ≥ 65 (OR 2.96, 95%CI 1.13-7.73), male sex (OR 2.12; 95%CI 1.01–4.45), receiving multiple antithrombotic agents (OR 2.70, 95%CI 1.74-4.21) and lesion size ≥ 20 mm (OR 1.67, 95%CI 1.08-2.59) were independent risk factors for post-ESD bleeding in patients taking anticoagulants, and that cessation of anticoagulants without heparin-bridging therapy was associated with a low risk of bleeding (OR 0.32; 95%CI 0.14–0.76). However, the multivariate analysis identified no significant independent increased risk factors for post-ESD bleeding and demonstrated that dabigatran was associated with a significantly lower risk of bleeding (OR 0.04, 95%CI 0.16-0.97)[84]. Further, in a nationwide multicenter retrospective study of 10320 patients, multivariate analysis conducted by Hatta *et al*[36] showed that taking anticoagulants was an independent risk factor for post-ESD bleeding (OR 8.16; 95%CI 4.74-14.04). Although the number of patients registered in each of these previous studies is relatively small (*n* = 21-261), both reported post-ESD bleeding in 8.7%-20.8% of gastric cancer patients receiving DOACs, considered to be equivalent to that in patients receiving warfarin (17.5%-22.7%) and higher than that in patients not receiving anticoagulants (Table 5).

Few studies have been conducted on esophageal, duodenal and colorectal ESD in patients receiving DOACs. Horie *et al*[85] reported that the post-endoscopic resection bleeding rate in esophageal cancer patients receiving DOACs (14 patients received ESD and 2 patients received EMR) was significantly higher than that in those not receiving antithrombotic drugs [13% (95%CI 1.6%–38%) *vs* 0.3% (95%CI 0.1%–1%), *P* = 0.003]. Moreover, the post-ESD bleeding rate in colorectal tumor patients receiving DOACs was 16.0%-23.3%, which is equivalent to that in those receiving warfarin (7.7%-26.3%) (Table 5).

Thus, despite the small number of DOAC patients who received ESD in previous studies, the post-ESD delayed bleeding rate appears to vary among different organs in patients not receiving DOACs, but not in patients receiving DOACs.

**FUTURE OF ESD FOR PATIENTS RECEIVING DOACS**

There is no doubt that patients receiving DOACs are at higher risk of post-ESD bleeding than patients not taking DOACs or receiving antithrombotic drugs. As mentioned above, although examining plasma DOAC level and anti-Xa activity in relation to CYP metabolic enzymes or glycoprotein transporter gene polymorphisms may serve as predictive markers for selecting DOAC patients with higher risk of post-ESD delayed bleeding, no studies have been conducted with such considerations. Although scoring systems such as the BEST-J score are being developed to assess the risk of post-ESD delayed bleeding by stratifying multiple possible risk factors in clinical practice, we propose the need for a new scoring system that considers pharmacological parameters of DOACs, namely plasma DOAC level and anti-Xa activity.

DOACs is current recommended for not only patients with nonvalvular atrial fibrillation and venous thrombosis (VTE), but also those with cancer due to prevention of VTE by clinical guidelines[86]. Treatment or prophylaxis of VTE for patients with cancer must always balance the risk of incidence or recurrent VTE with the increased risk of major bleeding and take into consideration the consequences of these outcomes (including mortality, financial cost, quality of life)[86]. Developing a system that easily measures the anti–FXa activity and plasma level could be an important way to monitor the anticoagulant effect of DOACs and may help physicians to treat DOAC patients receiving ESD, endoscopic treatment, and surgical treatment and with cancer in clinical practice.

**CONCLUSION**

Post-ESD delayed bleeding for gastrointestinal tumors is a major adverse event, with an incidence of around 5%-8% for gastric cancer and 2%-4% for esophageal, duodenum and colorectal tumors. Of the many risk factors for bleeding, taking anticoagulants, including DOACs, is currently the biggest. In fact, the post-ESD bleeding rate in DOAC patients is 13% in esophageal cancer, 8.7%-20.8% in gastric cancer and 7.7%-26.3% in colorectal cancer. Compared with warfarin, the anticoagulant effects of which can be monitored using prothrombin time and international normalized ratio tests, there is currently no established method for monitoring the effects of DOACs. Thus, it is important to develop simple and accurate methods to evaluate the pharmacokinetics (*e.g.*, plasma DOAC level at trough and Tmax) and pharmacodynamics (*e.g.*, anti-factor Xa activity) of DOACs. In the future, a scoring system that includes pharmacological parameters of DOACs may be useful for stratifying risk of post-ESD delayed bleeding in clinical practice.

**REFERENCES**

1 **Gotoda T**, Yamamoto H, Soetikno RM. Endoscopic submucosal dissection of early gastric cancer. *J Gastroenterol* 2006; **41**: 929-942 [PMID: 17096062 DOI: 10.1007/s00535-006-1954-3]

2 **Tanabe S**, Ishido K, Higuchi K, Sasaki T, Katada C, Azuma M, Naruke A, Kim M, Koizumi W. Long-term outcomes of endoscopic submucosal dissection for early gastric cancer: a retrospective comparison with conventional endoscopic resection in a single center. *Gastric Cancer* 2014; **17**: 130-136 [PMID: 23576197 DOI: 10.1007/s10120-013-0241-2]

3 **Ono H**, Yao K, Fujishiro M, Oda I, Nimura S, Yahagi N, Iishi H, Oka M, Ajioka Y, Ichinose M, Matsui T. Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer. *Dig Endosc* 2016; **28**: 3-15 [PMID: 26234303 DOI: 10.1111/den.12518]

4 **Pimentel-Nunes P**, Libânio D, Bastiaansen BAJ, Bhandari P, Bisschops R, Bourke MJ, Esposito G, Lemmers A, Maselli R, Messmann H, Pech O, Pioche M, Vieth M, Weusten BLAM, van Hooft JE, Deprez PH, Dinis-Ribeiro M. Endoscopic submucosal dissection for superficial gastrointestinal lesions: European Society of Gastrointestinal Endoscopy (ESGE) Guideline - Update 2022. *Endoscopy* 2022; **54**: 591-622 [PMID: 35523224 DOI: 10.1055/a-1811-7025]

5 **Tanaka S**, Kashida H, Saito Y, Yahagi N, Yamano H, Saito S, Hisabe T, Yao T, Watanabe M, Yoshida M, Kudo SE, Tsuruta O, Sugihara KI, Watanabe T, Saitoh Y, Igarashi M, Toyonaga T, Ajioka Y, Ichinose M, Matsui T, Sugita A, Sugano K, Fujimoto K, Tajiri H. JGES guidelines for colorectal endoscopic submucosal dissection/endoscopic mucosal resection. *Dig Endosc* 2015; **27**: 417-434 [PMID: 25652022 DOI: 10.1111/den.12456]

6 **Ishihara R**, Arima M, Iizuka T, Oyama T, Katada C, Kato M, Goda K, Goto O, Tanaka K, Yano T, Yoshinaga S, Muto M, Kawakubo H, Fujishiro M, Yoshida M, Fujimoto K, Tajiri H, Inoue H; Japan Gastroenterological Endoscopy Society Guidelines Committee of ESD/EMR for Esophageal Cancer. Endoscopic submucosal dissection/endoscopic mucosal resection guidelines for esophageal cancer. *Dig Endosc* 2020; **32**: 452-493 [PMID: 32072683 DOI: 10.1111/den.13654]

7 **Draganov PV**, Wang AY, Othman MO, Fukami N. AGA Institute Clinical Practice Update: Endoscopic Submucosal Dissection in the United States. *Clin Gastroenterol Hepatol* 2019; **17**: 16-25.e1 [PMID: 30077787 DOI: 10.1016/j.cgh.2018.07.041]

8 **Fujishiro M**, Yahagi N, Kakushima N, Kodashima S, Muraki Y, Ono S, Kobayashi K, Hashimoto T, Yamamichi N, Tateishi A, Shimizu Y, Oka M, Ogura K, Kawabe T, Ichinose M, Omata M. Successful nonsurgical management of perforation complicating endoscopic submucosal dissection of gastrointestinal epithelial neoplasms. *Endoscopy* 2006; **38**: 1001-1006 [PMID: 17058165 DOI: 10.1055/s-2006-944775]

9 **Tanaka M**, Ono H, Hasuike N, Takizawa K. Endoscopic submucosal dissection of early gastric cancer. *Digestion* 2008; **77** Suppl 1: 23-28 [PMID: 18204258 DOI: 10.1159/000111484]

10 **Cao Y**, Liao C, Tan A, Gao Y, Mo Z, Gao F. Meta-analysis of endoscopic submucosal dissection versus endoscopic mucosal resection for tumors of the gastrointestinal tract. *Endoscopy* 2009; **41**: 751-757 [PMID: 19693750 DOI: 10.1055/s-0029-1215053]

11 **Yoshizawa Y**, Sugimoto M, Sato Y, Sahara S, Ichikawa H, Kagami T, Hosoda Y, Kimata M, Tamura S, Kobayashi Y, Osawa S, Sugimoto K, Miyajima H, Furuta T. Factors associated with healing of artificial ulcer after endoscopic submucosal dissection with reference to Helicobacter pylori infection, CYP2C19 genotype, and tumor location: Multicenter randomized trial. *Dig Endosc* 2016; **28**: 162-172 [PMID: 26331711 DOI: 10.1111/den.12544]

12 **Otsuka T**, Sugimoto M, Ban H, Nakata T, Murata M, Nishida A, Inatomi O, Bamba S, Andoh A. Severity of gastric mucosal atrophy affects the healing speed of post-endoscopic submucosal dissection ulcers. *World J Gastrointest Endosc* 2018; **10**: 83-92 [PMID: 29774087 DOI: 10.4253/wjge.v10.i5.83]

13 **Yano T**, Tanabe S, Ishido K, Suzuki M, Kawanishi N, Yamane S, Watanabe A, Wada T, Azuma M, Katada C, Koizumi W. Different clinical characteristics associated with acute bleeding and delayed bleeding after endoscopic submucosal dissection in patients with early gastric cancer. *Surg Endosc* 2017; **31**: 4542-4550 [PMID: 28378078 DOI: 10.1007/s00464-017-5513-1]

14 **Sato C**, Hirasawa K, Koh R, Ikeda R, Fukuchi T, Kobayashi R, Kaneko H, Makazu M, Maeda S. Postoperative bleeding in patients on antithrombotic therapy after gastric endoscopic submucosal dissection. *World J Gastroenterol* 2017; **23**: 5557-5566 [PMID: 28852315 DOI: 10.3748/wjg.v23.i30.5557]

15 **Muto M**, Minashi K, Yano T, Saito Y, Oda I, Nonaka S, Omori T, Sugiura H, Goda K, Kaise M, Inoue H, Ishikawa H, Ochiai A, Shimoda T, Watanabe H, Tajiri H, Saito D. 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**: 1566-1572 [PMID: 20177025 DOI: 10.1200/JCO.2009.25.4680]

16 **Dohi O**, Yagi N, Naito Y, Fukui A, Gen Y, Iwai N, Ueda T, Yoshida N, Kamada K, Uchiyama K, Takagi T, Konishi H, Yanagisawa A, Itoh Y. Blue laser imaging-bright improves the real-time detection rate of early gastric cancer: a randomized controlled study. *Gastrointest Endosc* 2019; **89**: 47-57 [PMID: 30189197 DOI: 10.1016/j.gie.2018.08.049]

17 **Ono S**, Kawada K, Dohi O, Kitamura S, Koike T, Hori S, Kanzaki H, Murao T, Yagi N, Sasaki F, Hashiguchi K, Oka S, Katada K, Shimoda R, Mizukami K, Suehiro M, Takeuchi T, Katsuki S, Tsuda M, Naito Y, Kawano T, Haruma K, Ishikawa H, Mori K, Kato M; LCI-FIND Trial Group. Linked Color Imaging Focused on Neoplasm Detection in the Upper Gastrointestinal Tract : A Randomized Trial. *Ann Intern Med* 2021; **174**: 18-24 [PMID: 33076693 DOI: 10.7326/M19-2561]

18 **Sugimoto M**, Koyama Y, Itoi T, Kawai T. Using texture and colour enhancement imaging to evaluate gastrointestinal diseases in clinical practice: a review. *Ann Med* 2022; **54**: 3315-3332 [PMID: 36420822 DOI: 10.1080/07853890.2022.2147992]

19 **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]

20 **Muto M**, Katada C, Sano Y, Yoshida S. Narrow band imaging: a new diagnostic approach to visualize angiogenesis in superficial neoplasia. *Clin Gastroenterol Hepatol* 2005; **3**: S16-S20 [PMID: 16012987 DOI: 10.1016/s1542-3565(05)00262-4]

21 **Kim JS**, Kim BW, Shin IS. Efficacy and safety of endoscopic submucosal dissection for superficial squamous esophageal neoplasia: a meta-analysis. *Dig Dis Sci* 2014; **59**: 1862-1869 [PMID: 24619279 DOI: 10.1007/s10620-014-3098-2]

22 **Dubecz A**, Solymosi N, Stadlhuber RJ, Schweigert M, Stein HJ, Peters JH. Does the Incidence of Adenocarcinoma of the Esophagus and Gastric Cardia Continue to Rise in the Twenty-First Century?-a SEER Database Analysis. *J Gastrointest Surg* 2013 [PMID: 24234242 DOI: 10.1007/s11605-013-2345-8]

23 **Yang D**, Zou F, Xiong S, Forde JJ, Wang Y, Draganov PV. Endoscopic submucosal dissection for early Barrett's neoplasia: a meta-analysis. *Gastrointest Endosc* 2018; **87**: 1383-1393 [PMID: 28993137 DOI: 10.1016/j.gie.2017.09.038]

24 **Suzuki H**, Takizawa K, Hirasawa T, Takeuchi Y, Ishido K, Hoteya S, Yano T, Tanaka S, Endo M, Nakagawa M, Toyonaga T, Doyama H, Hirasawa K, Matsuda M, Yamamoto H, Fujishiro M, Hashimoto S, Maeda Y, Oyama T, Takenaka R, Yamamoto Y, Naito Y, Michida T, Kobayashi N, Kawahara Y, Hirano M, Jin M, Hori S, Niwa Y, Hikichi T, Shimazu T, Ono H, Tanabe S, Kondo H, Iishi H, Ninomiya M; Ichiro Oda for J-WEB/EGC group. Short-term outcomes of multicenter prospective cohort study of gastric endoscopic resection: 'Real-world evidence' in Japan. *Dig Endosc* 2019; **31**: 30-39 [PMID: 30058258 DOI: 10.1111/den.13246]

25 **Tanabe S**, Ishido K, Matsumoto T, Kosaka T, Oda I, Suzuki H, Fujisaki J, Ono H, Kawata N, Oyama T, Takahashi A, Doyama H, Kobayashi M, Uedo N, Hamada K, Toyonaga T, Kawara F, Tanaka S, Yoshifuku Y. Long-term outcomes of endoscopic submucosal dissection for early gastric cancer: a multicenter collaborative study. *Gastric Cancer* 2017; **20**: 45-52 [PMID: 27807641 DOI: 10.1007/s10120-016-0664-7]

26 **Zullo A**, Manta R, De Francesco V, Manfredi G, Buscarini E, Fiorini G, Vaira D, Marmo R. Endoscopic submucosal dissection of gastric neoplastic lesions in Western countries: systematic review and meta-analysis. *Eur J Gastroenterol Hepatol* 2021; **33**: e1-e6 [PMID: 32804845 DOI: 10.1097/MEG.0000000000001886]

27 **Tao M**, Zhou X, Hu M, Pan J. Endoscopic submucosal dissection versus endoscopic mucosal resection for patients with early gastric cancer: a meta-analysis. *BMJ Open* 2019; **9**: e025803 [PMID: 31874864 DOI: 10.1136/bmjopen-2018-025803]

28 **Libânio D**, Costa MN, Pimentel-Nunes P, Dinis-Ribeiro M. Risk factors for bleeding after gastric endoscopic submucosal dissection: a systematic review and meta-analysis. *Gastrointest Endosc* 2016; **84**: 572-586 [PMID: 27345132 DOI: 10.1016/j.gie.2016.06.033]

29 **Bureau**. MoIAaCS. Population estimates. [cited 3 April 2023]. Available from: http://wwwstatgojp/data/jinsui/

30 **Sugimoto M**, Hatta W, Tsuji Y, Yoshio T, Yabuuchi Y, Hoteya S, Doyama H, Nagami Y, Hikichi T, Kobayashi M, Morita Y, Sumiyoshi T, Iguchi M, Tomida H, Inoue T, Mikami T, Hasatani K, Nishikawa J, Matsumura T, Nebiki H, Nakamatsu D, Ohnita K, Suzuki H, Ueyama H, Hayashi Y, Murata M, Yamaguchi S, Michida T, Yada T, Asahina Y, Narasaka T, Kuribayashi S, Kiyotoki S, Mabe K, Fujishiro M, Masamune A, Kawai T. Risk Factors for Bleeding After Endoscopic Submucosal Dissection for Gastric Cancer in Elderly Patients Older Than 80 Years in Japan. *Clin Transl Gastroenterol* 2021; **12**: e00404 [PMID: 34644281 DOI: 10.14309/ctg.0000000000000404]

31 **Zou J**, Chai N, Linghu E, Zhai Y, Li Z, Du C, Li L. Clinical outcomes of endoscopic resection for non-ampullary duodenal laterally spreading tumors. *Surg Endosc* 2019; **33**: 4048-4056 [PMID: 30756173 DOI: 10.1007/s00464-019-06698-x]

32 **Inoue T**, Uedo N, Yamashina T, Yamamoto S, Hanaoka N, Takeuchi Y, Higashino K, Ishihara R, Iishi H, Tatsuta M, Takahashi H, Eguchi H, Ohigashi H. Delayed perforation: a hazardous complication of endoscopic resection for non-ampullary duodenal neoplasm. *Dig Endosc* 2014; **26**: 220-227 [PMID: 23621427 DOI: 10.1111/den.12104]

33 **Watanabe D**, Hayashi H, Kataoka Y, Hashimoto T, Ichimasa K, Miyachi H, Tanaka S, Toyonaga T. Efficacy and safety of endoscopic submucosal dissection for non-ampullary duodenal polyps: A systematic review and meta-analysis. *Dig Liver Dis* 2019; **51**: 774-781 [PMID: 31014942 DOI: 10.1016/j.dld.2019.03.021]

34 **Kato M**, Ochiai Y, Fukuhara S, Maehata T, Sasaki M, Kiguchi Y, Akimoto T, Fujimoto A, Nakayama A, Kanai T, Yahagi N. Clinical impact of closure of the mucosal defect after duodenal endoscopic submucosal dissection. *Gastrointest Endosc* 2019; **89**: 87-93 [PMID: 30055156 DOI: 10.1016/j.gie.2018.07.026]

35 **Fuccio L**, Hassan C, Ponchon T, Mandolesi D, Farioli A, Cucchetti A, Frazzoni L, Bhandari P, Bellisario C, Bazzoli F, Repici A. Clinical outcomes after endoscopic submucosal dissection for colorectal neoplasia: a systematic review and meta-analysis. *Gastrointest Endosc* 2017; **86**: 74-86.e17 [PMID: 28254526 DOI: 10.1016/j.gie.2017.02.024]

36 **Hatta W**, Tsuji Y, Yoshio T, Kakushima N, Hoteya S, Doyama H, Nagami Y, Hikichi T, Kobayashi M, Morita Y, Sumiyoshi T, Iguchi M, Tomida H, Inoue T, Koike T, Mikami T, Hasatani K, Nishikawa J, Matsumura T, Nebiki H, Nakamatsu D, Ohnita K, Suzuki H, Ueyama H, Hayashi Y, Sugimoto M, Yamaguchi S, Michida T, Yada T, Asahina Y, Narasaka T, Kuribasyashi S, Kiyotoki S, Mabe K, Nakamura T, Nakaya N, Fujishiro M, Masamune A. Prediction model of bleeding after endoscopic submucosal dissection for early gastric cancer: BEST-J score. *Gut* 2021; **70**: 476-484 [PMID: 32499390 DOI: 10.1136/gutjnl-2019-319926]

37 **Kagawa Y**, Fukuzawa M, Sugimoto M, Nemoto D, Muramatsu T, Shinohara H, Matsumoto T, Madarame A, Yamaguchi H, Uchida K, Morise T, Koyama Y, Sugimoto A, Yamauchi Y, Kono S, Naito S, Yamamoto K, Kishimoto Y, Inuyama M, Kawai T, Itoi T. Validation of the BEST-J score, a prediction model for bleeding after endoscopic submucosal dissection for early gastric cancer: a multicenter retrospective observational study. *Surg Endosc* 2022; **36**: 7240-7249 [PMID: 35194665 DOI: 10.1007/s00464-022-09096-y]

38 **Ban H**, Sugimoto M, Otsuka T, Murata M, Nakata T, Hasegawa H, Fukuda M, Inatomi O, Bamba S, Kushima R, Andoh A. Letter: a potassium-competitive acid blocker vs a proton pump inhibitor for healing endoscopic submucosal dissection-induced artificial ulcers after treatment of gastric neoplasms. *Aliment Pharmacol Ther* 2017; **46**: 564-565 [PMID: 28776744 DOI: 10.1111/apt.14202]

39 **Li R**, Cai S, Sun D, Shi Q, Ren Z, Qi Z, Li B, Yao L, Xu M, Zhou P, Zhong Y. Risk factors for delayed bleeding after endoscopic submucosal dissection of colorectal tumors. *Surg Endosc* 2021; **35**: 6583-6590 [PMID: 33237467 DOI: 10.1007/s00464-020-08156-5]

40 **Seo M**, Song EM, Cho JW, Lee YJ, Lee BI, Kim JS, Jeon SW, Jang HJ, Yang DH, Ye BD, Byeon JS. A risk-scoring model for the prediction of delayed bleeding after colorectal endoscopic submucosal dissection. *Gastrointest Endosc* 2019; **89**: 990-998.e2 [PMID: 30521794 DOI: 10.1016/j.gie.2018.11.029]

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; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011; **365**: 981-992 [PMID: 21870978 DOI: 10.1056/NEJMoa1107039]

42 **Hu PT**, Lopes RD, Stevens SR, Wallentin L, Thomas L, Alexander JH, Hanna M, Lewis BS, Verheugt FW, Granger CB, Jones WS. Efficacy and Safety of Apixaban Compared With Warfarin in Patients With Atrial Fibrillation and Peripheral Artery Disease: Insights From the ARISTOTLE Trial. *J Am Heart Assoc* 2017; **6** [PMID: 28096100 DOI: 10.1161/JAHA.116.004699]

43 **Easton JD**, Lopes RD, Bahit MC, Wojdyla DM, Granger CB, Wallentin L, Alings M, Goto S, Lewis BS, Rosenqvist M, Hanna M, Mohan P, Alexander JH, Diener HC; ARISTOTLE Committees and Investigators. Apixaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of the ARISTOTLE trial. *Lancet Neurol* 2012; **11**: 503-511 [PMID: 22572202 DOI: 10.1016/S1474-4422(12)70092-3]

44 **Rose DK**, Bar B. Direct Oral Anticoagulant Agents: Pharmacologic Profile, Indications, Coagulation Monitoring, and Reversal Agents. *J Stroke Cerebrovasc Dis* 2018; **27**: 2049-2058 [PMID: 29753603 DOI: 10.1016/j.jstrokecerebrovasdis.2018.04.004]

45 **Conway SE**, Hwang AY, Ponte CD, Gums JG. Laboratory and Clinical Monitoring of Direct Acting Oral Anticoagulants: What Clinicians Need to Know. *Pharmacotherapy* 2017; **37**: 236-248 [PMID: 27983747 DOI: 10.1002/phar.1884]

46 **Cuker A**, Siegal DM, Crowther MA, Garcia DA. Laboratory measurement of the anticoagulant activity of the non-vitamin K oral anticoagulants. *J Am Coll Cardiol* 2014; **64**: 1128-1139 [PMID: 25212648 DOI: 10.1016/j.jacc.2014.05.065]

47 **Frost C**, Song Y, Barrett YC, Wang J, Pursley J, Boyd RA, LaCreta F. A randomized direct comparison of the pharmacokinetics and pharmacodynamics of apixaban and rivaroxaban. *Clin Pharmacol* 2014; **6**: 179-187 [PMID: 25419161 DOI: 10.2147/CPAA.S61131]

48 **Reilly PA**, Lehr T, Haertter S, Connolly SJ, Yusuf S, Eikelboom JW, Ezekowitz MD, Nehmiz G, Wang S, Wallentin L; RE-LY Investigators. The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients: the RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy). *J Am Coll Cardiol* 2014; **63**: 321-328 [PMID: 24076487 DOI: 10.1016/j.jacc.2013.07.104]

49 **Chen A**, Stecker E, A Warden B. Direct Oral Anticoagulant Use: A Practical Guide to Common Clinical Challenges. *J Am Heart Assoc* 2020; **9**: e017559 [PMID: 32538234 DOI: 10.1161/JAHA.120.017559]

50 **Derebail VK**, Rheault MN, Kerlin BA. Role of direct oral anticoagulants in patients with kidney disease. *Kidney Int* 2020; **97**: 664-675 [PMID: 32107019 DOI: 10.1016/j.kint.2019.11.027]

51 **Martin K**, Beyer-Westendorf J, Davidson BL, Huisman MV, Sandset PM, Moll S. Use of the direct oral anticoagulants in obese patients: guidance from the SSC of the ISTH. *J Thromb Haemost* 2016; **14**: 1308-1313 [PMID: 27299806 DOI: 10.1111/jth.13323]

52 **Lee SR**, Choi EK, Park CS, Han KD, Jung JH, Oh S, Lip GYH. Direct Oral Anticoagulants in Patients With Nonvalvular Atrial Fibrillation and Low Body Weight. *J Am Coll Cardiol* 2019; **73**: 919-931 [PMID: 30819360 DOI: 10.1016/j.jacc.2018.11.051]

53 **Fralick M**, Juurlink DN, Marras T. Bleeding associated with coadministration of rivaroxaban and clarithromycin. *CMAJ* 2016; **188**: 669-672 [PMID: 26811362 DOI: 10.1503/cmaj.150580]

54 **Mueck W**, Kubitza D, Becka M. Co-administration of rivaroxaban with drugs that share its elimination pathways: pharmacokinetic effects in healthy subjects. *Br J Clin Pharmacol* 2013; **76**: 455-466 [PMID: 23305158 DOI: 10.1111/bcp.12075]

55 **Ueshima S**, Hira D, Fujii R, Kimura Y, Tomitsuka C, Yamane T, Tabuchi Y, Ozawa T, Itoh H, Horie M, Terada T, Katsura T. Impact of ABCB1, ABCG2, and CYP3A5 polymorphisms on plasma trough concentrations of apixaban in Japanese patients with atrial fibrillation. *Pharmacogenet Genomics* 2017; **27**: 329-336 [PMID: 28678049 DOI: 10.1097/FPC.0000000000000294]

56 **Staatz CE**, Goodman LK, Tett SE. Effect of CYP3A and ABCB1 single nucleotide polymorphisms on the pharmacokinetics and pharmacodynamics of calcineurin inhibitors: Part I. *Clin Pharmacokinet* 2010; **49**: 141-175 [PMID: 20170205 DOI: 10.2165/11317350-000000000-00000]

57 **Ieiri I**. Functional significance of genetic polymorphisms in P-glycoprotein (MDR1, ABCB1) and breast cancer resistance protein (BCRP, ABCG2). *Drug Metab Pharmacokinet* 2012; **27**: 85-105 [PMID: 22123128 DOI: 10.2133/dmpk.dmpk-11-rv-098]

58 **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; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; **361**: 1139-1151 [PMID: 19717844 DOI: 10.1056/NEJMoa0905561]

59 **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; ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013; **369**: 2093-2104 [PMID: 24251359 DOI: 10.1056/NEJMoa1310907]

60 **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; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011; **365**: 883-891 [PMID: 21830957 DOI: 10.1056/NEJMoa1009638]

61 **Weitz JI**, Connolly SJ, Patel I, Salazar D, Rohatagi S, Mendell J, Kastrissios H, Jin J, Kunitada S. Randomised, parallel-group, multicentre, multinational phase 2 study comparing edoxaban, an oral factor Xa inhibitor, with warfarin for stroke prevention in patients with atrial fibrillation. *Thromb Haemost* 2010; **104**: 633-641 [PMID: 20694273 DOI: 10.1160/TH10-01-0066]

62 **Salazar DE**, Mendell J, Kastrissios H, Green M, Carrothers TJ, Song S, Patel I, Bocanegra TS, Antman EM, Giugliano RP, Kunitada S, Dornseif B, Shi M, Tachibana M, Zhou S, Rohatagi S. Modelling and simulation of edoxaban exposure and response relationships in patients with atrial fibrillation. *Thromb Haemost* 2012; **107**: 925-936 [PMID: 22398655 DOI: 10.1160/TH11-08-0566]

63 **Sakaguchi T**, Osanai H, Murase Y, Ishii H, Nakashima Y, Asano H, Suzuki S, Takefuji M, Inden Y, Sakai K, Murohara T, Ajioka M. Monitoring of anti-Xa activity and factors related to bleeding events: A study in Japanese patients with nonvalvular atrial fibrillation receiving rivaroxaban. *J Cardiol* 2017; **70**: 244-249 [PMID: 28017463 DOI: 10.1016/j.jjcc.2016.11.013]

64 **Sin CF**, Wong KP, Wong HM, Siu CW, Yap DYH. Plasma Rivaroxaban Level in Patients With Early Stages of Chronic Kidney Disease-Relationships With Renal Function and Clinical Events. *Front Pharmacol* 2022; **13**: 888660 [PMID: 35662694 DOI: 10.3389/fphar.2022.888660]

65 **Chan EW**, Lau WC, Leung WK, Mok MT, He Y, Tong TS, Wong IC. Prevention of Dabigatran-Related Gastrointestinal Bleeding With Gastroprotective Agents: A Population-Based Study. *Gastroenterology* 2015; **149**: 586-95.e3 [PMID: 25960019 DOI: 10.1053/j.gastro.2015.05.002]

66 **Ollier E**, Hodin S, Basset T, Accassat S, Bertoletti L, Mismetti P, Delavenne X. In vitro and in vivo evaluation of drug-drug interaction between dabigatran and proton pump inhibitors. *Fundam Clin Pharmacol* 2015; **29**: 604-614 [PMID: 26392328 DOI: 10.1111/fcp.12154]

67 **Bolek T**, Samoš M, Škorňová I, Galajda P, Staško J, Kubisz P, Mokáň M. Proton Pump Inhibitors and Dabigatran Therapy: Impact on Gastric Bleeding and Dabigatran Plasma Levels. *Semin Thromb Hemost* 2019; **45**: 846-850 [PMID: 31537027 DOI: 10.1055/s-0039-1695735]

68 **Desai J**, Granger CB, Weitz JI, Aisenberg J. Novel oral anticoagulants in gastroenterology practice. *Gastrointest Endosc* 2013; **78**: 227-239 [PMID: 23725876 DOI: 10.1016/j.gie.2013.04.179]

69 **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]

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

71 **Kato M**, Uedo N, Hokimoto S, Ieko M, Higuchi K, Murakami K, Fujimoto K. Guidelines for Gastroenterological Endoscopy in Patients Undergoing Antithrombotic Treatment: 2017 Appendix on Anticoagulants Including Direct Oral Anticoagulants. *Dig Endosc* 2018; **30**: 433-440 [PMID: 29733468 DOI: 10.1111/den.13184]

72 **Veitch AM**, Radaelli F, Alikhan R, Dumonceau JM, Eaton D, Jerrome J, Lester W, Nylander D, Thoufeeq M, Vanbiervliet G, Wilkinson JR, Van Hooft JE. Endoscopy in patients on antiplatelet or anticoagulant therapy: British Society of Gastroenterology (BSG) and European Society of Gastrointestinal Endoscopy (ESGE) guideline update. *Gut* 2021; **70**: 1611-1628 [PMID: 34362780 DOI: 10.1136/gutjnl-2021-325184]

73 **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,ASGE Standards of Practice Committee. 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]

74 **Lim H**, Gong EJ, Min BH, Kang SJ, Shin CM, Byeon JS, Choi M, Park CG, Cho JY, Lee ST, Kim HG, Chun HJ. Clinical Practice Guideline for the Management of Antithrombotic Agents in Patients Undergoing Gastrointestinal Endoscopy. *Clin Endosc* 2020; **53**: 663-677 [PMID: 33242928 DOI: 10.5946/ce.2020.192]

75 **Chan FKL**, Goh KL, Reddy N, Fujimoto K, Ho KY, Hokimoto S, Jeong YH, Kitazono T, Lee HS, Mahachai V, Tsoi KKF, Wu MS, Yan BP, Sugano K. Management of patients on antithrombotic agents undergoing emergency and elective endoscopy: joint Asian Pacific Association of Gastroenterology (APAGE) and Asian Pacific Society for Digestive Endoscopy (APSDE) practice guidelines. *Gut* 2018; **67**: 405-417 [PMID: 29331946 DOI: 10.1136/gutjnl-2017-315131]

76 **Dunn A**. Perioperative management of oral anticoagulation: when and how to bridge. *J Thromb Thrombolysis* 2006; **21**: 85-89 [PMID: 16475048 DOI: 10.1007/s11239-006-5582-9]

77 **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]

78 **Beyer-Westendorf J**, Gelbricht V, Förster K, Ebertz F, Köhler C, Werth S, Kuhlisch E, Stange T, Thieme C, Daschkow K, Weiss N. Peri-interventional management of novel oral anticoagulants in daily care: results from the prospective Dresden NOAC registry. *Eur Heart J* 2014; **35**: 1888-1896 [PMID: 24394381 DOI: 10.1093/eurheartj/eht557]

79 **Shindo Y**, Matsumoto S, Miyatani H, Yoshida Y, Mashima H. Risk factors for postoperative bleeding after gastric endoscopic submucosal dissection in patients under antithrombotics. *World J Gastrointest Endosc* 2016; **8**: 349-356 [PMID: 27076874 DOI: 10.4253/wjge.v8.i7.349]

80 **Yamamoto Y**, Kikuchi D, Nagami Y, Nonaka K, Tsuji Y, Fujimoto A, Sanomura Y, Tanaka K, Abe S, Zhang S, De Lusong MA, Uedo N. Management of adverse events related to endoscopic resection of upper gastrointestinal neoplasms: Review of the literature and recommendations from experts. *Dig Endosc* 2019; **31** Suppl 1: 4-20 [PMID: 30994225 DOI: 10.1111/den.13388]

81 **Jaruvongvanich V**, Sempokuya T, Wijarnpreecha K, Ungprasert P. Continued versus interrupted aspirin use and bleeding risk after endoscopic submucosal dissection of gastric neoplasms: a meta-analysis. *Ann Gastroenterol* 2018; **31**: 344-349 [PMID: 29720860 DOI: 10.20524/aog.2018.0251]

82 **Dong J**, Wei K, Deng J, Zhou X, Huang X, Deng M, Lü M. Effects of antithrombotic therapy on bleeding after endoscopic submucosal dissection. *Gastrointest Endosc* 2017; **86**: 807-816 [PMID: 28732709 DOI: 10.1016/j.gie.2017.07.017]

83 **Nagata N**, Yasunaga H, Matsui H, Fushimi K, Watanabe K, Akiyama J, Uemura N, Niikura R. Therapeutic endoscopy-related GI bleeding and thromboembolic events in patients using warfarin or direct oral anticoagulants: results from a large nationwide database analysis. *Gut* 2018; **67**: 1805-1812 [PMID: 28874418 DOI: 10.1136/gutjnl-2017-313999]

84 **Tomida H**, Yoshio T, Igarashi K, Morita Y, Oda I, Inoue T, Hikichi T, Sumiyoshi T, Doyama H, Tsuji Y, Nishikawa J, Hatta W, Mikami T, Iguchi M, Sumiyama K, Yamamoto K, Kitamura K, Kuribayashi S, Yanagitani A, Uraoka T, Yada T, Hasatani K, Kawaguchi K, Fujita T, Nishida T, Hiasa Y, Fujishiro M; FIGHT-Japan Study Group. Influence of anticoagulants on the risk of delayed bleeding after gastric endoscopic submucosal dissection: a multicenter retrospective study. *Gastric Cancer* 2021; **24**: 179-189 [PMID: 32683602 DOI: 10.1007/s10120-020-01105-0]

85 **Horie Y**, Horiuchi Y, Ishiyama A, Tsuchida T, Yoshimizu S, Hirasawa T, Fujisaki J, Maetani I, Yoshio T. The effect of antithrombotic drug use on delayed bleeding with esophageal endoscopic resection. *J Gastroenterol Hepatol* 2022; **37**: 1792-1800 [PMID: 35844140 DOI: 10.1111/jgh.15944]

86 **Lyman GH**, Carrier M, Ay C, Di Nisio M, Hicks LK, Khorana AA, Leavitt AD, Lee AYY, Macbeth F, Morgan RL, Noble S, Sexton EA, Stenehjem D, Wiercioch W, Kahale LA, Alonso-Coello P. American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer. *Blood Adv* 2021; **5**: 927-974 [PMID: 33570602 DOI: 10.1182/bloodadvances.2020003442]

87 **Samoš M**, Bolek T, Stančiaková L, Péč MJ, Brisudová K, Škorňová I, Staško J, Mokáň M, Kubisz P. Tailored Direct Oral Anticoagulation in Patients with Atrial Fibrillation: The Future of Oral Anticoagulation? *J Clin Med* 2022; **11** [PMID: 36362597 DOI: 10.3390/jcm11216369]

88 **Yoshio T**, Tomida H, Iwasaki R, Horiuchi Y, Omae M, Ishiyama A, Hirasawa T, Yamamoto Y, Tsuchida T, Fujisaki J, Yamada T, Mita E, Ninomiya T, Michitaka K, Igarashi M. Effect of direct oral anticoagulants on the risk of delayed bleeding after gastric endoscopic submucosal dissection. *Dig Endosc* 2017; **29**: 686-694 [PMID: 28295638 DOI: 10.1111/den.12859]

89 **Sanomura Y**, Oka S, Tanaka S, Yorita N, Kuroki K, Kurihara M, Mizumoto T, Yoshifuku Y, Chayama K. Taking Warfarin with Heparin Replacement and Direct Oral Anticoagulant Is a Risk Factor for Bleeding after Endoscopic Submucosal Dissection for Early Gastric Cancer. *Digestion* 2018; **97**: 240-249 [PMID: 29421806 DOI: 10.1159/000485026]

90 **Saito H**, Igarashi K, Hirasawa D, Okuzono T, Suzuki K, Abe Y, Nawata Y, Tanaka Y, Tanaka I, Unno S, Nishikawa Y, Tsubokura M, Nakahori M, Chonan A, Matsuda T. The risks and characteristics of the delayed bleeding after endoscopic submucosal dissection for early gastric carcinoma in cases with anticoagulants. *Scand J Gastroenterol* 2020; **55**: 1253-1260 [PMID: 32924673 DOI: 10.1080/00365521.2020.1817542]

91 **Choi J**, Cho SJ, Na SH, Lee A, Kim JL, Chung H, Kim SG. Use of direct oral anticoagulants does not significantly increase delayed bleeding after endoscopic submucosal dissection for early gastric neoplasms. *Sci Rep* 2021; **11**: 9399 [PMID: 33931685 DOI: 10.1038/s41598-021-88656-z]

92 **Yamashita K**, Oka S, Tanaka S, Boda K, Hirano D, Sumimoto K, Mizumoto T, Ninomiya Y, Tamaru Y, Shigita K, Hayashi N, Sanomura Y, Chayama K. Use of anticoagulants increases risk of bleeding after colorectal endoscopic submucosal dissection. *Endosc Int Open* 2018; **6**: E857-E864 [PMID: 29978006 DOI: 10.1055/a-0593-5788]

93 **Ogiyama H**, Inoue T, Maekawa A, Yoshii S, Yamaguchi S, Nagai K, Yamamoto M, Egawa S, Horimoto M, Ogawa H, Nishihara A, Komori M, Kizu T, Tsutsui S, Tsujii Y, Hayashi Y, Iijima H, Takehara T. Effect of anticoagulants on the risk of delayed bleeding after colorectal endoscopic submucosal dissection. *Endosc Int Open* 2020; **8**: E1654-E1663 [PMID: 33140021 DOI: 10.1055/a-1244-2097]

94 **Harada H**, Nakahara R, Murakami D, Suehiro S, Nagasaka T, Ujihara T, Sagami R, Katsuyama Y, Hayasaka K, Tounou S, Amano Y. The effect of anticoagulants on delayed bleeding after colorectal endoscopic submucosal dissection. *Surg Endosc* 2020; **34**: 3330-3337 [PMID: 31482349 DOI: 10.1007/s00464-019-07101-5]

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**Figure Legends**



**Figure 1 Post-endoscopic submucosal dissection bleeding-related factors.** DOACs: Direct oral anticoagulants; NSAIDs: Non-steroidal anti-inflammatory drugs; CHADS: Congestive heart failure, Hypertension, Age > 75 years, Diabetes mellitus, and Stroke.

**Table 1 Possible methods for monitoring the anticoagulant ability of direct oral anticoagulants**[**49,71,87**]

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Qualitative methods** | **Quantitative methods** | **Other** |
| aPTT | TT | PT | Anti-FIIalevels | Anti-FXalevels | Plasma level | dTT | ECT/ECA | CBC | CMP |
| Dabigatran | 2 | 2 | 2 | 1 |  | 1 | 2 | 2 | 2 | 2 |
| Apixaban |  |  | 2 |  | 1 | 1 |  |  | 2 | 2 |
| Edoxaban |  |  | 2 |  | 1 | 1 |  |  | 2 | 2 |
| Rivaroxaban |  |  | 2 |  | 1 | 1 |  |  | 2 | 2 |

1Possible excellent markers.

2Possible sensitive markers.

APTT: Activated partial thromboplastin time; CBC: Complete blood count; CMP: Comprehensive metabolic panel; dTT: Dilute thrombin time; ECA: Ecarin chromogenic assay: ECT: Ecarin clotting time; FXa: Activated factor X; PT: Prothrombin time; TT: Thrombin time.

**Table 2 Pharmacological characteristics of direct oral anticoagulant**[**71,87**]

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Dabigatran** | **Apixaban** | **Edoxaban** | **Rivaroxaban** |
| Target factor | Thrombin (Factor IIa) | Factor Xa | Factor Xa | Factor Xa |
| Half-time (h) | 10.7-11.8 | 6.12-8.11 | 6.21-6.70 | 5.7-12.6 |
| Time to peak effect (h) | 4 | 3.0-3.5 | 1-1.5 | 1.4-3.3 |
| Distribution volume (L) | 50-70 | 21 | 107 | 50 |
| Renal excretion (%) | 85 | 27 | 35.4-50 | 50 |
| Fecal excretion (%) | 6 | 25 | 62.2 | 50 |
| Hepatic metabolism | No | CYP3A4/5 | CYP3A4 | CYP3A4 and CYP2J2 |
| Transporter | P-gP | P-gP/BCRP | P-gP | P-gP/BCRP |
| Protein binding (%) | 28.2-31.5 | 87 | 40.0-58.9 | 92-95 |
| Dialyzable | Yes | No | No | No |
| Prodrug | Yes | No | No | No |
| Bioavailability (%) | 6.5 | 50 | 61.8 | 66-112 |
| Dose for AF (in Japan) | 150 mg | 5 mg | 60 mg | 15 mg |
| Dosing time | Twice daily | Twice daily | Once daily | Once daily |
| Reversal agent | Idarucizumab | Andexanet alfa | Andexanet alfa | Andexanet alfa |
| FDA-approvedindications | Nonvalvular AF, VTE (T, SP, P) | Nonvalvular AF, VTE (T, SP, P) | Nonvalvular AF, VTE (T) | Nonvalvular AF, VTE (T, SP, P) |
| Japanese insurance system-approved indications | Nonvalvular AF (P) | Nonvalvular AF (P), VTE (T, SP) | Nonvalvular AF (P), VTE (T, SP) | Nonvalvular AF (P), VTE (T, SP) |
| Non-pharmacologicinteractions | Age, reduced GFR | Age, reduced body weight, reduced GFR, probable severe liver damage | Reduced GFR, probable severe liver damage | Age, reduced GFR, probable severe liver damage |
| Drug interactions | Dose reduction: Concomitant P-gp inhibitor, gastric acid inhibitory drug | Avoid: Concomitant P-gp and CYP3A4 inhibitors | Avoid: Concomitant rifampin | Avoid: Rivaroxaban with concomitant dual P-gp and CYP3A4 inhibitors |
| Contraindications | Ccr: < 30mL/min | Nonvalvular AF: Ccr: < 15mL/min, VTE:Ccr: < 30mL/min | Nonvalvular AF: Ccr: < 15mL/min, VTE:Ccr: < 30mL/min | Nonvalvular AF: Ccr: < 15mL/min, VTE:Ccr: < 30mL/min |

AF: Atrial fibrillation; P: Prophylaxis; SP: Secondary prevention; T: Treatment; VTE: Venous thromboembolism; FDA: Food and Drug Administration; Ccr: Creatinine clearance.

**Table 3 Comparison of clinical trials on patients receiving direct oral anticoagulant: Major bleeding**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Dabigatran** | **Apixaban** | **Edoxaban** | **Rivaroxaban** |
| Trial name | RE-LY[4] | ARISTOTLE[5] | ENGAGE AF TIMI48[6] | ROCKET AF[7]/J-ROCKET AF |
| Number of patients | 18113 | 18201 | 21105 | 14264 |
| Method | PROBE | RCT | RCT | RCT |
| Primary endpoints | Stroke or systemic embolism | Ischemic or hemorrhagic stroke or systemic embolism | Stroke or systemic embolism | Stroke or systemic embolism |
| Period (years) | 2.0 | 1.8 | 2.8 | 1.9 |
| CHADS2 score (mean) | 2.2 | 2.1 | 2.8 | 3.48 (J-ROCKET: 3.25) |
| Dosing dose | 150 mg/10 mg bid | 5 mg bid | 60 mg/30 mg qd | 20 mg od (J-ROCKET: 15 mg od) |
| Evaluation |  |  |  |  |
| Thrombus/embolism *(vs* warfarin) | 110 mg: Non-inferior, 150 mg: Superior | Superior | 60 mg: Similar, 30 mg: Similar | On treatment: Superior, Intention-to-treat: Non-inferior |
| Outcomes: Stroke or systemic embolism | War: 1.69%/yr, D (110): 1.51%/yr, D (150): 1.11%/yr | War: 1.50%/yr, A: 1.27%/yr | War: 1.81%/yr, E (30): 2.06%/yr, E (60): 1.57%/yr | War: 2.2%/yr, R: 1.7%/yr |
| Major bleeding (*vs* warfarin) | 110 mg: Superior, 150 mg: Similar | Superior | Superior | Similar |
| Bleeding rate | War: 3.36%/yr, D (110): 2.71%/yr, D (150): 3.11%/yr | War: 3.09%/yr, A: 2.13%/yr | War: 3.43%/yr, E (30): 1.61%/yr, E (60): 2.75%/yr | War: 3.4%/yr, R: 3.6%/yr |
| Intracranial bleeding | War: 0.74%/yr, D (110): 0.23%/yr, D (150): 0.30%/yr | War: 2.27%/yr, A: 1.79%/yr | War: 0.85%/yr, E (30): 0.26%/yr, E (60): 0.39%/yr | War: 0.7%/yr, R: 0.5%/yr |
| Gastrointestinal bleeding | War: 1.02%/yr, D (110): 1.12%/yr, D (150): 1.51%/yr | War: 0.86%/yr, A: 0.76%/yr | War: 1.23%/yr, E (30): 0.82%/yr, E (60): 1.51%/yr | War: 2.2%/yr, R: 3.2%/yr1 |
| Minor bleeding (*vs* warfarin) | War: 16.37%/yr, D (110): 13.16%/yr, D (150): 14.84%/yr | War: 6.01%/yr, A: 4.07%/yr | War: 4.89%/yr, E (30): 3.52%/yr, E (60): 4.12%/yr | War: 11.4%/yr, R: 11.8%/yr |
| Mortality rate | War: 4.13%/yr, D (110): 3.75%/yr, D (150): 3.64%/yr | War: 3.94%/yr, A: 3.52%/yr | War: 4.35%/yr, E (30): 3.80%/yr, E (60): 3.99%/yr | War: 2.2%/yr, R: 1.9%/yr |

A: Apixaban; D: Dabigatran; E: Edoxaban; R: Rivaroxaban; war: Warfarin; RCT: Randomized clinical trial; CHADS: Congestive heart failure, Hypertension, Age > 75 years, Diabetes mellitus, and Stroke; PROBE: Prospective randomized open blinded-endpoint.

**Table 4 Summary of international guidelines concerning withdrawal of direct oral anticoagulants during gastroenterological endoscopy**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Standard endoscopy** | **Biopsy** | **Low risk of bleeding** | **High risk of bleeding, including** **ESD** |
| Japan[71] | 1 | 2Avoid peak plasma level | 2Avoid peak plasma level | 3(1) Withdraw on the day of treatment; and (2) Heparin replacement |
| Europe[72] | 1 | 3Withdraw on the day of treatment | 3Withdraw on the day of treatment | 3(1) Withdraw 3 d before treatment; (2) Withdraw 5 d before treatment for dabigatran patients at Ccr 30–50 mL/min; and (3) No heparin bridging |
| United States[73] | 1 | 1 | 1 | 3(1) Withdraw; and (2) Bridge therapy required for patients at high risk for thromboembolic events |
| Korea[74] | 1 | 1 | 1 | 3Withdraw 2 d before treatment |
| Asia-Pacific[75] | 1 | 1 | 1 | 3Withdraw 2 d before treatment |

1Withdrawal is not required.

2Withdrawal is not required but possible.

3Withdrawal is required.

ESD: Endoscopic submucosal dissection; Ccr: Creatinine clearance.

**Table 5 Delayed bleeding after endoscopic submucosal dissection in patients receiving direct oral anticoagulants**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Authors** | **Yr** | **Country** | **Type** | **Organ** | **DOAC patients** | **Bleeding rate** | **Non-DOAC patients** | **Bleeding rate** |
| Nagata *et al*[83] | 2018 | Japan | Retrospective | Upper GI | 275 | 39.6% | 301 (warfarin) | 45.8% |
| Horie *et al*[85] | 2022 | Japan | Retrospective | Esophagus | 161 | 13% | 8692 | 0.3%1 |
| Yoshio *et al*[88] | 2017 | Japan | Retrospective | Stomach | 24 | 20.8% | 73 (warfarin) | 24.6% |
| Sanomura *et al*[89] | 2018 | Japan | Retrospective | Stomach | 21 | 19.0% | 40 (warfarin) | 17.5% |
| Saito *et al*[90] | 2020 | Japan | Retrospective | Stomach | 77 | 19.5% | 66 (warfarin) | 22.7% |
| Hatta *et al*[36] | 2021 | Japan | Retrospective | Stomach | 253 | 17.0% | 10,067 | 4.4%1 |
| Tomida *et al*[84] | 2021 | Japan | Retrospective | Stomach | 261 | 14% | 467 (warfarin) | 18% |
| Choi *et al*[91] | 2021 | Korea | Retrospective | Stomach | 23 | 8.7% | 1499 | 3.0% |
| Kagawa *et al*[37] | 2022 | Japan | Retrospective | Stomach | 39 | 15.4% | 752 | 4.3%1 |
| Nagata *et al*[83] | 2018 | Japan | Retrospective | Lower GI | 121 | 13.2% | 111 (warfarin) | 25.9% |
| Yamashita *et al*[92] | 2018 | Japan | Retrospective | Colon | 9 | 22.0% | 19 (warfarin) | 26.3% |
| Ogiyama *et al*[93] | 2020 | Japan | Retrospective | Colon | 43 | 23.3% | 44 (warfarin) | 11.4% |
| Harada *et al*[94] | 2020 | Japan | Retrospective | Colon | 25 | 16.0% | 26 (warfarin) | 7.7% |

1Included 2 EMR patients.

2Included no antithrombotic drug patients.

DOAC: Direct oral anticoagulants.