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Comparison of bleeding following gastrointestinal endoscopic biopsy in patients treated with and without direct oral anticoagulants

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ABSTRACT

Background and study aims Despite the widespread use of direct oral anticoagulants (DOACs), the association between DOAC use and complications (e. g., bleeding) following gastrointestinal endoscopic biopsy remains unclear. This study aimed to evaluate complications after biopsy in patients treated with DOACs in Japan, where biopsies would be generally performed without DOAC withdrawal based on guideline recommendations.

Patients and methods Using a Japanese nationwide database, we identified patients taking DOACs who underwent gastrointestinal endoscopic biopsy (n = 2,769, DOAC group) and those not taking DOACs (n = 129,357, control group) from April 2015 to November 2020. We conducted 1:4 propensity score (PS) matching and overlap PS-weighting analyses with adjustment for background characteristics to compare occurrence of post-procedure hemorrhage and stroke within 1 week after biopsy, and thrombin use on the day of biopsy without a diagnosis of hemorrhage.

Results In total, 578 patients (0.44 %) developed post-procedure hemorrhage, and 13 patients (0.01 %) developed stroke. The DOAC group had more comorbidities than the control group. The PS matching analysis revealed no significant differences in post-procedure hemorrhage (odds ratio, 1.52 [95 % confidential interval, 0.96–2.41]) or stroke (1.00 [0.21–4.71]), whereas the DOAC group received thrombin more often than the control group (1.60 [1.30–1.95]). The results were equivalent in the overlap PS-weighting analysis.

Conclusions The PS analyses showed no significant differences in complications following gastrointestinal endoscopic biopsy between DOAC users and non-users. These results suggest the safety of endoscopic biopsy without DOAC withdrawal although the need for careful hemostasis remains.

Introduction

Oral anticoagulants are widely used for stroke prevention in patients with atrial fibrillation [1–3] and the treatment and secondary prevention of venous thromboembolism [4, 5]. Recently, direct oral anticoagulants (DOACs) that directly inhibit thrombin and factor Xa have commonly replaced vitamin K antagonists such as warfarin [6–8]. DOACs are characterized by rapid onset of action, short half-lives, and predictable pharmacokinetic and therapeutic effects at a fixed dose [9]. However, there are no routine clinical tests that can quantitatively assess the anticoagulant effect of DOACs [10]. Furthermore, there is still a lack of evidence regarding the appropriate timing of discontinuation and resumption before and after procedures [11, 12].

Although the management of anticoagulants before a procedure requires a risk-benefit balance (i. e., post-procedure hemorrhage versus thrombosis) [13], the incidence of complications following gastrointestinal endoscopy in patients treated with DOACs remains unclear. Observational studies in Japan comprising 560 biopsies and 101 biopsies on patients with anticoagulant medication showed no significant association between post-procedure bleeding and DOACs use [14, 15]. In a report on 529 cases from Italy, the patients who withdrew DOACs on the morning of the endoscopic procedure exhibited decreased bleeding, but the difference was not statistically significant [9]. Due to the small number of patients in these studies, stroke occurrence following biopsy was not assessed. Consequently, there are inconsistent guideline recommendations regarding the management of DOACs in patients undergoing gastrointestinal endoscopy [16–19].

In Japan, biopsies in gastrointestinal endoscopy generally have been performed without DOAC withdrawal based on reports and Japanese guidelines [14–16, 20]. This study aimed to compare the occurrence of complications after endoscopic biopsy between patients who continued DOACs and those not treated with anticoagulants.

Patients and methods

Data collection

We conducted a retrospective study using an administrative claims database, the DeSC database (DeSC Healthcare Inc. Tokyo, Japan), covering over one million individuals. The database was created by anonymizing and processing data from the health insurance claims database provided by several Japanese public health insurers [21, 22]. Three types of insurers were included: (1) society-managed, employment-based health insurance association (provided for employees of Japanese companies and their families); (2) national health insurance (provided for individuals below 75 years of age who are not covered by other public health insurance); and (3) latter-stage elderly healthcare system (provided for individuals over 75 years old). Diagnoses were recorded based on the International Classification of Diseases, 10th revision (ICD-10) codes, and the nationally standardized Japanese diagnosis. Each diagnostic record included the date of treatment initiation for the condition. Drugs and procedures were recorded using the European Pharmaceutical Market Research Association codes and Japanese medical procedure codes, respectively. A validation study confirmed the accuracy of the diagnosis and procedure in the database [21]. The study was approved by the Institutional Review Board of the University of Tokyo (approval number: 10862-(1); June 13, 2018). Given the de-identified nature of the data, the requirement for informed consent was waived.

Study protocol

We retrospectively identified patients in the DeSC database who underwent gastrointestinal endoscopic biopsy from April 2015 to November 2020. We excluded patients who: (1) underwent endoscopic treatments (e. g., polypectomy, endoscopic mucosal resection, and endoscopic submucosal dissection); (2) underwent a procedure for the bile duct or pancreas; (3) received warfarin within 6 months before the biopsy; and (4) joined the insurance organization included in the database within 6 months preceding the biopsy (window period). We categorized eligible patients into patients who received DOACs within 3 months before the biopsy (DOAC group) and those not treated with DOACs within 3 months preceding the biopsy (control group).

The primary outcome was post-procedure hemorrhage ("post-procedure hemorrhage" or "afterbleeding" in the nationally standardized Japanese diagnosis record). The secondary outcomes were gastrointestinal bleeding (ICD-10 code: K92.2) and stroke including embolism and thrombosis (I26, I74, T82.8). These outcomes were defined by diagnoses with the date of treatment initiation within 1 week after the biopsy. We also investigated outcomes with interventions: thrombin use and transfusion with the aforementioned diagnoses of bleeding (post-procedure hemorrhage or gastrointestinal bleeding); and thrombin use on the day of the biopsy without a bleeding diagnosis.

We examined the following background characteristics in each group: sex, age, gastrointestinal malignancy (upper and lower tract), comorbidities, concomitant medications (antiplatelet drugs, histamine 2-receptor antagonists, and proton pump inhibitors) within 3 months before the biopsy, type of endoscopy (esophagogastroduodenoscopy or colonoscopy), national health insurance, and treatment year. Age was categorized into five groups: <50, 50–59, 60–69, 70–79, and ≥80 years. We investigated comorbidities defined in the Charlson comorbidity index, CHA_2DS_2-VaSc score, and HAS-BLED score; their definitions in the ICD-10 codes are presented in Supplemental Table 1 [23, 24]. These background characteristics were adjusted for in the subsequent analyses.

Statistical analysis

We conducted two propensity score analyses to compare the DOAC and control groups [25]. We calculated the propensity score with a logistic regression model using the aforementioned background characteristics.

First, we conducted a 1:4 propensity score matching analysis. Each patient in the DOAC group was matched with four patients in the control group with the closest estimated propensi-

ty score within a caliper (≤ 0.2 of the pooled standard deviation of estimated logits) using the nearest-neighbor method with replacement. We calculated the C-statistic using the area under the receiver operating characteristic curve to evaluate the ability of the model to predict medication. We also calculated standardized differences to examine the balance in the baseline variables of patients between the two groups in all patients and the 1:4 propensity score-matched pair cohort. A standardized difference of 10 % denoted a negligible difference between the two groups [26].

Second, we also conducted overlap propensity score weighting analysis, which is an extension of the propensity score method to balance covariates between the two groups [27–30]. Each patient was weighted by the probability (i. e., propensity score) of that patient being assigned to the opposite group. This method minimizes the asymptotic variance of the nonparametric estimate of the weighted average treatment effect within the class of balancing weights and yields an exact balance between groups regarding the means of each covariate included in the model [29]. The resulting population weighted by this method mimics randomized trials without excluding study participants from the available sample [28].

We used a generalized linear model to calculate the odds ratio of outcomes in the DOAC group with reference to the control group in the all-patient cohort without adjustment, in the 1:4 propensity score-matched cohort, and in the overlap propensity score-weighted cohort. All tests of hypotheses had a two-sided significance level of 0.05. All statistical analyses were conducted using Stata/MP 16.0 (StataCorp, College Station, Texas, United States).

We also described the number of outcomes stratified by treatment year in the 1:4 propensity score-matched patients.

Results

A total of 156,813 patients underwent gastrointestinal endoscopic biopsies between April 2015 and November 2020. We excluded 24,777 patients who fulfilled the following exclusion criteria: (1) 2,714 patients underwent other endoscopic procedures; (2) 47 patients underwent procedures for the bile duct or pancreas; (3) 1,088 patients received warfarin within 6 months preceding the biopsy; and (4) 20,928 patients obtained insurance within 6 months preceding the biopsy. Of the 132,036 eligible patients, the DOAC group comprised 2,679 patients, and the control group comprised 129,357 patients.

▶ **Table 1** shows the baseline characteristics of all patients and the propensity score-matched patients in the main analysis. Before matching, the DOAC group was more likely to be older, have comorbidities, and receive antiplatelet drugs than the control group. After propensity score matching, the DOAC group comprised 2,677 patients, and the control group comprised 10,706 patients. The background characteristics did not differ between the matched DOAC and control groups. The C-statistic was 0.88. The overlap propensity score-weighted patients exhibited an exact match regarding the background characteristics between the two groups (Supplemental Table 2).

▶ **Table 2** shows a comparison of outcomes between the two groups. Post-procedure hemorrhage occurred in 0.44 %, gastrointestinal bleeding in 0.68 %, and stroke in 0.01 % of all patients. On the day of biopsy without a bleeding diagnosis, thrombin was used in 1.3 % of all patients. The number of outcomes stratified by treatment year is shown in Supplemental Table 3.

The results of the generalized linear model are shown in ▶ **Fig. 1** and ▶ **Table 3**. The DOAC group showed higher occurrence for all outcomes in the unadjusted models. However, in the propensity score-adjusted models, there were no significant differences for post-procedure hemorrhage (odds ratio, 1.52 [95 % confidence interval, 0.96–2.41] in the 1:4 propensity score matching model; and 1.39 [0.89–2.16] in the overlap propensity score weighting model), gastrointestinal bleeding (1.26 [0.91–1.77] and 1.14 [0.82–1.57], respectively), or stroke. Thrombin use and transfusion with a bleeding diagnosis demonstrated similar tendencies. Thrombin was significantly more often used on the day of biopsy without bleeding diagnoses in the DOAC group than in the control group (1.60 [1.30–1.95] and 1.74 [1.43–2.13], respectively).

Discussion

We compared the complications following gastrointestinal endoscopic biopsy between patients with and without DOAC treatment using a Japanese nationwide database. The propensity score analyses revealed no significant differences in the occurrence of post-procedure hemorrhage and stroke between the two groups. Endoscopic biopsies generally would be performed in the current Japanese population without DOAC withdrawal in the current Japanese cohort, and these results suggest that endoscopic biopsy is indeed safe without the need for DOAC withdrawal.

Several guidelines have addressed endoscopic procedures during anticoagulant treatment due to the widespread use of anticoagulants such as warfarin and DOACs [16–20]. Although all guidelines recommend DOAC cessation for high-risk procedures such as endoscopic submucosal dissection, the recommendation for mucosal biopsy has been inconsistent. Because bleeding complications after biopsy are rare (0.002 %-0.37 % in the general population [31–33]), previous studies have not evaluated sufficient case numbers to make firm conclusions regarding the effect of anticoagulants on complications [9, 14, 15]. Moreover, anticoagulant management must always balance risks (i. e., hemorrhage resulting from the procedure versus thrombosis if antithrombotic medication is discontinued or modified); therefore, the occurrence of stroke following the procedure should be assessed [13]. To our knowledge, the current study is the first to analyze the association between DOAC use and the occurrence of hemorrhage as well as stroke following endoscopic biopsy, using a large-scale database.

Previous studies have reported that patients taking DOACs had several comorbidities other than atrial fibrillation and history of stroke and venous thromboembolism [11, 12, 34, 35]. Actually, the DOAC group exhibited higher proportions of most comorbidities and included a larger number of patients

▶ **Table 1** Comparison of baseline characteristics between patients treated with direct oral anticoagulants and those without anticoagulant administration.

	All patients					1:4 PS matched-pair patients				
	DOAC		Control		ASD[1]	DOAC		Control		ASD[1]
Baseline characteristics	**n = 2,679**		**n = 129,357**		**(%)**	**n = 2,679**		**n = 10,714**		**(%)**
Female sex	854	(32)	57,854	(45)	26.7	854	(32)	3,644	(34)	4.5
Age, years										
▪ <50	37	(1.4)	30,013	(23)	70.5	37	(1.4)	72	(0.7)	7.0
▪ 50–59	132	(4.9)	24,530	(19)	44.3	132	(4.9)	526	(4.9)	0.1
▪ 60–69	620	(23)	38,375	(30)	14.8	620	(23)	2,435	(23)	1.0
▪ 70–79	1,065	(40)	26,466	(20)	43.0	1,065	(40)	4,227	(39)	0.6
▪ ≥80	825	(31)	9,973	(7.7)	61.2	825	(31)	3,454	(32)	3.1
Gastrointestinal malignancy										
▪ Upper tract	395	(15)	7,753	(6.0)	29.0	395	(15)	1,526	(14)	1.4
▪ Lower tract	159	(5.9)	3,689	(2.9)	15.1	159	(5.9)	615	(5.7)	0.8
Charlson comorbidities										
▪ Cerebrovascular disease	898	(34)	12,904	(10)	59.5	898	(34)	3,726	(35)	2.7
▪ Chronic pulmonary disease	737	(28)	22,058	(17)	25.3	737	(28)	3,003	(28)	1.2
▪ Congestive heart failure	1,438	(54)	9,053	(7.0)	117.9	1,438	(54)	5,737	(54)	0.3
▪ Dementia	164	(6.1)	1,819	(1.4)	25.0	164	(6.1)	699	(6.5)	1.7
▪ Diabetes without chronic complication	202	(7.5)	3,435	(2.7)	22.3	202	(7.5)	768	(7.2)	1.4
▪ Diabetes with chronic complication	255	(9.5)	6,478	(5.0)	17.4	255	(9.5)	1,051	(9.8)	1.0
▪ Hemiplegia/paraplegia	53	(2.0)	687	(0.5)	13.0	53	(2.0)	210	(2.0)	0.1
▪ Liver disease, mild	802	(30)	26,545	(21)	21.8	802	(30)	3,261	(30)	1.1
▪ Liver disease, moderate or severe	21	(0.8)	790	(0.6)	2.1	21	(0.8)	104	(1.0)	2.0
▪ Malignancy (non-GI)	1,076	(40)	27,973	(22)	41.0	251	(9.4)	966	(9.0)	1.2
▪ Metastatic solid tumor	133	(5.0)	3,311	(2.6)	12.7	133	(5.0)	533	(5.0)	0.0
▪ Myocardial infarction	103	(3.8)	1,336	(1.0)	18.3	103	(3.8)	416	(3.9)	0.2
▪ Peptic ulcer disease	858	(32)	40,449	(31)	1.6	858	(32)	3,367	(31)	1.3
▪ Peripheral vascular disease	462	(17)	10,387	(8.0)	28.0	462	(17)	1,903	(18)	1.4
▪ Renal disease	271	(10)	4,236	(3.3)	27.6	271	(10)	1,116	(10)	1.0
▪ Rheumatic disease	152	(5.7)	3,297	(2.5)	15.8	152	(5.7)	660	(6.2)	2.1
Other comorbidities										
▪ Alcohol abuse	67	(2.5)	1,978	(1.5)	6.9	67	(2.5)	258	(2.4)	0.6
▪ Altered kidney function	272	(10)	4,342	(3.4)	27.3	272	(10)	1,096	(10)	0.3
▪ Altered liver function	801	(30)	26,384	(20)	22.0	801	(30)	3,245	(30)	0.8
▪ Bleeding predisposition	2,356	(88)	92,049	(71)	42.5	2,356	(88)	9,476	(88)	1.6
▪ Hypertension	2,147	(80)	49,811	(39)	93.6	2,147	(80)	8,890	(83)	7.3
▪ Stroke/TIA/embolism	493	(18)	3,809	(2.9)	51.7	493	(18)	2,018	(19)	1.1
▪ Vascular disease	466	(17)	9,490	(7.3)	30.9	466	(17)	1,894	(18)	0.7
Concomitant medication										
▪ Antiplatelet medication	482	(18)	10,824	(8.4)	28.7	482	(18)	2,251	(21)	7.6

▶ **Table 1** (Continuation)

	All patients					1:4 PS matched-pair patients				
	DOAC		Control		ASD[1]	DOAC		Control		ASD[1]
Baseline characteristics	n = 2,679		n = 129,357		(%)	n = 2,679		n = 10,714		(%)
▪ Histamine 2-receptor antagonist	188	(7.0)	7,602	(5.9)	4.6	188	(7.0)	781	(7.3)	1.1
▪ Proton pump inhibitor	998	(37)	20,661	(16)	49.6	998	(37)	3,876	(36)	2.2
Endoscopy type										
▪ Esophagogastroduodenoscopy	2,331	(87)	110,805	(86)	3.9	2,331	(87)	9,365	(87)	1.2
▪ Colonoscopy	770	(29)	34,780	(27)	4.1	770	(29)	3,029	(28)	1.0
National insurance user	906	(34)	46,396	(36)	4.3	906	(34)	3,674	(34)	1.0
Treatment year										
▪ 2015	23	(0.9)	5,089	(3.9)	20.2	23	(0.9)	109	(1.0)	1.6
▪ 2016	111	(4.1)	17,371	(13)	33.3	111	(4.1)	395	(3.7)	2.4
▪ 2017	151	(5.6)	17,888	(14)	27.9	151	(5.6)	582	(5.4)	0.9
▪ 2018	274	(10)	21,779	(17)	19.4	274	(10)	1,126	(11)	0.9
▪ 2019	1,142	(43)	38,796	(30)	26.5	1,142	(43)	4,544	(42)	0.4
▪ 2020	978	(37)	28,434	(22)	32.3	978	(37)	3,958	(37)	0.9

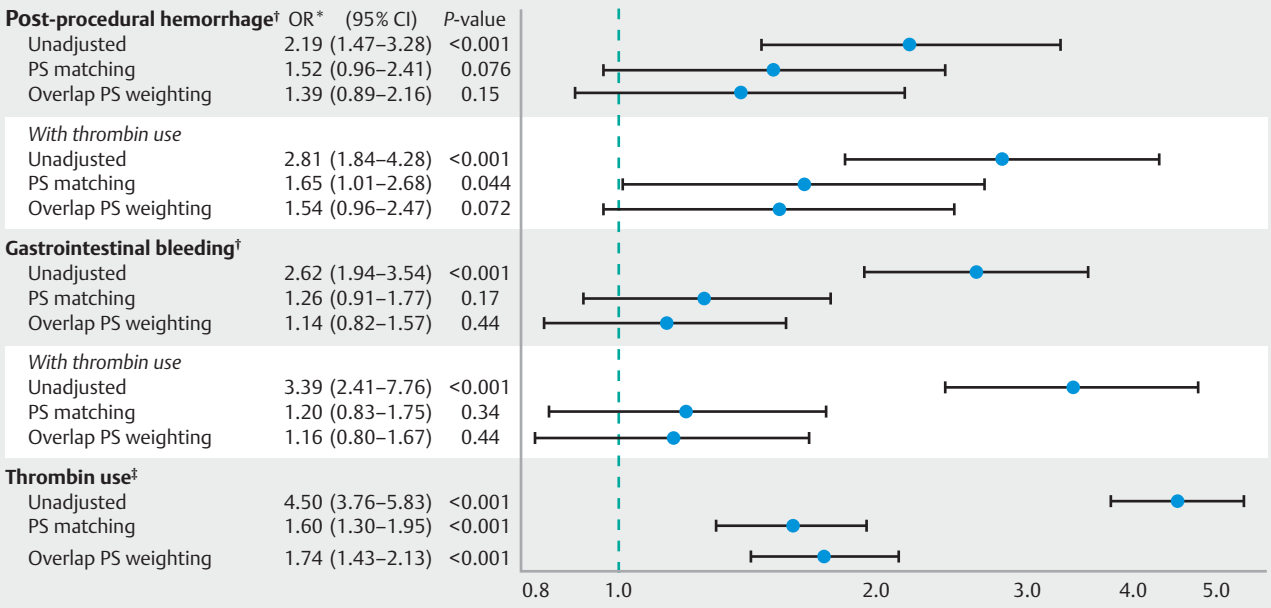
Data are presented as n (%).
PS, propensity score; DOAC, direct oral anticoagulants; ASD, absolute standardized difference; TIA, transient ischemic attack.
[1] An ASD ≤ 10 % denotes a negligible difference between the two groups.

▶ **Table 2** Comparison of outcomes between patients treated with direct oral anticoagulants and those without anticoagulant administration.

	All patients				1:4 PS matched-pair patients				Overlap PS-weighted patients	
	DOAC		Control		DOAC		Control		DOAC	Control
	n = 2,679		n = 129,357		n = 2,679		n = 10,714			
Post-procedure hemorrhage[1]	25	(0.93)	553	(0.43)	25	(0.93)	66	(0.62)	(0.93)	(0.67)
▪ With thrombin use	23	(0.86)	398	(0.31)	23	(0.86)	56	(0.52)	(0.85)	(0.56)
▪ With blood transfusion	1	(0.04)	2	(0.00)	1	(0.04)	1	(0.01)	(0.04)	(0.01)
Gastrointestinal bleeding[1]	46	(1.72)	856	(0.66)	46	(1.72)	146	(1.36)	(1.60)	(1.41)
▪ With thrombin use	35	(1.31)	518	(0.40)	36	(1.34)	120	(1.12)	(1.26)	(1.10)
▪ With blood transfusion	4	(0.15)	37	(0.03)	4	(0.15)	23	(0.21)	(0.14)	(0.16)
Thrombin use[2]	137	(5.1)	1532	(1.2)	137	(5.1)	350	(3.3)	(4.8)	(2.8)
Stroke[1]	2	(0.07)	11	(0.01)	2	(0.07)	8	(0.07)	(0.08)	(0.08)

Data are presented as n (%).
PS, propensity score; DOAC, direct oral anticoagulant.
[1] Within 1 week after biopsy.
[2] On the day of biopsy without diagnoses of post-procedure hemorrhage or gastrointestinal bleeding.

>70 years of age than the control group. Such differences would explain a relatively higher occurrence of complications in the DOAC group of the unadjusted all-patient cohort. A Japanese prospective survey reported similar proportions to the current results (0.81 % in patients with antithrombic medications and 0.37 % in those without) [33]. In particular, the significantly higher occurrence of stroke in the DOAC group than in the control group is understandable because the DOAC group was likely to have factors included in the CHA_2DS_2-VaSc score, a risk score for predicting stroke [36, 37]. Clinicians performing endoscopy should be aware that patients taking DOACs are generally more prone to stroke than patients not taking anticoagulants. Additionally, unnecessary withdrawal of DOACs might increase the risk of stroke in such patients.



▶ **Fig. 1** Propensity score analysis of direct oral anticoagulants on outcomes. OR, odds ratio; CI, confidence interval; PS, propensity score. * Odds ratio with reference to the control group. †Within 1 week after biopsy; ‡On the day of biopsy without diagnoses of post-procedure hemorrhage or gastrointestinal bleeding.

▶ **Table 3** Results of propensity score analysis of direct oral anticoagulants on rare outcomes.

	Unadjusted			1:4 PS matching			Overlap PS weighting		
	OR[1]	95% CI	P-value	OR*	95% CI	*P* value	OR[1]	95% CI	P value
Post-procedure hemorrhage[2]									
With blood transfusion	24.2	2.19–266	0.009	4.00	0.25–64.0	0.33	6.29	0.51–77.2	0.15
Gastrointestinal bleeding[2]									
With blood transfusion	5.22	1.86–14.7	0.002	0.70	0.24–2.01	0.50	0.89	0.29–2.75	0.84
Stroke[2]	8.79	1.95–39.7	0.005	1.00	0.21–4.71	0.99	1.10	0.23–5.32	0.90

PS, propensity score; OR, odds ratio; CI, confidence interval.
[1] Odds ratios with reference to the control group.
[2] Within 1 week after the biopsy.

However, analyses with propensity score adjustment for background characteristics revealed that endoscopic biopsy was performed safely in patients who received DOACs, with similar outcomes to those not taking anticoagulants. Because endoscopic biopsies would be generally performed without DOAC withdrawal in Japan based on a Japanese guideline [14–16, 20], the current results support Asian and American guidelines that recommend biopsy without DOAC withdrawal [16–18]. Moreover, overlap propensity score weighting analysis shows the average effect of moving an entire population from untreated to treated [29]. The current results that show no significant differences in the overlap propensity score weighting analysis indicate that DOAC medication does not affect complications regardless of comorbidities in low-risk procedures like endoscopic biopsy, unlike high-risk procedures like submucosal dissection [38, 39].

Thrombin use without a bleeding diagnosis was observed significantly more often in the DOAC group than in the control group. We presume that the thrombin was used for hemostasis immediately after a biopsy, and lesions of the DOAC group would have presumably bled more. Indeed, the Japanese guidelines recommend confirming hemostasis at the end of endoscopy in anticoagulant users [20]. In a study involving 112 patients who underwent endoscopic biopsy, three patients required more than 7 minutes to achieve hemostasis, although none developed gastrointestinal bleeding 2 weeks after the biopsy [14]. Careful observation and hemostasis in the DOAC group may have prevented post-procedure hemorrhage and gastrointestinal bleeding.

Because diagnoses recorded within an administrative database can be inaccurate, we investigated the outcomes that were defined by a combination of diagnosis and procedure (e. g., thrombin use and transfusion). Such definitions that combine diagnosis and procedure are generally considered to convey high validity in research using an administrative database [40]. These outcomes demonstrated similar results to the primary outcomes; therefore, we consider that the current results are robust.

In the current study, we were unable to obtain information regarding whether patients actually continued DOAC medication on the day of the biopsy. As such, the effects of DOAC administration on post-procedure hemorrhage might have been underestimated. However, the recent Japanese guidelines published in 2018 clearly outlined how to avoid DOAC withdrawal and peak blood concentration (for example, performing a biopsy in the morning before the morning dose or in the afternoon, hours after the morning dose). This was in addition to the first guideline published in 2012 [16, 20] with similar recommendations. Thus, we believe that clinicians would not have directed patients to discontinue DOAC therapy prior to endoscopy. Indeed, a previous Japanese multicenter study reported that 277 biopsies were conducted without the withdrawal of DOACs [15]. Moreover, in the DOAC group, more thrombin would have been used for easily-bleeding lesions during biopsy presumably due to the continuation of DOACs. The current results, based on a nationwide database, demonstrated that in Japanese real-world clinical practice, where patients on DOAC therapy did not withhold therapy prior to the procedure, they underwent endoscopic biopsy generally as safely as patients not taking anticoagulants. Thus, we consider that the current results imply that endoscopic biopsy can be safely performed without DOAC withdrawal.

Biopsy without the withdrawal of DOACs can reduce the burden on patients and physicians. If DOACs must be withdrawn before biopsy, patients taking DOACs cannot immediately undergo biopsy when a lesion is detected by endoscopy. Repeated endoscopy for a biopsy would be burdensome for both patients and physicians, particularly in colonoscopy [41]. The current study indicates that endoscopic biopsy without withdrawal of DOACs is acceptable, and repeated endoscopy for the purpose of biopsy only in patients taking DOACs is unnecessary.

This study had several limitations. First, since the current study was a retrospective administrative database study, information regarding whether patients actually continued DOAC medication on the day of the biopsy was unavailable, as stated above. Because the number of cases before 2017 was small (as shown in Supplemental Table 3), we were also unable to observe any impact of the issuing of the guidelines that recommend DOAC continuation. To accurately investigate whether non-withdrawal of DOACs increased the risk of bleeding, we would like to conduct future research comparing the outcomes with and without withholding doses in DOAC users, if there should be large-scale real-world data containing information regarding skipped doses. Second, the database did not contain information on hemorrhage during endoscopy. We considered thrombin use on the day of biopsy without a bleeding diagnosis as a proxy for hemorrhage occurring immediately after biopsy during endoscopy. Third, we were unable to obtain information on the number of biopsies performed, which could have affected the outcomes. However, because the Japanese guidelines recommend minimizing the number of biopsies in anticoagulant users [20], the number of biopsies as well as thrombin use during a biopsy are intermediate factors (i. e., a factor that can be affected by an exposure [DOAC use]). Therefore, the number of biopsies should not be adjusted in the analysis to overadjustment, since the adjustment with an intermediate factor will usually bias results toward the null [42].

Conclusions

In conclusion, complications after gastrointestinal endoscopic biopsy were rare, and DOAC administration was not associated with complications such as bleeding and stroke in a large-scale cohort. Endoscopic biopsy would be generally performed without DOAC withdrawal in Japan as recommended by the Asian and American guidelines; the current analysis suggests that endoscopic biopsy can be safely performed without DOAC withdrawal although the necessity for careful hemostasis remains.

Competing interests

The authors declare that they have no conflict of interest.

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