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Original article

The association between direct oral anticoagulant concentration upon acute stroke and stroke outcome

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ABSTRACT

Background: This study aimed to investigate the association between direct oral anticoagulant (DOAC) concentration upon acute ischemic stroke (IS) or intracranial hemorrhage (ICH) and stroke outcomes.
Methods: Patients aged ≥20 years treated with DOACs, including dabigatran, rivaroxaban, apixaban, or edoxaban, and developed acute IS or ICH were enrolled to measure DOAC concentration at the time of hospital presentation by using ultrahigh-performance liquid chromatography with tandem mass spectrometry. Ischemic stroke patients was categorized into low (<50 ng/mL) and effective (≥50 ng/mL) groups. The primary outcome was poor functional outcomes at 3 months (modified Rankin Scale scores of 4–6).
Results: A total of 138 patients were enrolled, including 105 IS (76.1%) and 33 ICH patients. In the IS cohort, the average DOAC concentration was 85.7 ± 88.6 ng/mL (low DOAC concentration: 42.9%). Low level group had numerically higher NIHSS (14 versus 9, $p = 0.37$), significantly poorer functional outcomes at 3 months (odds ratio [OR], 5.08 [1.32, 19.63]), and higher chance of stroke-in-evolution (OR, 6.83 [1.64, 28.41]). In the ICH cohort, the average DOAC concentration was 128.9 ± 111.9 ng/mL. Reversal therapy was administered in 60.6% of patients. Hematoma growth occurred in 35.7% patients. The DOAC concentration was similar across patients with or without reversal therapy, and with or without hematoma growth.
Conclusion: Among DOAC users who developed IS, low drug concentrations at hospital presentation predicted poor outcomes.

1. Introduction

Direct oral anticoagulants (DOAC), including dabigatran, rivaroxaban, apixaban, and edoxaban, are commonly used to prevent thromboembolism in various populations. Nevertheless, ischemic stroke (IS) and intracranial hemorrhage (ICH) still occur during DOAC therapy and are difficult to manage [1]. Several studies have reported on the effects of preceding anticoagulant (AC) therapy on stroke severity. In the case of acute IS, data from the Get With the Guidelines–Stroke (GWTG-Stroke) Registry in the United States revealed that therapeutic warfarin and DOACs reduced the odds of moderate or severe stroke and in-hospital mortality in patients receiving this treatment compared to AC non-users [2]. Similarly, data from the Korean Stroke Registry (KSR) showed that the pre-hospitalization use of AC therapy was associated with mild neurological deficit, defined as an initial National Institutes of Health Stroke Scale (NIHSS) score of ≤5, and favorable outcomes at discharge [3]. Conversely, in the case of acute ICH, preceding AC therapy enhances stroke severity. According to the GWTG-Stroke Registry, using warfarin or DOAC prior to hospitalization was associated with increased in-hospital mortality or discharge to hospice care compared with not using this treatment. Notably, compared to warfarin, DOAC still resulted in lower rates of in-hospital mortality or discharge to hospice care [4].

The management of acute IS or ICH among warfarin users is driven by international normalized ratio (INR) levels. In case of DOAC use, the most appropriate management strategy remains uncertain. According to the Erlangen Registry of Patients on Oral Anticoagulation (ER-NOAC), a low DOAC concentration is associated with higher NIHSS scores at

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admission and persisting neurologic deficit after acute IS [5]. Importantly, administering systemic thrombolytic therapy to IS patients with low DOAC concentrations did not increase the risk of excessive bleeding [6]. These data support the concentration-guided management of acute stroke in patients receiving preceding DOAC therapy; this has also been suggested by the European Heart Rhythm Association [1]. Currently, data on the DOAC concentration at the time of acute stroke are sparse. Therefore, in our study, we aimed to investigate the association between the DOAC concentration and stroke outcomes in patients who developed acute IS or ICH during treatment.

2. Patients and methods

2.1. Participants and study setting

This prospective observational study was conducted at a tertiary hospital in Taiwan. The inclusion criteria were as follows: (1) age ≥20 years; (2) receiving treatment with DOACs, including dabigatran, rivaroxaban, apixaban, or edoxaban; (3) development of acute cerebral ischemia or ICH; and (4) DOAC concentration measured at hospital arrival. Cerebral ischemia included IS and transient ischemic attack (TIA). The exclusion criteria were as follows: (1) traumatic or spontaneous subarachnoid hemorrhage, (2) ICH associated with cerebral venous sinus thrombosis, and (3) ICH associated with hemorrhagic transformation or development of hemorrhagic transformation after acute IS. The diagnosis of IS, TIA, or ICH was reached by experienced neurologists (S.C. Tang and C.H. Chen) and was based on brain computed tomography (CT) or magnetic resonance imaging (MRI). Brain CT angiography or perfusion was performed in patients suspected of having large vessel occlusion stroke. TIA was defined as a transient or reversible episode of neurological dysfunction lasting less than 24 h [7]. The study protocol conformed with World Medical Association Declaration of Helsinki, was approved by the NTUH Research Ethics Committee (No. 202112164RINA) and was registered at clinicaltrials.gov (NCT05283174). Each participant provided informed consent before enrollment in the study.

2.2. Study process

In all participants, blood samples were collected upon hospital presentation in order to measure the DOAC concentration using ultrahigh-performance liquid chromatography with tandem mass spectrometry. The method has been validated and published previously, and the details are listed in the Supplementary Texts [8]. The index date was defined as the onset date of IS, TIA, or ICH. All participants were prospectively followed up from the index date to the occurrence of the study outcomes, the time of death, the end of the medical record in our main or branch hospitals, or 3 months after the index date, whichever came first.

The cutoff value of DOAC concentration to define active pharmacological effect remained unclear. According to the ER-NOAC, low DOAC concentration was defined as <50 ng/mL, at which point thrombolytic therapy can be administered [5,6]. Because the protocol of ER-NOAC has been tested and proved not to increase risk of symptomatic ICH, we used the cutoff value in present study [5,6]. Low DOAC concentration was defined as a drug level <50 ng/mL, at which value intravenous (IV) recombinant tissue plasminogen activator (rt-PA) can be administered. Due to the small patient number, we did not further categorize patient into DOAC level into intermediate activity (50–100 ng/mL), or high activity (>100 ng/mL), at which value IV rtPA should be carefully evaluated or avoided, respectively. Instead, we define DOAC concentration ≥50 ng/mL as the effective drug level group. For ICH, because data was lacking, we applied the same criteria as cerebral ischemia. The universal cutoff value for different DOAC may not display similar pharmacological activity. Therefore, we performed a sensitivity analysis by applying the lower expected range of trough concentration reported in clinical trials to see if the finding changed. The cutoff value is 28 ng/mL for dabigatran, 12 ng/mL for rivaroxaban, 34 ng/mL for apixaban and 12 ng/mL for edoxaban [1].

2.3. Study outcomes

The primary outcome was functional status, which was reflected by the modified Rankin Scale (mRS) score calculated 3 months after the index stroke. Poor functional outcomes were defined as mRS scores of 4–6 points. The secondary outcomes included stroke-in-evolution in case of cerebral ischemia; hematoma growth in case of ICH; or the composite outcomes of recurrent IS, TIA, ICH, major bleeding, or death at 3 months. Stroke-in-evolution was defined as a change of ≥3 points in the NIHSS score occurring within 72 h, excluding that caused by hemorrhagic transformation or by other attributable medical or systemic causes [9]. Hematoma expansion was defined as an increase of ≥6 mL in the hematoma volume or of ≥33% on the follow-up image (usually obtained 24–48 h after the initial scans) [10]. The hematoma volume was calculated by using the ABC/2 formula [11]. Major bleeding was classified according to the platelet inhibition and patient outcome (PLATO) criteria [12]. Major life-threatening bleeding was defined as ICH, intrapericardial bleeding, overt bleeding leading to hemorrhagic shock, hypotension requiring inotropic agents or surgical intervention, a reduction of >5 g/dL in hemoglobin levels, or requirement of a packed red blood cell transfusion of ≥4 U. Other major bleeding events were significant disabling bleeding or bleeding that resulted in a drop of 3–5 g/dL in hemoglobin levels, requiring a packed red blood cell transfusion of 2 to 3 U [12].

Moreover, the following outcomes were assessed in patients who received endovascular thrombectomy (EVT): (1) successful reperfusion, defined as modified thrombolysis in cerebral infarction (mTICI) graded with a score of 2B, 2C or 3; (2) early neurological improvement, defined as a reduction of 8 points or more in the NIHSS score at 3 days; and (3) symptomatic ICH, defined as parenchymal hematoma type 2 observed within 36 h after treatment combined with an increase of at least 4 points from the baseline NIHSS score. Clinical outcomes were evaluated by S.C. Tang and C.H. Chen blinded to the DOAC concentration results.

2.4. Statistical analysis

Descriptive analysis was used to obtain the means, standard deviations, medians, and ranges. To compare between-group differences, Student's *t*-test or the Mann-Whitney U test was used for continuous variables, and the chi-square test or Fisher's exact test was used for categorical variables. Ordinal logistic regression was performed to compare the primary outcome: mRS score at 3 months. To investigate the factors associated with poor functional outcomes, stroke-in-evolution, and hematoma expansion, univariable logistic regression was performed first. Subsequently, the factors with a p-value of <0.1, DOAC concentration, and CHA_2DS_2-VASc score were adjusted for in the multivariable logistic regression model. A Cox proportional hazard model was used to investigate the factors associated with composite outcomes at 3 months. In all the analyses, statistical significance was defined as a p-value <0.05.

3. Results

3.1. Participant enrollment

A total of 208 patients were enrolled in this study between March 2018 and April 2022, and 148 patients measured DOAC concentration upon hospital presentation. After applying the exclusion criteria, 105 patients with IS and 33 patients with ICH were enrolled in the statistical analysis. The participant enrollment process is shown in Fig. 1.

Among patients with available data of DOAC administration time (n = 100, 72.5%), the median sampling time was 14.0 h (interquartile range [IQR], 7.3 to 23.5 h) from last DOAC dose. The DOAC dosing

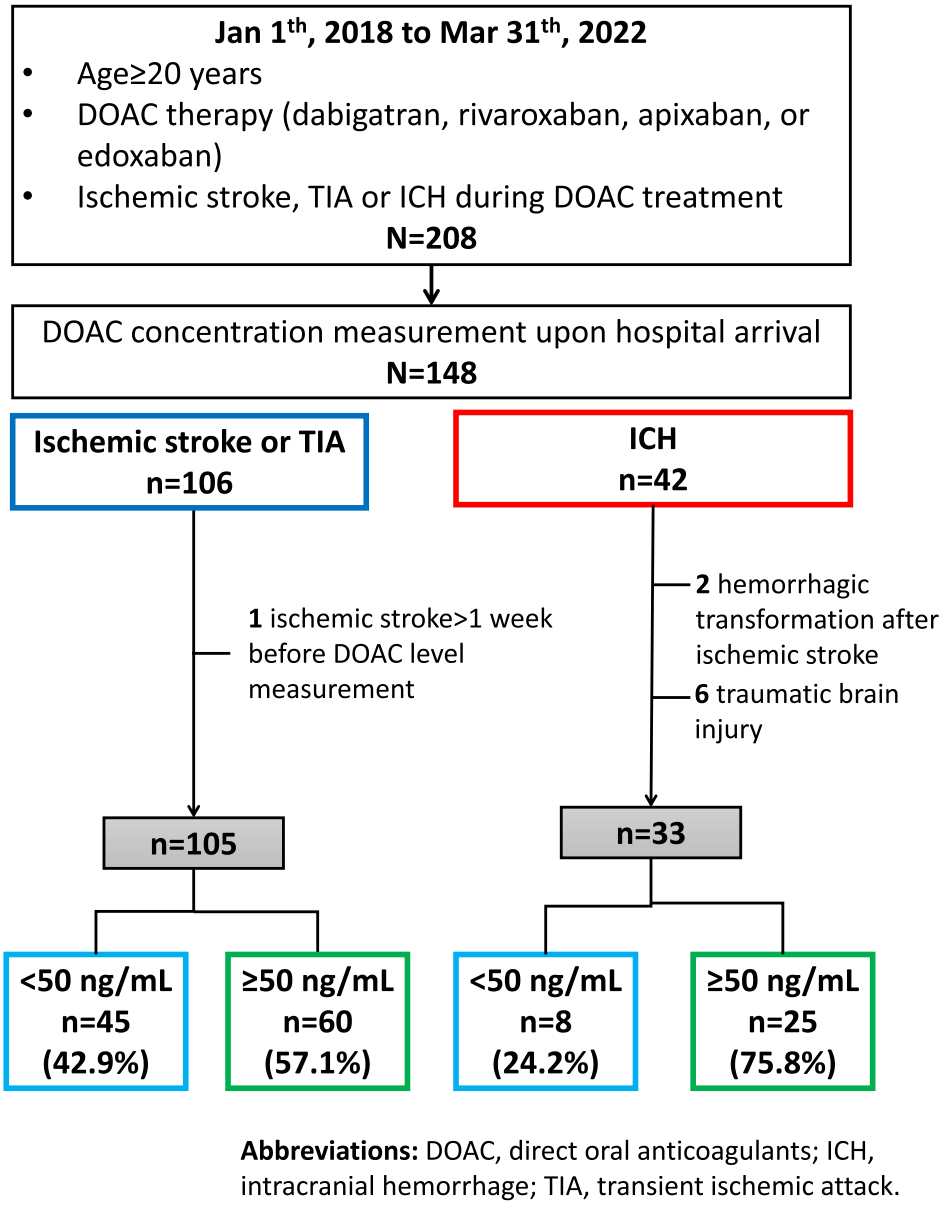

Fig. 1. The process of participant enrollment.

information was available in 94.2% patients. Among them, 58.7% used on label dosing regimen, 33.3% used off label underdose regimen and 2.2% used off label overdose regimen.

3.2. Basic characteristics and DOAC concentrations among cerebral ischemia patients

Among the 105 patients with cerebral ischemia, 90 (85.7%) had IS, and 15 (14.3%) had TIA. The indication for DOAC therapy was AF for 87 patients (82.9%) and venous thromboembolism (VTE) for 18 patients (17.1%). The type of DOACs before IS/TIA were as following: dabigatran (n = 26, 24.8%), rivaroxaban (n = 13, 12.4%), apixaban (n = 32, 30.5%), and edoxaban (n = 34, 32.4%). The average DOAC concentration was 85.7 ± 88.6 ng/mL, and 45 patients (42.9%) had DOAC concentration <50 ng/mL. The baseline characteristics and stroke presentation were generally similar between patients with DOAC concentrations <50 ng/mL and those with concentrations ≥50 ng/mL. Regarding laboratory test results, the low DOAC concentration group exhibited a lower prothrombin time (PT) and activated partial thromboplastin time (aPTT), as presented in Table 1.

Details of stroke presentation, management, and outcomes are listed in Table 2. The median NIHSS score was numerically higher in patients with DOAC concentrations <50 ng/mL than in those with DOAC concentrations ≥50 ng/mL (median 14 vs. 9, p = 0.37). The proportion of patients with NIHSS scores of >10 was 59.5% among those with DOAC concentration <50 ng/mL in contrast to 44.8% among those with DOAC concentration ≥50 ng/mL (p = 0.15). A total of 6 patients received alteplase therapy. Among them, 2 patients administered idarucizumab for dabigatran reversal before initiating thrombolytic therapy. None of the patients developed symptomatic ICH within 24 h after thrombolytic therapy.

A total of 29 patients underwent EVT, and 15 patients (51.7%) had DOAC concentration <50 ng/mL. Only one patient received alteplase therapy preceding EVT. The initial presentation of cerebral ischemia among those underwent EVT was similar between patients with and without DOAC concentration <50 ng/mL, as presented in Table S1. Successful reperfusion was achieved in 73.3% of patients with DOAC concentration <50 ng/mL in contrast to in 100.0% of patients with DOAC concentration ≥50 ng/mL (p = 0.10).

Table 1
Baseline characteristics between patients with different DOAC concentrations.

	Ischemic stroke / TIA		
	<50 ng/mL (*n* = 45)	**≥50 ng/mL (*n* = 60)**	**p-value**
Drug level	16.2 ± 16.3	137.9 ± 84.8	**<0.001**
Characteristics			
Male	20 (44.4)	34 (56.7)	0.22
Age (year)	75.7 ± 12.4	75.7 ± 11.8	1.00
Atrial fibrillation	35 (77.8)	52 (86.7)	0.23
CHA_2DS_2-VASc score[†]	4.5 ± 1.4	4.7 ± 1.8	0.68
IS/TIA history	21 (46.7)	37 (61.7)	0.13
Hypertension	27 (60.0)	38 (63.3)	0.73
Diabetes mellitus	10 (22.2)	20 (33.3)	0.21
Cancer history	17 (37.8)	14 (23.3)	0.11
ICH history	2 (4.4)	3 (5.0)	1.00
Laboratory tests			
CrCl (mL/min)	55.1 ± 28.5	51.0 ± 23.3	0.42
Hb (g/dL)	12.1 ± 2.5	13.4 ± 2.5	**0.01**
Platelet (K/uL)	193.4 ± 69.5	203.3 ± 87.4	0.53
ALT (U/L)	18.9 ± 11.2	31.9 ± 38.3	**0.03**
PT (*sec*)	11.4 ± 0.9	12.0 ± 1.3	**0.01**
aPTT (*sec*)	28.6 ± 4.4	31.9 ± 7.1	**0.01**
INR	1.1 ± 0.1	1.1 ± 0.1	**0.02**
d-dimer	5.0 ± 8.4	3.6 ± 7.3	0.10
T-CHO (mg/dL)	157.1 ± 48.3	148.7 ± 35.0	0.35
LDL-C (mg/dL)	94.7 ± 34.4	85.2 ± 28.1	0.15
Triglycerin (mg/dL)	101.9 ± 51.9	104.6 ± 52.3	0.81
HbA1c (%)	5.8 ± 0.8	6.3 ± 1.2	**0.04**
From last DOAC dose (hour)	34.5 ± 31.1	14.9 ± 17.9	**<0.001**
DOAC regimen			
On labeled dose	22 (53.7)	37 (62.7)	0.42
Off label underdose	19 (46.3)	21 (35.6)	
Off label overdose	0 (0)	1 (1.7)	

Data are presented as number (proportion) or mean ± standard deviation. Bold number indicates statistical significance.
Abbreviations: ALT, alanine transaminase; aPTT, activated partial thromboplastin time; CrCl, creatinine clearance estimated by using the Cockcroft-Gault formulation; DOAC, direct oral anticoagulant; Hb, hemoglobin; HbA1c, hemoglobin A1c; ICH, intracranial hemorrhage; INR, international normalized ratio; IS, ischemic stroke; LDL-C, low density lipoprotein cholesterol; PT, prothrombin time; T-CHO, total cholesterol; TIA, transient ischemic attack.
[†] The CHA_2DS_2-VASc score was only calculated among patients with atrial fibrillation.

3.3. Three-month functional outcomes in patients who developed cerebral ischemia during DOAC therapy

The median mRS score at 3 months was 4 (IQR, 2–5) in patients with DOAC concentration <50 ng/mL in contrast to 3 (IQR, 1–4) in patients with DOAC concentration ≥50 ng/mL (common odds ratio [OR], 2.35 [1.01, 5.47]; $p = 0.047$). The proportion of patients with poor functional outcomes at 3 months was 53.3% ($n = 24$) in the DOAC concentration <50 ng/mL group and 33.3% ($n = 20$) in the DOAC concentration ≥50 ng/mL group ($p = 0.04$, Table 2 and Fig. 2A). After adjustments, DOAC concentrations of <50 ng/mL remained a significant predictor of poor functional outcomes at 3 months (OR, 5.08 [1.32, 19.63]; $p = 0.02$; Table 3). The details of the univariable and multivariable regression models are presented in Table S2.

The outcomes of cerebral ischemia in patients who underwent EVT are presented in Table S1. The proportion of patients with poor functional outcomes was 66.7% among patients with DOAC concentration <50 ng/mL in contrast to 42.9% among patients with DOAC concentration ≥50 ng/mL ($p = 0.20$).

3.4. Other stroke outcomes in patients who developed cerebral ischemia during DOAC therapy

Stroke-in-evolution occurred in 40.0% of patients with DOAC concentrations <50 ng/mL compared to in 21.7% of patients with DOAC concentrations ≥50 ng/mL ($p = 0.04$, Table 2). After adjustments, DOAC concentration <50 ng/mL (OR, 6.83 [1.64, 28.41]; $p = 0.01$) and the initial NIHSS score (OR, 1.15 [1.05, 1.27]; $p = 0.003$) predicted stroke-in-evolution (Tables 3 and S1).

Table 2
Stroke presentation, management and outcomes between warfarin and DOAC groups.

	Ischemic stroke / TIA		
	<50 ng/mL (*n* = 45)	**≥50 ng/mL (*n* = 60)**	**p-value**
Initial presentation			
GCS[†]	15 (11–15)	14 (11–15)	0.87
NIHSS[†]	14 (4–21)	9 (5–19)	0.37
SBP (mmHg)	148.1 ± 27.8	148.9 ± 26.5	0.89
DBP (mmHg)	80.4 ± 13.6	84.9 ± 18.7	0.17
hematoma size (mL)	N/A	N/A	N/A
> 30 mL	N/A	N/A	N/A
ICH score	N/A	N/A	N/A
Management			
Reperfusion therapy	18 (40.0)	16 (26.7)	0.15
rtPA	4 (8.9)	2 (3.3)	0.40
EVT	15 (33.3)	14 (23.3)	0.26
Reversal agent[‡]	0 (0)	2 (3.3)	N/A
Outcomes			
Stroke-in-evolution	18 (40.0)	13 (21.7)	**0.04**
Hematoma expansion	N/A	N/A	N/A
mRS at 3M[†]	4 (2–5)	3 (1–4)	0.12
Poor functional outcome at 3M[§]	24 (53.3)	20 (33.3)	**0.04**
Composite outcome at 3M	13 (28.9)	9 (15.0)	0.08

Data are presented as number (proportion) or mean±standard deviation.
Abbreviations: DBP, diastolic blood pressure; EVT, endovascular thrombectomy; GCS; Glasgow coma scale; ICH, intracranial hemorrhage; M, months; mRS, modified Rankin scale; N/A, non-applicable; NIHSS, National Institutes of Health Stroke Scale; rtPA, recombinant tissue-type plasminogen activator; SBP, systolic blood pressure.
[†] The data is represented as median (interquartile range).
[‡] Two IS patients who used dabigatran before stroke administered idarucizumab before starting rtPA therapy.
[§] Poor functional outcome was defined as mRS 4 to 6 points.

The incidence of the composite outcomes at 3 months, including recurrent IS, TIA, ICH, major bleeding, and death from any cause, was 13.9% (8.4%–23.0%) per month among patients with an initial DOAC concentration of <50 ng/mL in contrast to 6.3% (3.4%–11.9%) per month among patients with an initial DOAC concentration of ≥50 ng/mL (log-rank test, $p = 0.08$, Fig. S1A). After adjustments, an initial DOAC concentration of <50 ng/mL (HR [hazards ratio], 4.27 [1.10, 16.56]; $p = 0.04$) was the only predictor of the composite outcomes at 3 months (Table S2).

Among patients who underwent EVT, patients with DOAC concentrations ≥50 ng/mL displayed a trend toward being more likely to have early neurological improvement than those with DOAC concentration of <50 ng/mL (50 versus 40%, $p = 0.72$). The incidence of composite outcomes at 3 months was 27.3% (10.0%−59.4%) per month in patients with DOAC concentration <50 ng/mL in contrast to 13.3% (3.6%–34.1%) per month in patients with DOAC concentration ≥50 ng/mL (log rank test, $p = 0.52$, Fig. S2).

3.5. Outcome at 3 months for ischemic stroke patients with or without atrial fibrillation

We performed subgroup analyses among patients who used DOAC for AF (87 patients). The results were in line with the main analysis. DOAC concentration <50 ng/mL predicted worse functional outcome at 3 months (OR=4.80 [1.23, 18.73], $P = 0.02$), stroke-in-evolution (OR=6.02 [1.55, 23.42], $P = 0.01$) and composite outcomes at 3 months (0.98 [1.83, 50.04], $P = 0.01$), as listed in Table S3.

Among patients without AF (18 patients), all used DOAC for VTE. A total of 16 patients (88.9%) also had cancer, and the most common type

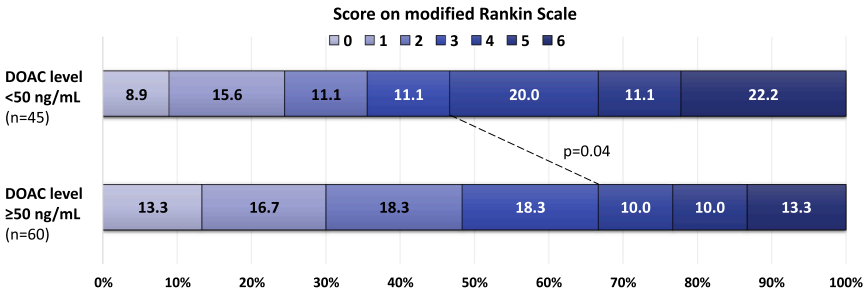

Fig. 2. Modified Rankin scale among ischemic stroke patients with different drug concentration.

Table 3
Factors associated with clinical outcomes among patients with ischemic stroke.

Poor functional outcome at 3 months[†]		
Factors	**Odds ratio**	**P-value**
Initial NIHSS	1.23 (1.12, 1.34)	**<0.001**
CHA_2DS_2-VASc score	1.61 (1.02, 2.53)	**0.04**
Cancer history	1.35 (0.31, 5.88)	0.69
Drug level < 50 ng/mL	5.08 (1.32, 19.63)	**0.02**
Stroke in-evolution		
Factors	**Odds ratio**	**P-value**
HbA1c	0.52 (0.20, 1.38)	0.19
Initial NIHSS	1.15 (1.05, 1.27)	**0.003**
Reperfusion therapy[‡]	1.01 (0.23, 4.51)	0.99
CHA_2DS_2-VASc score	0.63 (0.38, 1.02)	0.06
Cancer history	1.90 (0.40, 8.97)	0.42
Drug level < 50 ng/mL	6.83 (1.64, 28.41)	**0.01**

[†] Poor functional outcome was defined as modified Rankin Scale 4 to 6 points.
[‡] Reperfusion therapy is defined as rt-PA administration or endovascular thrombectomy.
Abbreviations: NIHSS, National Institutes of Health Stroke Scale.

of cancer was lung cancer (11 patients), followed by pancreatic cancer (3 patients). The average age for non-AF patients was 66.4 ± 11.9 years, mean CrCl was 67.0 ± 33.0 mL/min and mean DOAC concentration was 67.8 ± 84.9 ng/mL (<50 ng/mL, 55.6%). The proportion of patients with clinical outcome in low DOAC concentration group in contrast to the rest of patients were listed as following: Poor functional outcome at three months, 40.0% versus 25.0% (P = 0.64), stroke-in-evolution, 30.0% versus 62.5% (P = 0.34), and composite outcome at three months, 30.0% versus 75.0% (P = 0.15).

3.6. Sensitivity analysis of individualized cutoff value for different DOAC

The lower expected range of trough reported in clinical trials for each DOAC was used to reclassify patient with low DOAC concentration. The proportion of patients with DOAC concentration less than the lower expected range of trough concentration was 24.8% (26 patients, 23.1% of dabigatran users, 46.2% of rivaroxaban users, 28.1% of apixaban users and 14.7% of edoxaban users). The proportion of patients with poor functional outcomes at 3 months was 53.8% in lower-than-expected-range DOAC concentration group and 38.0% among the rest of patients (p = 0.16). After adjustments, lower-than-expected-range DOAC concentrations was a significant predictor of poor functional outcomes at 3 months (OR, 5.60 [1.40, 22.38]; p = 0.02). Stroke-in-evolution occurred in 46.2% of patients with lower-than-expected-range DOAC concentration compared to 24.1% of the rest of patients (p = 0.03). After adjustments, lower-than-expected-range DOAC concentration (OR, 5.56 [1.41, 21.93]; p = 0.01) and the initial NIHSS score (OR, 1.15 [1.05, 1.26]; p = 0.003) predicted stroke-in-evolution. The composite outcomes at 3 months occurred in 10 (38.5%) patients in the lower-than-expected-range DOAC concentration group, in contrast to 12 (15.2%) patients in the other group (p = 0.01). After adjustments, lower-than-expected-range DOAC concentration (HR 6.19 [1.76, 21.82]; p = 0.005) was the only significant predictor for composite outcome at 3 months. The results of sensitivity analyses were displayed in Table S4.

3.7. Basic characteristics and DOAC concentrations among ICH patients

Among the DOAC users who developed ICH, 3 (9.1%) patient used dabigatran, 7 (21.2%) used rivaroxaban, 14 (42.4%) used apixaban and 9 (27.3%) used edoxaban. Their mean age was 77.8 ± 9.3 years and CrCl was 44.9 ± 13.3 mL/min. The indication for DOAC therapy was AF for 27 patients (81.8%), VTE for 3 patients (9.1%) and unknown for 3 patients (9.1%). The median DOAC concentration was 128.9 ± 111.9 ng/mL.

3.8. ICH patients underwent reversal therapy

A total of 20 (60.6%) patients received treatment with reversal agents: one dabigatran user administered idarucizumab, and 19 factor Xa inhibitor users were administered prothrombin complex concentrate. The comparison of ICH presentation and outcomes between patients with or without reversal therapy were listed in Table S5. The average duration from the last DOAC dose to hospital presentation was significantly shorter in patients receiving reversal treatment than in those not receiving this treatment (10.5 ± 9.8 vs. 26.7 ± 17.2 h, P = 0.01). The average DOAC concentration was 106.2 ± 108.4 ng/mL in reversal group, in contrast to 163.9 ± 112.2 ng/mL in non-reversal group (P = 0.15). Patient in reversal group had numerically lower initial NIHSS (8 [IQR, 4 −13] versus 19 [IQR, 2–28], P = 0.28) and smaller baseline hematoma (12.7 ± 12.9 mL versus 18.4 ± 16.2 mL, P = 0.32). Poor functional outcome at three months occurred in 40% of patients receiving reversal therapy, in contrast to 53.8% of patients without reversal therapy (P = 0.44).

3.9. Hematoma expansion among DOAC users with ICH

Hematoma volume was unable to be estimated in 5 patients with subdural hemorrhage. Among the rest 28 patients, hematoma expansion occurred in 10 (35.7%) patients. The basic characteristics, stroke presentation and outcomes were listed in Table S5. The DOAC concentration was 82.6 ± 65.4 ng/mL in hematoma expansion group, in contrast to 166.3 ± 128.8 ng/mL for hematoma non-expansion group (P = 0.09, Table S5). Patient in reversal group had numerically lower initial NIHSS (6 [IQR, 4 −15] versus 11 [IQR, 4–27], P = 0.52) and smaller baseline hematoma (19.3 ± 18.8 mL versus 12.1 ± 10.4 mL, P = 0.45).

4. Discussion

The present study reports the DOAC concentration during acute stroke and its association with stroke outcomes. Our data showed that in approximately 60% of cases, cerebral ischemia occurred while the DOAC concentrations were exerting active pharmacological effects. In

addition, a low DOAC concentration predicted poor functional outcomes at 3 months and stroke-in-evolution.

In studies reporting the DOAC concentration in different cohorts of patients with acute IS, the proportion of patients with low DOAC exposure ranged from 27 to 67% [5,13]. The proportion in our study was approximately 40%, which was within this range. Notably, the DOAC concentration at the time of acute stroke is associated with stroke severity. As mentioned previously, data from the ER-NOAC registry showed that low DOAC concentrations were associated with higher initial NIHSS scores [5]. Another study on a German cohort reported similar results: low DOAC exposure was linked to increased stroke severity [13]. In our cohort, patients with low DOAC concentrations also exhibited numerically higher initial NIHSS scores than the rest of the patients did. The association between DOAC concentrations and stroke outcomes has not been discussed extensively. Rizos et al. reported that stroke severity and premorbid functional outcomes, but not DOAC exposure, were predictors of unfavorable outcomes [13]. Conversely, our data showed that low DOAC concentrations were associated with worse stroke outcomes, including a higher mRS score at 3 months, higher risk of stroke-in-evolution, and higher likelihood of developing composite outcomes at 3 months.

In patients being treated with DOAC therapy who develop acute cerebral ischemia, EVT is an effective treatment option for large vessel occlusion, especially in cases in which alteplase therapy is unsuitable [14]. A meta-analysis showed that in comparison with not using DOACs, preceding DOAC therapy did not increase the rate of successful reperfusion in EVT, but increased the risk of poor functional outcomes [15]. Of note, the risk of symptomatic ICH after the procedure was similar. Nevertheless, there was a lack of data regarding the DOAC concentration at the time of acute cerebral ischemia. Our results showed that patients with active DOAC concentrations, defined as those $\geq$50 ng/mL, exhibited the following trends: they were more likely to have successful reperfusion and early neurological improvement and were less likely to have poor functional outcomes or to develop the composite outcomes at 3 months. However, the incidence of symptomatic ICH was low in our cohort, and we were not able to reach a conclusion on whether preceding DOAC treatment increased the risk of ICH in comparison with not using DOACs.

The association between low DOAC concentration and increased risk of IS / systemic thromboembolism has been reported in real-world observational study [16,17]. Of note, investigations conducted in patients under steady-state DOAC therapy used individualized cutoff value to define low concentration varied across different DOAC [16,17]. Contractively, our main analysis used a universal cutoff value (i.e., $<$ 50 ng/mL) to define low DOAC concentration, which can be debatable. There were some rationales behind our design. First, the time of DOAC concentration measurement is random, neither peak nor trough. In addition, delayed or additional DOAC dose can happen during acute IS, leading to non-steady-state of DOAC therapy. Using the concentration range for peak or trough elucidated at steady-state as reference to define high or low drug level is inappropriate. Second, the main purpose of DOAC concentration measurement upon acute stroke is to guide the decision of thrombolytic therapy. A universal cutoff value with absent or low DOAC pharmacological effect for all DOAC is feasible for this purpose and easy to apply in clinical practice. The cutoff value to determine low DOAC concentration was inconclusive. Unlike the ER-NOAC registry which defined low DOAC concentration as $<$50 ng/mL, the 2021 European Heart Rhythm Association practical guide on NOAC proposed the feasibility of thrombolytic therapy among patients with DOAC concentration lower than 30 ng/mL [18]. Because the cutoff value of 30 ng/mL has not been tested in real-world practice, we used the cutoff value applied in the ER-NOAC registry. In sensitivity analysis, we used individualized cutoff value to define low DOAC concentration, and the results were in line with the main analysis. Although the most appropriate cutoff value is unclear, our data proves the link between low DOAC concentration upon acute IS and worse outcome or stroke-in-evolution.

The incidence of ICH during DOAC therapy is low at approximately 0.2%, according to real-world data [19–22], which may explain the difficulty in the participant enrollment in our ICH cohort. Despite the small sample size, our investigation is the first one to report real-world DOAC concentration in patients with acute ICH. In our cohort, approximately 60% of ICH patients received reversal treatment, which reflects the awareness of physicians in the management of DOAC-associated ICH. Upon acute treatment, the DOAC concentration was not disclosed. The decision for reversal therapy is driven by clinical presentation and medication history. Therefore, we did not find a correlation between DOAC concentration and reversal therapy. In Taiwan, the reversal agent for factor Xa inhibitors, andexanet alpha, is not available. In addition, patients need to pay out of pocket to treat with prothrombin complex concentration. Introducing the test to evaluate anticoagulant effect with rapid turnaround time, such as chromogenic anti-Factor Xa activity assay, is essential to guide acute management. We did not find increased DOAC concentration among patients with hematoma growth, neither. In addition, these patients paradoxically displayed a trend of numerically lower initial NIHSS and smaller initial hematoma size. However, hematoma growth is affected by the time from symptom onset to hospital presentation, which can occur before hospital arrival in patients with delayed transposition.

These data elucidate the DOAC concentration at the time of acute IS or ICH, which is a strength of this study. In addition, we demonstrated an association between low DOAC concentrations and worse outcomes in IS/TIA, which has not been discussed in previous studies. Nevertheless, we acknowledge the following limitations. First, the sample size of this study was small; therefore, we were not able to draw a robust conclusion, especially in the case of patients with ICH. Second, we did not implement DOAC concentration-guided management of acute stroke in this observational study. Therefore, we were not able to judge whether the use of a concentration-based decision tree for treating acute stroke during DOAC therapy would improve stroke outcomes. And we were not able to answer the most appropriate cutoff value to determine the feasibility of thrombolytic therapy. Third, we collected the results of only one DOAC concentration measurement performed at the time of hospital presentation, which may not accurately reflect the extent of DOAC exposure before stroke. However, DOAC concentration after hospital presentation can be affected by the reversal agent, which may not be appropriate for pharmacokinetic parameter estimation.

5. Conclusion

Our data showed that low DOAC concentrations at the time of acute IS were associated with poor functional outcomes, stroke-in-evolution, and worse clinical outcomes. The measurement of DOAC concentration at the time of acute IS is essential, as it could serve as a guide in acute management and identifying patients who are at a risk of deterioration.

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CRediT authorship contribution statement

Shin-Yi Lin: Conceptualization, Investigation, Data curation, Formal analysis, Writing – original draft, Writing – review & editing, Funding acquisition. **Sung-Chun Tang:** Conceptualization, Investigation. **Ching-**

Hua Kuo: Resources, Formal analysis, Data curation, Funding acquisition. **Chih-Hao Chen:** Conceptualization, Investigation, Data curation, Formal analysis. **Yuan-Chang Chao:** Investigation. **Chih-Fen Huang:** Writing – review & editing. **Jiann-Shing Jeng:** Conceptualization, Investigation, Data curation, Formal analysis.

Declaration of Competing Interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2023.03.023.

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