



# Influence of anticoagulants on the risk of delayed bleeding after gastric endoscopic submucosal dissection: a multicenter retrospective study

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## Abstract

**Background and aims** Delayed bleeding after gastric endoscopic submucosal dissection (ESD) in patients receiving anticoagulants remains an unpreventable adverse event. Although direct-acting oral anticoagulants (DOACs) have superior efficacy in preventing thromboembolism, their effects on the occurrence of delayed bleeding remain unclear. This study aimed to elucidate the clinical effect of DOACs on delayed bleeding after gastric ESD.

**Patients and methods** We retrospectively examined 728 patients who received anticoagulants and were treated for gastric neoplasms with ESD in 25 institutions across Japan. Overall, 261 patients received DOACs, including dabigatran (92), rivaroxaban (103), apixaban (45) and edoxaban (21), whereas 467 patients were treated with warfarin.

**Results** Delayed bleeding occurred in 14% of patients taking DOACs, which was not considerably different in patients receiving warfarin (18%). Delayed bleeding rate was significantly lower in patients receiving dabigatran than in those receiving warfarin and lower than that observed for other DOACs. Multivariate analysis showed that age  $\geq 65$ , receiving multiple antithrombotic agents, resection of multiple lesions and lesion size  $\geq 30$  mm were independent risk factors, and that discontinuation of anticoagulants was associated with a decreased risk of bleeding. In multivariate analysis among patients taking DOACs, dabigatran therapy was associated with a significantly lower risk of delayed bleeding.

**Conclusions** The effects of DOACs on delayed bleeding varied between agents, but dabigatran therapy was associated with the lowest risk of delayed bleeding. Switching oral anticoagulants to dabigatran during the perioperative period could be a reasonable option to reduce the risk of delayed bleeding after gastric ESD.

**Keywords** Gastric endoscopic submucosal dissection · Delayed bleeding · Direct-acting oral anticoagulants · Dabigatran

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## Introduction

Endoscopic submucosal dissection (ESD) is a globally performed, minimally invasive treatment for node-negative, early gastric cancer (EGC) [1] with relatively favorable long-term outcomes, comparable to those of surgical treatment [2]. However, post-ESD delayed bleeding occurs as an uncontrolled adverse event, in 3.1%–6.5% of cases [3, 4], a rate which has not decreased over the past decade.

In the aging society, the number of patients taking antithrombotic agents may be expected to rise as a preventative therapy for cardio- and cerebrovascular diseases.

Accordingly, we are observing an increasing number of patients undergoing ESD within the context of ongoing treatments with antithrombotic agents including anticoagulants and antiplatelet agents. Antithrombotic agents may increase the risk of delayed bleeding, depending on their type and dose, and on whether they are discontinued or continued during the perioperative period [5–9]. Anticoagulants, which include warfarin and direct-acting oral anticoagulants (DOACs), are difficult to manage during the perioperative period of gastric ESD because anticoagulant therapies represent most potent risk factors of delayed bleeding [7, 9] and of secondary thrombotic events [7, 10, 11]. In the past, heparin-bridging therapy (HBT) together with discontinuation of warfarin therapy was used as an approach to prevent thrombotic surgery-related events [12]. However, HBT caused a remarkable risk of delayed bleeding following surgical and interventional procedures [13] as well as gastric ESD [7, 9, 14]. Recent studies further revealed that HBT does not reduce perioperative arterial thromboembolism [15–17]. These findings underscore the need for new strategies to manage warfarin during the perioperative period. While the continuation of warfarin therapy and switching warfarin to DOACs are candidate approaches, data supporting their use are still lacking [10].

Several studies demonstrated an increased risk of gastrointestinal bleeding among DOACs-treated patients [18–20]. However, these results do not apply to patients receiving endoscopic treatment, and those who may have post-procedural wounds in specific organs rather than spontaneous bleeding. Moreover, these studies assessed effects on patients treated with warfarin and not on those receiving individual DOACs.

We previously reported that patients receiving dabigatran had a lower risk of delayed bleeding after gastric ESD than those receiving rivaroxaban [9]. However, this study was not adequately powered to establish the comparative clinical efficacy of different DOACs, due to the small number of patients being treated with DOACs (particularly with apixaban and edoxaban). Several studies have been conducted to determine the effect of anticoagulants on endoscopic procedures; DOACs has been more favorable in bleeding complications than warfarin [21], and high-risk procedures have been associated with a substantial risk of delayed major bleeding that varies with the type of procedure [22]. HBT increases the risk of bleeding without providing clinical benefit to these patients. However, all included many types of endoscopic procedures without focusing on specific procedures or organs [21, 22].

Hence, in the present study, we conducted a nationwide multicenter study in Japan, and examined a large number of patients receiving DOACs and warfarin, to compare the clinical efficacy of the various DOACs and conventional warfarin treatment on post-gastric ESD bleeding.

## Materials and methods

### Patients

We conducted a multicenter, retrospective study at 25 institutions in Japan. Data were included of 728 consecutive patients receiving anticoagulants, i.e., warfarin or DOACs, who underwent ESD for gastric neoplasms between November 2011 and October 2016. All indicated lesions were pre-operatively confirmed to be adenocarcinomas or suspected adenocarcinomas. We excluded the following cases: (1) administration of anticoagulants was not resumed after ESD; (2) the ESD procedure was not completed; (3) ESD for other upper gastrointestinal neoplasia was performed within 30 days after the gastric ESD; (4) additional surgical resection was performed within 30 days after the ESD and (5) cases had missing data.

All authors had access to the study data and reviewed and approved the final manuscript. This study was carried out in accordance with the Declaration of Helsinki and was approved by the institutional review board of the participating institutions (The Ethics Committee of Ehime Prefectural Central Hospital Registry number: 28-79). Written informed consent was obtained from all patients enrolled in this study.

### ESD procedure

Performance of ESD was principally indicated for possible node-negative EGC, following criteria described by Gotoda et al. [1]. ESD was performed according to standard procedures. Briefly, the procedure included: (1) marking around the lesion; (2) submucosal injection of 0.2–0.4% sodium hyaluronic acid solution; (3) application of a mucosal incision outside of the marked region and submucosal dissection with a cutting device; (4) hemostasis of active bleeding, as well as prophylactic coagulation of visible vessels on the mucosal defect using hemostatic forceps or placement of clips either during submucosal dissection or during the final step of ESD. In some cases, the mucosal defect was closed using an endoloop and endoclips when completing the ESD procedure [23]. In other cases, the mucosal defect was covered with polyglycolic acid (PGA) sheets and fibrin glue during the completion of the ESD procedure [24].

### Management of anticoagulants and antiplatelet agents

The administered anticoagulants included warfarin and DOACs such as dabigatran, rivaroxaban, apixaban and edoxaban. Antiplatelet agents provided to the patients included aspirin, cilostazol, ticlopidine and clopidogrel.

The duration of withdrawal of antithrombotic agents were determined according to the guidelines published in 2014 by the Japan Gastroenterological Endoscopy Society (JGES) [12]: 3–5 days for warfarin, 1–2 days for DOACs, three to 5 days for aspirin, 1 day for cilostazol, and 5–7 days for ticlopidine and clopidogrel before the procedure, and were resumed 1 day after ESD. Patients who received anticoagulant therapy preoperatively were recommended for HBT as per the JGES guidelines from 2014. However, patients who were considered to have a low risk of thromboembolism, for instance, based on the CHADS2 or CHA2DS2-VASc score, were excluded from HBT [25]. The decision to discontinue anticoagulants or to perform HBT in patients undergoing ESD was based on the judgment of the prescribing physician and endoscopists.

### Adverse events

Delayed bleeding was defined as an event requiring emergency endoscopy with endoscopic hemostasis or transfusion for the management of hematemesis or melena, or a decrease > 2 g/dL of hemoglobin levels after ESD. This definition did not include cases of preventive hemostasis for exposed vessels on the mucosal defect without the clinical criterion of bleeding on second-look endoscopy.

### Statistical analysis

All continuous variables were expressed as median and range. Statistical analyses were performed using Fisher exact tests, Mann–Whitney *U* tests, log-rank tests or the Kaplan–Meier method, as appropriate. We used Cochran–Armitage tests to assess correlations between the number of antiplatelets combined with anticoagulants and delayed bleeding rate. Multivariate logistic regression models were used to examine the effect of independent variables on delayed bleeding. Multivariate models included factors suggested in studies associated with delayed bleeding and those that were statistically significant ( $p < 0.05$ ) in univariate analysis. To reduce confounding effects of covariates, we used logistic regression to perform propensity score matching (PSM) with the following independent variables: gender, age, chronic kidney disease, lesion size, cessation of anticoagulant, and concomitant use of antiplatelet agent. Patients receiving dabigatran were matched with those receiving other DOACs according to the generated PSM using a caliper width of 0.2. On the completion of matching, we examined the influence of DOACs on delayed bleeding. A  $p$  value < 0.05 was considered as statistically significant. Statistical analyses were performed using the EZR version 1.41, which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

## Results

### Characteristics of patients and lesions

We treated 849 gastric neoplasms by gastric ESD in 728 patients, who were being treated with anticoagulant medication, 467 of whom received warfarin and 261 of whom received DOACs. Of the latter group, 92 patients received dabigatran, 103 rivaroxaban, 45 apixaban and 21 edoxaban. Twenty-three percent of the patients received antiplatelet agents.

Characteristics of the patients and their lesions are shown in Table 1. The median age of the patients was 76 years (range 48–90 years), and 86% were males. The proportion of males among DOAC-treated patients was higher than that in the warfarin-treated group. The frequency of atrial fibrillation (AF) was higher in the DOAC group than in the warfarin group, because DOACs are prescribed for non-valvular AF and deep-vein thrombosis based on standards implemented in the Japanese health insurance system. In addition, patients in the DOAC group had fewer severe comorbidities (e.g., ischemic heart disease) than those in the warfarin group. Therefore, antiplatelet agents were used less often in the DOAC group. However, the median CHADS2 and CHA2DS2-VASc scores were identical in the two groups and no between-group difference was found in lesions.

### Perioperative managements of gastric ESD

The proportions of patients receiving HBT in the warfarin- and DOAC groups were 60% and 16%, respectively (Table 2). Although JGES guidelines recommend the application of HBT to patients treated with warfarin, ESD was carried out without HBT in 36% of these patients, and with uninterrupted warfarin therapy maintained in 4% of the patients. Thirty percent (37/122) of patients on warfarin therapy and 26% (11/31) of patients on DOACs continued their intake of antiplatelet agents on the day of ESD, although 21% (9/42) of the patients on thienopyridine derivatives were given replacement with aspirin or cilostazol during the perioperative period.

The proportions of patients who received endoscopic closure or tissue-shielding method with PGA sheets and fibrin glue to prevent delayed bleeding were 3 and 7%, respectively, in the warfarin group, and 3 and 6% in the DOAC-treated group. There were no differences between the two groups in the proportion of patients treated with proton-pump inhibitors (PPI) or mucosa-protecting agents after ESD, or with intravenous PPI on the day of the ESD procedure.

**Table 1** Characteristics of patients and lesions according to the type of anticoagulant

	Warfarin ( <i>n</i> = 467)	DOACs ( <i>n</i> = 261)	<i>p</i> value
<b>Patients</b>			
Age, median (range), years	76 (64–88)	74 (53–84)	0.11
Gender (male/female), <i>n</i>	394/73	234/27	<b>0.04</b>
Antiplatelets (0/1/2), <i>n</i>	345/104/18	219/42/0	<b>&lt; 0.01</b>
<b>Comorbidities, <i>n</i> (%)</b>			
Atrial Fibrillation	328 (70)	232 (89)	<b>&lt; 0.01</b>
Deep vein thrombosis	25 (5.4)	7 (2.7)	0.09
Cardiac valve replacement	22 (4.7)	9 (3.4)	0.41
Congestive heart failure	119 (25)	55 (21)	0.18
Hypertension	297 (64)	142 (54)	<b>0.01</b>
Diabetes mellitus	133 (28)	62 (24)	0.16
Prior stroke or transient ischemic attacks	101 (22)	44 (17)	0.12
Ischemic heart disease	117 (25)	41 (16)	<b>&lt; 0.01</b>
Chronic kidney disease	168 (36)	88 (34)	0.54
CHADS2 score, median (range) <sup>a</sup>	2 (0–6)	2 (0–6)	
Thrombotic risk (low; score ≤ 2/moderate or high; score ≥ 3)	293/174	179/82	0.12
CHA2DS2-VASc score, median (range) <sup>a</sup>	3 (0–8)	3 (0–7)	
Thrombotic risk (low; score ≤ 4/moderate or high; score ≥ 5)	352/115	213/48	0.06
<b>Lesions</b>			
Number of resected lesion (1/2/3 <), <i>n</i>	404/48/15	231/23/7	0.44
Lesion size, median (range), mm	15 (1–122)	15 (1–60)	0.42
Lesion location (U/M/L), <i>n</i>	85/198/184	36/120/105	0.29
Macroscopic type (Protruding/Flat/Depressed), <i>n</i>	255/10/198	110/7/142	<b>&lt; 0.01</b>
Ulceration in lesion (±), <i>n</i>	30/432	15/245	0.69
Histology (differentiated/undifferentiated/adenoma), <i>n</i>	408/11/44	242/6/12	0.06
Depth of invasion in cancer (mucosa/submucosa), <i>n</i>	361/58	215/33	0.90

<sup>a</sup>Patients with atrial fibrillation

DOACs direct oral anticoagulants, U upper third of stomach, M middle third of stomach, L lower third of stomach

All *p* values less than 0.05 were shown in bold

## Treatment outcome of the DOACs and warfarin groups

The rate of delayed bleeding in the DOAC group was not different from that in the warfarin group (Table 2). In comparisons between individual agents, delayed bleeding rates were different for each agent (Fig. 1a). In patients taking dabigatran, the delayed bleeding rate was the lowest of patients taking anticoagulants. Furthermore, the delayed bleeding rate in dabigatran-treated patients was lower than that of warfarin-treated ones (8% vs 18%, *p* = 0.018), and lower than that of patients treated with other DOACs (8% vs 17%, *p* = 0.033; Fig. 1b). In warfarin-treated patients, delayed bleeding was more frequently seen among those receiving HBT. Compared with patients who did not receive HBT, the delayed-bleeding rate was higher in patients undergoing HBT, and higher yet in patients receiving continued anticoagulant therapy without cessation, and this occurred equally in the warfarin and in the DOAC Group (Fig. 1c). The

amount of time between the ESD and the onset of delayed bleeding did not differ between warfarin- and DOAC groups (Fig. 1b), and was the same regardless of whether patients underwent HBT or not. In regard to the combined use of antiplatelet agents, delayed bleeding rates of patients receiving either no antiplatelet agent, a single antiplatelet agent, or dual antiplatelet agents were 12%, 27%, and 50%, respectively. It was observed that the delayed bleeding rate rose as the number of antiplatelet agents increased (*p* < 0.001; Fig. 1d). In patients who had undergone closure of mucosal defect using endoloop and endoclips, delayed bleeding occurred in two out of the 22 cases (9%; Fig. 1e), which did not differ significantly from patients who did not receive these preventive measures. However, notably, 18 patients with complete closures of the mucosal defect did not develop delayed bleeding, although two out of four patients with incomplete closures showed delayed bleeding. However, in patients who underwent preventative procedures using PGA sheets and fibrin glue to cover their mucosal defect, delayed

**Table 2** Perioperative management and treatment outcome of gastric ESD for different anticoagulants

	Warfarin ( <i>n</i> = 467)	DOACs ( <i>n</i> = 261)	<i>p</i> value
Management of anticoagulants			<b>&lt; 0.01</b>
Cessation (without HBT), <i>n</i> (%)	166 (36)	206 (79)	
Heparin bridging therapy, <i>n</i> (%)	280 (60)	41 (16)	
Continuation (Without cessation), <i>n</i> (%)	21 (4)	4 (5)	
Management of antiplatelets			0.69
Cessation, <i>n</i> (%)	85 (18)	31 (12)	
Continuation (without cessation), <i>n</i> (%)	37 (8)	11 (4)	
Perioperative managements			
Closure of mucosal defect, <i>n</i> (%)	15 (3)	7 (3)	0.68
Covering mucosal defect with PGA sheet, <i>n</i> (%)	32 (7)	15 (6)	0.56
Gastric acid inhibitor, <i>n</i> (%)			0.56
Proton pump inhibitor	421 (90)	226 (87)	
Potassium competitive acid blocker	40 (9)	35 (13)	
Intravenous PPI, <i>n</i> (%)	366 (78)	193 (74)	0.17
Mucosa protecting agents, <i>n</i> (%)	272 (58)	146 (56)	0.54
Treatment outcome			
En bloc resection, <i>n</i> (%)	465 (99)	260 (99)	1
Delayed bleeding, <i>n</i> (%)	82 (18)	36 (14)	0.20
With/without HBT, <i>n</i>	55/27	8/28	<b>&lt; 0.01</b>
Periods until delayed bleeding, median (range), day	6 (0–18)	7 (0–29)	0.75
With/without HBT, median, day	6/8	7/10	0.12
Blood transfusion, <i>n</i> (%)	35 (7)	5 (2)	<b>&lt; 0.01</b>
Perforation, <i>n</i> (%)	6 (1)	2 (1)	0.71
Thrombotic event, <i>n</i> (%)	0	0	1
Period of HBT after ESD, median (range) day	5 (1–23)	2 (1–12)	<b>&lt; 0.01</b>
Hospitalization period, median (range), day	13 (4–53)	9 (4–32)	<b>&lt; 0.01</b>

*HBT* heparin bridging therapy, *PGA* polyglycolic acid, *PPI* proton pump inhibitor, *ESD* endoscopic submucosal dissection

All *p* values less than 0.05 were shown in bold

bleeding occurred in 10 of 47 cases (21%), which was not different from the patients who did not receive these preventive treatments.

### Clinical risk factors for delayed bleeding

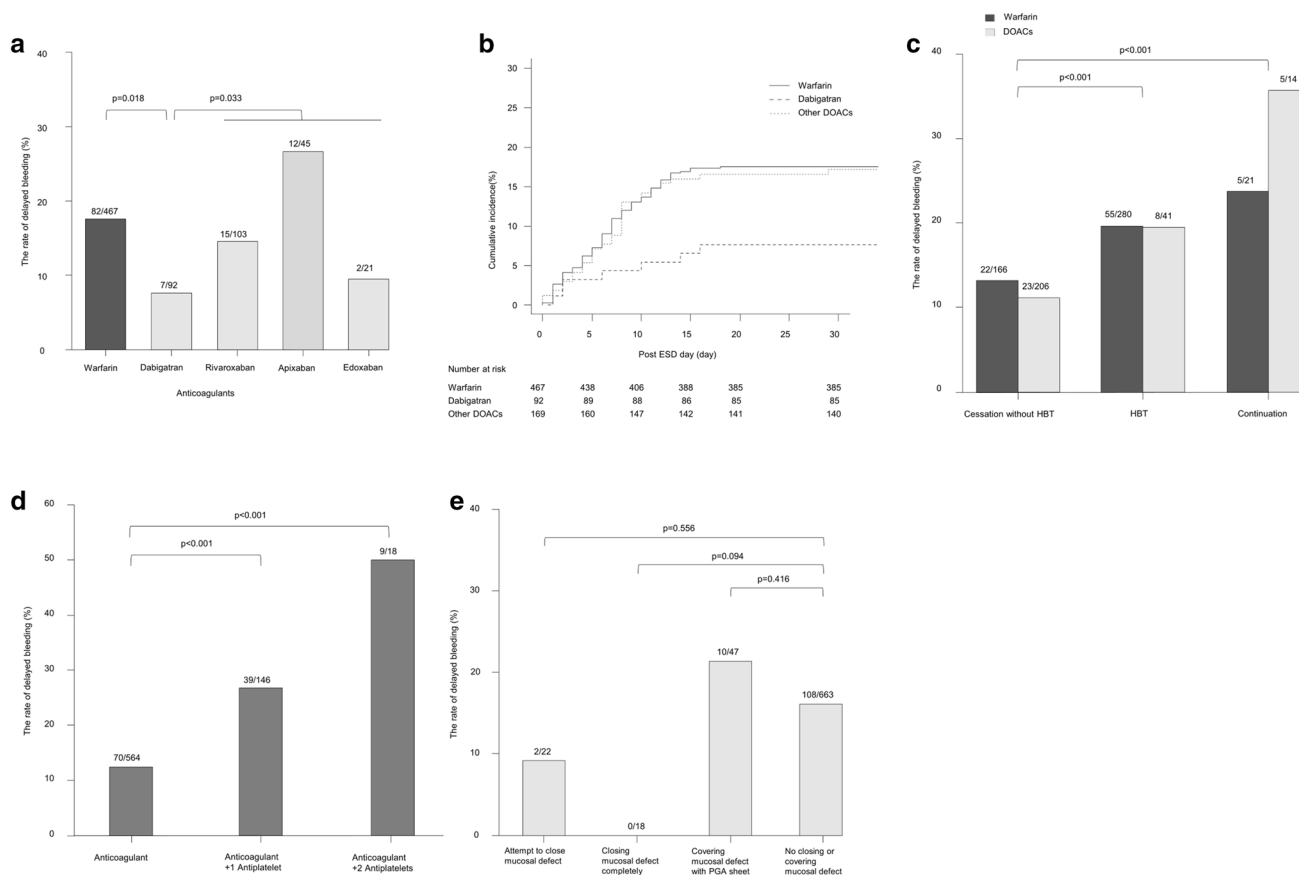
We compared the lesions and characteristics of patients to those without delayed bleeding. Univariate analysis showed that an increased risk of delayed bleeding was associated with having an age > 65 years, being male, receiving HBT after ESD, being treated with combined antiplatelet agents, resection of multiple lesions and the presence of lesions > 20 mm (Table 3). Both Dabigatran treatment and cessation of anticoagulants without HBT reduced the risk of delayed bleeding. In multivariate analysis, age > 65 years (OR 2.96; 95% CI 1.13–7.73), being treated with combined antiplatelet agents (OR 2.70; 95% CI 1.74–4.21), being male (OR 2.12; 95% C 1.01–4.45) and lesions > 20 mm (OR 1.67; 95% CI 1.08–2.59) were independent risk factors for delayed bleeding, whereas

cessation of anticoagulants without HBT was associated with a low risk of delayed bleeding (OR 0.32; 95% CI 0.14–0.76).

Patients with bleeding within 6 days after ESD and those with bleeding after 7 days of ESD were compared with patients without bleeding (Supplementary Tables 1 and 2). In the early bleeding group, presence of ulceration (OR 2.74; 95% CI 1.08–6.97), being treated with combined antiplatelet agents (OR 2.15; 95% CI 1.19–3.89), lesions in the lower third of the stomach (OR 2.07; 95% CI 1.18–3.63), and lesions of > 20 mm (OR 1.85; 95% CI 1.05–3.27) were independent risk factors for delayed bleeding, and cessation of anticoagulants without HBT was associated with a low risk of delayed bleeding (OR 0.42; 95% CI 0.23–0.76). In the late bleeding group, being treated with combined antiplatelet agents was the only independent risk factor for delayed bleeding (OR 3.17; 95% CI 1.80–5.58).

We also conducted the univariate and multivariate analysis for delayed bleeding exclusively in patients receiving DOACs, to assess the optimal, appropriate use of DOACs.





**Fig. 1** **a** The delayed-bleeding rates in patients receiving warfarin and DOACs. **b** Time-to-event curve of delayed bleeding after gastric ESD in the different patient groups. **c** The delayed-bleeding rates in patients without HBT, patients with HBT and patients receiving continuous anticoagulants. **d** Rates of delayed bleeding in patients receiving

only anticoagulants, one antiplatelet combined with an anticoagulant, and two antiplatelets combined with an anticoagulant. **e** Rates of delayed bleeding in patients who attempted to close mucosal defect, in whom defect was closed completely, in whom defect covered with PGA sheet, and in those who did not undergo both the methods

Dabigatran and cessation of DOACs were independent low-risk factors for delayed bleeding after ESD (Table 4).

To identify differences of delayed-bleeding rates between dabigatran and other DOACs, we applied a PSM procedure (Supplementary Table 3). Ninety-one matched dabigatran-other DOAC patient pairs were formed. The two groups did not differ in terms of patient characteristics or lesions. However, the delayed bleeding rate of the patients taking dabigatran was significantly lower than that of patients receiving other DOACs.

## Discussion

In the present study, we examined the efficacies of DOACs in gastric ESD patients by comparisons with warfarin treatment in a large cohort of 728 patients from institutions across Japan. This is the largest study of gastric ESD to date in patients treated with anticoagulant therapy, partly because the ratio of patients taking anticoagulants among all gastric

ESD cases is only 2.3%–5.7% [5, 7, 8]. However, the number of patients taking anticoagulants is surely expected to rise with the ongoing aging of the society, and the proportion of DOAC users in this study has been also steadily increased from year to year (Supplementary Fig. 1). Therefore, this study may contribute to the perioperative management of anticoagulants to reduce delayed bleeding after ESD of EGC in patients treated with anticoagulants.

We previously reported that the delayed bleeding risk of patients receiving dabigatran was significantly lower than those treated with rivaroxaban because of different pharmacokinetics of the two drugs. However, in the previous study, the number of patients receiving DOACs was small [9]. In this present study, dabigatran was again shown to significantly lower delayed-bleeding risk relative to other DOACs, as confirmed by both univariate and multivariate analyses (Table 4). In a PSM analysis conducted to reduce selection bias in patients, the rate of delayed bleeding in patients on dabigatran was significantly lower than that in patients receiving other DOACs (Supplementary Table 3).

**Table 3** Univariate and multivariate analysis of risk factors for delayed bleeding after gastric ESD

	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	<i>p</i> value	Odds ratio	95% CI	<i>p</i> value
Age ( $\geq 65$ years)	2.97	1.17–9.65	<b>0.01</b>	2.96	1.13–7.73	<b>0.02</b>
Gender (male)	2.12	1.02–4.94	<b>0.03</b>	2.12	1.01–4.45	<b>0.04</b>
Anticoagulants						
Warfarin	1.33	0.86–2.10	0.21			
Dabigatran	0.39	0.15–0.87	<b>0.01</b>	0.49	0.21–1.15	0.10
Rivaroxaban	0.86	0.45–1.58	0.77			
Apixaban	1.97	0.90–4.08	0.05			
Edoxaban	0.53	0.06–2.27	0.55			
Cessation of anticoagulants without HBT	0.53	0.35–0.81	<b>&lt; 0.01</b>	0.32	0.14–0.76	<b>0.01</b>
Heparin bridging therapy after ESD	1.56	1.03–2.37	<b>0.03</b>			
Antiplatelets (concomitant use)	2.91	1.87–4.52	<b>&lt; 0.01</b>	2.70	1.74–4.21	<b>&lt; 0.01</b>
Continued use of antiplatelets	0.86	0.37–1.91	0.85	0.51	0.22–1.17	0.11
Resection of multiple lesions ( $\geq 2$ )	2.00	1.14–3.41	<b>0.01</b>	1.73	0.99–3.01	0.05
Lesion size ( $> 20$ mm)	1.82	1.18–2.80	<b>&lt; 0.01</b>	1.67	1.08–2.59	<b>0.02</b>
Location (lower third of stomach)	1.46	0.96–2.21	0.06	1.51	0.98–2.30	0.05
Macroscopic type (depressed type)	1.06	0.69–1.64	0.83			
Presence of ulceration	1.72	0.76–3.61	0.14	2.02	0.91–4.43	0.08
Histology (differentiated type)	1.49	0.34–13.7	1			
Depth of invasion (mucosa)	1.10	0.59–2.19	0.87			
Gastric acid inhibitor (P-cab)	1.21	0.60–2.29	0.51			
Intravenous PPI	1.15	0.70–1.94	0.63			
Mucosa protecting agents	1.30	0.85–2.00	0.22			
Closing mucosal defect	0.50	0.05–2.14	0.56			
Covering mucosal defect with PGA sheet	1.43	0.62–3.05	0.31			

*HBT* heparin bridging therapy, *ESD* endoscopic submucosal dissection, *P-cab* potassium competitive acid blocker, *PPI* proton pump inhibitor, *PGA* polyglycolic acid

All *p* values less than 0.05 were shown in bold

DOACs have different properties from warfarin, but individual DOACs have distinct pharmacological properties. Warfarin targets vitamin K epoxide reductase in the liver to block the function of the coagulation factors II, III, IX, and X. In contrast to warfarin, which exerts a systemic anticoagulant effect, DOACs directly target coagulation proteins and have both systemic and local effects on the gastric mucosa, with the exception of dabigatran. Dabigatran is administrated as a prodrug that does not exhibit anticoagulant activity and is converted to its active form by hepatic and serum esterases [26]. Therefore, dabigatran may not have local anticoagulant effect in the stomach, whereas other DOACs may have direct anticoagulant effect in post-gastric ESD ulcer sites and potentially induce local bleeding [25, 27]. These differences may explain the variance in the risk of delayed bleeding between warfarin and DOACs, and between dabigatran and other DOACs.

It was also reported previously that dabigatran is more effective than other DOACs in inducing clotting after vascular injury [28]. This observation was consistent with other

studies that showed a low rate of intracranial hemorrhage during dabigatran therapy [29] and a low rate of bleeding complications during catheter ablation in patients receiving dabigatran [30]. We suspect that a similar response to vascular injury of the post-ESD ulcers could support favorable outcomes, reflected by a difference in bleeding risk between patients treated with dabigatran or other DOACs.

Although the number of patients who received continued anticoagulants during the perioperative period was limited, continuation of warfarin and DOACs was associated with higher delayed-bleeding rates, i.e., 24% (5/21) in warfarin-treated- and 36% (5/14) in DOAC-treated patients (Fig. 1c). Thus, for the patients on DOACs, a one- or two-day therapeutic discontinuation without HBT would be appropriate because no higher risk of delayed bleeding or thrombosis would occur. For patients on warfarin, a continuation of warfarin treatment would seem a good option, because warfarin requires 5 days of discontinuation before diminishing its reported effects to cause one percent of thrombotic event [31] or a nine-percent (2/22) higher rate of delayed bleeding,

**Table 4** Multivariate analysis of risk factors for delayed bleeding after gastric ESD in patients taking DOACs

	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	<i>p</i> value	Odds ratio	95% CI	<i>p</i> value
Age ( $\geq 65$ years)	3.59	0.54–153	0.32			
Gender (male)	2.12	0.48–19.2	0.39			
DOACs						
Dabigatran	0.39	0.14–0.98	<b>0.03</b>	0.40	0.16–0.97	<b>0.04</b>
Other DOACs	2.50	1.01–7.08	<b>0.03</b>			
High dosage of DOACs	0.72	0.33–1.56	0.36			
Cessation of anticoagulants without HBT	0.40	0.18–0.95	<b>0.02</b>	0.40	0.18–0.87	<b>0.02</b>
Heparin bridging therapy after ESD	1.65	0.60–4.15	0.32			
Antiplatelets (concomitant use)	1.93	0.73–4.72	0.14	1.47	0.60–3.55	0.39
Continued use of antiplatelets	2.45	0.39–10.9	0.18			
Resection of multiple lesions ( $\geq 2$ )	1.28	0.36–3.79	0.58			
Lesion size ( $> 20$ mm)	1.80	0.79–3.97	0.11	1.85	0.86–3.96	0.11
Location (lower third of stomach)	1.22	0.55–2.63	0.58			
Macroscopic type (depressed type)	1.05	0.49–2.30	1			
Presence of ulceration	0.95	0.10–4.51	1			
Depth of invasion (mucosa)	1.18	0.37–4.93	1			
Gastric acid inhibitor (P-cab)	1.35	0.42–3.69	0.59			
Intravenous PPI	1.53	0.61–4.38	0.41			
Mucosa protecting agents	1.11	0.51–2.46	0.85			

DOACs direct oral anticoagulants, ESD endoscopic submucosal dissection, HBT heparin bridging therapy, P-cab potassium competitive acid blocker, PPI proton pump inhibitor

All *p* values less than 0.05 were shown in bold

as reported recently [32]. A larger study is needed to assess the actual risk of continuing warfarin when carrying out ESD procedures. When the patients receiving anticoagulant treatment have a low risk of thrombosis, e.g., a history of deep-vein thrombus or AF with a CHADS2 score of 1 and they could discontinue it, these patients significantly had a low risk of delayed bleeding in multivariate analysis (Tables 3, 4), although the patients rarely can discontinue anticoagulant treatment during the perioperative period [33]. HBT was still performed, but especially in warfarin-treated patients delayed bleeding occurred significantly more often in patients who received HBT than in those who were not (Fig. 1c), an observation that confirmed results of previous studies [7, 9, 14, 33]. Although former Japanese guidelines recommended HBT for warfarin-treated patients, new guidelines issued in 2017 do no longer recommend HBT and merely suggest whether to continue warfarin treatment or switching to DOACs without HBT [34] backed by sufficient supportive data.

Three guidelines that are currently available suggest the of implementation of a drug withdrawal period from a pharmacological perspective and do not reflect the results of clinical studies on ESD [35–37]. Although thromboembolism is serious and potentially fatal, gastrointestinal bleeding is often controllable, and measures to control bleeding

while maintaining anticoagulant effectiveness should be considered.

With respect of how to deal with ongoing anticoagulant treatments to minimize the risk of delayed bleeding, a reasonable option would be to switch current anticoagulant treatment to dabigatran, especially after discontinuation of apixaban, rivaroxaban, and warfarin, for a one-month long postoperative period after ESD, because the delayed bleeding rate of dabigatran (8%) is lower than that of apixaban (27%), rivaroxaban (15%), and even warfarin (18%; Fig. 1a). We consider dabigatran to be the better alternative for warfarin and other DOACs because of the results of the present study.

In some patients, tissue shielding using a PGA sheet and fibrin glue [24], and closure of mucosal defects using endoloop and endoclips [23] were performed to prevent delayed bleeding. However, bleeding was not significantly reduced in comparison with patients who did not undergo these procedures (Fig. 1e). The PGA-shielding method showed no effect on the prevention of delayed bleeding, confirming another recent report [38]. The complete closure of mucosal defects was achieved in 82% (18/22) of patients in whom such closures were attempted and the patients who did not show mucosal defects had no delayed bleeding. The closure of mucosal defects itself could be



useful; however, the success to close all mucosal defects critically depends on the location and the size. Although we still have to overcome a number of technical difficulties, closing the mucosal defect could be a good countermeasure to prevent post-bleeding in patients receiving antithrombotic agents.

A number of limitations of the current study should be noted. The first is that this was a retrospective study, albeit of a large number of cases in treated in multiple centers. Second, the management of anticoagulants varied in several ways, especially for DOACs, because there was no statement about DOACs other than the use of dabigatran in the guidelines [12] during the examined period. Thirdly, we could not conduct a systematic evaluation of the effect of edoxaban, because the number of included patients receiving edoxaban was insufficient. Fourth, the risk of thromboembolism could not be examined, because no case with a thrombotic event emerged.

In conclusion, this is the first study to directly compare and clarify the effects of DOACs surrounding endoscopic treatment in a large number of patients. Patients taking oral anticoagulants had a higher risk of delayed bleeding after gastric ESD, but the delayed bleeding rate varied with the specific type of drug administered. In the present study, dabigatran was associated with a lower rate of delayed bleeding than other anticoagulants, i.e., warfarin and other DOACs. Although this was a retrospective study, its multicenter character and the large number of cases included in the analysis support the validity of the present results. The superior efficacy of dabigatran to reduce delayed bleeding after gastric ESD should be demonstrated in future prospective studies. Changing oral anticoagulants to dabigatran in the perioperative period could be a good treatment choice for reducing delayed bleeding after gastric ESD.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.


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