


 **Original Article** 

# Use of Direct Oral Anticoagulation for Isolated Distal Deep Vein Thrombosis in Japanese Orthopedic Patients

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**Objectives:** Although direct oral anticoagulants (DOAC) have become widely used, little is known about the efficacy of DOAC for isolated distal deep vein thrombosis (DVT).

**Methods:** In-hospitalized orthopedic patients with isolated distal DVT who were diagnosed from 2016 to 2018 were enrolled and were followed for 1 year. Embolic events included symptomatic pulmonary embolism (PE) and DVT extension above the knee. Bleeding events were determined in the presence of bleeding academic research consortium (BARC) 2, 3 or 5 bleeding.


**Results:** Of 196 orthopedic patients, 84% of patients (n = 164) received DOAC (DOAC+ group), whereas 16% of patients (n = 32) did not (DOAC– group). Cumulative incidence of embolic events was observed in 1.5% of the DOAC+ group and none of the DOAC– group (p = 0.443). Cumulative incidence of bleeding events was observed in 5.1% of the DOAC+ group and none of the DOAC– group (p = 0.157). The majority of bleeding events (80%) occurred in patients with HAS-BLED scores of 3 or greater.

**Conclusions:** There were no significant differences in embolic events and bleeding events in retrospective data. Balancing thrombotic risk and bleeding risk remains to be key for isolated distal DVT.

**Keywords:** isolated distal deep vein thrombosis, anticoagulant therapy, direct oral anticoagulants, orthopedic patients

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## Introduction

Anticoagulant therapy for isolated distal deep vein thrombosis (DVT) has not been frequently recommended owing to its potential to increase bleeding events in patients who rarely deteriorate.<sup>1)</sup> However, isolated distal DVT could be a potential embolic source that causes significant pulmonary embolism (PE),<sup>2)</sup> and anticoagulant therapy has also been reported to be effective in DVT exacerbation and recurrence.<sup>3)</sup>

A previous randomized, double-blind, placebo-controlled trial (CACTUS) enrolled low-risk outpatients without cancer or previous venous thromboembolic disease with a first acute symptomatic DVT in the calf (n = 259) and assigned (1:1) patients to receive either the low-molecular-weight heparin nadroparin or placebo for 6 weeks. In their study, PE or extension of calf DVT developed in 3% in the nadroparin group and 5% in the placebo group, respectively (p = 0.54), whereas bleeding occurred in 4% in the nadroparin group and no patients in the placebo group, respectively (p = 0.03).<sup>1)</sup> Therefore, direct oral anticoagulants (DOAC) for calf DVT is not recommended recently. Moreover, distal DVT has a lower relapse rate than central DVT.<sup>4)</sup>

The emergence of DOAC has markedly changed our daily practice, replacing warfarin, which had been the golden standard for most oral anticoagulation therapies.<sup>5)</sup> All clinical studies comparing DOAC and warfarin for proximal DVT have shown the equivalent efficacy for embolic events but significantly fewer bleeding events in DOAC.<sup>6–10)</sup> Furthermore, food control and close monitoring are not necessary in DOAC, which is beneficial for both patients and physicians.<sup>11)</sup> Data from an atrial fibrillation (AF) study showed that the rate of patients receiving any type of oral anticoagulant (OAC) significantly increased from 53% to 70% in the last decade.<sup>5)</sup> Therefore, it is quite natural that some physicians are beginning to use DOAC even for isolated DVT. However, to date, clear evidence showing the significance of DOAC for distal DVT is not available.

The American College of Chest Physicians (ACCP) guidelines recommend that patients with low-risk distal DVT are not encouraged to take anticoagulant therapy.<sup>12)</sup> Only central extension cases or high-risk patients are recommended for anticoagulant therapy, with follow-up ultrasonography at 7–14 days.<sup>12)</sup> Japanese guidelines basically follow this strategy. (Japanese Guideline for Prevention of Venous Thromboembolism [revised edition in 2017]). However, an Asian paradox states that patients from Asia tend to experience more bleeding risk rather than embolic risk.<sup>13)</sup> Accordingly, real-world Japanese data in this category are lacking and needed.

This study aims to evaluate the use of DOAC in daily practice and to assess the efficacy and bleeding risk of DOAC in Japanese orthopedic patients with isolated distal DVT.

## Materials and Methods

We retrospectively enrolled consecutive orthopedic patients with isolated distal DVT from January 2016 to December 2018. We excluded patients younger than 20 years of age, hemodialysis patients, patients with active cancer, distal DVT associated with a popliteal or more proximal DVT, or clinically suspected PE. We also excluded patients on heparin only and on warfarin. The diagnosis of DVT was established using ultrasonography or enhanced computed tomography (CT). D-dimer was routinely checked in these patients by an orthopedic surgeon. Even if they were asymptomatic, echo or CT was performed aggressively in patients with elevated D-dimer before or after surgery or those who require long-term rest. Not only symptomatic DVT but also non-symptomatic DVT was included. Each orthopedic physician decided on the indication of DOAC and implementation of follow-up. We defined as DOAC+ group which received DOAC, and the DOAC– group which did not receive DOAC.

Hypertension was defined as blood pressure  $\geq 140/90$  mmHg or the use of anti-hypertensive drugs. Dyslipidemia was defined as a low-density lipoprotein cholesterol level of  $\geq 140$  mg/dl, high-density cholesterol level of  $\leq 40$  mg/dl, triglyceride level of  $\geq 150$  mg/dl, or the use of lipid-lowering medications. Diabetes was defined as fasting plasma glucose level of  $\geq 126$  mg/dl, casual glucose level of  $\geq 200$  mg/dl, 2-hour level of  $\geq 200$  mg/dl, hemoglobinA1c  $\geq 6.5\%$ , or the use of medications for diabetes. Chronic heart failure (CHF) was defined as a history of heart failure or diuretic medication use. Ischemic heart disease (IHD) was defined as receiving percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).

HAS-BLED was defined as the sum of 1 point for hypertension (uncontrolled, systolic blood pressure  $>160$  mmHg), 1 point for the presence of renal or liver impairment (maximum of 2 points), 1 point for stroke

(previous history, particularly lacunar), 1 point for bleeding history or predisposition (anemia), 1 point for labile international normalized ratio (INR) (e.g., therapeutic time in range  $<60\%$ ), 1 point for elderly ( $>65$  years), 1 point for drug (e.g., antiplatelet agents and nonsteroidal anti-inflammatory drugs), and 1 point for alcohol excess.<sup>14)</sup>

Embolic events were defined as symptomatic PE or symptomatic DVT extension above the knee. The diagnosis was established using ultrasonography or CT. Bleeding events were defined as bleeding academic research consortium (BARC) 2 (an actionable sign of hemorrhage that requires nonsurgical, medical intervention by a healthcare professional, leading to hospitalization or increased level of care, or prompting evaluation), or BARC 3 (any transfusion with overt bleeding, bleeding requiring surgical intervention for control, bleeding requiring intravenous vasoactive agents, or intracranial hemorrhage), or BARC 5 (fatal bleeding).<sup>15)</sup> These data were followed for 1 year.

The normality of data was evaluated using the Shapiro–Wilk test. Continuous variables were expressed as the means  $\pm$  standard deviations or the median value (25th–75th percentiles) as appropriate unless specified. Categorical variables were expressed as numbers (percentages). Comparisons of continuous variables with normal distribution were evaluated using Student's t-test. Comparisons of continuous variables with non-normal distribution were examined using the Wilcoxon test. Categorical variables were analyzed using the chi-squared test or Fisher's exact test, as appropriate. Statistical analyses were performed using JMP 16 (SAS Institute, Cary, NC, USA). P-values of  $<0.05$  were considered statistically significant. The Institutional Review Board of Showa University Fujigaoka Hospital approved this study (F2017C28).

## Results

A total of 196 patients including 164 patients with DOAC and 32 patients without DOAC were analyzed. The baseline clinical characteristics of the participants are presented in **Table 1**. The mean age of the participants was 75 years, and 85.2% were females. There were no significant differences in lifestyle-related diseases including hypertension, dyslipidemia, and diabetes. No significant differences were found in the history of venous thromboembolism or heart disease. There were no significant differences in creatinine, hemoglobin (Hb), or D-dimer levels. The use of oral steroid therapy and antiplatelet drugs did not differ between the groups. The majority of distal DVT patients, except a few of them (4.1%), did not have DVT-related symptoms. In terms of DOAC selection, edoxaban was the most frequently selected DOAC (90.2%, 148 of 164 patients) followed by apixaban (7.3%, 12 of 164 patients) and rivaroxaban (2.4%, 4 of 164 patients). The loading

**Table 1** Baseline clinical characteristics

	Overall (N = 196)	DOAC+ (N = 164)	DOAC- (N = 32)	P value
Age, years	75 (69–82)	74 (73–76)	68 (56–80)	0.591
Female sex, n (%)	167 (85.2%)	145 (88.4%)	22 (68.8%)	0.008
Body mass index	23.7 (21.5–26.3)	24.4 (23.6–25.1)	24.4 (21.4–27.3)	0.697
Hypertension, n (%)	112 (57.1%)	94 (57.3%)	18 (56.3%)	0.531
Hyperlipidemia, n (%)	59 (30.1%)	48 (29.3%)	11 (34.4%)	0.674
Diabetes, n (%)	32 (16.3%)	25 (15.2%)	7 (21.9%)	0.431
Stroke, n (%)	13 (6.6%)	8 (4.9%)	5 (15.6%)	0.042
Previous history of DVT, n (%)	5 (2.6%)	5 (3.1%)	0 (0%)	0.406
Chronic heart failure, n (%)	21 (10.7%)	19 (11.6%)	2 (6.3%)	0.537
Ischemic heart disease, n (%)	15 (7.7%)	11 (6.7%)	4 (12.5%)	0.275
Atrial fibrillation, n (%)	14 (7.1%)	9 (7.9%)	5 (7.7%)	0.675
Hb (g/dl)	11.0 (9.4–12.1)	10.2 (9.9–10.5)	11.2 (9.9–12.6)	0.055
Plt ( $\times 10^4/\text{mm}^3$ )	22.3 (18.5–28.4)	23.4 (22.2–24.6)	26.1 (23.1–29.1)	0.058
D-dimmer ( $\mu\text{g/ml}$ )	5.4 (2.8–10.0)	7.6 (6.5–8.7)	6.3 (4.5–7.9)	0.917
Cre (mg/dl)	0.59 (0.50–0.71)	0.58 (0.55–0.61)	0.84 (0.42–1.25)	0.106
Use of oral antiplatelet drug, n (%)	31 (15.8%)	24 (14.6%)	7 (21.9%)	0.298
Use of oral steroid therapy, n (%)	15 (7.7%)	12 (7.3%)	3 (9.4%)	0.716
DVT-related symptom, n (%)	8 (4.1%)	7 (4.3%)	1 (3.1%)	0.767
HAS-BLED score	1.7 (1.6–1.9)	1.8 (0.1–1.6)	1.5 (0.2–1.1)	0.227

DOAC: direct oral anticoagulant; DVT: distal deep vein thrombosis; Hb: hemoglobin; Plt: platelet; Cre: creatinine

**Table 2** The underlying orthopedic disease

	Overall (N = 196)	DOAC+ (N = 164)	DOAC- (N = 32)	P value
With orthopedic surgery, n (%)	127 (64.8%)	114 (69.5%)	13 (40.6%)	0.002
Fracture, n (%)	8 (4.1%)	7 (4.3%)	1 (3.1%)	0.767
Arthritis, n (%)	119 (60.7%)	107 (65.2%)	12 (37.5%)	0.005
Without orthopedic surgery, n (%)	69 (35.2%)	50 (30.5%)	19 (59.4%)	0.002
Fracture, n (%)	16 (8.2%)	6 (3.7%)	10 (31.3%)	<0.001
Arthritis, n (%)	53 (27.0%)	44 (26.8%)	9 (28.1%)	0.666

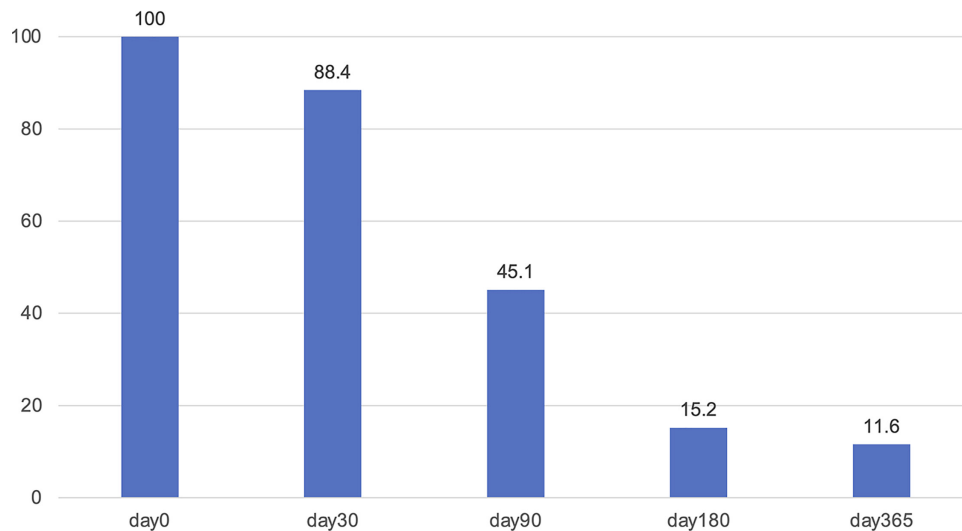
DOAC: direct oral anticoagulant

dose for DVT was not used in this study population. For patients prescribed edoxaban, a reduced dose (30 mg) was frequently used (67.4%). For patients prescribed apixaban and rivaroxaban, standard maintenance dose for Japanese (10mg for apixaban and 15mg for rivaroxaban) was mostly used (83.3% for apixaban and 100% for rivaroxaban).

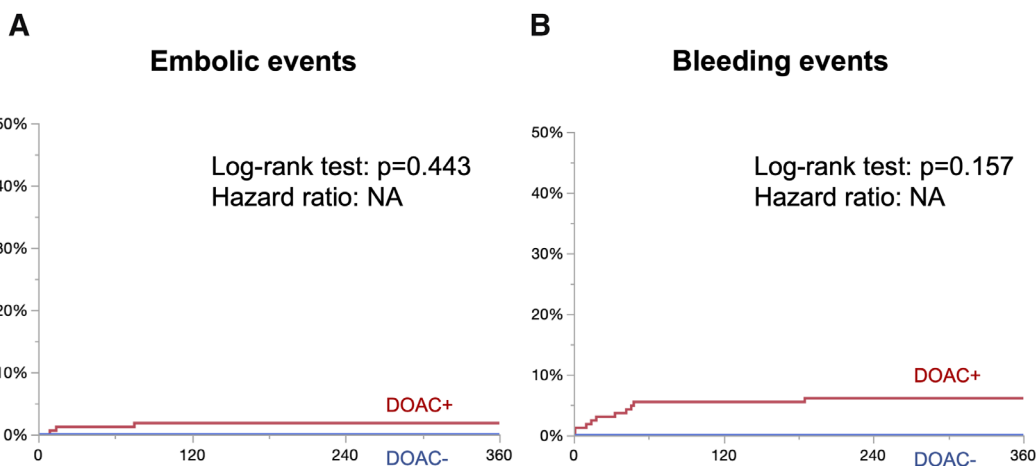
The underlying orthopedic diseases are shown in **Table 2**. All the DVT with orthopedic surgery occurred after the operations. DVT after orthopedic surgery was observed in 64.8% of the study population, whereas DVT without surgery was observed in 35.2% of the study population. The majority of the patients who underwent orthopedics extremity surgery received DOAC (89.0%, 113 of 127 patients). On the other hand, patients with fractures who did not undergo surgery did not receive DOAC (62.5%, 10 of 16 patients). Each orthopedic physician tended to discontinue DOAC when patients began to be physically active (**Fig. 1**).

Cumulative incidence of embolic events and bleeding events are shown in **Figs. 2A** and **2B**. A tiny proportion of patients developed embolic events in the DOAC+ group, whereas no patients developed embolic events in the DOAC- group (log-rank test,  $p = 0.443$ ; hazard ratio, NA) (**Fig. 2A**). Similarly, a tiny proportion of patients developed bleeding events in the DOAC+ group, whereas no patients developed bleeding events in the DOAC- group (log-rank test,  $p = 0.157$ ; hazard ratio, NA) (**Fig. 2B**). All embolic events are listed in **Supplementary Table 1**, which were all DVT extension above the knee and occurred while taking DOAC. Similarly, all bleeding events are listed in **Supplementary Table 2**, which were mostly primary disease and procedure-related and occurred while taking DOAC. Patient characteristics and HAS-BLED scores were compared between patients with bleeding and those without in the DOAC+ group (**Table 3**). In patients with bleeding events, body mass index (BMI) and hemoglobin levels

### continue rate of DOAC



**Fig. 1** Continue rates of DOAC. The continued rates of DOAC were 88.4%, 45.1%, 15.2%, and 11.6% in days 30, 90, 180, and 365, respectively. Approximately half of the patients discontinued DOACs within 90 days. DOAC: direct oral anticoagulant



**Fig. 2** Kaplan–Meier curve. **(A)** Embolic events. No significant differences in embolic events were noted between the 2 groups (log-rank test,  $p = 0.443$ ; hazard ratio, NA). **(B)** Bleeding events (BARC >2). No significant differences in bleeding events were observed between the 2 groups (log-rank test,  $p = 0.157$ ; hazard ratio, NA). DOAC: direct oral anticoagulant; BARC: bleeding academic research consortium

were significantly lower, whereas D-dimer and HAS-BLED scores were significantly greater. Patients with bleeding events mostly had >2 HAS-BLED scores and had significantly high-risk bleeding events (positive predictive value [PPV], 1/4 [85.7%]; area under the curve [AUC], 0.843).

### Discussion

The main findings of this study can be summarized as follows. DOAC was prescribed in most of the patients, accounting for 84% of our study population. No symptomatic PE

events were observed in either group. Few cases of DVT extension above the knee were observed in the DOAC+ group. Bleeding events were observed only in the DOAC+ group; however, these events were mostly primarily disease-related or procedure-related in patients with relatively high bleeding risk. A statistically significant difference was not observed between the groups in terms of embolic events and bleeding events.

Warfarin, which used to be the gold standard for anticoagulant therapy, was occasionally avoided owing to concerns about bleeding complications and the inconvenience

**Table 3** Predictors of bleeding events (only in the DOAC+ group)

	Overall (N = 164)	Bleeding event+ (N = 10)	Bleeding event- (N = 154)	P value
Age, years	74 (73–76)	76.8 (71.2–82.4)	74.8 (73.4–76.2)	0.522
Female sex, n (%)	145 (88.4%)	9 (90.0%)	136 (88.3%)	0.719
Body mass index	24.4 (23.6–25.1)	22.0 (20.5–23.6)	24.6 (24.0–25.3)	0.018
Hypertension, n (%)	94 (57.3%)	7 (70.0%)	87 (56.5%)	0.519
Hyperlipidemia, n (%)	48 (29.3%)	2 (20.0%)	46 (29.9%)	0.725
Diabetes, n (%)	25 (15.2%)	4 (40.0%)	21 (13.6%)	0.047
Stroke, n (%)	8 (4.9%)	1 (10.0%)	7 (4.6%)	0.923
Previous history of DVT, n (%)	5 (3.1%)	0 (0.0%)	5 (3.3%)	0.727
Chronic heart failure, n (%)	19 (11.6%)	0 (0.0%)	19 (12.3%)	0.607
Ischemic heart disease, n (%)	11 (6.7%)	0 (0.0%)	11 (7.1%)	0.489
Atrial fibrillation, n (%)	9 (7.9%)	0 (0.0%)	9 (5.8%)	0.427
Hb (g/dl)	10.2 (9.9–10.5)	9.6 (8.2–11.0)	10.8 (10.5–11.1)	0.036
Plt ( $\times 10^4/\text{mm}^3$ )	23.4 (22.2–24.6)	20.2 (16.3–24.1)	23.6 (22.4–24.8)	0.221
D-dimer ( $\mu\text{g/ml}$ )	7.6 (6.5–8.7)	12.8 (6.3–19.2)	7.2 (6.0–8.5)	0.007
Cre (mg/dl)	0.58 (0.55–0.61)	0.64 (0.50–0.79)	0.62 (0.59–0.66)	0.783
Use of oral antiplatelet drug, n (%)	24 (14.6%)	1 (10.0%)	23 (14.9%)	0.554
Use of oral steroid therapy, n (%)	12 (7.3%)	0 (0.0%)	12 (7.8%)	0.457
DVT-related symptom, n (%)	7 (4.3%)	1 (10.0%)	6 (3.9%)	0.362
HAS-BLED score	1.8 (0.1–1.6)	3 (2.3–3.7)	1.7 (1.6–1.8)	<0.001

In patients with bleeding events, body mass index and hemoglobin were significantly lower, whereas D-dimer and HAS-BLED scores were significantly greater.

DOAC: direct oral anticoagulant; DVT: distal deep vein thrombosis; Hb: hemoglobin; Plt: platelet; Cre: creatinine

of PT-INR adjustment.<sup>5)</sup> DOAC made this problem easier and is currently the main drug used for anticoagulant therapy. The proportion of Japanese patients on oral anticoagulants for AF was 53% in 2011, which increased to 70% in 2022.<sup>5)</sup> Similar to the situation of AF, anticoagulant therapy using DOAC became easier to introduce even for DVT. Around 2015, anticoagulant therapy using DOAC was indicated for DVT in Japan.<sup>6–10)</sup> Although a randomized placebo-controlled trial of anticoagulant therapy using DOAC for isolated distal DVT has not been conducted, DOAC can be prescribed.

The benefits of anticoagulant therapy in isolated distal DVT have been unclear.<sup>16)</sup> In 2008, the ACCP guidelines recommended a 3-month of anticoagulant therapy; however, since 2012, it has been recommended that patients with low-risk distal DVT should not take anticoagulant therapy, and only central extension cases or high-risk patients should take anticoagulant therapy, with follow-up ultrasonography at 7–14 days.<sup>12,16–18)</sup> Distal DVT is not covered by the NICE guidelines because it does not become severe.<sup>19)</sup> The CACTUS trial, which was a double-blind randomized controlled trial (RCT), reported that nadroparin was not superior to placebo in preventing the extension of calf DVT to the proximal veins, contralateral proximal DVT, and symptomatic PE, and led to significantly increased major and clinically relevant non-major bleeding events.<sup>1)</sup> These are the rationale for the current Japanese guidelines not

to uniformly administer anticoagulant therapy in patients with distal DVT. However, in our study, 84% of the orthopedic patients received DOAC. It was likely that attending physicians initiated DOAC despite the potential risk of bleeding in patients postoperatively.

Sevitt et al.<sup>20)</sup> reported from autopsy data that the most frequent site of DVT was the soleal vein. According to a study at Tottori University, distal DVT was a PE source when the isolated thrombosis of the large soleal vein was >7 mm in diameter, and the soleal vein was the most frequent and significant location of calf DVT, suggesting that these were an occasional embolic source of critical PE.<sup>2)</sup> Based on the above, to prevent PE, treating soleus DVT at its source in the first place may be imperative. Moreover, a study on anticoagulant therapy using heparin for patients with asymptomatic isolated distal DVT during hospitalization showed that the rate of DVT extension above the knee was higher in orthopedic patients, patients with malignancies, and patients with immobility, and recommended anticoagulant therapy in these patients until they are ambulatory or have a negative echo.<sup>21)</sup>

In this study, bleeding events were numerically greater in the DOAC+ group but not statistically significant. The use of anticoagulant therapy frequently comes with balancing embolic and bleeding risks.<sup>14)</sup> The HAS-BLED score assesses major bleeding events in patients with AF,



and a score of  $>3$  indicates a high bleeding risk.<sup>14</sup> Similarly, in our study, the HAS-BLED score of patients with bleeding events was significantly  $>2$  (Table 3). We may need to be more cautious when patients have a high HAS-BLED score  $>2$ .

This study had some limitations. First, each attending physician decided whether to take the DOAC and period. Significant selection bias existed in our study population. Depending on the subjectivity of the attending physician, administration, and duration of DOAC use were determined. It was likely that orthopedic physicians were motivated to administrate DOAC for patients with the operation. Second, isolated distal DVT developed few embolic and bleeding events, and it may be not easy to conclude from our study.

## Conclusion

A substantial proportion of orthopedic patients received DOAC for isolated distal DVT. Regardless of DOAC prescription, thrombotic events were very rare in this population. Although bleeding events occurred in patients receiving DOAC, these events were mostly primarily disease related and procedure related in patients with high bleeding risk. DOAC could be an option when thrombotic and bleeding risks were carefully evaluated.

## Declarations

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### Disclosure statement

All authors have no conflicts of interest to disclose.

### Author contributions

Study conception: AO, MS, and HM

Data collection: AO and MS

Analysis: AO and HM

Investigation: AO, MS, and HM

Manuscript preparation: AO and HM

Funding acquisition: HS

Critical review and revision: all authors

Final approval of the article: all authors

Accountability for all aspects of the work: all authors.

### Supplementary information

Supplementary Table 1 Embolic event cases.

Supplementary Table 2 Bleeding event cases.

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