Intravenous Thrombolysis in Patients Taking Direct Oral Anticoagulation Treatment Before Stroke Onset: Results from the Safe Implementations of Treatments in Stroke International Stroke Registry

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Objectives: Intravenous thrombolysis (IVT) is contraindicated for acute ischemic stroke (AIS) patients taking direct oral anticoagulants (DOACs) within 48 hours before index stroke. Limited data exist on off-label use of IVT for these patients. We compared the safety and outcomes of IVT in AIS patients with DOAC treatment and patients with no OAC before index stroke.

Methods: We analyzed data from the Safe Implementations of Treatments in Stroke (SITS) International Stroke Thrombolysis Registry during 2013–2024. Outcomes were symptomatic intracerebral hemorrhage (SICH) by the SITS Monitoring Study and European Cooperative Acute Stroke Study II definitions, functional independency (modified Rankin Scale score 0–2), and death by 3 months. Propensity score matching with a nearest neighbor matching algorithm with a ratio of 1:2 was used for relevant clinical variables. We also analyzed the time from last DOAC dose to IVT treatment.

Results: A total of 1,311 DOAC and 129,384 no OAC patients were included. We matched 894 patients with DOAC to 1,788 with no OAC. The mean age was 75 years versus 76 years, and the median National Institutes of Health Stroke Scale score 11 versus 12, respectively. Patients with DOAC had a similar proportion of outcomes compared with patients with no OAC: SICH per SITS Monitoring Study (1.1 vs 1.5%, $p = 0.50$), SICH per European Cooperative Acute Stroke Study II (4.0 vs 4.3%, $p = 0.82$), any parenchymal hematoma (6.3 vs 7.8, $p = 0.22$), and functional independency (47.9 vs 46.4%, $p = 0.59$) and death (25.1 vs 24.0%, $p = 0.65$) at 3-month follow-up. The time from last DOAC dose to IVT did not affect outcomes.

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Interpretation: In this observational study, we did not find any difference in outcomes after IVT therapy in AIS patients with DOAC compared with no OAC treatment before index stroke.

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Intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator within 4.5 hours of ischemic stroke onset is an established and approved treatment.[1,2] Depending on the definition, approximately 2–7% of patients treated with IV thrombolysis suffer symptomatic intracerebral hemorrhage (SICH) as a complication, leading to death in 1.5–2%, and worsening functional outcome in survivors.[3] Treatment with direct oral anticoagulant (DOAC) is now commonly used for patients with atrial fibrillation to prevent embolic events, such as an ischemic stroke.[4–8] IVT is formally contraindicated in patients taking DOAC within 48 hours. There are currently limited data and no results from randomized controlled trials on reperfusion therapy in acute ischemic stroke (AIS) patients with ongoing DOAC treatment.[9–12] However, recent studies indicate that IVT is safe in patients taking DOAC.[13–15] Regarding endovascular treatment (EVT), observational data indicates no increased risk of hemorrhagic transformations and SICH after EVT with patients taking DOAC.[16] Although some guidelines recommend IVT when appropriate laboratory tests, such as aPTT, INR, ecarin clotting time, thrombin time, or direct factor Xa activity assays, are normal or when the patient has not taken a dose of these DOACs for >48 hours and renal function is normal, the evidence level for this recommendation is regarded as low.[2,17] It is therefore important to examine real-world data regarding the choice, safety, and timing of revascularization therapies in patients who suffer AIS despite DOAC treatment before stroke onset.

The aim of this study was to investigate the safety and outcomes of IVT treatment in AIS patients taking DOACs before stroke onset.

Methods

Study Design and Registry Data

This was an observational, multinational, multicenter, study of patients taking DOAC and presenting with ischemic acute stroke, based on data recorded in the Safe Implementation of Treatment in Stroke (SITS) International Stroke Thrombolysis Register (ISTR).[18,19] The SITS-ISTR is an academic-driven, international stroke registry. SITS encourages participating centers to adhere to current guidelines regarding certification for evaluating National Institute of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS), but does not require registration of the certificates.

We included AIS patients aged ≥18 years and treated with IVT with or without EVT during the period from January 1, 2013 to February 1, 2024. We collected baseline and demographic characteristics, including premorbid mRS, stroke severity per the NIHSS, medication history, imaging data at admission and follow up, time logistics, type of DOAC and whether reversal agents were used before IVT start, and 3-month death and functional independence defined as a mRS of 0–2. Time of last dose of DOAC taken before onset of AIS was introduced in a later phase in the registry, and these data were used for a subgroup analysis. We identified IVT-treated AIS patients taking DOAC before stroke symptom onset and compared them with patients without any OAC before stroke onset.

All assessments of imaging studies, and neurological and functional status were carried out according to clinical routine at centers participating in the SITS-ISTR.

This study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[20]

Study Population

We included all patients that were treated with IVT and had data on OAC treatment (either with currently ongoing treatment, or specifically without ongoing treatment) in the SITS-ISTR registry. Patients with prophylactic heparinoid treatment before stroke onset were not included in this study. Patients with missing or unknown data for anticoagulant treatment were excluded from this study. We divided the study population into the following groups:

DOAC group: Patients with ongoing treatment with dabigatran, apixaban, rivaroxaban, or edoxaban before stroke onset.

No OAC group: Patients not receiving any DOAC or warfarin, or any other anticoagulant treatment before stroke onset.

Outcomes

The main outcomes were safety, as defined by SICH as defined per the SITS Monitoring Study[18] local or remote parenchymal hemorrhage type 2 at 22–36-hour follow-up computed tomography scan, and (1) neurological deterioration of ≥4 NIHSS points from baseline or the lowest score during the first 24 hours after treatment; or (2) death and European Cooperative Acute Stroke Study II (ECASS II) definitions[21] (any sign of hemorrhage on computed tomography scan, and clinical deterioration, or adverse events indicating clinical worsening or causing an increase

of ≥4 NIHSS points), parenchymal hematoma (PH), and death within 3 months.

Other outcomes were functional independence, as measured by a mRS score of 0–2.

Statistical Analysis

We performed descriptive statistics for baseline and demographic characteristics comparing patients taking DOAC and patients without any OAC treatment before stroke onset. For univariate comparisons, we used Student *t* test, Mann–Whitney *U* test, and Pearson's χ^2-test for continuous, ordinal, and categorical variables, respectively.

For outcome analyses, we performed propensity score matching (PSM) analysis matching patients taking DOAC with patients without OAC before stroke onset. We chose variables to be included in the matching algorithm based on clinical relevance for risk of SICH. Variables that were included in the matching algorithm were: age, sex, baseline NIHSS, baseline mRS, onset to IVT treatment time, history of atrial fibrillation, history of hypertension, history of diabetes mellitus, congestive heart failure, previous stroke, endovascular treatment, and treatment with antiplatelet therapy before stroke onset. The corresponding propensity score of the DOAC variable was calculated for each participant, and a nearest neighbor matching algorithm with a 1:2 ratio allocation was then used to match patients in the DOAC group to patients in the control group within 0.2*SD of the logit of the propensity score. To determine whether the PSM achieved balance in the selected variables, we compared the same baseline and demographic characteristics through univariate analyses before and after PSM. We also presented the log odds ratios, 95% confidence intervals, and standard error of the regression models used to calculate the propensity score for the PSM. We evaluated the robustness of our PSM results using a doubly robust approach by an augmented inverse propensity weighted (AIPW) estimator model.[22] Additionally, an explorative analysis was performed on the PSM population, investigating the importance of the variables included in the PSM for the outcomes. Backwards stepwise multivariable logistic regression analyses were performed for the outcome variables, where all variables in the PSM (including prior DOAC/no OAC) were included as covariates. Only variables with a $p < 0.05$ were included in the final models.

We performed a secondary analysis to examine the association between time of last dose of DOAC taken and outcomes in all patients with the available data on DOAC treatment before stroke onset. The last dose of DOAC taken data were divided into time intervals of hours: 0–4 hours, 4–8 hours ago, 8–12 hours ago, 12–24 hours ago, and >24 hours but within 72 hours. For univariate comparison of the time intervals as a categorical variable on a group level, we used Pearson's χ^2-test. Additionally, we performed multivariable analyses to examine if the time of the last dose of DOAC taken as an ordinal variable was an independent predictor for the outcomes, using the same time categories in the following order (where the upper value is included into the interval): 0–4 hours, 4–8 hours, 8–12 hours, 12–24 hours, and >24 hours. We selected covariates for adjustment of the multivariable models based on their clinical significance and potential for confounding. The selected covariates were: age, sex, baseline NIHSS, onset to IVT treatment time, history of atrial fibrillation, history of hypertension, history of hyperlipidemia, history of diabetes mellitus, history of congestive heart failure, and treatment with endovascular thrombectomy.

Several sensitivity analyses were performed, to investigate the outcomes within selected subgroups. For the first sensitivity analysis, we performed the analyses on patients that did not receive DOAC reversal agents. The SITS database collects data on the use of idarucizumab for dabigatran reversal, but does not collect data on any other reversal agents for other DOACs. This sensitivity analysis was performed on all DOAC patients that did not receive any reversal agent. For the second and third sensitivity analyses, we divided the DOAC-treated patients into groups based on the mechanism of action for the DOAC, namely thrombin inhibitors (dabigatran) versus factor Xa inhibitors (FXa; apixaban, edoxaban, and rivaroxaban), respectively. PSM was then performed for each sensitivity analysis comparing the DOAC with non-DOAC patients, using the same matching variables as for the primary analysis. For the second and third sensitivity analyses, we also presented tables with results based on the analyses of time from last dose of DOAC taken, using the same methods as for the secondary outcomes.

A p value of <0.05 was considered statistically significant. Statistical analysis was performed by the software R version 4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria).

Standard Protocol Approvals, Registrations, and Consent

Requirements for ethical approval and patient consent for participation in the SITS-ISTR differed among participating countries. Ethical approval and patient consent were obtained in countries that required this, whereas other countries approved the register for conduct as an anonymized audit. The SITS Register was approved by the Research Ethics Committee in Stockholm, Sweden, and any subsequent amendment by the Swedish National Ethics Review Authority.

Results

The study flow chart (Fig 1) shows the number of patients included in the study. Of 135,194 patients with data on OAC treatment or not before stroke onset and treated with IVT, 1,311 patients were taking DOAC, whereas 129,384 patients did not have any OAC or other anticoagulation treatment. Patients taking DOAC before stroke onset and treated with IVT were registered from 33 countries and 289 centers from Europe, the Middle East, and Asia.

Before PSM, many of the risk factors were unbalanced between groups (Table S1). After PSM, 894 patients were matched into the DOAC group, and 1,788 into the no OAC group (coefficients for the propensity score calculations in Table S2). Baseline and demographic characteristics that were matched on were well balanced between the groups after PSM (Table 1). After PSM, patients with DOAC before stroke had a higher proportion of hyperlipidemia (36.2 vs 28.4%), lower mean baseline systolic blood pressure (152 vs 155 mmHg), and longer median onset to IVT time (165 vs 150 min).

There was no statistically significant difference in any outcome parameter between the groups after PSM (Table 2). The results were largely mirrored in the AIPW analysis, which showed similar point estimates with narrower confidence intervals for the outcomes (Table S3). The point estimate for PHr1, although statistically not significant, did change direction in the AIPW as compared with the PSM results (PSM: odds ratio [OR] 1.1, 95% confidence interval [CI] 0.53–2.2; AIPW: 0.88, 0.76–1.02).

The mRS score distribution after PSM was even between the groups (Fig 2). For the sensitivity analysis after removal of DOAC patients that received reversal agents, 786 patients were matched in the DOAC group, and 1,572 in the no OAC group (coefficients for the propensity score calculations in Table S4). There was no statistically significant difference for any of the outcomes between the groups (Table 3). For the sensitivity analyses with specific DOAC mechanisms, 324 patients on dabigatran where matched with 648 patients in the no OAC group, and 570 patients on a FXa were matched with 1,140 patients in the no OAC group (coefficients for the propensity score calculations in Tables S5 and S6, respectively). Dabigatran-treated patients showed a significantly lower odds of any PH at radiological follow-up (OR 0.50, 85% CI 0.28–0.87). The remaining outcomes for dabigatran patients, as all outcomes for FXa patients, did not show statistically significant results (Tables S7 and S8, respectively).

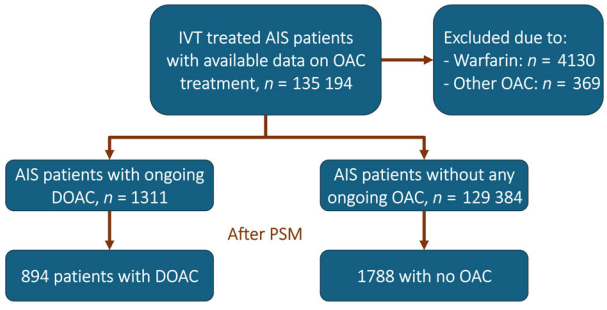

Fig 1: Study flow chart. AIS = acute ischemic stroke; DOAC = direct acting oral anticoagulants; IVT = intravenous thrombolysis; OAC = oral anticoagulants. [Color figure can be viewed at www.annalsofneurology.org]

When analyzing outcomes per the time intervals of the last dose of DOAC taken before stroke onset, on a group level, there were no statistically significant differences in any of the outcomes within the primary analysis population (Table 4). The same was seen with the sensitivity analyses of dabigatran and FXa patients (Tables S9 and S10, respectively).

In the multivariable analysis of the last dose of DOAC taken, an ordinal predictor, longer time since the last dose of DOAC taken before index stroke was associated with a higher risk for PH2 (OR 1.40, 95% CI 1.10–2.00) and a trend toward a lower chance for mRS 0–2 at 3 months (OR 0.91, 95% CI 0.83–1.00), but not with the other outcomes (Table 5). For the sensitivity analyses, patients treated with dabigatran showed that longer time from last DOAC intake was associated with a lower odds ratio for SICH by ECASS II definition (OR 0.21, 95% CI 0.03–0.67) and death by 3-month follow-up (OR 0.64, 95% CI 0.42–0.93), but not with the remaining outcomes (Table S11). The sensitivity analysis with patients treated with FXa did not show any statistically significant results (Table S12).

The explorative analyses of the variables that were the most associated with the outcomes yielded lists of variables that for no outcome included DOAC treatment before stroke onset in those lists (Tables S13–S22).

Discussion

In this large international registry-based study of patients with ongoing DOAC therapy before stroke onset, we did not observe any safety issue regarding PH, SICH, and death after IVT treatment compared with patients with no OAC therapy. Our results are consistent with previous observational studies and meta-analyses.[9–12] A registry study investigated the association of SICH after IVT in AIS patients taking DOAC within the past 48 hours of stroke onset, and they did not find any increased risk of SICH or harm after IVT in this patient group.[13] The authors concluded that there was no evidence that an intake of DOAC within 48 hours before IVT treatment had a negative outcome, which is in line with our findings.

Table 1. Baseline and Demographic Characteristics After Propensity Score Matching

	DOAC	No OAC	*p* value
n	894	1,788	
Previous atrial fibrillation	81.9 (732/894)	83.8 (1,499/1,788)	0.361
Age (yr)	75.2 (11.6)	75.7 (11.2)	0.221
Systolic blood pressure, baseline (mmHg)	152.1 (24.9)	154.7 (24.9)	0.012
Diastolic blood pressure, baseline (mmHg)	85.0 (15.2)	85.1 (15.2)	0.907
Glucose, baseline (mmol/l)	7.9 (5.2)	7.7 (3.6)	0.275
Cholesterol, baseline (mmol/l)	4.5 (2.1)	4.8 (4.1)	0.175
APTT (baseline)	28.9 (10.8)	26.9 (9.8)	<0.001
Onset to door (min)	89.0 (59, 136)	84 (57, 126)	0.070
Onset to imaging (min)	111 (76, 169)	107.5 (76, 155)	0.258
Onset to IVT (min)	165 (113, 224.5)	150 (110, 204)	0.002
NIHSS score (baseline)	11 (6, 18)	12 (7, 18)	0.491
mRS score (baseline)	0 (0, 1)	0 (0, 1)	0.647
Sex (M)	51.1 (457/894)	51.7 (925/1,788)	0.795
Previous hypertension	83.0 (742/894)	84.6 (1,512/1,788)	0.323
Previous hyperlipidemia	36.2 (319/880)	28.4 (496/1,744)	<0.001
Previous diabetes mellitus	23.3 (208/894)	22.3 (399/1,788)	0.613
Previous congestive heart failure	19.2 (172/894)	20.0 (357/1,788)	0.693
Previous TIA	8.3 (74/892)	4.5 (80/1,780)	<0.001
Previous stroke	22.6 (202/894)	21.6 (386/1,788)	0.586
Smoking, current and previous	16.5 (141/852)	19.3 (327/1,691)	0.097
Antiplatelet treatment (baseline)	9.2 (82/894)	11.5 (206/1,788)	0.074
Antihypertensive treatment (baseline)	80.9 (653/807)	74.8 (1,244/1,662)	0.001
Statin treatment (baseline)	36.9 (328/890)	22.8 (405/1,777)	<0.001
Antidiabetic treatment (baseline)	18.3 (148/807)	15.8 (262/1,661)	0.121
Apixaban (baseline)	20.0 (179/894)	0	
Dabigatran (baseline)	36.2 (324/894)	0	
Edoxaban (baseline)	5.1 (46/894)	0	
Rivaroxaban (baseline)	38.6 (345/894)	0	
Idarucizumab	14.7 (108/733)	0	
Endovascular thrombectomy treatment	20.9 (187/894)	20.7 (371/1,788)	0.960

Note: Mean (standard deviation), median (interquartile range), and percentage (number of cases/number of patients with data) presented for continuous, ordinal, and categorical variables, respectively. *p* values calculated by Student *t* test, Mann–Whitney *U* test, and Pearson's χ^2-test for continuous, ordinal, and categorical variable, respectively.

Abbreviations: DOAC = direct acting oral anticoagulant; IVT = intravenous thrombolysis; mRS = modified Rankin Scale; n = number of patients; NIHSS = National Institute of Health Stroke Scale; OAC = oral anticoagulant; PSM = propensity score matching; TIA = transient ischemic attack.

Table 2. Univariate Results After Propensity Score Matching for the Primary Analysis

	DOAC	No OAC	Odds ratios	*p* value
n	894	1,788		
SICH by SITS-MOST	1.1 (9/854)	1.5 (25/1,699)	0.71 (0.31–1.5)	0.493
SICH by ECASS2	4.0 (34/844)	4.3 (73/1,695)	0.93 (0.61–1.4)	0.823
mRS 0–2 at 3-month follow-up	47.9 (287/599)	46.4 (540/1,163)	1.1 (0.87–1.3)	0.589
Death by 3-month follow-up	25.1 (156/622)	24.0 (288/1,201)	1.1 (0.85–1.3)	0.645
Any PH	6.3 (51/808)	7.8 (128/1,647)	0.8 (0.57–1.1)	0.221
PH1	2.7 (22/807)	3.3 (55/1,645)	0.81 (0.48–1.3)	0.484
PH2	2.0 (16/807)	3.0 (50/1,645)	0.65 (0.35–1.1)	0.166
PHr1	1.5 (12/805)	1.3 (22/1,640)	1.1 (0.53–2.2)	0.911
PHr2	1.0 (8/805)	0.7 (12/1,640)	1.4 (0.53–3.3)	0.662
Major extracranial hemorrhage by 3-month follow-up	0.0 (0/424)	0.2 (2/809)	-	0.780

Note: *p* values per Pearson's χ^2-test. Unadjusted odds ratios after propensity score matching, with 95% confidence intervals within parentheses.
Abbreviations: DOAC = direct-acting oral anticoagulants; ECASS = European Cooperative Acute Stroke Study; MOST = Safe Implementation of Treatment in Stroke Monitoring Study; n = number of patients; OAC = oral anticoagulants; PSM = propensity score matching; SICH = symptomatic intracranial hemorrhage; SITS-PH = parenchymal hemorrhage.

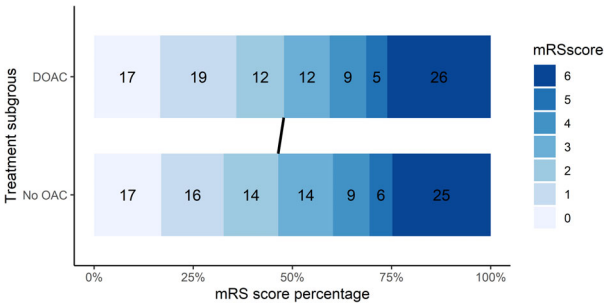

Fig 2: Modified Rankin Scale (mRS) score distribution after propensity score matching for the study population. Solid black line shows limit between mRS score 2 and 3. DOAC = direct acting oral anticoagulants; mRS = modified Rankin Scale; OAC = oral anticoagulants. [Color figure can be viewed at www.annalsofneurology.org]

Our secondary analyses of only DOAC patients regarding the time from last intake of DOAC to IVT treatment observed no difference in univariate analyses regarding any of the outcomes. For the hemorrhage variables, this may be due to relatively low numbers of hemorrhages, leading to a lack of statistical power. Still, no clear trend of increasing risk of hemorrhage, despite recent DOAC intake before IVT treatment, was observed, in both the primary and sensitivity analyses. In contrast, our ordinal multivariable analysis showed that longer time from last intake of DOAC before IVT treatment was associated with more PH2 and a trend toward a lower chance of functional independency at 3 months. Although these results may be more difficult to explain, they too do not support the inherent assumption of a higher risk of hemorrhage with more recent DOAC intake before IVT treatment. In the sensitivity analysis of patients with dabigatran treatment, the association of longer time from last intake of DOAC with a lower risk of SICH by ECASS II definition and death by 3-month follow-up is mainly driven by higher rates of these events in the <4 hours subgroup.

Whether these finding are due to a difference in outcomes based on the mechanism of DOAC or by chance is difficult to explain, as the number of events in the dabigatran multivariable analyses were low, with a higher number of events in the 0–4-hour time period, but a stable proportion in the remaining time periods. Importantly, the SICH per ECASS II definition includes hemorrhagic infarction type 1 and 2, and in our results there was no association with an increase of PH or more conservative definitions of SICH per the SITS Monitoring Study with the time of last dose of DOAC taken. Additionally, our explorative analysis for finding the most significantly associated variables with the outcomes did not yield prior DOAC treatment as an independent variable in any of the final regression models, suggesting that prior DOAC treatment in general may not have as much an importance for hemorrhage after IVT as one might expect. Together, these results raise questions about the assumed dynamics of the last DOAC intake before IVT treatment and its association with outcomes, with data on DOAC intake available for as early as within 4 hours of stroke onset.

Table 3. Univariate Results After Propensity Score Matching for the Sensitivity Analysis After Removing Direct-Acting Oral Anticoagulants Patients that Received Reversal Agents

Outcomes	OAC	No OAC	Odds ratios	*p* value
n	786	1,572		
SICH by SITS-MOST	1.1 (8/751)	1.8 (26/1,484)	0.6 (0.25–1.3)	0.285
SICH by ECASS2	4.2 (31/741)	5.0 (75/1,488)	0.82 (0.53–1.2)	0.430
mRS 0–2 at 3-month follow-up	47.7 (259/543)	47.0 (497/1,058)	1.0 (0.84–1.3)	0.825
Death by 3-month follow-up	25.0 (141/563)	24.6 (267/1,084)	1.0 (0.81–1.3)	0.901
Any PH	6.8 (48/709)	8.0 (115/1,432)	0.83 (0.58–1.2)	0.343
PH1	3.0 (21/708)	3.0 (43/1,432)	0.99 (0.57–1.7)	1.000
PH2	2.1 (15/708)	3.2 (46/1,432)	0.65 (0.35–1.1)	0.196
PHr1	1.7 (12/706)	2.0 (28/1,424)	0.86 (0.42–1.7)	0.797
PHr2	0.8 (6/706)	0.8 (11/1,424)	1.1 (0.38–2.9)	1.000
Major extracranial hemorrhage by 3-month follow-up	0.0 (0/382)	1.0 (7/734)	–	0.130

Note: *p* values per Pearson's χ^2-test. Unadjusted odds ratios after propensity score matching, with 95% confidence intervals within parentheses.
Abbreviations: DOAC = direct-acting oral anticoagulants; ECASS = European Cooperative Acute Stroke Study; n = number of patients; OAC = oral anticoagulants; PH = parenchymal hemorrhage; PSM = propensity score matching; SICH = symptomatic intracranial hemorrhage; SITS-MOST = Safe Implementation of Treatment in Stroke Monitoring Study.

Our results from these analyses would suggest that DOAC intake close to stroke onset does not seem to affect outcomes negatively on the population as a whole, as might be intuitively believed. Our observational data may help guide clinicians make a better-informed decision when presented with patients with disabling stroke

Table 4. Outcomes by Last Dose of Direct-Acting Oral Anticoagulants Taken

	≤4 h	4–8 h	8–12 h	12–24 h	>24 h	*p* value
n	77	86	115	158	388	
SICH by SITS-MOST	1.4 (1/74)	1.2 (1/81)	1.0 (1/105)	0.0 (0/139)	0.9 (3/347)	0.802
SICH by ECASS2	8.1 (6/74)	2.5 (2/81)	2.9 (3/105)	2.9 (4/138)	3.5 (12/345)	0.291
mRS 0–2 at 3-month follow-up	42.2 (19/45)	45.1 (23/51)	53.1 (34/64)	46.7 (50/107)	48.6 (108/222)	0.818
Death by 3-month follow-up	31.9 (15/47)	21.2 (11/52)	23.4 (15/64)	25.5 (28/110)	23.8 (55/231)	0.762
Any PH	4.3 (3/69)	5.2 (4/77)	4 (4/100)	4.5 (6/132)	6.2 (21/336)	0.876
PH1	2.9 (2/69)	3.9 (3/77)	2.0 (2/100)	1.5 (2/131)	3.0 (10/335)	0.841
PH2	0.0 (0/69)	1.3 (1/77)	2.0 (2/100)	1.5 (2/131)	1.2 (4/335)	0.844
PHr1	0.0 (0/69)	0.0 (0/76)	1.0 (1/100)	1.5 (2/132)	2.1 (7/335)	0.504
PHr2	1.4 (1/69)	0.0 (0/76)	1.0 (1/100)	0.0 (0/132)	0.6 (2/335)	0.645
Major extracranial hemorrhage by 3-month follow-up	0.0 (0/33)	0.0 (0/40)	0.0 (0/47)	0.0 (0/81)	0.6 (1/164)	0.873

Note: *p* values per Pearson's χ^2-test.
Abbreviations: DOAC = direct-acting oral anticoagulants; ECASS = European Cooperative Acute Stroke Study; n = number of patients; PH = parenchymal hemorrhage; SICH = symptomatic intracranial hemorrhage; SITS-MOST = Safe Implementation of Treatment in Stroke Monitoring Study.

Table 5. Multivariable Analysis for Time of Last Dose of Direct-Acting Oral Anticoagulants Taken Before Stroke Onset, as an Ordinal Variable of Time Intervals 0–4, 4–8, 8–12, 12–24, and >24 hours

	Odds ratios	*p* values
SICH by SITS-MOST	1.20 (0.87–1.80)	0.303
SICH by ECASS 2	0.99 (0.85–1.20)	0.904
mRS 0–2 by 3-month follow-up	0.91 (0.83–1.00)	0.063
Death by 3-month follow-up	1.00 (0.93–1.10)	0.575
Any PH	1.10 (0.95–1.30)	0.233
PH1	0.97 (0.79–1.20)	0.796
PH2	1.40 (1.10–2.00)	0.020
PHr1	1.00 (0.76–1.40)	0.976
PHr2	1.10 (0.74–1.70)	0.736
Major extracranial hemorrhage by 3-month follow-up	1.30 (0.57–5.50)	0.575

Note: *p* values for the ordinal variable last dose of direct-acting oral anticoagulants taken before stroke onset as a predictor in the multivariable models of each outcome. Multivariable models adjusted for: age, sex, baseline National Institute of Health Stroke Scale, onset to intravenous thrombolysis treatment time, history of atrial fibrillation, history of hypertension, history of hyperlipidemia, history of diabetes mellitus, history of congestive heart failure, and treatment with endovascular thrombectomy.

Abbreviations: DOAC = direct acting oral anticoagulants; ECASS = European Cooperative Acute Stroke Study; PH = parenchymal hemorrhage; SICH = symptomatic intracranial hemorrhage; SITS-MOST = Safe Implementation of Treatment in Stroke Monitoring Study.

symptoms with ongoing DOAC treatment where IVT is the only reperfusion option, such as when EVT is not a treatment option due to distal/no visible occlusion or EVT is not available in the center or region.

Common wisdom would suggest that anticoagulant intake may increase the risk of hemorrhagic transformation after IVT through some form of combined effect, and current guidelines have accepted this view.[1,2] Yet, more specific considerations about this potential mechanism may raise questions about its validity, and thus provide a possible explanation for our findings. First, unlike heparin and vitamin K antagonists, DOACs have only one target in the coagulation pathway—thrombin for dabigatran and factor Xa for apixaban, rivaroxaban, and edoxaban—making these drugs as effective as the older drug, but safer, with a lower incidence of bleeding complications.[23] Second, hemostasis is not solely based on the coagulation cascade, but results from a complex interplay between endothelium, platelets, von Willebrand factor, and coagulation factors.[24] Third, DOACs and recombinant tissue plasminogen activator have different mechanisms of action and functions: anticoagulants prevent the formation of new blood clots by acting at a different site of the coagulation cascade, but ultimately inhibiting fibrin formation, whereas recombinant tissue plasminogen activator dissolves existing clots by activating mainly fibrin-bound plasminogen and consequently depolymerizing fibrin (Fig S1).[25] In principle, the two pathways are different from each other, thus there is no obvious potentiation of the risk of hemorrhage between them.[26] In light of these considerations, our results may not be as surprising or counterintuitive as one might initially assume.

Our findings are also in agreement with other large systematic reviews and meta-analyses. A study by Shahjouei et al.[9] also supports the findings that an intake of DOAC within 48 hours in combination with IVT treatment did not increase the risk of SICH. Our results are also comparable with more recent studies.[14,27] Similar to these studies, our unadjusted DOAC population was older and had a higher prevalence of cardiovascular risk factors compared with the no OAC group. These studies did not find any difference in the risk of SICH between DOAC and no OAC patients in the adjusted analysis, which mirrors our results. However, these studies were limited to smaller study populations or DOAC intake within 7 days before stroke onset.

There were several limitations to our study. The main limitations were the observational retrospective, register-based study design with inherent risk of biases, and the missing data. Approximately 34% of patients had missing mRS at 3 months. However, this applies to both the DOAC and no OAC groups. Data on PH and SICH were available for 90% and 96%, respectively. We could classify more patients as no SICH based on clinical data (no clinical deterioration), even though imaging data were missing. We also had limited data on the exact time of the last DOAC dose taken, which could lead to some unknown bias regarding the main analysis. Finally, we do not know if patients in the DOAC group had any abnormal levels of INR or direct factor Xa activity assays. Additionally, for previous antiplatelet therapy, we did not differentiate between single or dual regimen, which could affect this variable. The main strengths of our study were the clinically valuable data, pending results from future randomized controlled trials, and a relatively large cohort from a worldwide stroke registry with available outcomes on SICH, as well as PH.

Conclusions

In this observational study based on data from an international registry, we did not find any difference in safety outcome regarding PH, SICH, and death or functional outcomes at 3 months after IVT therapy between AIS patients with ongoing DOAC and no OAC treatment. These findings remained stable in our secondary and sensitivity analyses, including no change in outcomes when analyzing patients that did not receive DOAC reversal. Our study results, together with other published observational data, indicate no observed harm of IVT treatment in patients with recent intake of DOAC before index stroke. Further prospective studies are needed to shed light on this topic and help guide physicians' decisions when no randomized controlled trials are available, with investigation into the role of the time from the last dose of DOAC much warranted.

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Author Contributions

M.M., M.S., and N.A. contributed to the conception and design of the study. All authors contributed to the acquisition and analysis of the data. All authors contributed to the drafting of the manuscript and its figures.

Potential Conflicts of Interest

M.M. has received financial support from SITS International, from which the data for this study were acquired. N.A. is the chairman of SITS International, from which the data for this study were acquired. The remaining authors have nothing to report.

Data availability

Access to the anonymized data for this study will be available from the corresponding author upon reasonable request from qualified researchers, contingent on approval by the SITS Scientific Committee.

References

1. Berge E, Whiteley W, Audebert H, et al. European stroke organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke. Eur Stroke J 2021;6:I–LXII. https://doi.org/10.1177/2396987321989865.
2. Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 guidelines for the early Management of Patients with Acute Ischemic Stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2018;49:e46–e110. https://doi.org/10.1161/str.0000000000000158.
3. Emberson J, Lees KR, Lyden P, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. Lancet 2014;384:1929–1935. https://doi.org/10.1016/s0140-6736(14)60584-5.
4. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014;383:955–962. https://doi.org/10.1016/s0140-6736(13)62343-0.
5. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013;369:2093–2104. https://doi.org/10.1056/NEJMoa1310907.
6. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883–891. https://doi.org/10.1056/NEJMoa1009638.
7. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139–1151. https://doi.org/10.1056/NEJMoa0905561.
8. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981–992. https://doi.org/10.1056/NEJMoa1107039.
9. Shahjouei S, Tsivgoulis G, Goyal N, et al. Safety of intravenous thrombolysis among patients taking direct Oral anticoagulants: a systematic review and meta-analysis. Stroke 2020;51:533–541. https://doi.org/10.1161/strokeaha.119.026426.
10. Xian Y, Federspiel JJ, Hernandez AF, et al. Use of intravenous recombinant Tissue plasminogen activator in patients with acute ischemic stroke who take non-vitamin K antagonist Oral anticoagulants before stroke. Circulation 2017;135:1024–1035. https://doi.org/10.1161/circulationaha.116.023940.
11. Seiffge DJ, Hooff RJ, Nolte CH, et al. Recanalization therapies in acute ischemic stroke patients: impact of prior treatment with novel oral anticoagulants on bleeding complications and outcome. Circulation 2015;132:1261–1269. https://doi.org/10.1161/circulationaha.115.015484.
12. Suzuki K, Aoki J, Sakamoto Y, et al. Low risk of ICH after reperfusion therapy in acute stroke patients treated with direct oral anti-coagulant. J Neurol Sci 2017;379:207–211. https://doi.org/10.1016/j.jns.2017.06.004.
13. Meinel TR, Wilson D, Gensicke H, et al. Intravenous thrombolysis in patients with ischemic stroke and recent ingestion of direct Oral anticoagulants. JAMA Neurol 2023;80:233–243. https://doi.org/10.1001/jamaneurol.2022.4782.
14. Kam W, Holmes DN, Hernandez AF, et al. Association of Recent use of non-vitamin K antagonist Oral anticoagulants with intracranial hemorrhage among patients with acute ischemic stroke treated with

alteplase. JAMA 2022;327:760–771. https://doi.org/10.1001/jama.2022.0948.

15. Behnoush AH, Khalaji A, Bahiraie P, Gupta R. Meta-analysis of outcomes following intravenous thrombolysis in patients with ischemic stroke on direct oral anticoagulants. BMC Neurol 2023;23:440. https://doi.org/10.1186/s12883-023-03498-8.
16. Kurowski D, Jonczak K, Shah Q, et al. Safety of endovascular intervention for stroke on therapeutic anticoagulation: multicenter cohort study and meta-analysis. J Stroke Cerebrovasc Dis 2017;26:1104–1109. https://doi.org/10.1016/j.jstrokecerebrovasdis.2016.12.027.
17. Ahmed N, Audebert H, Turc G, et al. Consensus statements and recommendations from the ESO-Karolinska stroke update conference, Stockholm 11-13 November 2018. Eur Stroke J 2019;4:307–317. https://doi.org/10.1177/2396987319863606.
18. Wahlgren N, Ahmed N, Davalos A, et al. Thrombolysis with alteplase for acute ischaemic stroke in the safe implementation of thrombolysis in stroke-monitoring study (SITS-MOST): an observational study. Lancet 2007;369:275–282. https://doi.org/10.1016/s0140-6736(07)60149-4.
19. Ahmed N, Wahlgren N, Grond M, et al. Implementation and outcome of thrombolysis with alteplase 3-4.5 h after an acute stroke: an updated analysis from SITS-ISTR. Lancet Neurol 2010;9:866–874. https://doi.org/10.1016/s1474-4422(10)70165-4.
20. von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007;370:1453–1457. https://doi.org/10.1016/s0140-6736(07)61602-x.
21. Hacke W, Kaste M, Fieschi C, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Lancet 1998;352:1245–1251. https://doi.org/10.1016/s0140-6736(98)08020-9.
22. Zhong Y, Kennedy EH, Bodnar LM, Naimi AI. AIPW: an R package for augmented inverse probability-weighted estimation of average causal effects. Am J Epidemiol 2021;190:2690–2699. https://doi.org/10.1093/aje/kwab207.
23. Chai-Adisaksopha C, Crowther M, Isayama T, Lim W. The impact of bleeding complications in patients receiving target-specific oral anticoagulants: a systematic review and meta-analysis. Blood 2014;124:2450–2458. https://doi.org/10.1182/blood-2014-07-590323.
24. Sang Y, Roest M, de Laat B, et al. Interplay between platelets and coagulation. Blood Rev 2021;46:100733. https://doi.org/10.1016/j.blre.2020.100733.
25. Collen D, Lijnen HR, Todd PA, et al. A review of its pharmacology and therapeutic use as a thrombolytic agent. Drugs 1989;38:346–388. https://doi.org/10.2165/00003495-198938030-00003.
26. Frol S, Pretnar Oblak J, Kermer P, et al. Higher efficacy of intravenous thrombolysis in patients with acute ischemic stroke taking direct oral anticoagulants-a new relevant hypothesis. Front Neurol 2024;15:1458697. https://doi.org/10.3389/fneur.2024.1458697.
27. Bücke P, Jung S, Kaesmacher J, et al. Intravenous thrombolysis in patients with recent intake of direct oral anticoagulants: a target trial analysis after the liberalization of institutional guidelines. Eur Stroke J 2024;9:23969873241252751. https://doi.org/10.1177/23969873241252751.