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ORIGINAL ARTICLE - ENDOSCOPY

Rates and risk factors of bleeding after gastric endoscopic submucosal dissection with continuous warfarin or 1-day withdrawal of direct oral anticoagulants

Shoichiro Hirata,[*] Kenta Hamada,[†] Masaya Iwamuro,[*] Hirokazu Mouri,[‡] Koji Miyahara,[§] Takao Tsuzuki,[¶] Kenji Yamauchi,[**,††] Sayo Kobayashi,[‡‡] Sakuma Takahashi,[††] Ryuta Takenaka,[§§] Shinichiro Hori,[¶,¶¶] Masafumi Inoue,[***] Tatsuya Toyokawa,[†††] Mamoru Nishimura,[‡‡‡] Shuhei Ishiyama,[§§§] Jiro Miyaike,[¶¶¶] Ryo Kato,[****,††††] Minoru Matsubara,[‡‡‡‡] Naoko Yunoki,[§§§§] Hiromitsu Kanzaki,[*,§§] Yoshiro Kawahara,[†] Hiroyuki Okada,[*,¶] Hideki Ishikawa,[¶¶¶¶] Motoyuki Otsuka[*] and Okayama Gut Study Group

[*]Department of Gastroenterology and Hepatology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, [†]Department of Practical Gastrointestinal Endoscopy, Okayama University, [***]Department of Gastroenterology, Japanese Red Cross Okayama Hospital, [‡‡‡]Department of Internal Medicine, Okayama City Hospital, [§§§]Department of Internal Medicine, Okayama Saiseikai General Hospital, [††††]Department of Gastroenterology, Okayama Rosai Hospital, Okayama, [‡]Department of Gastroenterology and Hepatology, Kurashiki Central Hospital, Kurashiki, [§]Department of Internal Medicine, Hiroshima City Hospital, Hiroshima, [¶]Department of Gastroenterology, Japanese Red Cross Society Himeji Hospital, Himeji, [**]Department of Gastroenterology, Mitoyo General Hospital, Kanonji, [††]Department of Gastroenterology, Kagawa Prefectural Central Hospital, Takamatsu, [‡‡]Department of Internal Medicine, Fukuyama City Hospital, [†††]Department of Gastroenterology, National Hospital Organization Fukuyama Medical Center, Fukuyama, [§§]Department of Internal Medicine, Tsuyama Chuo Hospital, Tsuyama, [¶¶]Department of Endoscopy, National Hospital Organization Shikoku Cancer Center, Matsuyama, [¶¶¶]Department of Internal Medicine, Saiseikai Imabari Hospital, Imabari, [****]Department of Gastroenterology, National Hospital Organization Iwakuni Clinical Center, Iwakuni, [‡‡‡‡]Department of Internal Medicine, Sumitomo Besshi Hospital, Niihama, [§§§§]Department of Internal Medicine, Akaiwa Medical Association Hospital, Akaiwa, [¶¶¶¶]Department of Molecular-Targeting Prevention, Kyoto Prefectural University of Medicine, Osaka, Japan

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Correspondence
Kenta Hamada, Department of Practical Gastrointestinal Endoscopy, Okayama University, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan.
Email: paosishou@yahoo.co.jp

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Abstract

Background and Aim: The 2017 Japanese guidelines recommend continuing warfarin therapy during the perioperative period or discontinuing direct oral anticoagulants (DOACs) only on the day of endoscopic submucosal dissection for early gastric cancer. However, their safety has not been sufficiently explored. This study aimed to validate this management method.
Methods: This retrospective, multicenter study analyzed the characteristics and outcomes of patients who underwent gastric endoscopic submucosal dissection between July 2017 and June 2019. The patients were categorized according to the use of warfarin or DOACs.
Results: Among the 62 eligible patients, 53 (85%) were male (median age, 76 years). Warfarin was used in 10 patients (16%) and DOACs in 52 patients (84%). Fourteen patients taking DOACs (27%) used concomitant antiplatelet agents, with seven patients (13%) continuing treatment at the time of the endoscopic procedure. No postprocedural bleeding occurred in patients receiving warfarin (0%), whereas 10 cases (19%) of bleeding occurred in patients receiving DOACs: rivaroxaban, 0% (0/22); dabigatran, 0% (0/2); edoxaban, 43% (6/14); and apixaban, 29% (4/14). The type of anticoagulant ($P < 0.01$) and continuation of antiplatelet therapy ($P = 0.02$) were risk factors for postprocedural bleeding in patients receiving DOACs. Intraprocedural bleeding requiring transfusion or symptomatic thromboembolic events were not reported.
Conclusions: Continuous warfarin therapy is preferred. DOAC withdrawal 1 day before a procedure is associated with a high bleeding rate, which may differ for different types of anticoagulants. The continuation of antiplatelet medications in patients receiving DOACs carries a high risk of bleeding and is a future challenge.

Introduction

Endoscopic submucosal dissection (ESD) is the most effective and minimally invasive procedure for early gastric cancer. In recent years, with a surge in the prevalence of elderly individuals, the number of patients receiving anticoagulant agents, including warfarin and direct oral anticoagulants (DOACs), for the secondary prevention of cerebrovascular disorders and thromboembolic diseases has increased. According to the guidelines proposed by the Japan Gastroenterological Endoscopy Society in 2012,[1] endoscopic treatment with heparin replacement of anticoagulants is recommended to prevent thrombotic events.

Postprocedural bleeding after gastric ESD is the most frequent adverse event, particularly in patients receiving antithrombotic therapy.[2–4] Although heparin replacement has traditionally served as the standard bridging therapy for high-risk patients with thromboembolic complications, our previous report revealed that patients undergoing heparin replacement exhibited an increased susceptibility to postprocedural bleeding following gastric ESD.[5] Several studies have reported that heparin replacement is a risk factor for bleeding after gastric ESD or colorectal endoscopic resection,[6–9] while continuous oral anticoagulant therapy might have a lower risk of postprocedural bleeding than heparin replacement.[10,11]

According to the guidelines published in 2017,[12] maintaining continuous warfarin administration within the therapeutic range or temporarily discontinuing DOACs solely on the day of endoscopic procedures is recommended. However, the available evidence remains inadequate and warrants further investigation. We conducted a retrospective multicenter study to elucidate the safety of gastric ESD while continuously administering warfarin or discontinuing DOAC on the day of the procedure.

Methods

Patients. Patients eligible for enrolment were those who underwent ESD for early gastric cancer or a suspected malignancy between July 2017 and June 2019 at 17 collaborating institutions across Japan (Okayama Gut Study Group). Inclusion criteria were as follows: (i) patients who underwent the procedure with continued warfarin or 1-day withdrawal of DOAC, including apixaban, dabigatran, edoxaban, or rivaroxaban; (ii) patients aged over 20 years old; (iii) patients with hemoglobin level ≥ 9 g/dL; (iv) patients with platelet count $\geq 100\ 000/mm^3$; and (v) patients with transaminase ≤ 150 U/L. The exclusion criteria were as follows: (i) switching from warfarin to DOAC because no specific method is indicated in the guidelines, (ii) discontinuing warfarin after ESD, (iii) resuming DOACs two or more days after ESD, (iv) simultaneous ESD for more than two lesions, (v) a history of gastrectomy or gastric tube reconstruction because of special cases, (vi) systemic administration of corticosteroids or nonsteroidal anti-inflammatory drugs, (vii) endoscopic closure for ulcers resulting from ESD, and (viii) patients undergoing dialysis.

The study protocol was approved by the institutional review board of each hospital in accordance with the Declaration of Helsinki.

Study methods. Gastric ESD was performed using a high-frequency generator (VIO 300D; Erbe Elektromedizin GmbH, Tübingen, Germany), ITknife2 (KD-611L; Olympus Medical Systems, Co. Ltd., Tokyo, Japan), DualKnife (KD-650L; Olympus Medical Systems, Co. Ltd.), ITknife (KD-610L; Olympus Medical Systems, Co. Ltd.), ITknife nano (KD-612; Olympus Medical Systems, Co. Ltd.), and hemostatic forceps (Coagrasper; FD-411UR; Olympus Medical Systems, Co. Ltd.). En bloc resection was defined as the resection of the tumor in one piece with no endoscopic residual disease. A complete resection was defined as an en bloc resection with histologically confirmed negative horizontal and vertical margins.

The prothrombin time–international normalized ratio was measured in all patients receiving warfarin treatment and confirmed to be within the therapeutic level 1.6–2.6. Apixaban was administered at a dose of 5 or 2.5 mg twice daily. Dabigatran was administered at a dose of 150 or 110 mg twice daily. Edoxaban was administered at a dose of 60 or 30 mg daily. Rivaroxaban was administered at a dose of 15 or 10 mg daily. The DOAC dosage was determined by the prescribing physician with reference to age, body weight, renal function, and bleeding risk. Proton pump inhibitors or potassium-competitive acid blockers (vonoprazan) were received for 5–8 weeks after the procedure. The patients underwent second-look endoscopy (SLE) either before oral food intake or at discharge, with the addition of preventive hemostasis, if necessary.

Measured outcomes. The primary outcome of this study was the incidence of postprocedural bleeding after gastric ESD with continuous warfarin or 1-day withdrawal of DOAC in accordance with the guidelines. Postprocedural bleeding was defined as clinically evident bleeding, such as hematemesis or melena, which was confirmed by endoscopic examination with a decline of > 2 g/dL in the hemoglobin concentration. The incidence of intraprocedural and postprocedural bleeding requiring transfusion and symptomatic thromboembolic complications was also assessed. A blood transfusion was performed at the discretion of the attending physician. Complications were monitored for 28 days after the ESD. Additionally, this study aimed to identify the risk factors for postprocedural bleeding with 1-day withdrawal from DOAC. We divided patients taking DOACs into two groups based on bleeding rates by DOAC type and compared the patient backgrounds between the DOAC groups with high and low bleeding rates.

Statistical analysis. Differences were considered significant at P-values of < 0.05, as determined using Fisher's exact test for discontinuous variables and the Mann–Whitney U-test for continuous variables. JMP PRO version 17 software package (SAS Institute, Cary, NC, USA) was used for all statistical analyses.

Results

Enrolled patients. The patient flow is shown in Figure 1. Finally, 62 patients were included in the analysis, 10 of whom were taking warfarin, and 52 were taking DOAC. The DOACs used

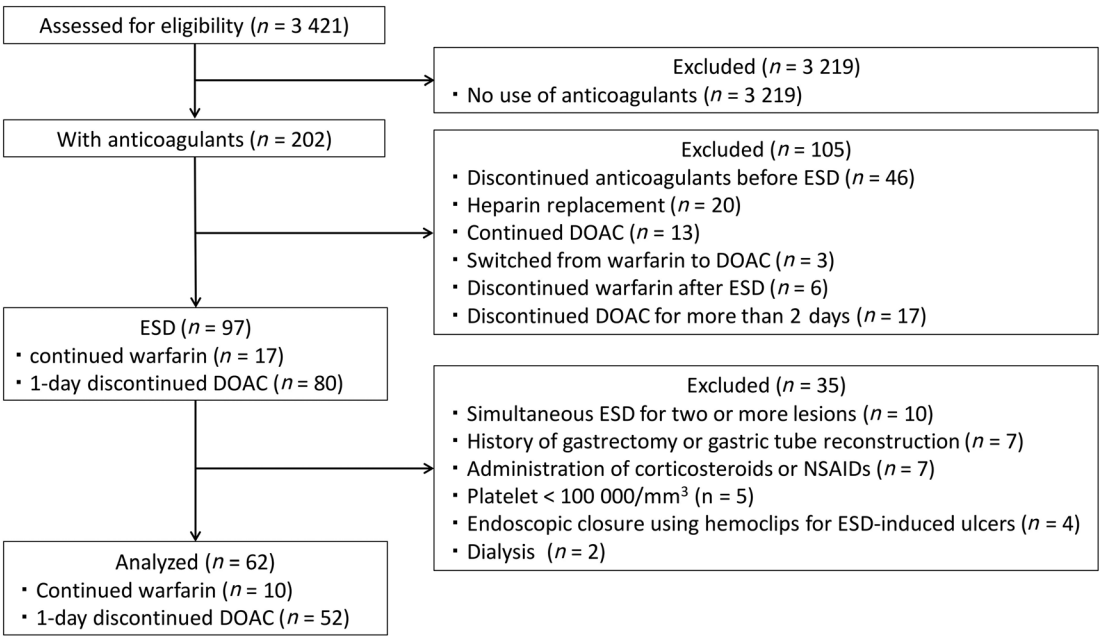

Figure 1 Flow diagram of the study participants. DOAC, direct oral anticoagulant; ESD, endoscopic submucosal dissection; NSAIDs, nonsteroidal anti-inflammatory drugs.

were as follows: rivaroxaban, 22 patients; edoxaban, 14 patients; apixaban, 14 patients; and dabigatran, 2 patients.

Characteristics of patients and antiplatelet agents. The baseline characteristics of the patients are summarized in Table 1. The study cohort consisted of 53 men and 9 women, with a median age of 76 years (range: 51–91 years). Among the participants, 16 patients were also receiving antiplatelet agents, with five patients prescribed with aspirin, four prescribed with clopidogrel, one prescribed with prasugrel, two prescribed with cilostazol, three prescribed with eicosapentaenoic acid, and two prescribed with limaprost alfadex.

Management of antiplatelet agents during the perioperative period and endoscopic submucosal dissection outcomes. Perioperative medication management details and ESD outcomes are summarized in Table 2. In all but two cases, antiplatelet agents were resumed on the day following ESD. The exceptions included one case in which the physician exercised discretion to resume after 2 days and another case in which resumption was delayed for 4 days due to minor intraprocedural bleeding. En bloc resection was successfully achieved in all cases, with a median procedure duration of 80 min (range: 16–279 min). Curative resection was performed in 60 (97%) patients.

Complications during and after endoscopic submucosal dissection. The complications are presented in Table 3. In this study, no instances of bleeding (0%) were observed in patients receiving warfarin, whereas 10 cases (19%, 95% confidence interval [CI] 11–32%) of bleeding occurred in patients receiving DOACs. Postprocedural bleeding occurred in 0 of 22 cases (0%), 0 of 2 cases (0%), 6 of 14 cases (43%, 95% CI 21–67%), and 4 of 14 cases (29%, 95% CI 12–55%) in patients taking rivaroxaban, dabigatran, edoxaban, and apixaban, respectively. The median timing of postprocedural bleeding was 8.5 days after ESD (range: 1–14 days), and no clear trend was observed. Blood transfusion was necessary in six instances (12%, 95% CI 5–23%) of patients receiving DOACs; however, hemostasis was successfully achieved endoscopically in all cases. Intraprocedural bleeding was controlled in all cases, and no transfusion was performed during the procedure. No symptomatic thromboembolic events or perforations were observed.

Risk factors for postprocedural bleeding complications in patients taking direct oral anticoagulants. As no postprocedural bleeding occurred in patients taking warfarin, we analyzed the risk factors for bleeding in patients taking DOACs. The background characteristics and clinical outcomes of the patients receiving DOACs for postprocedural bleeding (postprocedural bleeding group) and those without postprocedural bleeding (no postprocedural bleeding group) are presented in Table 4. The DOAC type was a risk factor for bleeding ($P < 0.01$). Of the patients who experienced postprocedural bleeding, 40% (4 out of 10 patients) had been continuously using antiplatelet medications. In contrast, only 7% (3 of 42 patients) of those without postprocedural bleeding were taking such medications, resulting in a significant difference ($P = 0.02$). The postprocedural bleeding rate was 57% (4/7) in patients who continued antiplatelet therapy and 13% (6/45) in those who did not. No significant differences were observed between the postprocedural bleeding and no postprocedural bleeding groups in the percentage of tumors larger than 2 cm in diameter (30% *vs*

Table 1 Characteristics of the patients, antithrombotic therapy, and lesions.

	Total *n* = 62	Warfarin *n* = 10	DOAC *n* = 52
Age (years)	76 (51–91)	79 (67–89)	76 (51–91)
Male	53 (85)	8 (80)	45 (86)
Performance status	0 (0–2)	0 (0–0)	0 (0–2)
Comorbidities associated with cardiovascular disease			
Atrial fibrillation	57 (92)	9 (90)	48 (92)
$CHADS_2$ score[†]	2 (0–5)	2 (1–5)	2 (0–5)
CHA_2DS_2-VASc score[†]	3 (0–7)	4 (2–6)	3 (0–7)
Hypertension	47 (76)	7 (70)	40 (77)
Dyslipidemia	26 (42)	2 (20)	24 (46)
Diabetes mellitus	13 (21)	2 (20)	11 (21)
Congestive heart failure	12 (19)	3 (30)	9 (17)
Valvular heart disease	7 (11)	1 (10)	6 (12)
Pulmonary hypertension	1 (2)	0 (0)	1 (2)
Cardiomyopathy	1 (2)	0 (0)	1 (2)
Peripheral artery disease	3 (5)	0 (0)	3 (6)
History associated with cardiovascular disease			
Stroke or transient ischemic attack	15 (24)	3 (30)	12 (23)
Deep vein thrombosis	4 (6)	1 (10)	3 (6)
Myocardial infarction	7 (11)	0 (0)	7 (13)
Antiplatelet agent	16 (26)	2 (20)	14 (27)
Aspirin	5 (8)	0 (0)	5 (10)
Clopidogrel	4 (6)	0 (0)	4 (8)
Prasugrel	1 (2)	0 (0)	1 (2)
Cilostazol	2 (3)	1 (10)	1 (2)
Eicosapentaenoic acid	3 (5)	0 (0)	3 (6)
Limaprost alfadex	2 (3)	1 (10)	1 (2)
Helicobacter pylori infection			
Positive	11 (18)	1 (10)	10 (19)
Negative	43 (69)	7 (70)	36 (69)
Unknown	8 (13)	2 (20)	6 (12)
Tumor located in the antrum	31 (50)	5 (50)	26 (50)
Pathological tumor size (mm)	14 (3–47)	10.5 (4–37)	14 (3–47)
Tumor with ulcer or scar	4 (6)	0 (0)	4 (8)

Data are presented as median (range) or *n* (%).

[†]$CHADS_2$ and CHA_2DS_2-VASc scores were evaluated in 61 patients with atrial fibrillation.

DOAC, direct oral anticoagulant; $CHADS_2$ score, Congestive heart failure or left ventricular dysfunction, Hypertension, Age, Diabetes mellitus, Stroke or transient ischemic attack 2; CHA_2DS_2-VASc, Congestive heart failure or left ventricular dysfunction, Hypertension, Age 2, Diabetes mellitus, Stroke or transient ischemic attack or thromboembolism 2 - Vascular disease, Age, Sex category.

21%), tumors located in the pyloric antrum (30% *vs* 55%), and SLEs performed (60% *vs* 81%).

Postprocedural bleeding rates and background characteristics according to direct oral anticoagulant. In the present study, postprocedural bleeding was observed in 43% (6 of 14 patients) of patients administered with edoxaban and 29% (4 of 14 patients) of patients receiving apixaban. Notably, no instances of postprocedural bleeding were recorded in patients receiving rivaroxaban or dabigatran (Table 4). Consequently, we compared the background characteristics of the edoxaban and apixaban (EA) groups with those of the rivaroxaban and dabigatran (RD) groups. The corresponding results are presented in Table 5. Despite the higher prevalence of patients with histories of myocardial infarction and diabetes in the EA group, no significant differences in the use or discontinuation of antiplatelet agents were observed. The preoperative activated partial thromboplastin time (APTT) tended to be longer in the RD group.

Table 2 Characteristics of perioperative management and ESD procedures and outcomes

	Total *n* = 62	Warfarin *n* = 10	DOAC *n* = 52
Continued antiplatelet treatment[†]	8 (13)	1 (10)	7 (13)
Acid suppressant	62 (100)	10 (100)	52 (100)
Proton pump inhibitor	23 (37)	2 (20)	21 (40)
Vonoprazan	39 (63)	8 (80)	31 (60)
Mucosal protective agent	46 (74)	6 (60)	40 (77)
ESD			
Procedural items			
ITknife2	23 (37)	6 (60)	17 (33)
DualKnife	16 (26)	2 (20)	14 (27)
ITknife	15 (24)	2 (20)	13 (25)
ITknife nano	4 (6)	0 (0)	0 (0)
FlushKnife	3 (5)	0 (0)	3 (6)
Others	1 (2)	0 (0)	1 (2)
Procedure time (min)	80 (16–279)	72.5 (25–191)	82.5 (16–279)
Resected specimen size (mm)	35 (20–63)	34.5 (20–60)	35 (20–63)
En bloc resection	62 (100)	10 (100)	52 (100)
Complete resection	60 (97)	10 (100)	50 (96)
SLE	49 (79)	9 (90)	40 (77)
Timing of SLE			
Before oral food intake	29 (47)	2 (20)	27 (52)
Before discharge	20 (32)	7 (70)	13 (25)
Not performed	13 (21)	1 (10)	12 (23)
Prophylactic hemostasis during SLE[‡]			
Yes	21 (34)	2 (20)	19 (37)
No	28 (45)	7 (70)	20 (39)

Data are presented as *n* (%) or median (range).

[†]Prasugrel was switched to aspirin in one patient.

[‡]One patient was excluded from the DOAC group because of postprocedural bleeding before the scheduled SLE.

DOAC, direct oral anticoagulant; ESD, endoscopic submucosal dissection; SLE, second-look endoscopy.

Discussion

In this study, no postprocedural bleeding (0%) was observed in patients receiving warfarin, whereas 10 cases (19%, 95% CI 11–32%) of bleeding occurred after gastric ESD in patients receiving DOACs. Although blood transfusion was necessary in six instances (12%, 95% CI 5–23%) of patients receiving DOACs, hemostasis was successfully achieved endoscopically in all cases. Intraprocedural bleeding was controlled in all cases. No symptomatic thromboembolic events were observed. The type of DOACs and continuation of antiplatelet agents were risk factors for postprocedural bleeding in patients receiving DOACs.

Table 3 Complications associated with gastric ESD

	Warfarin *n* = 10	DOAC *n* = 52	Rivaroxaban *n* = 22	Edoxaban *n* = 14	Apixaban *n* = 14	Dabigatran *n* = 2
Postprocedural bleeding	0 (0)	10 (19, 11–32)	0 (0)	6 (43, 21–67)	4 (29, 12–55)	0 (0)
Transfusion due to postprocedural bleeding	0 (0)	6 (12, 5–23)	0 (0)	2 (14, 4–40)	4 (29, 12–55)	0 (0)
Intraprocedural bleeding requiring transfusion	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Symptomatic thromboembolic complications	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Perforation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Data are presented as *n* (%, 95% CI).
CI, confidence interval; DOAC, direct oral anticoagulant; ESD, endoscopic submucosal dissection.

Table 4 A univariable analysis of the risk factors for postprocedural bleeding in the DOAC group

	Postprocedural bleeding *n* = 10	No postprocedural bleeding *n* = 42	*P*-value
DOAC			< 0.01
Rivaroxaban	0 (0)	22 (42)	
Edoxaban	6 (60)	8 (15)	
Apixaban	4 (40)	10 (19)	
Dabigatran	0 (0)	2 (4)	
Antiplatelet agent including cessation and continuation			0.43
Yes	4 (40)	10 (24)	
No	6 (60)	32 (76)	
Continued antiplatelet treatment			0.02
Yes	4 (40)	3 (7)	
No	6 (60)	39 (93)	
Acid suppressant			1.00
Proton pump inhibitor	4 (40)	17 (40)	
Vonoprazan	6 (60)	25 (60)	
Mucosal protective agent			0.21
Yes	6 (60)	34 (81)	
No	4 (40)	8 (19)	
Tumor size			0.68
> 2 cm	3 (30)	9 (21)	
≤ 2 cm	7 (70)	33 (79)	
Ulcer or scar in the tumor			1.00
Present	1 (10)	3 (7)	
Absent	9 (90)	39 (93)	
Tumor location			0.29
Antrum	3 (30)	23 (55)	
Body	7 (70)	19 (45)	
Second-look endoscopy			0.21
Yes	6 (60)	34 (81)	
No	4 (40)	8 (19)	

Data are presented as *n* (%).
DOAC, direct oral anticoagulant.

Continuous warfarin or 1-day withdrawal of DOACs is expected to have a lower risk of postprocedural bleeding than heparin replacement.[10,11] Accordingly, the revised guidelines for anticoagulants for gastric ESD in Japan were published in 2017.[12] In the present study, the incidence of postprocedural bleeding with continuous warfarin was 0%. Warfarin continuation may be a promising treatment, although it is based on a small number of cases. However, the postprocedural bleeding rate for 1-day withdrawal of DOACs was high (19%, 95% CI 11–32%), and further studies are needed.

Postprocedural bleeding was common in the EA group. Several studies have described the incidence of gastrointestinal bleeding associated with various DOACs.[13–16] Hakoda *et al*. revealed that the DOACs associated with postprocedural bleeding risk after gastric ESD were edoxaban, apixaban, rivaroxaban, and dabigatran in ascending order,[17] and Tomida *et al*. revealed that the postprocedural bleeding risk in patients taking dabigatran after gastric ESD was significantly lower than that in patients receiving other DOACs,[18] which is consistent with the results of this study. Although there are controversial results,[19–21] our study results suggest that when performing gastric ESD in patients receiving edoxaban or apixaban, switching to dabigatran or rivaroxaban should be considered. The favorable effects of dabigatran on postprocedural bleeding may be due to its different pharmacological mechanisms compared with other DOACs. Dabigatran is a prodrug that does not exhibit anticoagulant activity. It reaches the systemic circulation and is converted to its active form by hepatic and serum esterases.[22] Therefore, dabigatran may not exhibit local anticoagulant activity in the stomach. However, it is unclear why rivaroxaban has a lower bleeding risk, and further studies on the bleeding risk associated with each DOAC during endoscopic procedures are required. The preoperative APTT was longer in the RD group, which did not have postprocedural bleeding, suggesting that preoperative prothrombin time and APTT were not indicators of postprocedural bleeding.

To the best of our knowledge, this is the first study to report that the continuous use of antiplatelet agents is a risk factor for postprocedural bleeding after gastric ESD with 1-day withdrawal of DOACs. In our previous study, the continuation of aspirin was a risk factor for postprocedural bleeding after gastric ESD with heparin replacement with oral anticoagulants.[5] Irrespective of heparin replacement, the continuous use of antiplatelet agents is likely to increase the risk of postprocedural bleeding after gastric ESD with anticoagulation therapy. It is possible that the real risk factor for bleeding is not the continuation of antiplatelet agents themselves but a patient background that necessitates continuation of antiplatelet agents. Multivariate analysis could not be performed to exclude this possibility due to lack of power. However, a multicenter study and randomized trial reported that continued antiplatelet medication was a risk factor for postprocedural bleeding, which is consistent with the present study.[23,24] Furthermore, the rate of postprocedural bleeding was considerably high (57%) in

Table 5 Characteristics of the patients, antithrombotic therapy, and lesions according to DOAC

	Rivaroxaban or dabigatran $n = 24$	Edoxaban or apixaban $n = 28$	*P*-value
Postprocedural bleeding	0 (0)	10 (36)	< 0.01
Age (years)	76 (64–88)	76 (51–91)	0.69
Male	21 (88)	24 (86)	1.00
Performance status	0 (0–2)	0 (0–2)	0.05
Comorbidities associated with cardiovascular disease			
Atrial fibrillation	23 (96)	25 (89)	0.61
$CHADS_2$ score, median (range)[†]	2 (0–5)	2 (0–5)	0.70
CHA_2DS_2-VASc score, median (range)[†]	3 (0–6)	3 (0–7)	0.80
Hypertension	20 (83)	20 (71)	0.35
Dyslipidemia	13 (54)	11 (39)	0.40
Diabetes mellitus	2 (8)	9 (32)	0.05
Congestive heart failure	2 (8)	7 (25)	0.15
Valvular heart disease	2 (8)	4 (14)	0.67
Pulmonary hypertension	1 (4)	0 (0)	0.46
Cardiomyopathy	1 (4)	0 (0)	0.46
Peripheral artery disease	2 (8)	1 (4)	0.59
History associated with cardiovascular disease			
Stroke or transient ischemic attack	6 (25)	6 (21)	1.00
Deep vein thrombosis	1 (4)	2 (7)	1.00
Myocardial infarction	1 (4)	6 (21)	0.11
Antiplatelet agent	7 (29)	7 (25)	0.76
Aspirin	2 (8)	3 (11)	1.00
Clopidogrel	3 (13)	1 (4)	0.32
Prasugrel	0 (0)	1 (4)	1.00
Cilostazol	0 (0)	1 (4)	1.00
Eicosapentaenoic acid	2 (8)	1 (4)	0.59
Limaprost alfadex	0 (0)	1 (4)	1.00
Continued antiplatelet treatment	2 (8)	5 (18)	0.43
Prothrombin time–international normalized ratio[‡]	1.22 (1.03–2.4)	1.13 (0.93–2.02)	0.06
Activated partial thromboplastin time (s)[§]	38 (26.4–50.5)	33 (25.4–54.4)	0.05
Tumor located in the antrum	11 (46)	15 (54)	0.78
Pathological tumor size (mm)	13 (3–32)	14 (4–47)	0.90
Tumor with ulcer or scar	2 (8)	2 (7)	1.00

Data are presented as *n* (%) or median (range).
[†]$CHADS_2$ and CHA_2DS_2-VASc scores were evaluated in 51 patients with atrial fibrillation.
[‡]Prothrombin time–international normalized ratio was evaluated in 50 patients who were examined.
[§]Activated partial thromboplastin time was evaluated in 49 patients who were examined.
DOAC, direct oral anticoagulant.

patients who continuously used antiplatelet agents in addition to DOACs. Kobayashi *et al*. reported that endoscopic closure after gastric ESD may contribute to decreased postprocedural bleeding in patients undergoing antithrombotic therapy.[25] Therefore, when performing gastric ESD in patients continuously using antiplatelet agents in addition to DOACs, it would be useful to consider suturing the ulcer after resection.

This study has some limitations. First, the data were analyzed retrospectively, and the procedures were not strictly standardized. Second, the number of cases was small, as only two patients taking dabigatran were included. A few bleeding events occurred, and the influence of confounding factors could not be excluded. Patients taking warfarin, rivaroxaban, or dabigatran had no postprocedural bleeding events, and postprocedural bleeding occurred only in patients taking edoxaban or apixaban. There were insufficient cases to perform a multivariate logistic regression analysis. Therefore, further large-scale studies are required to confirm the safety of warfarin continuation and the discontinuation of DOAC on the day of the procedure.

In conclusion, continuous warfarin may be a promising method; however, the postprocedural bleeding rate after 1-day withdrawal of DOAC was high. However, postprocedural bleeding did not occur in patients receiving rivaroxaban or dabigatran, thereby necessitating further investigation to determine the risk of bleeding associated with each specific DOAC following gastric ESD. Notably, the rates of postprocedural bleeding increased in patients concurrently using antiplatelet agents and DOACs, warranting cautious monitoring of these patients for bleeding events.

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Data availability statement. The datasets used and analyzed during the present study are available from the corresponding author on reasonable request until October 13, 2025.

References

1 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**: 433–40.
2 Gotoda T, Hori K, Iwamuro M *et al*. Evaluation of the bleeding risk with various antithrombotic therapies after gastric endoscopic submucosal dissection. *Endosc. Int. Open* 2017; **5**: E653–62.
3 Sato C, Hirasawa K, Koh R *et al*. Postoperative bleeding in patients on antithrombotic therapy after gastric endoscopic submucosal dissection. *World J. Gastroenterol.* 2017; **23**: 5557–66.
4 Kono Y, Hirata I, Katayama T *et al*. Current evidence and issues of endoscopic submucosal dissection for gastric neoplasms during antithrombotic therapy. *Clin. J. Gastroenterol.* 2020; **13**: 650–9.

5 Hamada K, Kanzaki H, Inoue M *et al*. Continued aspirin treatment may be a risk factor of delayed bleeding after gastric endoscopic submucosal dissection under heparin replacement: a retrospective multicenter study. *Intern. Med.* 2020; **59**: 2643–51.
6 Toya Y, Endo M, Oizumi T *et al*. Risk factors for post-gastric endoscopic submucosal dissection bleeding with a special emphasis on anticoagulant therapy. *Dig. Dis. Sci.* 2020; **65**: 557–64.
7 Yoshio T, Nishida T, Kawai N *et al*. Gastric ESD under heparin replacement at high-risk patients of thromboembolism is technically feasible but has a high risk of delayed bleeding: Osaka University ESD Study Group. *Gastroenterol. Res. Pract.* 2013; **2013**: 365830.
8 Matsumoto M, Mabe K, Tsuda M *et al*. Multicenter study on hemorrhagic risk of heparin bridging therapy for periendoscopic thromboprophylaxis. *BMC Gastroenterol.* 2015; **15**: 89.
9 Inagaki K, Yamashita K, Oka S *et al*. Risk of bleeding after colorectal endoscopic resection in patients with continued warfarin use compared to heparin replacement: a propensity score matching analysis. *Gastroenterol. Res. Pract.* 2021; **2021**: 9415387.
10 Nagata N, Yasunaga H, Matsui H *et al*. 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**: 1805–12.
11 Harada H, Suehiro S, Murakami D *et al*. Continuous use of low-dose warfarin for gastric endoscopic submucosal dissection: a prospective study. *Endosc. Int. Open* 2017; **5**: E348–53.
12 Fujimoto K, Fujishiro M, Kato M *et al*. Guidelines for gastroenterological endoscopy in patients undergoing antithrombotic treatment. *Dig. Endosc.* 2014; **26**: 1–14.
13 Martinez BK, Sood NA, Bunz TJ, Coleman CI. Effectiveness and safety of apixaban, dabigatran, and rivaroxaban versus warfarin in frail patients with nonvalvular atrial fibrillation. *J. Am. Heart Assoc.* 2018; **7**: e008643.
14 Yao X, Abraham NS, Sangaralingham LR, Bellolio MF, McBane RD, Shah ND, Noseworthy PA. Effectiveness and safety of dabigatran, rivaroxaban, and apixaban versus warfarin in nonvalvular atrial fibrillation. *J. Am. Heart Assoc.* 2016; **5**: e003725.
15 Lopez-Lopez JA, Sterne JAC, Thom HHZ *et al*. Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis. *BMJ* 2017; **359**: j5058.
16 Tepper PG, Mardekian J, Masseria C *et al*. Real-world comparison of bleeding risks among non-valvular atrial fibrillation patients prescribed apixaban, dabigatran, or rivaroxaban. *PLoS ONE* 2018; **13**: e0205989.
17 Hakoda A, Takeuchi T, Kojima Y *et al*. Risk factors and prediction of bleeding after gastric endoscopic submucosal dissection in patients on antithrombotic therapy: newly developed bleeding prediction application software, SAMURAI model. *J. Clin. Biochem. Nutr.* 2022; **70**: 189–96.
18 Tomida H, Yoshio T, Igarashi K *et al*. Influence of anticoagulants on the risk of delayed bleeding after gastric endoscopic submucosal dissection: a multicenter retrospective study. *Gastric Cancer* 2021; **24**: 179–89.
19 Ono S, Ieko M, Tanaka I, Shimoda Y, Ono M, Yamamoto K, Sakamoto N. Bleeding after gastric endoscopic submucosal dissection focused on management of Xa inhibitors. *J. Gastric. Cancer* 2022; **22**: 47–55.
20 Saito H, Igarashi K, Hirasawa D *et al*. 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**: 1253–60.
21 Yoshio T, Tomida H, Iwasaki R *et al*. Effect of direct oral anticoagulants on the risk of delayed bleeding after gastric endoscopic submucosal dissection. *Dig. Endosc.* 2017; **29**: 686–94.
22 Saviano A, Brigida M, Petruzziello C, Candelli M, Gabrielli M, Ojetti V. Gastrointestinal bleeding due to NOACs use: exploring the molecular mechanisms. *Int. J. Mol. Sci.* 2022; **23**: 13955.
23 Miura Y, Tsuji Y, Yoshio T *et al*. Association between perioperative management of antiplatelet agents and risk of post–endoscopic submucosal dissection bleeding in early gastric cancer: analysis of a nationwide multicenter study. *Gastrointest. Endosc.* 2023; **97**: 889–97.
24 Dohi O, Uedo N, Gotoda T *et al*. Continuation of low dose aspirin during peri-gastric endoscopic submucosal dissection period and increased bleeding risk: a randomized non-inferiority trial. *Gastrointest. Endosc.* 2021; **93**: AB342.
25 Kobayashi N, Kobara H, Nishiyama N *et al*. Comparison of endoscopic closure versus non-closure for post-gastric endoscopic submucosal dissection artificial floor in antithrombotic therapy: a propensity score-matched analysis. *Ann. Gastroenterol.* 2023; **36**: 178–84.