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Ischemic stroke during anticoagulant interruption by healthcare professionals in stroke patients with atrial fibrillation

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ABSTRACT

Background: Anticoagulant therapy often requires temporary interruption. Nevertheless, the frequency and clinical characteristics of stroke patients who develop stroke during anticoagulant interruption are not fully known.

Methods: From March 2011 through May 2017, consecutive acute ischemic stroke patients with AF who were admitted to our stroke unit were retrospectively recruited. Patients who developed ischemic stroke during anticoagulant interruption were defined as those who developed ischemic stroke within 30 days from anticoagulant interruption. The frequency and clinical characteristics of patients during anticoagulant interruption were analyzed.

Results: A total of 561 patients with AF and acute ischemic stroke (237 women; median age 78 [IQR 71–85] years) were admitted during the study period. Of these, 21 (3.7%, 12 patients discontinued vitamin K antagonist [VKA] and 9 discontinued direct oral anticoagulants [DOACs]) patients were admitted during the period of anticoagulant interruption. Severity and functional outcomes in stroke patients during anticoagulant interruption were not different from those without anticoagulant treatment. The number of days between anticoagulant interruption and stroke onset was shorter in patients who discontinued DOACs (3 [3–5] days) than in those who discontinuedVKAs (10 [7–20] days, $p = .004$). The major reason for interruption was planning of invasive procedures (52%). Guideline deviations were suspected in 82% of such cases.

Conclusion: Patients developing stroke during anticoagulant interruption accounted for 3.7% of stroke patients with AF. Strokes occurred relatively early after interruption, especially in patients who discontinued DOACs. Guideline deviations was frequent.

1. Introduction

Anticoagulant therapy can effectively reduce the risk of thromboembolism in patients with atrial fibrillation (AF) [1], and anticoagulation is recommended for the majority of patients with AF [2,3]. In the clinical setting, anticoagulant therapy often requires temporary interruption, reported in up to 30% of anticoagulated patients [4], due to operations, invasive examinations, and hemorrhagic events. Appropriate anticoagulant therapy interruption strategies are particularly needed for AF patients to avoid preventable stroke, because the risk of postsurgical stroke is about twice as high in patients with than without AF [5]. However, a comprehensive approach for patients potentially needing anticoagulant therapy interruption has not been developed, e.g., who and which procedure requires discontinuation of anticoagulation, when to stop anticoagulation, and whether to bridge or not to bridge anticoagulation with heparin. Moreover, though some guidelines exist, deviations from guidelines for anticoagulant therapy interruption occur frequently [6].

Understanding the clinical characteristics of patients who actually develop ischemic strokes during anticoagulant therapy interruption is one of the bases for developing approaches for anticoagulant therapy interruption. Nevertheless, the frequency and clinical characteristics of AF patients who develop stroke during anticoagulant therapy interruption are not fully known, especially for patients treated with direct

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Table 1
Clinical background characteristics of the included patients.

Variable	Total	Interruption	On AC	p_*	No AC	$p^\dagger$
	n = 561	n = 21	n = 160		n = 380	
Female sex, n (%)	237 (42)	6 (29)	69 (43)	.244	162 (43)	.258
Age, y, median (IQR)	78 (71–85)	80 (74–86)	79 (73–85)	.690	78 (70–85)	.304
Risk factor						
Hypertension, n (%)	351 (63)	11 (52)	109 (68)	.218	231 (61)	.495
Dyslipidemia, n (%)	190 (34)	11 (52)	62 (39)	.246	117 (31)	.053
Diabetes mellitus, n (%)	95 (17)	6 (29)	33 (21)	.404	56 (15)	.114
Current smoker, n (%)	90 (16)	2 (10)	19 (12)	1.000	69 (18)	.555
Congestive heart failure, n (%)	115 (21)	7 (33)	46 (29)	.799	62 (16)	.068
Prior embolism, n (%)	138 (25)	5 (24)	69 (43)	.103	64 (17)	.381
History of vascular disease, n (%)	80 (14)	8 (38)	28 (18)	.039	44 (12)	.003
$CHADS_2$ score, median (IQR)	2 (1–3)	3 (2–3)	3 (2–4)	.235	2 (1–3)	.022
CHA_2DS_2-VASc score, median (IQR)	4 (2–5)	4 (4–5)	4 (3–6)	.367	3 (2–4)	.020
Chronic atrial fibrillation, n (%)	400 (71)	17 (81)	120 (75)	.787	263 (69)	.332
Preadmission mRS score, median (IQR)	0 (0–1)	0 (0–3)	0 (0–2)	.828	0 (0–0)	.110
Onset to arrival, h, median (IQR)	4.5 (2.0–14.0)	5.8 (3.0–16.1)	4.2 (1.6–18.8)	.277	4.4 (2.0–13.9)	.231
NIHSS score on admission, median (IQR)	9 (3 – 20)	9 (3–17)	10 (3–19)	.502	8 (3 – 21)	.533
Major artery occlusion at admission[a], n (%)	185 (33)	3 (14)	47 (29)	.197	135 (36)	.058
Reperfusion therapy, n (%)	182 (32)	7 (33)	51 (32)	1.000	124 (33)	1.000
Biochemistry results at admission, median (IQR)						
aPTT, *sec*	29.6 (26.9–33.7)	36.9 (29.1–40.3)	33.3 (29.2–38.2)	.260	28.5 (26.2–31.2)	< .001
PT-INR	1.13 (1.03–1.28)	1.26 (1.11–1.42)	1.37 (1.17–1.70)	.043	1.09 (1.01–1.16)	< .001
Blood glucose, mg/dL	120 (102–145)	119 (101–146)	120 (99–143)	.940	120 (104–148)	.770
eGFR, mL/min	61 (48–76)	60 (40–78)	59 (41–72)	.742	62 (50–77)	.639
D-dimer, μg/mL	1.4 (0.9–3.1)	2.4 (0.9–4.1)	1.3 (0.7–2.8)	.120	1.5 (0.9–3.2)	.650
Brain natriuretic peptide, pg/mL	194 (105–370)	208 (81–428)	196 (103–338)	.963	193 (108–379)	.915
Length of hospital stay, days, median (IQR)	18 (10 – 31)	15 (9–24)	17 (10–28)	.453	18 (11–34)	.194
mRS score at discharge, median (IQR)	3 (1–5)	3 (1–4)	3 (1–5)	.743	3 (1–5)	.535

AC, anticoagulant; IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; aPTT, activated partial thromboplastin time; PT-INR, prothrombin time-international normalized ratio; eGFR, estimated glomerular filtration rate.

[a] Defined as occlusion at the internal carotid artery, middle cerebral artery horizontal segment, or basilar artery.

[*] Stroke patients during anticoagulant therapy interruption vs. on anticoagulation.

[†] Stroke patients during anticoagulant therapy interruption vs. no anticoagulation.

oral anticoagulants (DOACs). The aims of the present study were to elucidate the prevalence and clinical features of AF patients who developed ischemic stroke during interruption of therapy with anticoagulants including DOACs.

2. Methods

2.1. Subjects

From March 2011 through May 2017, consecutive acute ischemic stroke patients with AF who were admitted to our stroke unit within 7 days from symptom onset were retrospectively recruited from a prospective registry [7,8]. There were no exclusion criteria in the present study. This study was approved by the institutional ethics committee. Written, informed consent was obtained from all patients or their next-of-kin.

2.2. Clinical characteristics

Clinical background characteristics, including sex, age, cardiovascular risk factors, and past medical histories, were recorded on admission. Cardiovascular risk factors were defined as: 1) hypertension, history of using antihypertensive agents, systolic blood pressure ≥ 140 mmHg, or diastolic blood pressure ≥ 90 mmHg before or ≥ 2 weeks after stroke onset; 2) diabetes mellitus, use of hypoglycemic agents, random glucose level ≥ 200 mg/dL, or glycosylated hemoglobin ≥6.5% on admission; 3) hyperlipidemia, use of antihyperlipidemic agents, or a serum total cholesterol level ≥ 220 mg/dL; and 4) current smoker. The prestroke $CHADS_2$ or CHA_2DS_2-VASc score was calculated for each patient based on the published guideline [9]. However, aortic plaque was not assessed as a component of the score. The index stroke was not counted as a “history of ischemic stroke”. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS), and functional status was evaluated with the modified Rankin scale (mRS). Routine blood biochemistry examinations were performed on admission. The site of arterial occlusion was assessed with magnetic resonance angiography on admission. Major artery occlusion was defined as internal carotid artery, middle cerebral artery horizontal segment, or basilar artery occlusion.

The medication history prior to the index stroke was obtained from prescription data that covered prescriptions from primary care sources and hospitals [7]. Anticoagulant therapy interruption was defined as discontinuing anticoagulant medications under the instruction of healthcare professionals, and patients who developed ischemic stroke during anticoagulant therapy interruption included those who developed ischemic stroke within 30 days from anticoagulant therapy interruption. Anticoagulant withdrawal due to patients' own lack of adherence was not treated as anticoagulant therapy interruption in the present study.

2.3. Statistical analysis

All included patients were divided into 3 groups based on anticoagulant status at stroke onset: the Interruption group consisted of patients who developed stroke during anticoagulant therapy interruption; the AC group consisted of patients taking any oral anticoagulant medications at stroke onset; and the No-AC group consisted of patients without preceding anticoagulant therapy for at least 30 days before stroke onset.

First, the frequency of patients in the cohort belonging to the Interruption group was evaluated. Second, clinical background characteristics were compared between the Interruption group and the AC

Table 2
Clinical characteristics of stroke patients during interruption of anticoagulant therapy: VKA vs. DOAC.

Variables	Total	VKA	DOAC	*p*
	n = 21	*n* = 12	*n* = 9	
Female sex, *n* (%)	6 (29)	2 (17)	4 (44)	.331
Age, y, median (IQR)	80 (74–86)	81 (77–85)	77 (69–88)	.702
Risk factor				
Hypertension, *n* (%)	11 (52)	8 (67)	3 (33)	.198
Dyslipidemia, *n* (%)	11 (52)	6 (50)	5 (56)	1.000
Diabetes mellitus, *n* (%)	6 (29)	3 (25)	3 (33)	1.000
Current smoker, *n* (%)	2 (10)	2 (17)	0 (0)	.486
Congestive heart failure, *n* (%)	7 (33)	4 (33)	3 (33)	1.000
Prior embolism*, *n* (%)	5 (24)	3 (25)	2 (22)	1.000
History of vascular disease**, *n* (%)	8 (38)	5 (42)	3 (33)	1.000
$CHADS_2$ score, median (IQR)	3 (2–3)	3 (1–4)	3 (2–3)	.651
CHA_2DS_2-VASc score, median (IQR)	4 (4–5)	4 (3–5)	4 (4–5)	.808
Days from AC interruption to stroke, median (IQR)	7 (3–15)	10 (7–20)	3 (3–5)	.004
Preadmission antiplatelet use, *n* (%)	1 (5)	1 (8)	0 (0)	1.000
Preadmission mRS score, median (IQR)	0 (0–3)	0 (0–3)	0 (0–2)	.808
Onset to arrival, h, median (IQR)	5.8 (3.0–16.1)	9.0 (3.1–55.3)	3.0 (2.3–11.0)	.193
NIHSS score on admission, median (IQR)	9 (3–17)	9 (2–17)	9 (5–15)	.862
Major artery occlusion at admission, *n* (%)	3 (14)	1 (8)	2 (22)	.553
Biochemistry results at admission, median (IQR)				
aPTT, *sec*	36.9 (29.1–40.3)	37.3 (30.5–40.4)	36.3 (26.1–43.6)	.382
PT-INR	1.26 (1.11–1.42)	1.30 (1.10–1.50)	1.23 (1.11–1.31)	.310
Blood glucose, mg/dL	119 (101–146)	112 (90–123)	136 (119–158)	.043
Creatinine, mg/dL	0.83 (0.70–1.22)	0.90 (0.71–1.37)	0.73 (0.66–1.01)	.148
eGFR, mL/min	60 (40–78)	62 (38–69)	58 (41–80)	.808
D-dimer, μg/mL	2.4 (0.9–4.1)	2.7 (0.7–4.3)	1.1 (0.9–2.5)	.412
Brain natriuretic peptide, pg/mL	208 (81–428)	211 (81–536)	206 (80–368)	.656
Chronic atrial fibrillation, *n* (%)	17 (81)	11 (92)	6 (67)	.272
mRS score at discharge, median (IQR)	3 (1–4)	3 (0–4)	3 (2–5)	.508

AC, anticoagulant; VKA, vitamin K antagonist; DOAC, direct oral anticoagulant; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; aPTT, activated partial thromboplastin time; PT-INR, prothrombin time-international normalized ratio; eGFR, estimated glomerular filtration rate; TIA, transient ischemic attack.

* Including ischemic stroke and systemic embolism.

** Including ischemic heart disease and peripheral artery disease.

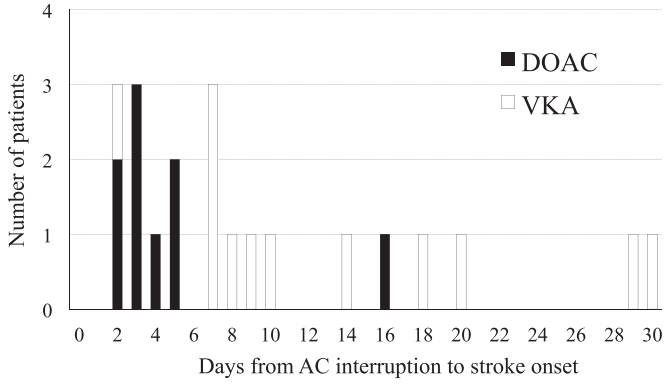

Fig. 1. The distribution of days from anticoagulant therapy interruption to stroke onset.
AC, anticoagulant; DOAC, direct oral anticoagulant; VKA, vitamin K antagonist.

or the No-AC group. Univariate analyses were performed using the chi-squared test, Fisher's exact test, and Mann-Whitney *U* test, as appropriate. Clinical characteristics were also compared between patients pretreated with a vitamin K antagonist (VKA) or DOACs in the Interruption group. Finally, the detailed features of each patient in the Interruption group, including reason for interruption and days from interruption to stroke onset, were assessed. Guideline deviations were also evaluated in patients during anticoagulant therapy interruption due to procedures. Based on the Japanese domestic guideline [10], the following 2 cases were regarded as guideline deviations in the present study: 1) anticoagulant therapy interruption for cataract surgery, tooth extraction, minor dermatologic procedures, and endoscopy (with low-risk procedures); or 2) discontinuing a VKA for > 5 days, dabigatran for > 4 days, rivaroxaban and edoxaban for > 1 day, or apixaban for > 2 days before major surgery or a high-risk procedure, and no subsequent heparin bridging. The data are presented as median values (interquartile range [IQR]) or numbers (%).

All statistical analyses were performed using PASW for Windows version 17.0 (SPSS Inc., Chicago, IL). Results were considered significant at $p < .05$.

3. Results

Overall, 561 consecutive patients with AF and acute ischemic stroke (237 women; median age 78 [IQR 71–85] years; NIHSS score 9 [3 − 20]) were admitted to our stroke center during the study period. Of these 561 patients, 21 (3.7%, 95% CI 2.2–5.3%) were in a period of anticoagulant therapy interruption (Interruption group), 160 (29%) were on anticoagulant medication (AC group), and 380 (68%) were on no anticoagulant medication (No-AC group) at stroke onset. For patients in the Interruption group ($n = 21$), the discontinued medication was a VKA in 12 (57%) patients and a DOAC in 9 (43%).

Table 1 shows the clinical background characteristics of the included patients. The proportion of patients having a history of vascular disease was higher in the Interruption group (38%) than in the AC (18%, $p = .039$) group or No-AC (12%, $p = .003$) group. The $CHADS_2$ (3 [2–3] vs. 2 [1–3], $p = .022$) and CHA_2DS_2-VASc scores (4 [4–5] vs. 3 [2–4], $p = .020$) were higher in the Interruption group than in the No-AC group. Activated partial thromboplastin time (aPTT) at admission was higher in the Interruption group (36.9 [29.1–40.3] s) than in the No-AC group (28.5 [26.2–31.2] s, $p < .001$), and the prothrombin

Table 3
Individual characteristics of stroke patients during anticoagulant therapy interruption.

Patient #	Sex	Age (y)	Reason for interruption	Heparinized	Days from interruption to stroke	Interrupted AC	Suspected guideline deviation	CHA_2DS_2-VASc score	Initial NIHSS	PT-INR on admission	mRS score at discharge
1	M	87	Change AC to DOAC	N/A	2	VKA	N/A	5	3	1.92	4
2	M	76	Poor general condition	N/A	7	VKA	N/A	3	7	1.56	0
3	M	85	High PT-INR value	N/A	7	VKA	N/A	5	1	1.47	3
4	M	73	Procedure (Lobectomy)	No	7	VKA	Yes	4	24	1.23	2
5	F	80	Procedure (Thoracic drainage)	No	8	VKA	Yes	5	18	1.04	0
6	M	63	High PT-INR value	N/A	9	VKA	N/A	1	2	1.04	0
7	M	79	Procedure (Hepatectomy)	Yes	10	VKA	No	4	2	1.42	1
8	M	80	Procedure (Hepatectomy)	No	14	VKA	Yes	2	2	1.20	4
9	M	81	Procedure (TAE)	No	18	VKA	Yes	4	10	1.31	4
10	F	89	Hemorrhage (ASDH)	N/A	20	VKA	N/A	7	18	1.51	5
11	M	85	Hemorrhage (Hematuria)	N/A	29	VKA	N/A	5	15	1.06	3
12	M	85	Hemorrhage (Alveolar)	N/A	30	VKA	N/A	4	12	1.28	4
13	M	71	Procedure (CAG)	No	2	Apixaban	Yes	3	3	1.26	2
14	M	90	Procedure (Tooth extraction)	No	2	Dabigatran	Yes	4	10	1.36	5
15	M	75	Procedure (Tooth extraction)	Yes	3	Apixaban	Yes	4	7	1.23	0
16	M	67	Procedure (Laminectomy)	No	3	Dabigatran	No	3	7	1.26	2
17	F	67	Procedure (Patella replacement)	No	3	Rivaroxaban	Yes	4	20	1.41	3
18	M	87	Hemorrhage (Gastrointestinal)	N/A	4	Rivaroxaban	N/A	4	10	1.22	4
19	F	81	Hemorrhage (Gastrointestinal)	N/A	5	Dabigatran	N/A	5	0	1.10	1
20	F	77	Procedure (ESWL)	No	5	Apixaban	Yes	6	9	1.04	6
21	F	88	Anemia (w/o apparent hemorrhage)	N/A	16	Apixaban	N/A	4	22	1.11	5

AC, anticoagulant; NIHSS, National Institutes of Health Stroke Scale; PT-INR, prothrombin time-international normalized ratio; mRS, modified Rankin Scale; DOAC, direct oral anticoagulant; VKA, vitamin K antagonist; TAE, transcatheter arterial embolization; ASDH, acute subdural hematoma; CAG, coronary angiography; ESWL, extracorporeal shock wave lithotripsy.

time-international normalized ratio (PT-INR) in the Interruption group (1.26 [1.11–1.42]) was between that of the AC (1.37 [1.17–1.70], $p = .043$) and the No-AC (1.09 [1.01–1.16], $p < .001$) groups. The NIHSS score, the rate of major artery occlusion on admission, and the mRS score at discharge were not different among the groups. In the Interruption group, the number of days between anticoagulant therapy interruption and stroke onset was shorter (3 [3–5] days vs. 10 [7–20] days, $p = .004$) and the serum glucose level on admission was higher (136 [119–158] mg/dL vs. 112 [90–123] mg/dL, $p = .043$) in patients who discontinued DOACs than in those who discontinued a VKA (Table 2 and Fig. 1).

Table 3 shows the clinical features of each case in the Interruption group. The major reasons for anticoagulant therapy interruption were planning invasive procedures (11 of 21 patients, 52%), followed by hemorrhagic events (5 patients, 24%). Two patients developed stroke during oral anticoagulant interruption and heparin bridging. For patients who discontinued anticoagulant medications due to invasive procedures, guideline deviations were suspected in 9 of 11 (82%) cases (4 with VKA and 5 with DOAC interruption). Anticoagulant therapy was restarted in the acute (< 7 days from onset) phase in all cases in the Interruption group, except for one case with parenchymal hemorrhagic transformation.

4. Discussion

The present study showed that patients developing ischemic stroke during anticoagulant therapy interruption accounted for about 4% of acute ischemic stroke and AF patients. Strokes occurred in the relatively early period (median 7 days) after interruption, especially after discontinuing DOACs (median 3 days). The major reason for interruption was planning invasive procedures, and guideline deviations were suspected in most such cases.

Patients developing ischemic stroke during anticoagulant therapy interruption accounted for 3.7% of acute stroke and AF patients. This percentage is slightly higher than that from a previous retrospective single-center study, which reported that 2.6% of stroke patients were in the period of anticoagulant therapy interruption [11]. A difference in the populations (acute stroke and AF patients in the present study and all acute stroke patients in the past study) may explain the slightly higher rate of patients in the period of anticoagulant therapy interruption in the present study. In patients with AF, strokes during anticoagulant therapy interruption accounted for about 4% of acute ischemic strokes. This is rare, but nevertheless, stroke during anticoagulant therapy interruption is a problem that needs to be solved, because, among ischemic stroke patients treated with anticoagulant medication prior to the stroke (patients belonging to the Interruption and the AC group, $n = 181$), 12% (21 of 181) developed stroke shortly after anticoagulant therapy interruption following the instructions of healthcare professionals.

Patients in the Interruption group had higher $CHADS_2$ or CHA_2DS_2-VASc scores than those in the No-AC group. Though a higher CHA_2DS_2-VASc score was reported to be associated with more severe symptoms or a higher rate of major artery occlusion in patients with stroke and AF [12], severity, rate of major artery occlusion, and functional outcomes of patients in the Interruption group were not different from those in the No-AC group. A short period from anticoagulant therapy interruption to stroke onset (median 7 days) or heparin bridging may contribute to this comparable severity or rate of major artery occlusion; the value of aPTT or PT-INR was higher in the Interruption group than in the No-AC group, and remaining anticoagulant activity after discontinuation of anticoagulant medication or bridging heparin might prevent large thrombus formation. The number of days from anticoagulant therapy interruption to stroke onset was less in patients who discontinued DOACs (median 3 days) than in those who discontinued a VKA (median 10 days). This is pharmacokinetically plausible; the anticoagulant effect of DOACs decreases more rapidly than that of a VKA [13–15].

In stroke patients whose anticoagulant therapy was interrupted due to the planning of procedures, guideline deviations were suspected in most cases. Guideline deviations were seen in both patients who discontinued a VKA and a DOAC. Although the precise reason for the high rate of guideline deviation in the present study was unclear, lack of clinical evidence in this field may contribute to this high rate. Indeed, the Japanese domestic guideline only offers level C suggestions about anticoagulant therapy interruption for procedures [10]. Guideline deviations in real-world clinical settings occurred frequently, as also indicated in a previous report [6]. In addition to disseminating guidelines, developing an evidence-based comprehensive approach to anticoagulated patients for whom procedures are planned is urgently needed, because strokes during anticoagulant therapy interruption can be, at least partly, preventable.

There were several limitations that need to be addressed. First, due to the retrospective and case-control nature of the study, there was no information about the prevalence and timing of stroke in AF patients whose anticoagulant therapy was interrupted; AF patients with anticoagulant therapy interruption but who did not develop ischemic stroke could not be included in the present study. Moreover, whether to discontinue anticoagulation or when to stop anticoagulation depended on attending physicians' discretion. Second, the number of included patients was relatively small, especially in the Interruption group. Moreover, only the short-term outcome was assessed. Third, because information about patients' drug adherence was not systematically collected in the present study, the effect of temporary anticoagulant therapy interruption due to patients' own lack of adherence could not be assessed. Patient classification was based on prescription data in the present study, and poorly adherent patients who were prescribed anticoagulant medications were classified into the AC group. Adherence was reported to be low among patients prescribed oral anticoagulants [16], so the frequency of stroke during anticoagulant therapy interruption or the effect of anticoagulant therapy interruption on stroke severity or the rate of major artery occlusion might be underestimated in the present study. Finally, some important clinical risk scores for patients with AF, such as the HAS-BLED score, could not be calculated due to lack of systematic collection of the information required. The present findings should be confirmed in a prospective cohort with information about medication adherence.

In conclusion, patients developing stroke during anticoagulant therapy interruption accounted for 3.7% of patients with stroke and AF. Strokes occurred relatively early in the period after interruption, especially among patients who discontinued DOACs. Guideline deviations were frequently seen, and developing and disseminating evidence-based guidelines seem to be urgently needed.

Conflict of interest

None.

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