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Editorial Board Member of *World Journal of Gastroenterology*, John K Triantafillidis, MD, PhD, FEBGH, Associate Professor of Medicine, Staff Physician, Iasi University of Medicine and Pharmacy, Romania, "Metropolitan General" Hospital, Holargos, Athens 15562, Greece. jktrian@gmail.com

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

Mitsushige Sugimoto, Masaki Murata, Takashi Kawai

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Mitsushige Sugimoto, Takashi Kawai, Department of Gastroenterological Endoscopy, Tokyo Medical University Hospital, Tokyo 160-0023, Japan

Masaki Murata, Department of Gastroenterology, National Hospital Organization Kyoto Medical Center, Kyoto 612-8555, Japan

Corresponding author: Mitsushige Sugimoto, AGAF, MD, PhD, Professor, Department of Gastroenterological Endoscopy, Tokyo Medical University Hospital, 6-7-1, Nishishinjuku, Shinjuku-ku, Tokyo 160-0023, Japan. sugimo@tokyo-med.ac.jp

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 T_{max}) 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.

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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 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 (I^2 : 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].

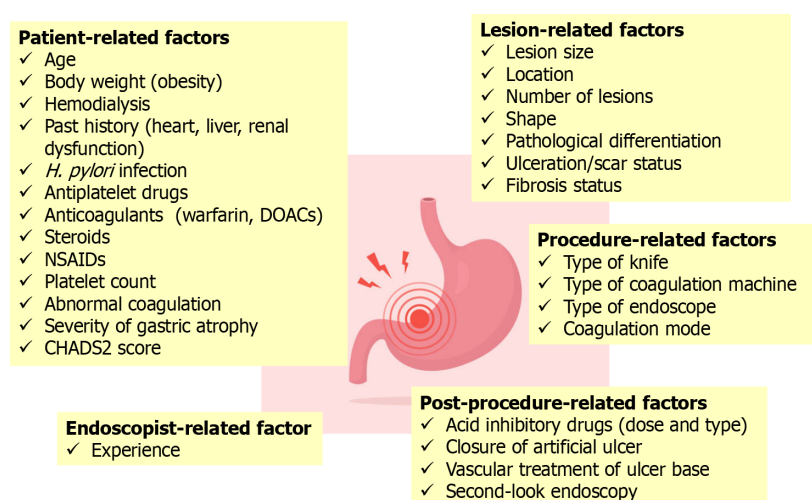
Libânio *et al*[28] showed in a meta-analysis of 74 articles that male sex (OR 1.25), cardiopathy (OR 1.54), antithrombotic drugs (OR 1.63), cirrhosis (OR 1.76), chronic kidney disease (CKD) (OR 3.38), tumor size > 20 mm (OR 2.70), resected specimen size > 30 mm (OR 2.85), localization in the lesser 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



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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.

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

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-FIIa levels	Anti-FXa levels	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.

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 (T_{max}) 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 T_{max} [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

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-approved indications	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-pharmacologic interactions	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.

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

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
CHADS ₂ 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 (<i>vs</i> 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 (<i>vs</i> 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%/yr ¹
Minor bleeding (<i>vs</i> 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.

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).

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

Ref.	Country	Standard endoscopy	Biopsy	Low risk of bleeding	High risk of bleeding, including ESD
[71]	Japan	¹	² Avoid peak plasma level	² Avoid peak plasma level	³ (1) Withdraw on the day of treatment; and (2) Heparin replacement
[72]	Europe	¹	³ Withdraw on the day of treatment	³ Withdraw 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
[73]	United States	¹	¹	¹	³ (1) Withdraw; and (2) Bridge therapy required for patients at high risk for thromboembolic events
[74]	Korea	¹	¹	¹	³ Withdraw 2 d before treatment
[75]	Asia-Pacific	¹	¹	¹	³ Withdraw 2 d before treatment

¹Withdrawal is not required.²Withdrawal is not required but possible.³Withdrawal is required.

ESD: Endoscopic submucosal dissection; Ccr: Creatinine clearance.

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

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

Ref.	Year	Country	Type	Organ	DOAC patients	Bleeding rate	Non-DOAC patients	Bleeding rate
Nagata <i>et al</i> [83]	2018	Japan	Retrospective	Upper GI	275	39.6%	301 (warfarin)	45.8%
Horie <i>et al</i> [85]	2022	Japan	Retrospective	Esophagus	16 ¹	13%	869 ²	0.3% ¹
Yoshio <i>et al</i> [88]	2017	Japan	Retrospective	Stomach	24	20.8%	73 (warfarin)	24.6%
Sanomura <i>et al</i> [89]	2018	Japan	Retrospective	Stomach	21	19.0%	40 (warfarin)	17.5%
Saito <i>et al</i> [90]	2020	Japan	Retrospective	Stomach	77	19.5%	66 (warfarin)	22.7%
Hatta <i>et al</i> [36]	2021	Japan	Retrospective	Stomach	253	17.0%	10,067	4.4% ¹
Tomida <i>et al</i> [84]	2021	Japan	Retrospective	Stomach	261	14%	467 (warfarin)	18%
Choi <i>et al</i> [91]	2021	Korea	Retrospective	Stomach	23	8.7%	1499	3.0%
Kagawa <i>et al</i> [37]	2022	Japan	Retrospective	Stomach	39	15.4%	752	4.3% ¹
Nagata <i>et al</i> [83]	2018	Japan	Retrospective	Lower GI	121	13.2%	111 (warfarin)	25.9%
Yamashita <i>et al</i> [92]	2018	Japan	Retrospective	Colon	9	22.0%	19 (warfarin)	26.3%
Ogiyama <i>et al</i> [93]	2020	Japan	Retrospective	Colon	43	23.3%	44 (warfarin)	11.4%
Harada <i>et al</i> [94]	2020	Japan	Retrospective	Colon	25	16.0%	26 (warfarin)	7.7%

¹Included 2 endoscopic mucosal resection patients.²Included no antithrombotic drug patients.

DOAC: Direct oral anticoagulants.

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 T_{max}) 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.

FOOTNOTES

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Country/Territory of origin: Japan

ORCID number: Mitsushige Sugimoto 0000-0002-9194-7392; Masaki Murata 0000-0002-4951-0584; Takashi Kawai 0000-0002-5320-8134.

S-Editor: Li L

L-Editor: A

P-Editor: Zhao S

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