Stroke

ORIGINAL CONTRIBUTION

Intravenous Thrombolysis in Patients With Recent Intake of Direct Oral Anticoagulants: A Target Trial Analysis and Comparison With Reversal Agent Use

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BACKGROUND: Intravenous thrombolysis (IVT) in patients with recent ingestion of direct oral anticoagulants (DOACs) is a frequent challenge and remains controversial. The benefit of DOAC reversal before IVT is uncertain.

METHODS: Using target trial methodology, we analyzed data from 28 comprehensive stroke centers. Patients on DOACs were included if they met IVT criteria, had a National Institutes of Health Stroke Scale score of ≥2, and last DOAC intake within 48 hours or was undeterminable. Safety and efficacy outcomes (symptomatic intracerebral hemorrhage, any intracerebral hemorrhage, major bleeding, 90-day mortality, and good functional outcome [modified Rankin Scale score of 0–2 or return to baseline]) were compared between those receiving IVT versus no IVT and IVT with versus without reversal. In addition, a comparison was made with patients from the New Zealand stroke registry, all of whom underwent reversal with idarucizumab. We adjusted for covariates known to be associated with safety and efficacy outcomes, including age, stroke severity, intended thrombectomy, blood glucose, blood pressure, DOAC reversal, and time from last intake.

RESULTS: Overall, 1342 patients fulfilled the target trial criteria. The median age was 80 (interquartile range, 73–86) years, median National Institutes of Health Stroke Scale score was 11, 50% were female, and 52% of patients received endovascular therapy. IVT was given in 342 of 1342 (25%) patients. Of these, 141 (41.2%) had verified DOAC intake <12 hours before admission, and 92 (26.9%) within 12 to 24 hours. Symptomatic intracerebral hemorrhage occurred in 10 of 328 (3.0%) of patients receiving IVT and 54 of 921 (5.9%) patients not receiving IVT (adjusted difference, −2.1% [95% CI, −5.3% to +1.2]). Patients receiving IVT were more likely to have good functional outcomes (adjusted difference, +14.4% [95% CI, +7.1% to +21.8%]). Comparing 289 patients with reversal (from the additional New Zealand registry) and 283 patients without reversal before IVT (from the target trial population), there was no significant difference in symptomatic intracerebral hemorrhage, major bleeding, or efficacy outcomes.

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CONCLUSIONS: This target trial confirms previous observational data regarding the safety of off-label IVT in patients with recent DOAC intake. More data and dedicated trials are needed for patients with confirmed high DOAC plasma levels and regarding the efficacy and safety of DOAC reversal before IVT.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: anticoagulants ■ atrial fibrillation ■ stroke ■ therapeutic thrombolysis

Nonstandard Abbreviations and Acronyms

CT	computed tomography
DOAC	direct oral anticoagulant
DO-IT	Direct Oral Anticoagulant–Intravenous Thrombolysis
EVT	endovascular therapy
ICH	intracerebral hemorrhage
IQR	interquartile range
IVT	intravenous thrombolysis
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
sICH	symptomatic intracerebral hemorrhage

Direct oral anticoagulants (DOACs) are approved for the primary and secondary prevention of ischemic stroke and systemic embolism in patients with nonvalvular atrial fibrillation.[1] DOAC use is steadily rising as a result of the increasing prevalence of atrial fibrillation among the aging population, as well as additional treatment indications such as for venous thromboembolism and preventing major cardiovascular events in stable atherosclerosis.[2] This has major implications as it is estimated that 1 in 6 patients with acute ischemic stroke otherwise eligible for intravenous thrombolysis (IVT) are on DOAC therapy.[3,4]

Current international guidelines generally advise against IVT use in patients who have taken a DOAC within 48 hours of the stroke if anticoagulant activity cannot be excluded, primarily due to concerns about the risk of symptomatic intracerebral hemorrhage (sICH).[5–7] However, this notion is challenged by data stemming from preclinical research,[8–12] observational clinical data[13,14] and randomized trials testing the thrombin inhibitor argatroban in addition to IVT,[15,16] which have not shown a significant increase in the risk of sICH.[15,17] Some guidelines recommend reversing dabigatran's anticoagulant effect with idarucizumab before administering IVT.[6] While dabigatran reversal has good safety data,[18] it is not clear whether reversal is needed or improves outcome. In addition, idarucizumab is of limited availability globally, is costly, and is associated with IVT treatment delays.

In this observational cohort study, we aimed to investigate the safety and efficacy of off-label IVT decisions. We designed the data collection and analysis using the principles of a hypothetical randomized controlled trial (target trial framework) to reduce the risk of bias in observational data sets.[19,20] Specifically, we compared outcomes in patients with recent DOAC intake who received IVT with those who did not. We hypothesized that off-label IVT use would not increase hemorrhagic complications, specifically sICH, and could potentially improve functional outcomes. In addition, we sought to compare DOAC patients receiving IVT with and without prior reversal with the hypothesis that safety and efficacy outcomes would not differ between groups.

METHODS

Study Design, Ethics, and Data Sharing

We conducted a retrospective, multicenter, observational cohort study, using target trial methodology to simulate the conditions of a randomized controlled trial.[19,20] This framework suggests developing a protocol of a hypothetical optimal randomized controlled trial on the topic of interest and to come as close as possible to this protocol for the observational data collection, time points, and analysis to avoid bias (eg, immortal time bias). One example is the inclusion of patients with verified intake within the last 48 hours only, rather than an ongoing prescription because in a trial also only patients with recent intake would be enrolled.

Retrospective data were drawn from prospective, ongoing stroke registries at 28 stroke centers and 1 national stroke registry not specifically designed for this study question (Table S1; Figure S1) and included cases between 2019 and 2023 internationally. For centers participating in the prior DO-IT (Direct Oral Anticoagulant–Intravenous Thrombolysis) project,[13] only newly enrolled patients who had not been included in the prior project were eligible for inclusion to prevent duplicate publication. Anonymized data was pooled centrally. Where applicable, approval from local ethics committees was obtained. We adhered to the STROBE guidelines to ensure accurate and transparent reporting of the study findings. The analysis plan was finalized and circulated before data collection and analysis. Individual patient data from this study cannot be shared due to data protection regulations; however, aggregated data can be provided upon request.

Patient Selection

Consecutive patients captured in the prospective registries of the participating comprehensive stroke centers were screened for eligibility. The inclusion criteria were (1) adult patients with a

confirmed diagnosis of acute ischemic stroke and an indication for IVT; (2) arrival within 12 hours of symptom onset; (3) a minimum National Institutes of Health Stroke Scale (NIHSS) score of 2, with the neurological deficit clinically judged to be disabling; (4) DOAC intake within 48 hours before the anticipated IVT bolus, or an active DOAC prescription with no verifiable last intake time in the emergency setting. Exclusion criteria were (1) evidence of acute or subacute intracerebral hemorrhage (ICH) on the initial brain imaging; (2) any contraindications for IVT other than the use of DOACs; (3) significant prestroke disability (modified Rankin Scale [mRS] score of 5) or advanced dementia; (4) known hypersensitivity or previous adverse reaction to IVT or its components; and (5) pregnancy or lactation. Local investigators evaluated all patients based on these criteria. Eligible patients were then categorized into 2 groups for further analysis: those who received IVT and those who did not.

Approach Toward IVT in DOAC Patients

The approaches varied between participating sites regarding IVT, despite DOAC treatment in the study timeframe. Whereas some centers excluded all patients with recent DOAC intake from IVT, others based their decision on plasma level measurements, offering IVT if levels were below predefined thresholds, or used IVT in dabigatran-treated subjects only after reversal with idarucizumab. Several centers, however, offered IVT regardless of plasma levels or prior DOAC reversal.[21,22]

Data Collection

Local investigators collected baseline characteristics and specific DOAC-related details from the electronic health records, including: (1) the type and dosage of the DOAC agent; (2) timing of the last dose, categorized as last intake <12 hours of symptom onset, 12 to 24 hours, 24 to 48 hours, or unverifiable in the emergency setting (eg, in a patient with aphasia but an ongoing DOAC prescription); (3) measured DOAC plasma levels or other surrogates of anticoagulation activity (anti-Xa activity, urine dipsticks). Imaging information was sourced from neuroradiological reports by site investigators (without central core laboratory) and included: (1) large vessel occlusion (carotid-T, M1/M2 segments of the middle cerebral artery, basilar artery); (2) Alberta Stroke Program Early Computed Tomography (CT) Score for CT scans, DWI–Alberta Stroke Program Early CT Score for magnetic resonance imaging scans, or posterior circulation Alberta Stroke Program Early CT Score for vertebrobasilar strokes; (3) white matter disease severity, quantified using the age-related white matter changes scale (age-related white matter changes scale).[23–26]

Outcome Measures

The primary safety outcome was sICH, defined by the criteria of the ECASS III (European Cooperative Acute Stroke Study III) and National Institute of Neurological Disorders and Stroke (Tables only) rt-PA Stroke Study Group.[27,28] Secondary safety outcomes included any ICH within 36 hours post-IVT, classified according to the Heidelberg Bleeding Classification,[29] as well as all-cause mortality, major bleeding events, and the occurrence of orolingual edema (see Table S2 for definitions).

The primary efficacy outcome was good functional outcome, defined as an mRS score of ≤2 at 90 days or a return to baseline mRS score. Secondary outcomes included (1) categorical shift in the mRS score at day 90 (±2 weeks) after admission; (2) stroke severity (NIHSS score) at 24±8 hours. Follow-up assessments were conducted either by telephone or by an in-person clinical visit, and functional outcome was assessed by each site.

Statistical Analysis

Distribution of ordinal, continuous, and categorical variables was described using medians with interquartile ranges (IQRs) or means with SD, as appropriate. Baseline characteristics were compared between groups using the Pearson χ^2 test for categorical variables and either the Student *t* test or Kruskal-Wallis test for continuous and ordinal variables.

For analyzing the efficacy outcomes, we prespecified to apply inverse probability of treatment weighting to address potential confounding factors, specifically baseline NIHSS score (continuous), age (continuous), endovascular therapy (EVT, binary), DOAC reversal (binary), DOAC plasma level category (ordinal) and other relevant baseline differences known to influence the outcome.[30] For causal effect estimation, we used inverse probability weighting and inverse probability weighting with regression adjustment in a doubly robust framework, which estimates the average treatment effect using inverse probability weighting for the treatment assignment using logistic regression models for binary outcomes and linear regression models for continuous outcomes. For the mRS score shift analysis, we used ordered logistic regression.

For the safety outcomes, we prespecified to adjust for known predictors of sICH (depending on the number of observed outcome events), including age (continuous), NIHSS score (continuous), prestroke disability, hypertension (binary), and systolic blood pressure (continuous). Sensitivity analyses on safety and efficacy outcomes were prespecified for patients ineligible for EVT and according to time from last DOAC intake, DOAC plasma levels, and reversal agent use. Adjusted outcome differences (in percentages) between the IVT and non-IVT groups were reported with corresponding 95% CIs.

All statistical analyses were conducted using STATA (StataCorp., 2019. Stata Statistical Software: Release 16; StataCorp LLC, College Station, TX). We performed complete case analysis (without the use of imputation), with 2-sided *P* values, and a threshold of $P<0.05$ was considered statistically significant without adjustment for multiple testing.

Sample Size Calculation

With this analysis, we aimed to rule out a worrying increase in sICH (exceeding 6% in total) associated with a more liberal IVT approach in DOAC-treated patients (ie, offering IVT despite recent intake, measurable plasma levels, and without reversal). A noninferiority framework was chosen because the primary clinical concern in this off-label setting is safety, with many clinicians likely to accept IVT if it does not significantly increase the risk of sICH, an end point considered more reliable than functional outcome, which is more prone to bias by indication. Estimating a 3% sICH rate from non-DOAC IVT patients and a noninferiority margin of 3% ($\alpha=0.05$, power=80%), we determined a target sample size of 800 patients (400 IVT, 400 controls) within this observational data set (target trial analysis).

As an exploratory analysis, Least Absolute Shrinkage and Selection Operator regression was applied to identify the most relevant predictors for sICH. Furthermore, we analyzed the main outcomes according to the availability of DOAC plasma levels (yes versus no), DOAC dosing (therapeutic versus subtherapeutic), and according to whether centers had a liberal approach (offering IVT to ≥20% of patients during the study timeframe versus <20%).

Comparison Between IVT Patients With and Without Reversal

In addition to the target trial population, IVT patients undergoing thrombolysis after reversal with idarucizumab were extracted from the New Zealand national stroke registry.[31] Using this sample of consecutive patients fulfilling the target trial criteria listed above and receiving idarucizumab, we compared the same outcomes between IVT patients receiving reversal versus not receiving DOAC reversal using the same statistical models specified above. For this analysis, the patients from the target population who received idarucizumab before IVT were combined with the New Zealand cohort (Figure S1).

RESULTS

Overall, the target trial cohort included 1342 individuals; the median age was 80 (IQR, 73–86) years, 50% were female, the median NIHSS score was 11 (6–18), and 88% had known atrial fibrillation as the indication for DOAC therapy. Of these, 342 patients (25%) received IVT. Compared with non-IVT patients, this group had lower stroke severity, less diabetes, and coronary heart disease, and were more often on dabigatran. Large vessel occlusion and EVT were less common among IVT-treated patients. See Table 1 for full demographics, baseline characteristics, and differences.

Among those undergoing IVT, DOAC levels were available in 230 of 342 (67%) and in 400 of 1000 (40%) not receiving IVT. The overall median DOAC plasma level was lower in the IVT group (29 versus 79 ng/mL). Overall, 85 of 342 (25%) patients receiving IVT had plasma levels of >50 ng/mL, and 35 of 342 (10%) had plasma levels >100 ng/mL. Last ingestion was reported within 12 hours for 141 (41%) and within 24 hours for 233 (68%) patients receiving IVT. Idarucizumab was administered in 59 of 72 patients with dabigatran before IVT. DOAC-specific information of both groups is presented in Table 2.

The primary safety outcome was assessable in 328 of 342 (96%) IVT patients and 921 of 1000 (92%) non-IVT patients. Ten IVT patients (3.0% [95% CI, 1.5%–5.5%]) experienced sICH versus 54 non-IVT patients (5.9% [95% CI, 4.4%–7.6%]; adjusted difference for IVT, −2.1% [95% CI, −5.3% to +1.2%]). The rates of sICH (National Institute of Neurological Disorders and Stroke criteria), any radiological ICH, or major bleeding did not differ between groups. We observed a numerical increase in orolingual edema after IVT (see Table 3 for safety outcomes). In the sensitivity analyses, there was no signal for increased sICH among those with documented DOAC plasma levels >100 ng/mL or proven ingestion within 12 hours and not receiving reversal agents, and sICH occurred in 2 of 102 patients in this subgroup (1.96% [95% CI, 0.2%–6.9%]).

Mortality at 90 days was numerically lower in the IVT group (15.7% [95% CI, 11.7%–20.3%]) versus non-IVT group (22.7% [95% CI, 20.1%–25.5%]; adjusted difference, −3.3% [95% CI, −9.5% to +2.9%]). Good functional outcome was more frequent in the IVT group (62.2% [95% CI, 56.4%–67.8%]) versus non-IVT group (43.7% [95% CI, 40.5%–47.0%]; adjusted difference for IVT, +14.4% [95% CI, +7.1% to +21.8%]). IVT was associated with lower disability categories in the ordinal regression shift analysis (adjusted odds ratio, 0.60 [95% CI, 0.45–0.80]). The adjusted difference between admission and 24-hour NIHSS score was not different across groups (weighted mean, 0.33 [95% CI, −0.58 to 1.24]).

Subgroup Analysis

Overall, 639 of 1342 (47.6%) patients on DOAC therapy did not receive EVT. Of these, 214 (33.5%) received IVT and 425 (66.6%) did not receive IVT. See Tables S3 and S4 for baseline characteristics (IVT versus no IVT). The rate of sICH was 1.5% (95% CI, 0.3%–4.2%) in those receiving IVT versus 1.7% (95% CI, 0.6%–3.7%) in those not receiving IVT (adjusted difference for IVT, −0.8% [95% CI, −2.8% to +1.2%]). There was a higher rate of good functional outcome in the IVT group 66.7% versus the no IVT group, 49.2%. They had a higher adjusted difference in good functional outcome with IVT (+19.8% [95% CI, +12.2% to +27.3%]).

In the exploratory subgroup analysis according to the availability of plasma levels and subtherapeutic dosing, the results were consistent with the overall findings and did not indicate relevant heterogeneity (Tables S5 and S6). However, the potential benefits of IVT were only tangible in those with a liberal approach. Namely, a significant association of IVT with better outcomes (dichotomized and shift) was only seen in centers offering IVT to >20% of the patient population without difference in safety outcomes (Table S7).

Comparison Between IVT Patients With and Without Reversal

In the New Zealand national stroke registry, 225 dabigatran patients received IVT after DOAC reversal with idarucizumab (in addition to the 59 patients from the target trial cohort). Thus, a total of 283 (49%) received no reversal, whereas 289 (51%) did receive reversal (all idarucizumab). There were significant differences between the groups: DOAC reversal patients were younger, less often

Table 1. Baseline Characteristics in DOAC Patients Receiving Versus Not Receiving Intravenous Thrombolysis

	Overall (N=1342)	No IVT (n=1000)	IVT (n=342)	*P* value
Age, y, median (IQR)	80 (73–86)	80 (73–86)	80 (73–86)	0.72
Female sex, n (%)	674 (50.3%)	500 (50.1%)	174 (50.9%)	0.79
Prestroke mRS score, median (IQR)	1 (0–2)	1 (0–2)	0 (0–2)	0.72
Cardiovascular risk factors, n (%)				
Known atrial fibrillation	1178 (87.8%)	881 (88.1%)	297 (86.8%)	0.54
Other reasons for DOAC use				
Previous venous thromboembolism or pulmonary embolism	100 (7.5%)	75 (7.5%)	25 (7.3%)	
Prophylaxis postsurgery	5 (0.4%)	3 (0.3%)	2 (0.6%)	
Rare causes (eg, thrombophilia)	5 (0.4%)	3 (0.3%)	2 (0.6%)	
Atherosclerosis (eg, limb ischemia)	16 (1.2%)	10 (1.0%)	6 (1.8%)	
Other (eg, cardiac thrombus)	11 (0.8%)	6 (0.6%)	5 (1.5%)	
Unclear	74 (5.5%)	67 (6.7%)	7 (2.0%)	
Hypertension	1083 (80.8%)	806 (80.6%)	277 (81.2%)	0.80
Hyperlipidemia	724 (54.0%)	538 (53.8%)	186 (54.7%)	0.77
Diabetes	388 (29.0%)	306 (30.6%)	82 (24.1%)	0.023
Active smoking	149 (11.5%)	109 (11.3%)	40 (12.1%)	0.69
Coronary heart disease	312 (23.3%)	247 (24.7%)	65 (19.1%)	0.033
Peripheral artery disease	169 (12.9%)	130 (13.0%)	39 (12.6%)	0.85
Previous ischemic stroke or TIA	444 (33.1%)	327 (32.7%)	117 (34.4%)	0.56
Stroke characteristics				
NIHSS score (admission), median (IQR)	11 (6–18)	12 (6–18)	9.5 (6–16)	0.002
Systolic blood pressure, mm Hg (admission; mean [SD])	152 (27)	152 (26)	154 (27)	0.14
Additional prior antiplatelet use, n (%)				
Single	100 (7.7%)	79 (7.9%)	21 (6.8%)	0.72
Double	10 (0.8%)	7 (0.7%)	3 (1.0%)	
Large vessel occlusion, n (%)*	766 (59.1%)	640 (65.0%)	126 (40.4%)	<0.001
Intended thrombectomy, n (%)	692 (52.0%)	565 (57.1%)	127 (37.2%)	<0.001
Imaging findings, median (IQR)				
ASPECTS/ pcASPECTS	10 (8–10)	9 (8–10)	10 (9–10)	<0.001
White matter hyperintensities (ARWMC criteria)	1 (1–2)	1 (1–2)	1 (1–2)	0.63
Blood sample analysis, median (IQR)				
Blood glucose levels, mmol/L	6.8 (5.8–8.3)	6.8 (5.8–8.4)	6.7 (5.7–8.2)	0.21
Creatinine clearance, mL/min	61 (45–79)	60 (45–78)	65 (48–81)	0.026
Platelet count, G/L	206 (165–262)	205 (163–260)	211 (172–266)	0.033
Hemoglobin, G/L	13.2 (11.9–14.4)	13.1 (11.8–14.3)	13.4 (12.1–14.8)	0.009

ARWMC indicates age-related white matter changes; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; DOAC, direct oral anticoagulant; IQR, interquartile range; IVT, intravenous thrombolysis; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; pc, posterior circulation; and TIA, transient ischemic attack.

*Carotid-T, M1/ M2 segments of the middle cerebral artery, basilar artery.

female, had fewer vascular risk factors, greater stroke severity, and more often underwent magnetic resonance imaging as the follow-up imaging modality (Tables S8 and S9). The rate of sICH was numerically, but not statistically significantly, lower in the nonreversal group (adjusted difference, −2.8% [95% CI, −6.9 to +1.3]). The rate of any ICH was higher in those without reversal than in those undergoing reversal, but other safety and efficacy outcomes did not differ between those without and with reversal (Table 3).

Exploratory Analysis

Using Least Absolute Shrinkage and Selection Operator regression, we found intended EVT, Alberta Stroke Program Early CT Score, platelet count, and glucose level to be independently associated with sICH in DOAC target trial patients. DOAC plasma levels, and time from last intake were not associated with sICH, neither in univariate nor multivariable analysis when added to this model (Table S10).

Table 2. DOAC-Specific Baseline Characteristics

	Overall (N=1342)	No IVT (n=1000)	IVT (n=342)	*P* value
Type of DOAC, n (%)				<0.001
Apixaban	567 (42.5%)	452 (45.4%)	115 (34.0%)	
Edoxaban	200 (15.0%)	159 (16.0%)	41 (12.1%)	
Rivaroxaban	415 (31.1%)	305 (30.7%)	110 (32.5%)	
Dabigatran	151 (11.3%)	79 (7.9%)	72 (21.3%)	
Therapeutic DOAC dose	1256 (93.6%)	943 (94.3%)	313 (91.5%)	0.070
Last DOAC intake, h, n (%)				<0.001
<12	689 (51.3%)	548 (54.8%)	141 (41.2%)	
12–24	351 (26.2%)	259 (25.9%)	92 (26.9%)	
24–48	128 (9.5%)	82 (8.2%)	46 (13.5%)	
Not verifiable in emergency setting	174 (13.0%)	111 (11.1%)	63 (18.4%)	
Blood sample analysis, mean (IQR)				
DOAC plasma levels, ng/mL, n (%)				<0.001
<50	269 (20.0%)	124 (12.4%)	145 (42.4%)	
50–99	159 (11.8%)	109 (10.9%)	50 (14.6%)	
100–199	142 (10.6%)	117 (11.7%)	25 (7.3%)	
200–299	35 (2.6%)	31 (3.1%)	4 (1.2%)	
300–599	25 (1.9%)	19 (1.9%)	6 (1.8%)	
Not available	712 (53.1%)	600 (60.0%)	112 (32.7%)	
INR	1.1 (1–1.23)	1.1 (1.01–1.3)	1.1 (1–1.2)	<0.001
Thrombin time, s	18 (15–26)	19 (15–26)	18 (16–27)	0.13
Reversal				
Idarucizumab		1 (0.1%)	59 (17.3%)	<0.001

DOAC indicates direct oral anticoagulant; INR, international normalized ratio; IQR, interquartile range; and IVT, intravenous thrombolysis.

DISCUSSION

In this international, multicenter, target trial emulation of patients with acute ischemic stroke who received IVT despite recent DOAC intake, there was no increase in sICH associated with off-label IVT. Importantly, selected patients receiving IVT showed improved rates of good functional outcomes as compared with those DOAC patients who did not receive IVT. When comparing patients undergoing IVT with and without reversal with idarucizumab, there was no significant difference in safety or clinical efficacy outcomes, although reduced rates of any hemorrhagic transformation after reversal were observed.

Previous studies mostly compared patients receiving IVT with recent DOAC intake to IVT patients not receiving anticoagulation rather than DOAC patients being treated with IVT to DOAC patients who did not receive IVT.[14] Thus, the risks and benefits in comparison to patients not receiving IVT from this exact population were hitherto unknown. To address this critical knowledge gap, we conducted a target trial emulation according to the protocol of a hypothetical randomized study to compare DOAC patients fulfilling the inclusion and exclusion criteria of this trial according to whether they received IVT or not.

Overall, we found that off-label IVT use in patients with recent DOAC intake did not increase the risk of sICH, major bleeding, or any radiological ICH. Most patients who had DOAC plasma levels measured had low or intermediate levels where these were measured. Importantly, our exploratory analyses indicated that this finding also applied to subgroups that would be expected to have the highest bleeding risk. Specifically, the nonsignificant association between the time from last DOAC intake as well as higher DOAC plasma levels with hemorrhage risk among IVT-treated patients challenges current expert opinion and guideline-recommended cutoffs for IVT use in these patients. Nevertheless, additional evidence is needed to determine safety in patients with high and very high plasma levels. Most patients who had DOAC plasma levels measured had low or intermediate levels. Our exploratory analysis regarding predictors of sICH in IVT patients indicated that established predictors such as higher glucose levels and greater stroke severity are also important in DOAC patients considered for IVT.

Another novel aspect of this article is the analysis comparing patients with and without specific reversal before IVT. The use of idarucizumab before IVT has been demonstrated to be feasible in retrospective cohort studies and case reports.[18,32–35] We found lower numbers of

Table 3. Safety and Efficacy Outcomes

	Patients receiving IVT vs not receiving IVT			IVT with vs without prior reversal		
	No IVT	IVT	Adjusted difference (95% CI)	No reversal	Reversal (all idarucizumab)	Adjusted difference, % (95% CI)
N (%)	n=1000	n=342		n=283	n=289	
Safety outcomes, n (%)						
sICH (ECASS III)*	54 (5.9%)	10 (3.0%)	−2.1% (−5.3% to +1.2)	10 (3.7%)	6 (2.1%)	−2.8% (−6.9 to +1.3)
sICH (NINDS)*	55 (6.5%)	9 (3.0%)	−1.1% (−5.2 to +2.9)			
Any radiological ICH*						
None	735 (78.1%)	264 (80.2%)	For any radiological ICH: −3.5% (−9.8 to +2.9)	213 (78.6%)	277 (96.2%)	For any radiological ICH: −16.4% (−22.9 to −10.1)
HI 1	92 (9.8%)	26 (7.9%)		21 (7.7%)	6 (2.1%)	
HI 2	47 (5.0%)	18 (5.5%)		18 (6.6%)	0 (0.0%)	
PH 1	13 (1.4%)	3 (0.9%)		2 (0.7%)	1 (0.3%)	
PH 2	22 (2.3%)	8 (2.4%)		8 (3.0%)	2 (0.7%)	
SAH	27 (2.9%)	9 (2.7%)		8 (3.0%)	2 (0.7%)	
Multiple types	5 (0.5%)	1 (0.3%)		1 (0.4%)	0 (0.0%)	
Any major bleeding†	21 (2.3%)	7 (2.3%)	+0.0% (−2.4 to +2.4)	6 (2.4%)	2 (0.7%)	−0.9% (−2.8 to +1.0)
Orolingual edema†	0 (0.0%)	4 (1.2%)	+1.2% (+0.03 to +2.4)	4 (1.5%)	3 (1.0%)	−0.0% (−1.7 to +1.6)
Mortality (90 d)†	219 (22.7%)	47 (15.7%)	−3.3% (−9.5 to +2.9)	42 (17.1%)	5 (9.3%)	−5.5% (−15.5 to +4.6)
Efficacy outcome, n (%)†						
mRS score of 0–2 or return to baseline (90 d)	405 (43.7%)	181 (62.2%)	+14.4% (+7.1% to +21.8%)	147 (62.0%)	159 (63.9%)	−2.6% (−10.9 to +5.7)
mRS score shift analysis			aOR, 0.60 (0.45 to 0.80)			aOR, 1.32 (0.92 to 1.88)
NIHSS score difference between admission and 24 h	2 (0–7)	3 (1–7)	+0.33 (−0.58 to 1.24)	3 (0–7)	4 (1–9)	+0.05 (−1.2 to +1.2)

aOR indicates adjusted odds ratio; DOAC, direct oral anticoagulant; ECASS III, European Cooperative Acute Stroke Study III; EVT, endovascular therapy; HI, hemorrhagic transformation; ICH, intracerebral hemorrhage; IVT, intravenous thrombolysis; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NINDS, National Institute of Neurological Disorders and Stroke; PH, parenchymal hemorrhage; SAH, subarachnoid hemorrhage; and sICH, symptomatic intracerebral hemorrhage.

*Adjustments for outcome ICH: age, stroke severity, intended thrombectomy, DOAC reversal, prestroke mRS, hypertension, systolic blood pressure on admission, blood glucose, and time from last intake.

†Adjustment for other safety and efficacy outcomes: age, stroke severity, intended thrombectomy, DOAC reversal, and time from last intake.

hemorrhagic transformation and numerically lower sICH rates among patients treated with idarucizumab, which, however, did not reach significance after adjustment. The IVT cohort receiving reversal predominantly stems from the New Zealand national stroke registry because this is one of the few countries where dabigatran has a very high market share. Given the differences in the cohorts and higher rate of magnetic resonance imaging follow-up (with higher sensitivity for hemorrhagic transformation) in the no-reversal group, further study is required to determine whether idarucizumab is beneficial before IVT; an important issue given its associated costs and limited global availability. The effectiveness and safety of DOAC reversal may also be highest in liberal IVT decision (ie, with higher DOAC levels), thus more data on a potential interaction are needed, especially for patients with confirmed high plasma levels. We suggest continuing the practice of dabigatran reversal before IVT when idarucizumab is directly available.[6] However, IVT without reversal might be reasonable if reversal would significantly delay treatment.[17]

Existing studies on off-label IVT in patients taking DOACs have primarily concentrated on safety outcomes, with limited data available regarding the potential benefits of IVT in this population. One meta-analysis indicated that patients on DOACs had a lower likelihood of achieving functional independence after IVT compared with those not on anticoagulation.[36] However, interpreting these findings is challenging due to limited information on baseline characteristics and stroke severity in the study cohorts. In contrast, other adjusted analyses have suggested better functional outcomes for IVT-treated DOAC patients compared with those without DOAC treatment, but had very few patients with confirmed recent intake.[3] In our cohort, good functional outcomes were more common in DOAC patients treated with IVT as compared with DOAC patients not receiving IVT. However, this finding should be interpreted with caution because baseline stroke severity and the prevalence of large vessel occlusion were higher in those who did not receive IVT. This aligns with the approach of most EVT-capable centers recommending direct EVT without IVT for confirmed large vessel occlusion cases.[14] Among patients who did not undergo EVT, the adjusted analysis continued to show a significant association between IVT and better functional outcomes.

Our findings underscore the necessity of ongoing prospective and randomized controlled trials to evaluate the safety and efficacy of IVT in patients with recent DOAC intake, such as the DO-IT (URL: https://www.clinicaltrials.gov; Unique identifiers: NCT06556446; NCT06571149) and ACT-GLOBAL trials (URL: https://www.clinicaltrials.gov; Unique identifier: NCT06352632). The provided estimates of patients with unknown intake, alternative treatment options (EVT), and potential treatment effects can help to inform those trials.

Strengths of this study include an international representation of centers and a recent study timeframe, as well as the granular data on the last intake of the DOAC medication. Limitations include those inherent to its retrospective design. Although the target trial methodology may have minimized biases, factors influencing IVT decisions (unmeasured confounding), cannot be ruled out and the observed difference in mortality rates (higher in non-IVT patients) as well as a better baseline profile of IVT patients (lower stroke severity, fewer LVO, fewer comorbidities (eg, diabetes, coronary artery disease) suggests a potential indication bias. Most participating centers were large academic stroke centers capable of performing EVT. The patients with DOAC reversal were mostly from another population (New Zealand stroke registry), limiting comparative analyses and interaction analyses, for example, according to liberal IVT decisions. Although most events were presumably cardioembolic, detailed stroke cause data (eg, TOAST classification) were not systematically available across all centers, limiting our ability to assess the influence of stroke subtype on outcomes. Lastly, the limited number of patients with DOAC plasma levels exceeding 100 ng/mL who were treated with IVT prevented us from conducting reliable subgroup analyses. The low number of patients from non-European sites hampered a comparison across geographic locations as originally foreseen in the analysis plan.

CONCLUSIONS

This target trial emulation confirms previous observational data regarding the safety of off-label IVT in patients with recent DOAC intake. However, more data and dedicated trials are needed for patients with confirmed high DOAC plasma levels. The outcome estimates of this observational cohort study can inform ongoing randomized controlled trials on this topic, including the efficacy and safety of DOAC reversal before IVT.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S10
Figure S1
STROBE Checklist

APPENDIX

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REFERENCES

1. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, 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. doi: 10.1016/S0140-6736(13)62343-0
2. Moras E, Gandhi K, Khan M, Moras A, Choi J, Frishman WH, Aronow WS. Direct oral anticoagulants: an overview of indications, pharmacokinetics, comorbidities, and perioperative management. *Cardiol Rev*. 2023;33:312–318. doi: 10.1097/crd.0000000000000618
3. Kam W, Holmes DJN, Hernandez AF, Saver JL, Fonarow GC, Smith EE, Bhatt DL, Schwamm LH, Reeves MJ, Matsouaka RA, 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. doi: 10.1001/jama.2022.0948
4. Meinel TR, Branca M, De Marchis GM, Nedeltchev K, Kahles T, Bonati L, Arnold M, Heldner MR, Jung S, Carrera E, et al; Investigators of the Swiss Stroke Registry. Prior anticoagulation in patients with ischemic stroke and atrial fibrillation. *Ann Neurol*. 2021;89:42–53. doi: 10.1002/ana.25917
5. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2019;50:e344–e418. doi: 10.1161/STR.0000000000000211
6. Berge E, Whiteley W, Audebert H, Marchis GMD, Fonseca AC, Padiglioni C, Ossa NP de la, Strbian D, Tsivgoulis G, Turc G. European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke. *Eur Stroke J*. 2021;6:I–LXII. doi: 10.1177/2396987321989865
7. Xian Y, Liang L, Smith EE, Schwamm LH, Reeves MJ, Olson DWM, Hernandez AF, Fonarow GC, Peterson ED. Risks of intracranial hemorrhage among patients with acute ischemic stroke receiving warfarin and treated with intravenous tissue plasminogen activator. *JAMA*. 2012;307:2600–2608. doi: 10.1001/jama.2012.6756
8. Sun L, Zhou W, Ploen R, Zorn M, Veltkamp R. Anticoagulation with dabigatran does not increase secondary intracerebral haemorrhage after thrombolysis in experimental cerebral ischaemia. *Thromb Haemost*. 2013;110:153–161. doi: 10.1160/TH12-12-0942
9. Kono S, Yamashita T, Deguchi K, Omote Y, Yunoki T, Sato K, Kurata T, Hishikawa N, Abe K. Rivaroxaban and apixaban reduce hemorrhagic transformation after thrombolysis by protection of neurovascular unit in rat. *Stroke*. 2014;45:2404–2410. doi: 10.1161/STROKEAHA.114.005316
10. Ploen R, Sun L, Zhou W, Heitmeier S, Zorn M, Jenetzky E, Veltkamp R. Rivaroxaban does not increase hemorrhage after thrombolysis in experimental ischemic stroke. *J Cereb Blood Flow Metab*. 2014;34:495–501. doi: 10.1038/jcbfm.2013.226
11. Monjazeb S, Chang HV, Lyden PD. Before, during, and after: an argument for safety and improved outcome of thrombolysis in acute ischemic stroke with direct oral anticoagulant treatment. *Ann Neurol*. 2024;96:871–886. doi: 10.1002/ana.27058
12. Pfeilschifter W, Bohmann F, Baumgarten P, Mittelbronn M, Pfeilschifter J, Lindhoff-Last E, Steinmetz H, Foerch C. Thrombolysis with recombinant tissue plasminogen activator under dabigatran anticoagulation in experimental stroke. *Ann Neurol*. 2012;71:624–633. doi: 10.1002/ana.23558
13. Meinel TR, Wilson D, Gensicke H, Scheitz JF, Ringleb P, Goganau I, Kaesmacher J, Bae H-J, Kim DY, Kermer P, et al. Intravenous thrombolysis in patients with ischemic stroke and recent ingestion of direct oral anticoagulants. *JAMA Neurol*. 2023;80:233. doi: 10.1001/jamaneurol.2022.4782
14. Ghannam M, AlMajali M, Galecio-Castillo M, Al Qudah A, Khasiyev F, Dibas M, Ghazaleh D, Vivanco-Suarez J, Morán-Mariños C, Farooqui M, et al. Intravenous thrombolysis for acute ischemic stroke in patients with recent direct oral anticoagulant use: a systematic review and meta-analysis. *J Am Heart Assoc*. 2023;12:e031669. doi: 10.1161/JAHA.123.031669
15. Chen HS, Cui Y, Zhou ZH, Dai YJ, Li GH, Peng ZL, Zhang Y, Liu XD, Yuan ZM, Jiang CH, et al; ARAIS Investigators. Effect of argatroban plus intravenous alteplase vs intravenous alteplase alone on neurologic function in patients with acute ischemic stroke: the ARAIS randomized clinical trial. *JAMA*. 2023;329:640–650. doi: 10.1001/jama.2023.0550
16. Adeoye O, Broderick J, Derdeyn CP, Grotta JC, Barsan W, Bentho O, Berry S, Concha M, Davis I, Demel S, et al. Adjunctive intravenous argatroban or eptifibatide for ischemic stroke. *N Engl J Med*. 2024;391:810–820. doi: 10.1056/NEJMoa2314779
17. Khan F, Meinel T, Lun R, Yu AYX, Campbell BCV. Should patients treated with direct oral anticoagulants receive intravenous thrombolytics for acute ischaemic stroke? *BMJ*. 2024;2021:1–7. doi: 10.1136/bmj-2024-079322
18. Barber PA, Wu TY, Ranta A. Stroke reperfusion therapy following dabigatran reversal with idarucizumab in a national cohort. *Neurology*. 2020;94:e1968–e1972. doi: 10.1212/WNL.0000000000009155
19. Hernán MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. *Am J Epidemiol*. 2016;183:758–764. doi: 10.1093/aje/kwv254
20. Hernán MA, Sauer BC, Hernáández-Díaz S, Platt R, Shrier I. Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses. *J Clin Epidemiol*. 2016;79:70–75. doi: 10.1016/j.jclinepi.2016.04.014
21. Bücke P, Jung S, Kaesmacher J, Goeldlin MB, Horvath T, Prange U, Beyeler M, Fischer U, Arnold M, Seiffge DJ, 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;9:959–967. doi: 10.1177/23969873241252751
22. Kleeberg A, Ringleb PA, Huber I, Jesser J, Möhlenbruch M, Purrucker JC. Hemorrhagic complications after stroke treatment with intravenous thrombolysis despite use of direct oral anticoagulants: an observational study. *Ther Adv Neurol Disord*. 2024;17:17562864241276206. doi: 10.1177/17562864241276206
23. Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. *Lancet*. 2000;355:1670–1674. doi: 10.1016/s0140-6736(00)02237-6
24. Sang H, Li F, Yuan J, Liu S, Luo W, Wen C, Zhu Q, Chen W, Lin M, Qi L, et al. Values of baseline posterior circulation acute stroke prognosis early

computed tomography score for treatment decision of acute basilar artery occlusion. *Stroke*. 2021;52:811–820. doi: 10.1161/strokeaha.120.031371
25. Yoshimoto T, Inoue M, Yamagami H, Fujita K, Tanaka K, Ando D, Sonoda K, Kamogawa N, Koga M, Ihara M, et al. Use of Diffusion-Weighted Imaging-Alberta Stroke Program Early Computed Tomography Score (DWI-ASPECTS) and ischemic core volume to determine the malignant profile in acute stroke. *J Am Heart Assoc*. 2019;8:1–9. doi: 10.1161/JAHA.119.012558
26. Wahlund LO, Barkhof F, Fazekas F, Bronge L, Augustin M, Sjögren M, Wallin A, Ader H, Leys D, Pantoni L, et al; European Task Force on Age-Related White Matter Changes. A new rating scale for age-related white matter changes applicable to MRI and CT. *Stroke*. 2001;32:1318–1322. doi: 10.1161/01.str.32.6.1318
27. Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, Larrue V, Lees KR, Medeghri Z, Machnig T, et al; ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. 2008;359:1317–1329. doi: 10.1056/NEJMoa0804656
28. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995;333:1581–1587. doi: 10.1056/NEJM199512143332401
29. Von Kummer R, Broderick JP, Campbell BCV, Demchuk A, Goyal M, Hill MD, Treurniet KM, Majoie CBLM, Marquering HA, Mazya MV, et al. The Heidelberg bleeding classification: classification of bleeding events after ischemic stroke and reperfusion therapy. *Stroke*. 2015;46:2981–2986. doi: 10.1161/STROKEAHA.115.010049
30. Kurth T, Walker AM, Glynn RJ, Chan KA, Gaziano JM, Berger K, Robins JM. Results of multivariable logistic regression, propensity matching, propensity adjustment, and propensity-based weighting under conditions of nonuniform effect. *Am J Epidemiol*. 2006;163:262–270. doi: 10.1093/aje/kwj047
31. Joshi P, Fink J, Barber PA, Davis A, Lanford J, Seymour A, Wright P, Busby W, Abernethy G, Ranta A. Stroke thrombolysis in New Zealand: data from the first 6 months of the New Zealand Thrombolysis Register. *N Z Med J*. 2016;129:42–47.
32. Kermer P, Eschenfelder CC, Diener HC, Grond M, Abdalla Y, Althaus K, Berrouschot J, Cangür H, Daffertshofer M, Edelbusch S, et al. Antagonizing dabigatran by idarucizumab in cases of ischemic stroke or intracranial hemorrhage in Germany—a national case collection. *Int J Stroke*. 2017;12:383–391. doi: 10.1177/1747493017701944
33. Giannandrea D, Caponi C, Mengoni A, Romoli M, Marando C, Gallina A, Marsili E, Sacchini E, Mastrocola S, Padiglioni C, et al. Intravenous thrombolysis in stroke after dabigatran reversal with idarucizumab: case series and systematic review. *J Neurol Neurosurg Psychiatry*. 2019;90:619–623. doi: 10.1136/jnnp-2018-318658
34. Karaszewski B, Szczyrba S, Jabłoński B, Gąsecki D, Kraszewski P, Wyszomirski A, Kowalski R, Kaliszan W, Dąbrowska M. Case report: first treatment of acute ischaemic stroke in a patient on active rivaroxaban therapy using andexanet alfa and rtPA combined with early complete recovery. *Front Neurol*. 2023;14:1269651. doi: 10.3389/fneur.2023.1269651
35. Romoli M, Matteo E, Migliaccio L, Gentile M, Mosconi MG, Scura GM, Naccarato M, Colangeli E, Candelaresi P, Andreone V, et al. Thrombolysis after dabigatran reversal: a nation-wide Italian multicentre study, systematic review and meta-analysis. *Eur Stroke J*. 2023;8:117–124. doi: 10.1177/23969873221131635
36. 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;23:1–9. doi: 10.1186/s12883-023-03498-8