Direct Oral Anticoagulants Increase Bleeding Risk After Endoscopic Sphincterotomy: A Retrospective Study

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Research article

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Abstract

Background: Bleeding is a serious adverse event of endoscopic sphincterotomy (EST). However, the risk of EST bleeding between direct oral anticoagulant (DOAC) users and those who received no antithrombotic agents has not been clarified. This study analyzed the risk factors for bleeding after EST in patients on DOAC and evaluated the Japan Gastroenterological Endoscopy Society (JGES) guidelines for gastroenterological endoscopy in patients undergoing antithrombotic treatment.

Methods: We retrospectively analyzed 524 patients treated with EST who received DOAC or no antithrombotic drug from May 2016 to August 2019. We investigated the risk factors for bleeding. Cessation and resumption of DOAC treatment were determined according to the JGES guidelines, although DOAC cessation or heparin replacement was determined by the attending physician.

Results: The number of patients on DOAC (DOAC group) and those without antithrombotic drug (no-drug group) were 42 (8.0%) and 482 (92.0%), respectively. DOAC was discontinued for <2 days in 24 (57.2%) patients and for ≥2 days in 18 (42.8%) patients. Of the 524 patients, 21 (4.0%) had EST bleeding. The bleeding rate was significantly higher in the DOAC group (14.3%, 6/42). Multivariate analysis showed that bleeding occurs more frequently in patients on DOAC, patients with low platelet counts (<100,000/µl), and elderly patients (>80 years old).

Conclusions: DOAC treatment, low platelet count, and old age (>80 years old) are significant risk factors for EST bleeding. Although the bleeding incidence increased in patients on DOAC, which was discontinued according to the JGES guidelines, successful hemostasis was achieved with endoscopy in all cases with bleeding, and no thrombotic events occurred after cessation of DOAC. Thus, the JGES guidelines are acceptable.

Background

Endoscopic sphincterotomy (EST) is an essential procedure for endoscopic retrograde cholangiopancreatography (ERCP). However, bleeding is an inevitable complication after EST. The rate of bleeding associated with EST is 1–5% [1–7]. The rates of severe bleeding associated with EST are significantly higher among anticoagulant users than among non-users [8]; however, the risk of EST bleeding is lower with direct oral anticoagulant (DOAC) use than with warfarin use [9, 10]. Moreover, the risk of EST bleeding between DOAC users and those who received no antithrombotic agents has not been clarified.

Recently, a guideline on gastroenterological endoscopy in patients undergoing antithrombotic treatment was published by the Japan Gastroenterological Endoscopy Society (JGES) [11, 12]. However, the evidence levels for several items in the guidelines are low, and the guidelines still need to be verified in clinical settings [12]. In addition, balancing the risks of bleeding against that of thromboembolism is difficult in patients with DOAC discontinuation [13, 14]. In this study, we aimed to investigate the risk
factors for bleeding after EST and to evaluate the JGES guidelines for gastroenterological endoscopy in patients receiving DOAC.

**Methods**

The study was reviewed and approved by the Future Medical Research Center Ethical Committee’s institutional review board (IRB No. TGE00934-024). All procedures have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

**Study population**

This retrospective study was conducted at Shonan Kamakura General Hospital in Japan. Study enrollment commenced in May 2016 and ended at the end of August 2019. This study included patients undergoing EST who had DOAC prior to EST and those who received no antithrombotic agent. Patients with warfarin or antiplatelet therapy were excluded. We investigated the patients’ characteristics, ERCP findings, incidence of EST bleeding, risk factors for bleeding, and DOAC cessation period. Under the conditions of $\alpha = 0.05$ and $\beta = 0.20$, 39 patients on DOAC and 448 patients without antithrombotic drug are required according to the EZR statistical software.

Of the 676 patients enrolled, 152 patients were excluded based on the exclusion criterion. A total of 524 patients were included in the final analysis (Fig. 1). Moreover, the number of patients on DOAC treatment (DOAC group) was 42 (8.0%) and that of patients without antithrombotic drug (no-drug group) was 482 (92.0%).

**Endoscopic procedure**

EST was basically performed with a pull-type sphincterotome (Clever Cut V3; Olympus, Tokyo, Japan) through a side-viewing endoscope (JF-260V, TJF-260V; Olympus, Tokyo, Japan). EST was performed by experts who had performed >1000 ERCP procedures. Sphincterotomy was performed using the 11–12 o’clock direction, an electrosurgical unit (ERBE ICC200; Surgical Technology Group, Hampshire, England, UK) was put in ENDOCUT mode, and 120-W power setting was employed. Medium EST, which extends from one third to two thirds of the total length of the ampulla, was performed in most cases. Small EST, which was within one third of the total length of the ampulla, was occasionally used (i.e., in patients with a potential risk of perforation such as those whose oral protraction of the ampulla was small). In patients in whom biliary cannulation was difficult, precut using a needle-type sphincterotome (KD-10Q-1; Olympus, Tokyo, Japan) or a transpancreatic precut sphincterotomy was performed.

**Antithrombotic agents**

In this study, DOAC was typically discontinued for <2 days based on the JGES guideline. However, DOAC cessation and heparin replacement were determined by the attending physician based on each patient’s status. The most common heparin-bridging technique before EST was to replace oral anticoagulants with
unfractionated heparin at 2–3 days after admission, with dose adjustments to attain the required activated partial thromboplastin time [11]. Heparin administration was stopped 4–6 h before EST and restarted 4–6 h after EST.

**Definitions**

EST bleeding was defined as bleeding during or after EST. Bleeding during EST was described as pulsatile bleeding or bleeding that continued at the end of the planned procedures, such as lithotripsy or stent replacement; bleeding after EST was defined as hematemesis, bloody stool, and bleeding that are not due to other causes of gastrointestinal bleeding confirmed by endoscopy within 2 weeks post-EST.

Hemostasis procedures, such as balloon compression and hypertonic saline epinephrine solution (HSE) administration, were indicated in patients whose point of bleeding could not be identified. After achieving hemostasis, additional procedures, such as coagulation or hemoclipping, were performed when the bleeding point was identified. In patients whose point of bleeding could be identified, coagulation with electrical devices was performed for oozing bleeding and hemoclipping for spurting bleeding or exposed vessels.

Low platelet count was defined as < 100,000/µl, which is a severe cholangitis classification in the Tokyo Guideline 2018 of cholangitis. Moreover, several studies also defined low platelet count as < 100,000/µl [10, 15]. An elderly patient was defined as a patient aged > 80 years, following the definition of Muro et al.'s who reported that this age group is at risk for EST bleeding [10].

**Statistical analysis**

The Mann-Whitney U-test was used to compare continuous variables, which were non-normally distributed, and $\chi^2$-test or Fisher’s exact test was used to compare categorical variables. A multivariate analysis was performed using logistic regression. Two-tailed p values < 0.05 were considered statistically significant. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander and was designed to allow additional statistical functions that are frequently used in biostatistics [16].

**Results**

**Patient characteristics**

The characteristics of the patients in the DOAC and no-drug groups are shown in Table 1. In the DOAC group, the median age was 82 (range 65–95) years and the male-to-female ratio was 1.21. The indications for EST were malignant stricture in 10 (23.8%), bile duct stone in 31 (73.8%), and acute cholecystitis in 1 (2.4%). Underlying diseases were present in 24 (57.1%) patients, including cardiovascular disease in 13 (31.0%), liver cirrhosis in 3 (7.1%), stroke in 13 (31.0%), and cerebral hemorrhage in 1 (2.4%). Moreover, cholangitis was found in 33 (78.6%) patients. The median platelet
count was $17.1 \times 10^4/\mu l$ (range 8.0–52.4 $\times 10^4/\mu l$), the median prothrombin time international normalized ratio (PT-INR) was 1.21 (range 1.02–1.72), and the median activated partial thromboplastin time (APTT) was 35.9 (range 26.0–62.6) seconds.

| Table 1 | Patient characteristics |
|---------|--------------------------|
|         | DOAC group n = 42 (8.0%) | No-drug group n = 482 (92.0%) | p value |
| Sex     | Male 23, Female 19       | Male 234, Female 248           | 0.52    |
| Age     | 82 (65 – 95) years       | 76 (25 – 106) years            | 0.00102 |
| Indication for ERCP | | | | |
| • Malignant biliary stricture | 10 (23.8%) | 108 (22.4%) | 0.848 |
| • Bile duct stone | 31 (73.8%) | 333 (68.1%) | 0.603 |
| • Cholecystitis | 1 (2.4%) | 22 (4.6%) | 1 |
| • Acute pancreatitis | 0 | 4 (0.8%) | 1 |
| • Chronic pancreatitis | 0 | 13 (2.7%) | 0.613 |
| Underlying disease‡ | | | | |
| • Total | 24 (57.1%) | 47 (9.8%) | 0.00000000000192 |
| • Hemodialysis | 3 (7.1%) | 6 (1.2%) | 0.0287 |
| • Liver cirrhosis | 13 (31.0%) | 25 (5.1%) | 0.00000112 |
| • Cardiovascular disease | 1 (2.4%) | 9 (1.9%) | 0.57 |
| • Cerebral hemorrhage | 13 (31.0%) | 10 (2.1%) | 0.000000000545 |
| Cholangitis | 33 (78.6%) | 314 (65.1%) | 0.0895 |
| Platelet (/µl) | 17.1 (8.0 – 52.4) | 20.5 (4.5 – 67.8) | 0.0133 |
| PT-INR | 1.21 (1.02 – 1.72) | 1.06 (0.81 – 2.46) | 0.000000000777 |
| APTT | 35.9 (26.0 – 62.6) | 29.8 (3.9 – 75.8) | 0.0000000000168 |

APTT: activated partial thromboplastin time; DOAC: direct oral anticoagulant; ERCP: endoscopic retrograde cholangiopancreatography; PT-INR: prothrombin time-international normalized ratio

‡ There are some duplicates in each group.
In the no-drug group, the median age was 76 (range 25–106) years, and the male-to-female ratio was 0.94. The indications for EST were malignant stricture in 108 (22.4%), bile duct stone in 333 (68.1%), acute cholecystitis in 22 (4.6%), acute pancreatitis in 2 (0.4%), and chronic pancreatitis in 4 (0.8%) patients. Underlying diseases were noted in 47 (9.8%) patients, including cardiovascular disease in 25 (5.1%), hemodialysis in 5 (1.0%), liver cirrhosis in 6 (1.2%), stroke in 10 (2.1%), and cerebral hemorrhage in 9 (1.9%). Cholangitis was observed in 314 (65.1%) patients. The median platelet count was 20.5 × 10^4/µl (range 4.5–67.8 × 10^4/µl), the median PT-INR was 1.06 (range 0.81–2.46), and the median APTT was 29.8 (range 3.9–75.8) seconds.

Age, cardiovascular disease, stroke, liver cirrhosis, PT-INR, and APTT in the DOAC group were significantly higher than those of the no-drug group. The platelet count was significantly lower in the DOAC group than in the no-drug group.

**ERCP findings**

In the DOAC group, periampullary diverticulum was found in 13 (31.0%) patients. Precut was performed in 1 (2.4%) patient, lithotripsy in 33 (78.6%) patients, and endoscopic papillary balloon dilation (EPLBD) in 5 (11.9%) patients. Self-expandable metallic stent (SEMS) was implanted in 2 (4.8%) patients and plastic stent in 5 (11.9%); endoscopic nasobiliary drainage tube (ENBD) was inserted in 3 (7.1%) patients. Complications were noted in 7 (16.7%) patients, including bleeding in 6 (14.3%) and acute cholecystitis in 1 (2.4%). Heparin replacement was induced in 12 (28.6%) patients.

In the no-drug group, periampullary diverticulum was observed in 134 (27.8%) patients. Precut was performed in 4 (0.8%) patients, lithotripsy in 345 (71.6%) patients, and EPLBD in 25 (5.2%) patients. SEMS was implanted in 50 (10.4%) patients and plastic stent in 100 (20.7%); ENBD was inserted in 28 (5.8%) patients. Complications were noted in 43 (8.9%) patients, including bleeding in 15 (3.1%), pancreatitis in 17 (3.5%), perforation in 3 (0.6%), acute cholecystitis in 5 (1.0%), and others in 4 (0.8%).

Only bleeding was significantly higher in the DOAC group than in the no-drug group. Table 2 shows the ERCP findings.
Table 2
Endoscopic retrograde cholangiopancreatography findings

|                     | No-drug group | DOAC group | p value |
|---------------------|---------------|------------|---------|
|                     | n = 482 (92.0%) | n = 42 (8.0%) |         |
| Periampullary diverticulum | 13 (31.0%)     | 134 (27.8%)  | 0.72    |
| Precut              | 1 (2.4%)       | 4 (0.8%)   | 0.343   |
| Lithotripsy         | 33 (78.6%)     | 345 (71.6%) | 0.375   |
| EPLBD               | 5 (11.9%)      | 25 (5.2%)  | 0.0819  |
| Metallic stent      | 2 (4.8%)       | 50 (10.4%)  | 0.415   |
| Plastic stent       | 5 (11.9%)      | 100 (20.7%) | 0.227   |
| ENBD                | 3 (7.1%)       | 28 (5.8%)  | 0.729   |
| **Complication‡**   |               |            |         |
| • Bleeding          | 0             | 17 (3.5%)  | 0.384   |
| • Pancreatitis      | 0             | 3 (0.6%)   | 1       |
| • Perforation       | 1 (2.4%)       | 5 (1.0%)   | 0.396   |
| • Cholecystitis     | 0             | 4 (0.8%)   | 1       |
| • Others            | 7 (16.7%)      | 43 (8.9%)  | 0.104   |
| **Total**           |               |            |         |
| Heparin replacement | 12 (28.6%)     | 0          | 0.0000000000000014 |

DOAC: direct oral anticoagulant; ENBD: endoscopic nasobiliary drainage; EPLBD: endoscopic papillary large balloon dilation

‡ There are some duplicates in each group.

**EST bleeding and outcomes**

Of 524 patients, 21 (4.0%) had bleeding. The bleeding rate in the DOAC group (14.3%, 6/42) was significantly higher than that of the no-drug group (3.1%, 15/482) (Table 3). In the DOAC group, bleeding occurred during ERCP in 2 (33.3%) patients and after ERCP in 4 (66.7%) patients. The rate of shock was 33.3% (2/6), and 16.7% (1/6) of the patients needed transfusion. The median change in hemoglobin level was −0.65 (range −7.3−0.7) g/dl. The change in hemoglobin level was defined as a change within 1 week before ERCP. The median duration of hospitalization was 8 (range 4–65) days.
In the no-drug group, bleeding was noted during ERCP in 8 (53.3%) patients and after ERCP in 7 (46.7%) patients. The rate of shock was 13.3% (2/15), and transfusion was needed in 20.0% (2/15) of the patients. The median change in hemoglobin level was −0.9 (range −5.1–1.7) g/dl. The median duration of hospitalization was 7 (range 3–71) days. No significant differences were found between the two groups. All patients with EST bleeding were successfully treated with endoscopy or conservative therapy. Interventional radiology or surgery was not needed to achieve hemostasis (Fig. 2).

**Multivariate analysis of risk factors for bleeding after EST**

Factors that are considered clinically significant were included in the multivariate analysis (Table 4). INR and APTT were difficult to interpret clinically because of the variable effects of DOAC on INR and APTT; thus, INR and APTT were not included in the analysis. Hemodialysis was considered to be not involved in EST bleeding in this study, since there were only 5 patients who had no bleeding. Therefore, it was not included in the multivariate analysis to not reduce the detection power of the multivariate analysis.
Table 4
Multivariate analysis of risk factors for bleeding after endoscopic sphincterotomy

| Multivariate analysis | Bleeding n = 21 | No bleeding n = 503 | p value | Odds ratio | 95% CI |
|-----------------------|-----------------|---------------------|----------|------------|--------|
| Age > 80 years        | 15 (76.2%)      | 205 (40.8%)         | 0.0369   | 3.18       | 1.07–9.42 |
| Underlying disease    |                 |                     |          |            |        |
| • Cardiovascular disease | 1 (4.8%) | 22 (4.4%) | 0.12 |            |        |
| • Stroke              | 0               | 9 (1.8%)            | 0.99     |            |        |
| • Liver cirrhosis     |                 |                     |          |            |        |
| DOAC use              | 6 (28.6%)       | 36 (7.2%)           | 0.00877  | 6.98       | 1.63–29.8 |
| Combination of DOAC and antiplatelet drugs | 2 (9.5%) | 10 (2.0%) | 0.28 |            |        |
| Platelet count < 100,000/µl | 5 (23.8%) | 17 (3.4%) | 0.000186 | 10.8 | 3.1–37.7 |
| ERCP findings         |                 |                     |          |            |        |
| • Periampullary diverticulum | 7 (33.3%) | 140 (27.8%) | 0.713 |            |        |
| • Precut              | 1 (4.8%)        | 4 (0.8%)            | 0.921    |            |        |
| • Lithotripsy         | 14 (66.7%)      | 364 (72.4%)         | 0.239    |            |        |
| • EPLBD               | 3 (14.3%)       | 27 (5.4%)           | 0.776    |            |        |
| • ENBD                | 2 (9.5%)        | 29 (5.8%)           | 0.426    |            |        |
| • SEMS                | 3 (14.3%)       | 49 (9.7%)           | 0.463    |            |        |
| • SpyGlass DS         |                 |                     |          |            |        |

Area under the ROC curve: 0.833; Multicollinearity: <5

CI: confidence interval; DOAC: direct oral anticoagulant; EPLBD: endoscopic papillary large balloon dilation; ENBD: endoscopic naso-biliary drainage; SEMS: self-expandable metallic stent; ROC, receiver-operating characteristic

Multivariate analysis showed that bleeding occurs more frequently in patients on DOAC (odds ratio [OR] 6.98, 95% confidence interval [CI] 1.63–29.8, p = 0.00877), those with low platelet count (< 100,000/µl) (OR 10.8, 95% CI 3.1–37.7, p = 0.000186), and elderly patients (> 80 years old) (OR 3.18, 95% CI 1.07–9.42,
p = 0.0369). In the model, the area under the receiver-operating characteristic curve was 0.833, and multicollinearity was < 5.

**DOAC cessation period**

Multivariate analysis revealed that DOAC is a risk factor for bleeding; hence, we examined the DOAC cessation period (Table 5). Forty-two patients on DOAC were divided into two groups according to the number of days DOAC was discontinued, that is, < 2 days (n = 24, 57.1%) and ≥ 2 days (n = 18; 42.9%).

| Table 5 | Direct oral anticoagulant cessation period |
|---------|-------------------------------------------|
|         | < 2 day cessation | ≥ 2 day cessation | p value |
| EST bleeding | n = 24 | n = 18 | 0.214 |
| Age > 80 years | 21 (87.5%) | 8 (44.4%) | 0.00584 |
| Underlying disease‡ | | | 1 |
| • Hemodialysis | 8 (33.3%) | 5 (27.8%) | 0.748 |
| • Cardiovascular disease | 7 (29.2%) | 6 (33.3%) | 1 |
| • Stroke | 3 (12.5%) | 0 | 0.247 |
| • Liver cirrhosis | | | |
| Combination of antiplatelet drugs | 8 (33.3%) | 4 (22.2%) | 0.506 |
| Heparin replacement | 3 (12.5%) | 9 (50.0%) | 0.0144 |
| Platelet count < 100,000/µl | 2 (8.3%) | 1 (5.6%) | 1 |
| ERCP findings | | | 1 |
| • Periampullary diverticulum | 0 | 1 (5.6%) | 0.429 |
| • Precut | 17 (70.8%) | 15 (83.3%) | 0.473 |
| • Lithotripsy | 2 (8.3%) | 3 (16.7%) | 0.636 |
| • EPLBD | 2 (8.3%) | 1 (5.6%) | 1 |
| • ENBD | | | |
| Thromboembolism | 0 | 0 | 1 |

ENBD: endoscopic naso-biliary drainage; EPLBD: endoscopic papillary large balloon dilation; EST: endoscopic sphincterotomy

For the < 2-day group, bleeding occurred in 5 (20.8%) patients, and 21 (87.5%) were elderly patients (> 80 years old). Underlying diseases were cardiovascular disease in 8 (33.3%), stroke in 7 (29.2%), and liver
cirrhosis in 3 (12.5%) patients. Eight (33.3%) patients used a combination of antiplatelet drugs and DOAC, 3 (12.5%) had heparin replacement, and 2 (8.3%) had a platelet count < 100,000. Periampullary diverticulum was found in 8 (33.3%) patients. Precut was not performed in any patient in this group, whereas lithotripsy was performed in 17 (70.8%) patients and EPLBD in 2 (8.3%) patients. ENBD was inserted in 2 (8.3%) patients.

In the ≥ 2-day group, bleeding was noted in 1 (5.6%) patient, and 8 (44.4%) were elderly patients (> 80 years old). Underlying diseases were cardiovascular disease in 5 (27.8%) patients, stroke in 6 (33.3%), and liver cirrhosis in 0. Four (22.2%) patients had a combination of antiplatelet drugs and DOAC, 9 (50.0%) patients had heparin replacement, and 1 (5.6%) patient had a platelet count < 100,000. Periampullary diverticulum was observed in 5 (27.8%) patients. Precut was performed in 1 (5.6%), lithotripsy in 15 (83.3%), and EPLBD in 3 (16.7%) patients. ENBD was inserted in 1 (5.6%) patient. No significant differences were found between the groups, except for the number of elderly patients and heparin replacement. Heparin tended to be used more often in the ≥ 2-day group; however, there was no significant difference in EST bleeding rates between the two group. Moreover, there was no EST bleeding in the case with heparin replacement. No thrombotic events occurred during hospitalization.

**Discussion**

Several single-center studies have analyzed the risk factors for EST bleeding [3, 15, 17–19]. Although most of these reports only included patients treated with warfarin, a few recent reports analyzed the risk factors for EST bleeding in patients treated with DOAC [9, 10]. However, these reports compared the risk of EST bleeding between DOAC and warfarin users, and patients not receiving an anticoagulant agent were not considered. As the population ages and the incidence of chronic disease rises, the need for anticoagulants also increases. Particularly, the use of DOAC has increased recently. Thus, the risk factors for bleeding after EST in patients on DOAC were analyzed and compared with those of patients without antithrombotic therapy.

Previous studies showed that the rate of bleeding associated with EST is 1–5% [1–7]. In this study, the rate of EST bleeding was 4.0% (21/524), and the bleeding rate in the DOAC group (14.3%, 6/42) was significantly higher than that in the no-drug group (3.1%, 15/482). While the bleeding rate in the DOAC group in this study was higher than that in previous studies, the bleeding rate in all cases was comparable to those of other reports [9, 10]. In addition, multivariate analysis revealed that the significant risk factors for EST bleeding are DOAC, low platelet count (< 100,000/µl), and old age (> 80 years old). Thus, the rate of EST bleeding in the DOAC group in our study was reliable. Moreover, among the studies that investigated the risk factors for EST bleeding [2, 20, 21], no report revealed the relationship between platelet count and EST bleeding. In our study, as all cases with a platelet count < 100,000 were not associated with liver cirrhosis or idiopathic thrombocytopenia, we suspected that the low platelet count was possibly due to an infection. Some reports described that heparin replacement is a risk factor for post-EST bleeding [9, 10, 15]. However, in our study, there was no EST bleeding in the case with heparin replacement. Therefore, we think that heparin was not related to EST bleeding in our study.
A previous study demonstrated that the rate of severe bleeding associated with EST among anticoagulant users is significantly higher than that among non-users [8]. In our study, although the EST bleeding rate was higher in the DOAC group than in the no-drug group, no significant differences in the extent of bleeding based on the rate of shock, necessity of transfusion, and change in hemoglobin level were found between the groups. In a recent study, the risk of EST bleeding was lower in DOAC users than in warfarin users [9, 10].

Our examination on the DOAC cessation period showed no significant difference in the rate of EST bleeding between DOAC cessation for < 2 days and that for ≥ 2 days. Nonetheless, to decrease the risk of EST bleeding in the DOAC group, a longer cessation of DOAC treatment may be necessary, which may, however, also increase the risk of thromboembolic events [22].

The incidence rate of thromboembolic events after temporary warfarin cessation was 0.7% in a large prospective cohort study that enrolled 6761 patients with 1293 episodes of anticoagulation interruption [23]. In another study, the incidence rate of thromboembolic events after temporary warfarin cessation was 4.2% (4/96) [22]. Moreover, long cessation of anticoagulant therapy of > 48 h was associated with thromboembolic events. Therefore, in patients at risk of thromboembolic events, early resumption of anticoagulant therapy after EST, i.e., within 48 h, may be recommended [22]. Our study followed the JGES guideline, and no thrombotic events were observed during hospitalization.

Various endoscopic approaches for the treatment of EST bleeding have been reported, including injection therapy with HSE [24], balloon compression [25], argon plasma coagulation [26], and hemoclip [27]. Although post-EST bleeding is not associated with increased mortality, morbidity rate and hospital stay duration as well as costs may increase [2]. In our study, all patients with EST bleeding were completely treated with endoscopic hemostasis or conservative therapy. No significant differences in hospital stay between the DOAC and no-drug groups were found. Hence, the JGES guideline was acceptable.

This study has several limitations. The study population was small. In addition, this was a single tertiary referral center retrospective study; thus, some uncontrolled confounding factors that affected the results possibly exist. Given these limitations, a prospective randomized multicenter study is warranted to standardize the approach for DOAC cessation.

**Conclusion**

Caution needs to be exercised when caring for patients on DOAC, those with low platelet count, and elderly patients after EST, as the occurrence of bleeding is more frequent in these populations. A longer DOAC cessation period may be necessary in the DOAC group to achieve the same bleeding rate as that of the no-drug group; nevertheless, this may result in thromboembolic events. Our study showed that hemostasis was achieved in all patients with EST bleeding and that no thromboembolic events occurred. Therefore, although the bleeding rate was higher in the DOAC group than in the no-drug group, EST based on short-term DOAC cessation according to the JGES guideline was considered valid because the prevention of thromboembolic event occurrence is as important as the achievement of hemostasis.
Further studies are required to broaden our understanding of DOAC, which has been increasingly used in the clinical setting, including a study on how the cessation period of DOAC relates to renal function.

**Abbreviations**

EST: endoscopic sphincterotomy, DOAC: direct oral anticoagulant, JGES: the Japan Gastroenterological Endoscopy Society, ERCP: endoscopic retrograde cholangiopancreatography, HSE: hypertonic saline epinephrine solution, PT-INR: the median prothrombin time international normalized ratio (PT-INR), APTT: the median activated partial thromboplastin time, EPLBD: endoscopic papillary balloon dilation, SEMS: Self-expandable metallic stent, ENBD: endoscopic nasobiliary drainage tube

**Declarations**

**Ethics approval and consent to participate:** This retrospective observational study was reviewed and approved by the Future Medical Research Center Committee's institutional review board (IRB no. TGE00934-024). Moreover, all procedures have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from all individual participants included in the study by the opt-out method of our hospital website and In-hospital posting (as it was a retrospective study using information contained in medical charts and computerized records). The ethics committee approved this.

**Consent for publication:** Not applicable

**Availability of data and materials:** The technical appendix, statistical code, and dataset are available from the corresponding author upon request. No additional data are available.

**Competing interests:** The authors declare that they have no competing interest.

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**Authors’ contributions:** SM and AS analyzed and interpreted the patient data regarding the bleeding risk after EST. SM and KK was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Figures
Figure 1

Study population Of the 676 patients treated with EST from May 2016 to August 2019, 152 patients were excluded based on the exclusion criteria (this study enrolled patients undergoing EST who were treated with either a DOAC prior to the EST or no antithrombotic agents). The exclusion criterion was the use of warfarin or antiplatelet therapy only. EST, endoscopic sphincterotomy; DOAC, direct oral anticoagulants.

Figure 2

- EST bleeding, n=21 (DOAC group: 6, No-drug group: 15)
  - Conservative therapy, n=3
  - IVR or surgery, n=0
  - Endoscopic treatment, n=18
    - Hemoclip 9
    - Balloon compression 6
    - HSE 2
    - APC 0
    - SEMS 2
    ※There were duplicates
Interventions for endoscopic sphincterotomy bleeding. Hemostasis was achieved with endoscopy or conservative therapy. Interventional radiology or surgery was not necessary. APC: argon plasma coagulation; HSE: hypertonic saline-epinephrine; SEMS: self-expandable metallic stent.