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A prospective multicenter observational study evaluating the risk of periendoscopic events in patients using anticoagulants: the Osaka GIANT Study

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ABSTRACT

Background and study aims An increasing number of patients have been using anticoagulants including anti-vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs); however, in patients using anticoagulants, limited data are available with regard to the risks of gastrointestinal bleeding and thromboembolic events during the peri-endoscopic period. We aimed to evaluate the peri-endoscopic bleeding and thrombotic risks in patients administered VKAs or DOACs.

Patients and methods Consecutive patients using anticoagulants who underwent endoscopic biopsy, mucosal resection, or submucosal dissection were prospectively enrolled across 11 hospitals. The primary outcome assessed was difference in incidence of post-procedural gastrointestinal bleeding in patients using VKAs and DOACs. Duration of hospitalization and peri-procedural thromboembolic events were also compared.

Results We enrolled 174 patients using VKAs and 37 using DOACs. In total, 16 patients using VKA were excluded from the analysis because of cancellation of endoscopic procedures and contraindications to the use of DOACs; 128 (81 %) patients using VKAs and 17 (46 %) using DOACs received heparin-bridging therapy (HB). The rate of post-procedural gastrointestinal bleeding in DOAC users was similar to that

in VKA users (16.2 % vs. 16.4 %, $P = 1.000$). Duration of hospitalization was significantly longer in patients using VKAs than in those using DOACs (median 15 vs. 7 days, $P < 0.0001$). Myocardial infarction occurred during pre-endoscopic HB in one patient using VKAs.

Conclusion DOAC administration showed similar post-procedural gastrointestinal bleeding risk to VKA administration in patients undergoing endoscopic procedures, but it shortened the hospital stay.

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Introduction

Anticoagulants are widely used to treat or prevent thromboembolic events in high risk patients such as those diagnosed with atrial fibrillation, acute coronary syndrome, and deep vein thrombosis [1 – 5], but are considered strong risk factors for gastrointestinal bleeding with an age- and gender-adjusted hazard ratio of 2.59 [6]. Management of anticoagulant therapy during invasive gastrointestinal endoscopic procedures is a perplexing issue because temporary cessation of antithrombotic drugs may be necessary to reduce the risk of gastrointestinal bleeding, although discontinuation of anticoagulants inversely raises the risk of thrombotic complications [7]. It has been shown that 1.06 % of patients developed cerebral infarction within a month of the endoscopic procedure when use of a vitamin K antagonist (VKA) such as warfarin was terminated without heparin bridging (HB) [8].

These results have led to a consensus that cessation of anticoagulants should be minimized during endoscopic procedures to prevent life-threatening cerebro-cardiovascular events. Uninterrupted antithrombotic therapy has been recommended for procedures with a low risk for gastrointestinal bleeding, such as endoscopic biopsy [5, 9]. HB is recommended when high risk endoscopic procedures, such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), are performed [9 – 11]. However, a study by our group and several other studies have reported that HB in patients using VKAs significantly increased the risk of peri-procedural gastrointestinal bleeding compared to patients who temporarily terminated VKAs without using heparin [12 – 14]. A recent meta-analysis has shown that VKA-treated patients who received peri-procedural HB demonstrated increased risks of both overall and major bleeding and showed a similar risk of thromboembolic events compared to VKA-treated patients who did not receive HB [15].

Recently, newer anticoagulants including direct thrombin inhibitors (dabigatran) and other direct Factor Xa inhibitors (e. g., rivaroxaban, apixaban, edoxaban) have been used as alternatives to VKA [16 – 18]. These drugs are collectively termed direct oral anticoagulant drugs (DOACs) or novel oral anticoagulant drugs (NOACs), and have been shown to be effective in preventing cardiogenic cerebral infarction in patients diagnosed with nonvalvular atrial fibrillation [1, 19]. DOACs show characteristics of a relatively short time to maximal effect and offset of action, and they can be prescribed at fixed doses without the need for close monitoring or dose adjustments [19, 20]. The rapid onset of anticoagulation and a short half-life of DOACs ensure easier initiation and interruption of anticoagulation than VKAs [21]. To date, most of the available data are retrospective with regard to evaluation of thrombotic and bleeding events during invasive endoscopic procedures in patients using anticoagulants especially for DOACs and even in VKA. Therefore, we conducted a prospective, multicenter observational study, the Osaka GastroIntestinal Anticoagulant (Osaka GIANT) Study, to evaluate the peri-procedural complications in patients using VKAs and DOACs.

Patients and methods

Patients and study design

This is a prospective, multicenter, observational study performed at 1 academic and 10 tertiary care hospitals participating in the Osaka Gut Forum. Patients using anticoagulants who underwent endoscopic procedures (biopsy, EMR, and ESD) were prospectively enrolled in the participating hospitals between September 2012 and December 2015 and these patients were followed up until 30 days after the endoscopic procedures. We obtained informed consent from the patients before endoscopic procedures when invasive endoscopic procedures were scheduled and the patients were registered at the Data Center. When it was uncertain whether endoscopic procedures such as biopsy would be performed, the patients were provisionally pre-registered at the Data Center and were formally registered when the invasive endoscopic procedures were actually performed. All clinical data were entered into case report forms before and after the endoscopic procedure and were submitted to the Data Center. The data analysis was completed in October 2016. This study was registered by the University Hospital Medical Information Network (UMIN) 000009109.

Inclusion and exclusion criteria

Inclusion criteria for recruitment into the study were: (1) Patients using anticoagulants: warfarin potassium (Warfarin, Eisai, Tokyo, Japan) or DOACs (dabigatran [Pradaxa, Boehringer Ingelheim, Ingelheim, Germany], apixaban [Eliquis, Pfizer Inc., New York, United States], edoxaban [Lixiana, Daiichi Sankyo, Tokyo, Japan], rivaroxaban [Xarelto, Bayer, Leverkusen, Germany]). (2) Patients aged ≥ 20 years. (3) Patients who required endoscopic biopsy or invasive procedures.

Exclusion criteria were: (1) Patients with unstable vital signs and a high risk associated with an endoscopic procedure. (2) Patients with apparent gastrointestinal bleeding before the endoscopy. (3) Pregnant women or those breast-feeding, and/or those with a high possibility of being pregnant. (4) Patients undergoing two or more procedures (biopsy, EMR, and ESD) in the same hospitalization. (5) Patients whose condition was not considered suitable for inclusion in this study. The analysis of post-procedural gastrointestinal bleeding excluded patients using medicines that could possibly interact with DOACs such as itraconazole [22] and those showing an allergy to DOACs. In addition, patients who underwent hemodialysis due to renal dysfunction and those with mechanical heart valve replacement were excluded from the analysis of post-procedural events because those conditions are contraindications to the use of DOACs and would lead to a selection bias to assess VKA.

Assessment of primary and secondary outcomes

Primary outcome was the prevalence of gastrointestinal bleeding within 30 days after the endoscopic procedures. Secondary outcomes were: (1) Duration of hospitalization. (2) Prevalence of cardiovascular, cerebral, and systemic thromboembolic events. (3) Rate of recurrent gastrointestinal bleeding, which required endoscopic evaluation. (4) Frequency of massive gastrointestinal bleeding. (5) Frequency of fatal gastrointestinal bleeding. (6) Frequency of cerebrovascular bleeding. Gastrointestinal bleeding was defined as the presence of melena or hematemesis, or a drop in hemoglobin level >2 g/dL that was not explained by the presence of other diseases such as oral, nasopharyngeal, and/or anal conditions, and active bleeding or attachment of blood at the lesion of endoscopic treatment or biopsy. Massive bleeding was defined as gastrointestinal bleeding necessitating transfusion of at least 2 units of red cells or symptoms secondary to bleeding in major organs. Fatal bleeding was defined as bleeding into critical sites (intracerebral, subarachnoid, and subdural hemorrhage), bleeding associated with a decrease in hemoglobin level >5 g/dL, documented transfusion of at least 9 units of red blood cells, hypotension requiring administration of intravenous catecholamine, and bleeding requiring surgical treatment.

Management of anticoagulants and antiplatelet agents

In principle, each drug holiday related to oral anticoagulants and antiplatelet drugs before and after performing a therapeutic endoscopy was determined based on the guidelines of the Japan Gastroenterological Endoscopy Society (JGES) [9]. In particular, for endoscopic mucosal biopsy or gastroenterological endoscopic procedures with low bleeding risk, aspirin, non-aspirin antiplatelet agents, or anticoagulants were continued when the patient was on antithrombotic monotherapy. For gastroenterological endoscopic procedures that carried a high risk of bleeding (EMR and ESD), warfarin or dabigatran was recommended to be suspended 3–5 days or 24–48 hours before endoscopy, respectively. There were no recommendations for DOACs other than dabigatran, but most procedures using other DOACs were performed similarly to dabigatran. Requirement of HB was evaluated by the patient's thromboembolic risk under consultation with specialists, such as cardiologists. Patients who required HB were instructed to discontinue use of anticoagulants or antiplatelet agents several days before the procedure and continuous intravenous administration of unfractionated heparin (Ajinomoto Pharmaceuticals Co., Ltd., Tokyo, Japan) was initiated after hospitalization. The dose of heparin was adjusted to attain the required activated partial thromboplastin time [9] and administration of heparin sodium was discontinued temporarily at least 3 hours before initiating the endoscopic treatment. After performing endoscopy, heparin sodium was restarted after confirming the absence of melena or development of anemia and its use was discontinued when the international normalized ratio of prothrombin time was observed to be elevated to approximately 1.50 in patients using VKAs. In some cases, the management of anticoagulants did not follow the guidelines, but all of the detailed data on the management of anticoagulants were collected.

Data collection

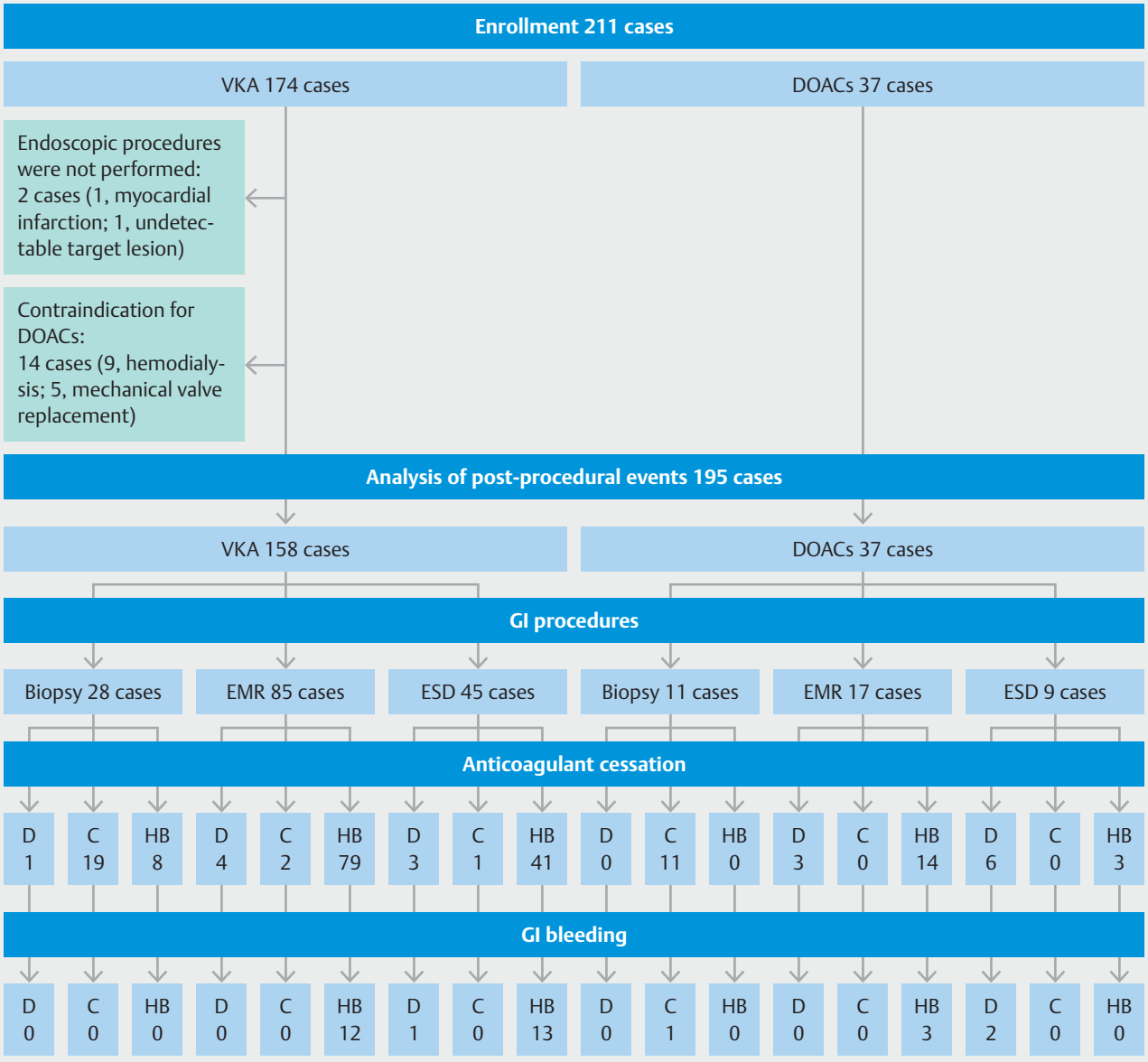
The following information was obtained from all patients before the endoscopic procedure: age, sex, height, weight, blood pressure, pulse, results of laboratory tests such as hemoglobin, stroke risk indices (CHADS2 [23], CHA2DS2-VASc [24]), bleeding risk index (HAS-BLED score) [22], name and dose of anticoagulants and antiplatelet drugs used, information regarding cessation of antithrombotic drugs, treatment with HB, history of hypersensitivity to DOACs, comorbidities, details of endoscopic procedures, and details regarding gastrointestinal bleeding. Patients were asked to visit the hospital 30 days after the endoscopic procedures in order to obtain information on subjective symptoms of gastrointestinal bleeding or thromboembolic events as well as information on vital signs and laboratory tests.

Estimation of sample size

We expected to recruit 450 patients during the study period. The ratio of VKA:DOAC use was 8:1 when generating the study protocol. Therefore, the estimated number of cases in the VKA group was 400 and in the DOAC group was 50. Our previous study showed that the post-procedural bleeding rate in patients using VKAs who underwent HB was 16%, and that in patients who temporarily terminated VKA use without HB was 3% [13]. We speculated that the rate of post-procedural bleeding would be similar in patients using DOACs without HB and in patients using VKAs without HB. The estimated accuracy in determining the bleeding rate was ±3.6% in the VKA group when the sample size was 400 and ±4.7% in the DOAC group when the sample size was 50 patients.

Statistical analysis

Baseline characteristics were expressed as medians (1st quartile, 3rd quartile) for continuous variables, and proportions for categorical variables. We used Wilcoxon rank-sum test for continuous variables, and Chi-squared test for categorical variables to compare baseline characteristics between the VKA and DOAC groups. Fisher's exact test was used to compare the pro-



▶ **Fig. 1** Study flow chart and the outcome of post-procedural gastrointestinal bleeding. Patients who received treatment with VKAs and DOACs were included and the numbers of patients with each type of endoscopic procedure, cessation method of anticoagulants, and post-procedural gastrointestinal bleeding are shown. D: discontinue anticoagulants without HB; C: continue anticoagulants without HB; GI: gastrointestinal; HB: heparin bridging.

portion of post-procedural gastrointestinal bleeding between the VKA and DOAC groups. Factors associated with post-procedural gastrointestinal bleeding were assessed using univariable and multivariable logistic regression models with penalized maximum likelihood estimations to correct for possible overfitting of models. These analyses were performed to identify independent risk factors associated with delayed bleeding. To compare the proportion of post-procedural gastrointestinal bleeding among patients with and without peri-procedural heparin bridge therapy, we used Fisher's exact test for each of the VKA and DOAC groups. The difference in the duration of hospital stay between the VKA and DOAC groups was compared using the Wilcoxon rank sum test. The relationship between drugs (VKAs or DOACs) and post-procedural gastrointestinal bleeding was assessed by performing a propensity score analysis with an augmented inverse probability weighted estimator [25] to avoid overfitting that could occur due to inclusion of too many variables into a logistic regression. A P value <0.05 was considered to be statistically significant. R version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria) was used for multivariate logistic regression models with penalized maximum likelihood estimations and Stata version 14 (College Station, Texas, United States) was used to perform propensity score analysis with an augmented inverse probability weighted

▶ **Table 1** Patient characteristics.

	All	VKAs	DOACs	*P* value
Total, n	195	158	37	
Age, y, median (1st, 3rd quartile)	74 (70, 79)	74 (70, 79)	75 (69, 78.5)	0.830
Sex, male, n (%)	152 (77.9)	128 (81.0)	24 (65.0)	0.033
$CHADS_2$ score, median (range)	2 (0 – 5)	2 (0 – 5)	2 (0 – 5)	0.356
$CHADS_2$-VASc score, median (range)	4 (0 – 8)	4 (0 – 8)	4 (1 – 7)	0.948
HAS-BLED score, median (range)	2 (0 – 5)	2 (0 – 5)	2 (0 – 4)	0.810
Comorbidities				
▪ Atrial fibrillation, n (%)	159 (81.5)	126 (79.7)	33 (89.1)	0.183
▪ Ischemic heart disease, n (%)	35 (17.9)	29 (18.4)	6 (16.2)	0.760
▪ Abnormal liver function test, n (%)	18 (9.2)	15 (9.5)	3 (8.1)	0.793
▪ Congestive heart failure, n (%)	46 (23.6)	41 (26.0)	5 (13.5)	0.581
▪ Hypertension, n (%)	144 (73.8)	116 (73.4)	28 (75.7)	0.778
▪ Diabetes mellitus, n (%)	53 (27.1)	41 (25.9)	12 (32.4)	0.425
▪ Cerebral infarction/TIA, n (%)	45 (23.1)	39 (24.7)	6 (16.2)	0.271
▪ Renal dysfunction, n (%)	63 (32.3)	52 (32.9)	11 (29.7)	0.710
Anticoagulants				
▪ Warfarin, n (%)	158 (81.0)	158 (100.0)		
▪ DOACs, n (%)	37 (18.9)		37 (100.0)	
▪ Dabigatran, n (%)	18 (9.2)		18 (48.6)	
▪ Rivaroxaban, n (%)	9 (4.6)		9 (24.3)	
▪ Apixaban, n (%)	8 (4.1)		8 (21.6)	
▪ Edoxaban, n (%)	2 (1.0)		2 (5.4)	
Antiplatelet drugs, n(%)	64 (32.8)	52 (32.9)	12 (27.0)	0.251
▪ Aspirin, n (%)	51 (26.1)	44 (27.8)	7 (18.9)	
▪ Clopidogrel, n (%)	8 (4.1)	5 (3.1)	3 (8.1)	
▪ Others, n (%)	11 (5.6)	9 (5.6)	2 (5.4)	
Number of antiplatelet drugs				
▪ 0, n (%)	131 (67.2)	106 (67.1)	25 (67.6)	
▪ 1, n (%)	55 (28.2)	45 (28.5)	10 (27.0)	
▪ 2, n (%)	9 (4.6)	7 (4.4)	2 (5.4)	
Region				
▪ Upper gastrointestinal tract, n (%)	84 (43.0)	65 (41.1)	19 (51.4)	0.259
Type of procedure				
▪ EMR, n (%)	106 (54.3)	89 (56.3)	17 (45.9)	0.081
▪ ESD, n (%)	47 (24.1)	40 (25.3)	7 (18.9)	
▪ Biopsy, n (%)	42 (21.5)	29 (18.4)	13 (35.1)	

▶ **Table 1** (Continuation)

	All	VKAs	DOACs	*P* value
Peri-procedural anticoagulants				
▪ Termination without heparin bridge, n (%)	17 (8.7)	8 (5.0)	9 (24.3)	<0.0001
▪ Continue, n (%)	33 (16.9)	22 (13.9)	11 (29.7)	
▪ Heparin bridge, n (%)	145 (74.4)	128 (81.0)	17 (45.9)	

DOACs, direct oral anticoagulants; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; TIA, transient ischemic attacks; VKAs, vitamin K antagonists.

▶ **Table 2** Post-procedural gastrointestinal bleeding in patients treated with VKAs and DOACs.

	VKAs (n = 158)	DOACs (n = 37)	*P* value*
Total post-procedural bleeding, n (%)	26 (16.4)	6 (16.2)	1.000
Massive bleeding, n (%)	14 (8.8)	3 (8.1)	1.000
Fatal bleeding, n (%)	2 (1.3)	0 (0.0)	1.000

DOACs, direct oral anticoagulants; VKAs, vitamin K antagonists.
* Fisher's exact test.

estimator. Other statistical analyses were performed using JMP 12.2.0 software (SAS Institute, North Carolina, United States).

Ethical considerations

This study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committees of Osaka University Hospital and participating hospitals. Written informed consent was obtained from each patient before performing the endoscopic procedures.

Results

Characteristics of patients and endoscopic procedures

The study was terminated before reaching the expected number of patients. Our study included 211 patients including 174 patients who used VKAs and 37 who used DOACs. Endoscopic treatment was not performed in two patients: one patient suffered a myocardial infarction during the cessation period of VKAs before the endoscopic procedure, and in one patient, the target lesion was not detected on the day of the endoscopic procedure. We also excluded 9 patients who underwent hemodialysis and 5 who underwent mechanical heart valve replacement (the use of DOACs was contraindicated) from the analysis of post-procedural events. Finally, 195 patients (158 VKAs and 37 DOACs) were analyzed to compare post-procedural gastrointestinal bleeding (▶ **Fig. 1**). The characteristics of patients analyzed for post-procedural events are shown in ▶ **Table 1**. The VKA group included a greater proportion of men than those in the DOAC group (81.0 % vs. 65.0 %, $P = 0.033$). A significantly larger proportion of patients received HB in the VKA group than in the DOAC group (81.0 % vs. 45.9 %, $P < 0.0001$; ▶ **Table 1**). There were no statistically significant differences in other background characteristics between the two groups.

Post-procedural gastrointestinal bleeding in patients using vitamin K antagonists and direct oral anticoagulants

The total post-procedural gastrointestinal bleeding rates within 30 days of an endoscopic procedure did not differ significantly between the VKA and the DOAC groups (16.4 % vs. 16.2 %, $P = 1.000$; ▶ **Table 2**). The proportion of patients with an abnormal liver function test was similar between the two groups (▶ **Table 1**). Four patients had a history of hematological disorders in the VKA group and none in the DOAC group. Both patients with liver dysfunction and hematological disorders did not experience post-procedural gastrointestinal bleeding. The post-procedural gastrointestinal bleeding rates and the proportion of patients who received HB associated with each type of DOAC use are shown in ▶ **Supplementary Table 1**. The rates of massive and fatal bleeding did not differ significantly between the two groups (▶ **Table 2**). All patients who developed massive and fatal bleeding were successfully treated using endoscopic hemostasis. There was no difference in the duration of bleeding after the endoscopic procedures and the rate of recurrent bleeding observed between patients using VKAs and DOACs (▶ **Supplementary Table 2**). No patient from either group developed any major extra-gastrointestinal bleeding.

To further confirm the anticoagulant-induced risks of post-procedural gastrointestinal bleeding, we compared the rate of gastrointestinal bleeding in matched patients receiving VKAs and DOACs using propensity score analysis with an augmented

▶ **Table 3** Characteristics of the patients with and without post procedural gastrointestinal bleeding.

	Without gastrointestinal bleeding (n = 163)	With gastrointestinal bleeding (n = 32)
DOACs, n (%)	31 (19.0)	6 (18.8)
Age, y, median (1st, 3rd quartile)	75.0 (70.0, 79.0)	73.0 (67.8, 77.3)
Sex, male, n (%)	125 (76.7)	27 (84.4)
Region, upper gastrointestinal tract, n (%)	68 (41.7)	16 (50.0)
Procedure, EMR, n (%)	90 (55.2)	16 (50.0)
Procedure, ESD, n (%)	33 (20.2)	14 (43.8)
Procedure, biopsy, n (%)	40 (24.5)	2 (6.2)
With heparin bridge, n (%)	113 (69.3)	26 (81.2)
Atrial fibrillation, n (%)	132 (81.0)	27 (84.4)
Ischemic heart disease, n (%)	27 (16.6)	8 (25.0)
Congestive heart failure, n (%)	38 (23.3)	9 (28.1)
Hypertension, n (%)	123 (75.5)	21 (65.6)
Diabetes mellitus, n (%)	47 (28.8)	6 (18.8)
Cerebral infarction/TIA, n (%)	36 (22.1)	9 (28.1)
Abnormal liver function test, n (%)	18 (11.0)	0 (0.0)
Renal dysfunction, n (%)	55 (33.7)	8 (25.0)
Antiplatelet drugs/NSAID use, n (%)	50 (30.7)	11 (34.4)

DOACs, direct oral anticoagulants; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; NSAID, non-steroidal anti-inflammatory drugs; TIA, transient ischemic attacks.

inverse probability weighted estimator. We used a logit model to predict the use of drugs (VKAs or DOACs) as a function of age, sex, size of the lesion, present or past history of hemorrhagic diathesis, serum creatinine, liver function tests, and type of endoscopic procedure, and we used a logit regression model for post-procedural gastrointestinal bleeding, using HB and endoscopic procedures as explanatory variables. This propensity score analysis showed no statistically significant difference between patients using VKAs and DOACs in terms of the mean treatment effect on post-procedural gastrointestinal bleeding ($P = 0.108$).

Univariable and multivariable analysis showing risk factors associated with post-procedural gastrointestinal bleeding

We further investigated the role of anticoagulants and other factors associated with post-procedural gastrointestinal bleeding in patients using anticoagulants by dividing patients into groups based on those with and those without post-procedural gastrointestinal bleeding. The characteristics of patients with and without post-procedural gastrointestinal bleeding are shown in ▶ **Table 3**. Univariable analysis revealed an ESD was a significant risk factor associated with post-procedural gastrointestinal bleeding (▶ **Table 4**). Multivariable analysis, however, revealed that none of the selected factors were associated with post-procedural gastrointestinal bleeding (▶ **Table 4**).

Risk of post-procedural gastrointestinal bleeding according to use of heparin bridging

We next compared the post-procedural gastrointestinal bleeding rates between the VKA and DOAC groups among the subgroups of patients who did and did not receive HB (▶ **Supplementary Table 3**). There was no significant difference in the gastrointestinal bleeding rate between VKA and DOAC groups. Next, we compared the gastrointestinal bleeding rate between patients in each group separately among those who did and did not receive HB. The post-procedural gastrointestinal bleeding rate was significantly higher in patients who received HB than in those without HB in the VKA group ($P = 0.049$, ▶ **Table 5**); however, it did not differ significantly in those using DOACs.

Assessment of peri-procedural thromboembolic events in patients using vitamin K antagonists versus direct oral anticoagulants

Among the 211 patients initially registered for the study, one patient from the VKA group suffered a myocardial infarction during the phase of temporary termination of VKAs. No patient reported cerebro-cardiovascular thromboembolic and bleeding events during the study period. Overall, the incidence of cerebro-cardiovascular thromboembolic events was not statistically significantly different between the VKA and DOAC groups (0.6 % [1/174] vs. 0 % [0/37], $P = 0.644$).

▶ **Table 4** Univariable and multivariable analysis of the factors associated with post-procedural gastrointestinal bleeding.

		Univariable			Multivariable		
	Category	**Odds ratio**	**95 %CI**	***P* value**	**Odds ratio**	**95 %CI**	***P* value**
DOACs	Yes/no	0.983	0.372 – 2.59	0.972	1.666	0.512 – 5.42	0.397
Age	1 year	0.724	0.464 – 1.13	0.154	0.664	0.398 – 1.11	0.117
Sex	Male/female	0.609	0.219 – 1.69	0.341	2.617	0.242 – 28.27	0.658
Region	Upper gastrointestinal/lower gastrointestinal tract	1.397	0.654 – 2.99	0.388	1.766	0.507 – 6.16	0.428
Heparin bridge	Yes/no	1.917	0.743 – 4.95	0.178	1.011	0.091 – 11.26	0.372
Atrial fibrillation	Yes/no	0.789	0.281 – 2.21	0.652	3.133	0.870 – 11.29	0.326
Ischemic heart disease	Yes/no	1.679	0.682 – 4.13	0.259	0.792	0.282 – 2.22	0.729
Congestive heart failure	Yes/no	1.287	0.549 – 3.02	0.561	0.578	0.194 – 1.72	0.274
Hypertension	Yes/no	1.611	0.715 – 3.63	0.250	1.667	0.667 – 4.16	0.603
Diabetes mellitus	Yes/no	0.570	0.220 – 1.47	0.246	0.750	0.176 – 3.20	0.213
Cerebral infarction/TIA	Yes/no	1.380	0.587 – 3.25	0.460	1.274	0.512 – 3.17	0.599
Renal dysfunction	Yes/no	0.655	0.276 – 1.55	0.336	1.276	0.514 – 3.17	0.215
Antiplatelet drugs/NSAID use	Yes/no	1.184	0.531 – 2.64	0.680	2.352	0.706 – 7.83	0.802
Endoscopic procedure	EMR/biopsy	0.528	0.232 – 1.20	1.000	0.548	0.212 – 1.42	0.993
Endoscopic procedure	ESD/biopsy	3.724	1.144 – 12.12	0.029	1.125	0.449 – 2.81	0.081

CI, confidence interval; DOACs, direct oral anticoagulants; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; NSAID, non-steroidal anti-inflammatory drugs; TIA, transient ischemic attacks.

▶ **Table 5** Rate of post-procedural bleeding in patients taking VKAs or DOACs with/without peri-procedural heparin bridge therapy.

	Without heparin bridge	**With heparin bridge**	***P* value***
VKAs, n (%)	1/29 (3.5)	25/129 (19.4)	0.049
DOACs, n (%)	3/20 (15.0)	3/17 (17.7)	1.000

CI, confidence interval; DOACs, direct oral anticoagulants; VKAs, vitamin K antagonists.
* Fisher's exact test.

▶ **Table 6** Duration of hospital stay in patients taking VKAs or DOACs.

	VKAs	**DOACs**	**Difference between groups**	**95 %CI**	***P* value***
Duration (range)	15 (1 – 48)	7 (227)	8.69	5.49 – 11.90	< 0.0001

CI, confidence interval; DOACs, direct oral anticoagulants; VKAs, vitamin K antagonists.
* Wilcoxon rank sum test.

Duration of hospital stay for patients using vitamin K antagonists versus those using direct oral anticoagulants

The proportion of patients who received HB was significantly lower in the DOAC group than in the VKA group (▶ **Table 1**), and the duration of hospitalization was significantly shorter in the DOAC group than in the VKA group (median 7 vs. 15 days, $P < 0.0001$; ▶ **Table 6**).

Discussion

DOACs are increasingly used as substitutes for VKAs because they obviate the need for dose adjustment and lower the risk of life-threatening bleeding and intracranial hemorrhage [26]. However, DOAC users are reportedly at a higher risk for the development of gastrointestinal hemorrhagic events than VKA users [27]. In this prospective, multicenter observational study, the rate of post-procedural gastrointestinal bleeding in pa-

tients using DOACs was similar to that in those using VKAs. We previously reported that HB increases the risk of post-procedural gastrointestinal bleeding in patients undergoing gastric ESD and colonic EMR [12, 13], and we initially speculated that concomitant use of VKA and heparin may increase the risk of post-procedural gastrointestinal bleeding. We therefore reckoned that DOACs, which can avoid or minimize heparin use, can reduce post-procedural gastrointestinal bleeding. Contrary to expectations, DOAC use showed a similar incidence rate of post-procedural gastrointestinal bleeding to that of VKA use with HB (▶ **Table 5**). Due to the short pre-intervention termination period and strong antithrombotic effects, the risk of gastrointestinal bleeding associated with DOACs may be similar to that associated with VKAs used with HB. A recent meta-analysis has revealed that DOACs are associated with a higher risk of gastrointestinal bleeding than the standard care using VKAs [27]. Based on these results, it is important for endoscopists to be aware of the risk of post-procedural gastrointestinal bleeding in patients using DOACs even in the absence of HB, which is similar to that in patients using VKA with HB.

The American Society for Gastrointestinal Endoscopy (ASGE) guidelines and JGES guidelines published in 2012 recommend bridge therapy for patients using VKAs before undergoing high risk endoscopic procedures in those who are at high risk for the development of thromboembolic events [5, 9]. However, previous studies by our own group have shown a high risk of gastrointestinal bleeding after HB [12, 13, 28]. Similar to these retrospective studies, our prospective study confirmed a higher risk of post-procedural gastrointestinal bleeding in patients using VKAs who received HB than in those who did not receive HB. Moreover, we observed that a patient from the VKA group suffered acute myocardial infarction during the temporary termination phase of anticoagulant therapy, although HB had been performed. The recently reported BRIDGE clinical trial, which included approximately 50 % of patients who underwent minor gastrointestinal procedures (low bleeding risk), revealed that forgoing peri-operative bridging anticoagulation was not inferior to peri-operative HB to prevent arterial thromboembolism and decrease the risk of major bleeding [29]. Recent ASGE guidelines recommend HB in patients using DOACs who are at a high risk for the development of thromboembolic events and that they undergo high risk endoscopic procedures only when a DOAC cannot be restarted within 24 hours after the endoscopic procedure has been performed [5]. European Society of Gastrointestinal Endoscopy (ESGE) guidelines do not recommend HB in patients using DOACs due to their fast on and off effects [21]. The recently revised Japanese guidelines also allow continuous use of VKA or DOAC use without HB in high risk procedures [30]. A recent prospective study, which primarily included non-therapeutic endoscopic procedures, showed that short-term interruption of DOACs was safe [31]. Temporary termination of DOACs and forgoing HB can theoretically be allowed because of their short T-max and half-life and can reduce the duration of hospitalization without increasing gastrointestinal bleeding and thromboembolic risks.

Our current study has several limitations: (1) This study was terminated before the recruitment of the expected number of the patients due to the scarcity of patients. Some of the cases with biopsy, which were not planned in advance, may be missed for registration because informed consent needed to be obtained before the endoscopic procedures. In addition, endoscopists may be hesitant to perform biopsy in cases with a low risk of malignancy judged from the endoscopic appearance. Although we could not collect the expected number of patients, our data showed that the bleeding rate in DOACs was much higher than we initially estimated and these data were considered very important in the situation of increasing DOAC users. (2) Because the sample size was small, our subgroup analysis of DOACs was not adequately performed. (3) We used intravenously administered unfractionated heparin because use of low-molecular-weight heparin (LMWH) is limited during hemodialysis and for the treatment of disseminated intravascular coagulation in our country, although use of LMWH is recommended in the ASGE and ESGE guidelines [5, 10]. LMWH can be used in an outpatient setting [32, 33] and the benefit of reduced duration of hospitalization may not be applicable to LMWH; however, using DOACs reduce heparin use and simplify the process of anticoagulant administration. (4) Most of the procedures were performed under the guidance of JGES guidelines, but some were performed by the decision of their own institution as some physicians were still concerned about gastrointestinal bleeding after endoscopic procedures with continuation of anticoagulants. Because sufficient evidence was still not available for the use of anticoagulant drugs, especially prospective studies, we conducted a prospective study and confirmed that continuation of anticoagulants is possible in low risk procedures such as biopsy.

In conclusion, peri-endoscopic procedural complications in patients taking DOACs were similar to those in patients taking VKAs; however, use of DOACs is shown to be beneficial because this class of drugs can significantly reduce the duration of hospitalization compared to VKA with HB.

Competing interests

These authors have the following financial conflicts of interest regarding this manuscript. Hideki Iijima, Yasushi Sakata, and Tetsuo Takehara received funding from Daiichi-Sankyo.

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▶ **Supplementary Table 1** Post-procedural gastrointestinal bleeding and heparin bridge in each type of DOAC.

	n	Post-procedural gastrointestinal bleeding, n (%)	Heparin bridge, n (%)
Dabigatran	18	2 (11.1)	9 (50.0)
Rivaloxaban	9	2 (22.2)	4 (44.4)
Apixaban	8	1 (12.5)	5 (62.5)
Edoxaban	2	1 (50.0)	0 (0)

DOAC, direct oralanticoagulant.

▶ **Supplementary Table 2** Bleeding period after endoscopic procedures and the rate of recurrent bleeding.

	VKAs	DOACs	*P* value
Bleeding period after endoscopic procedures (days), median (range)	3.5 (1 – 18)	5 (1 – 13)	0.592
Recurrent bleeding/total bleeding, n (%)	3/26 (11.5)	0/6 (0)	0.382

DOACs, direct oral anticoagulants; VKAs, vitaminK antagonists.

▶ **Supplementary Table 3** Rate of post-procedural bleeding in patients taking VKAs or DOACs with and without heparin bridge therapy.

	VKAs	DOACs	*P* value*
Without heparin bridge, n (%)	1/29 (3.4)	3/20 (15.0)	0.291
With heparin bridge, n (%)	25/129 (19.3)	3/17 (17.6)	1.000

DOACs, direct oral anticoagulants; VKAs, vitamin K antagonists.
* Fisher's exact test.