Use of Intravenous Recombinant Tissue Plasminogen Activator in Patients With Acute Ischemic Stroke Who Take Non–Vitamin K Antagonist Oral Anticoagulants Before Stroke

BACKGROUND: Intravenous rt-PA (recombinant tissue-type plasminogen activator) is effective in improving outcomes in ischemic stroke; however, there are few data on the use of rt-PA in patients who are receiving a non–vitamin K antagonist oral anticoagulant (NOAC).

METHODS: Using data from the American Heart Association Get With The Guidelines-Stroke Registry, we examined the outcomes of use of thrombolytic therapy in patients with ischemic stroke who received anticoagulation with NOACs versus those on warfarin (international normalized ratio <1.7) or not on anticoagulation from 1289 registry hospitals between October 2012 and March 2015.

RESULTS: Of 42 887 patients with ischemic stroke treated with intravenous rt-PA within 4.5 hours, 251 were taking NOACs (dabigatran 87, rivaroxaban 129, and apixaban 35) before their stroke, 1500 were taking warfarin, and 41 136 were on neither. Patients on NOACs or warfarin were older, had more comorbid conditions, and experienced more severe strokes than did those who were not on anticoagulation (median National Institutes of Health Stroke Scale 12, 13, and 9, respectively). Unadjusted rates of symptomatic intracranial hemorrhage in the NOAC, warfarin, and none groups were 4.8%, 4.9%, and 3.9%, respectively (P=0.11). In comparison with those not on anticoagulation, the adjusted odds ratio for symptomatic intracranial hemorrhage for those on NOACs was 0.92 (95% confidence interval, 0.51–1.65) and for those on warfarin the adjusted odds ratio was 0.85 (95% confidence interval, 0.66–1.10). There were also no significant differences in the risk for life-threatening/serious systemic hemorrhage, any rt-PA complication, in-hospital mortality, and modified Rankin Scale at discharge across 3 groups. Similar results were also found after propensity score matching.

CONCLUSIONS: Although experience of using rt-PA in patients with ischemic stroke on a NOAC is limited, these preliminary observations suggest that rt-PA appears to be reasonably well tolerated without prohibitive risks for adverse events among selected NOAC-treated patients. Future studies should evaluate the safety and efficacy of intravenous rt-PA in patients with ischemic stroke who are taking NOACs.

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Clinical Perspective

What Is New?

- Non–vitamin K antagonist oral anticoagulants (NOACs) have been increasingly used as alternatives to warfarin for stroke prevention in patients with atrial fibrillation.
- Despite the efficacy of NOACs, some patients may still experience an ischemic stroke.
- To date, the question of whether patients with ischemic stroke taking NOACs should be treated with intravenous rt-PA (recombinant tissue plasminogen activator) has been debated.
- We examined 42 887 patients with ischemic stroke treated with rt-PA at 1289 hospitals in the United States between 2012 and 2015.
- We found no statistically significant differences in the risk of symptomatic intracranial hemorrhage between patients who were taking NOACs, warfarin (international normalized ratio<1.7), or not taking any oral anticoagulant before stroke.

What Are the Clinical Implications?

- This study represents the largest clinical experience of stroke thrombolysis in patients receiving NOACs before stroke.
- rt-PA appears to be reasonably well tolerated without prohibitive risks for adverse events among selected NOAC-treated patients.
- However, our observations must be considered as preliminary because of the absence of coagulation parameters, timing of the last NOAC intake, and whether nonspecific reversal strategies may have been applied.

Clinical practice for the management of nonvalvular atrial fibrillation is rapidly changing.[1] Between 2010 and 2015, 4 non–vitamin K antagonist oral anticoagulants (NOACs), dabigatran (a direct thrombin inhibitor), rivaroxaban, apixaban, and edoxaban (direct factor Xa inhibitors) were approved by the US Food and Drug Administration for stroke prophylaxis in atrial fibrillation. Despite efficacy in preventing stroke, ≈1% to 2% of patients taking NOACs can be expected to experience an ischemic stroke per year.[2–5] To date, the question of whether patients with ischemic stroke taking NOACs should be treated with intravenous rt-PA (recombinant tissue-type plasminogen activator) has been debated. Although it is the only approved medical therapy to improve outcomes, treatment with rt-PA also carries the risk of symptomatic intracranial hemorrhage (sICH).[6] It remains unclear whether patients who are receiving NOACs and treated with rt-PA are at higher risk of sICH than patients not taking oral anticoagulants before stroke.

With the rapid adoption of NOACs in clinical practice, clinicians may expect to see an increasing number of patients with ischemic stroke on NOACs. At present, the evidence of intravenous rt-PA in patients who have had a stroke taking NOACs is limited to 29 case reports and 1 multicenter pilot study (n=45).[7–34] Although successful and safe thrombolysis cases have been noted in the literature, others reported fatal bleeding following rt-PA. On the basis of limited data, the current guidelines warn against administrating intravenous rt-PA to patients on NOACs unless sensitive laboratory tests are normal or the patient has not received NOACs for >48 hours before stroke (Class III, Level of Evidence C).[6,35] However, this recommendation is complex because of the lack of rapidly available tests to assess the degree of coagulation with NOACs.

Using data from the American Heart Association and American Stroke Association (AHA/ASA) Get With The Guidelines-Stroke (GWTG-Stroke) program, we evaluated the use of intravenous rt-PA among patients receiving NOAC therapy, relative to those treated with warfarin or those not on any anticoagulation. We hypothesized that there was no increased risk of sICH and tPA-related complications after intravenous rt-PA in NOAC patients in comparison with nonanticoagulated patients. In secondary analyses, we also examined in-hospital mortality, hospital discharge destination, ambulatory status, and modified Rankin Scale at hospital discharge.

METHODS

Study Design and Data Source

We performed a retrospective analysis of data from a registry of consecutive patients who had ischemic stroke in the United States. The primary data source was the GWTG-Stroke Registry, which is an ongoing, voluntary, national stroke registry sponsored by the AHA/ASA. Details of the design and conduct of the GWTG-Stroke Registry have been previously described.[36] Trained hospital personnel are instructed to use an Internet-based Patient Management Tool to collect patient-level data on acute stroke care provided to patients admitted to the GWTG-Stroke hospitals. The eligibility of each admission is confirmed through chart review. Standardized data collection includes patient demographics, medical history, medications before admission, diagnostic tests, brain imaging, treatment, and in-hospital outcomes. The validity and reliability of data collection in the GWTG-Stroke Registry database have been reported in previous research.[37] Quintiles, Inc. serves as the data collection and coordination center for the GWTG-Stroke Registry. The Duke Clinical Research Institute serves as the data analysis center and has an agreement to analyze the aggregate deidentified data for research purposes.

Study Population

For the purpose of the study, our analyses included patients with acute ischemic stroke who have been treated with intravenous rt-PA in GWTG-Stroke hospitals between October 1, 2012,

and March 31, 2015. Because the indications and guidelines regarding intra-arterial rt-PA or endovascular treatment may not be generalizable to the intravenous approach, we focused on intravenous rt-PA only without endovascular treatment.[6,38] We excluded patients who had missing information of anticoagulant or antiplatelet therapy before stroke, who received rt-PA beyond the 4.5-hour treatment window or investigational or experimental protocol for thrombolysis, as well as those who were transferred in or out because in-hospital care and outcomes could not be tracked after interhospital transfer. We further excluded patients treated with heparin or anticoagulants rather than NOACs or warfarin before stroke. For those on warfarin therapy, we limited patients to those with an international normalized ratio (INR) <1.7 according to AHA/ASA guidelines.[6] After these exclusions, our study population consisted of 42 887 patients who had ischemic stroke treated with intravenous rt-PA from 1289 hospitals in the United States (Figure).

Variables of Interest and Outcomes

According to GWTG-Stroke coding instructions, NOACs were defined as documentation of patients taking dabigatran, rivaroxaban, or apixaban within 7 days before hospital arrival. Edoxaban was approved by the Food and Drug Administration in January 2015 and was not collected in GWTG-Stroke during our study period. Warfarin therapy was defined in a similar fashion. On the basis of these data, our study population comprised 3 mutually exclusive cohorts: (1) 251 patients on NOACs; (2) 1500 patients on warfarin with INR <1.7; and (3) 41 136 patients who were not on any anticoagulants when they received intravenous rt-PA as the comparison group. With the exception of the admission INR, other coagulation parameters such as prothrombin time, activated partial thromboplastin time, thrombin time, dilute thrombin time, fibrinogen, ecarin clotting time, and antifactor Xa assay are not collected in the current version of the GWTG-Stroke case report form. The NOAC specific reversal agent idarucizumab was approved by the Food and Drug Administration in October 2015 and therefore was not commercially available during our study period. Data on the use of nonspecific reversal treatments, such as prothrombin complex concentrates, were not collected in the registry.

The primary outcomes were sICH, life-threatening or serious systemic hemorrhage within 36 hours, any rt-PA complication within 36 hours (sICH, life-threatening or serious systemic hemorrhage<36 hours, or other serious complications). The sICH was defined as intracranial hemorrhage within 36 hours, documented by computed tomography or MRI and the treating physician's notes indicating clinical deterioration attributable to hemorrhage. Secondary outcomes included in-hospital mortality, discharge destination (home, hospice, inpatient rehabilitation facility, and skilled nursing facility), ambulatory status, and modified Rankin Scale (mRS,

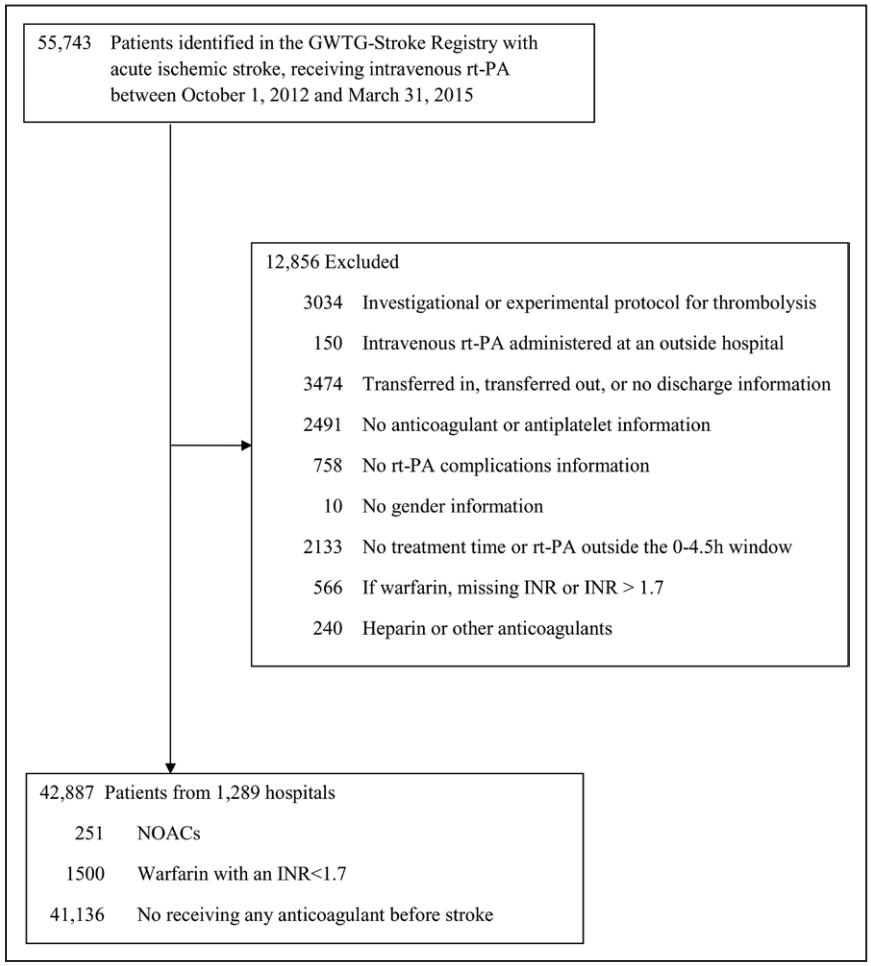

Figure. Study population.
GWTG indicates Get With The Guidelines-Stroke; INR, international normalized ratio; and rt-PA, recombinant tissue-type plasminogen activator.

a functional outcome measure ranging from 0 of no symptoms at all to 6 of death) at hospital discharge.

Statistical Analysis

Median and percentage were used to describe the distribution of continuous and categorical variables, respectively. Baseline characteristics were compared across 3 cohorts: NOACs, warfarin with an INR <1.7, and no oral anticoagulation. Multivariable logistic regression models were performed to investigate the relationships between prestroke anticoagulation (NOACs versus no anticoagulation and warfarin versus no anticoagulation) with each individual outcome. These analyses adjusted for baseline patient demographic, clinical variables, and hospital-level factors that are expected to be predictive of outcome and used in prior GWTG-Stroke analyses.[39–42] Patient-level variables included age, sex, race, baseline National Institutes of Health Stroke Scale (NIHSS, a measure of neurological deficits ranging from 0 to 42, with a higher score indicating greater stroke severity), systolic blood pressure, blood glucose, door-to-needle time, medical history of atrial fibrillation, coronary artery disease, prior stroke or transient ischemic attack, heart failure, carotid stenosis, hypertension, diabetes mellitus, dyslipidemia, peripheral vascular disease, smoking status, emergency medical services transport, arrival time during regular working hours (7 AM to 6 PM Monday through Friday), prestroke antiplatelet therapy. We also examined the interaction between prestroke antiplatelet and anticoagulant therapy and did not find significant interaction effect (NOACs and antiplatelet P=0.45; warfarin and antiplatelet P=0.68). Because NIHSS score is a critical predictor of outcomes,[41–43] a multiple imputation method was used to impute missing NIHSS values (2.1%, n=910). Hospital-level factors included hospital bed size, academic status, stroke center status, annual ischemic stroke volume, annual rt-PA volume, hospital region, and rural location. These analyses also accounted for within-hospital clustering using a generalized estimating equations approach. To account for differences in baseline characteristics of patients who were on NOACs, warfarin, and those who were not, we also performed a triple group propensity score matching as a sensitivity analysis.

To determine whether treatment selection exists regarding rt-PA treatment in NOACs, we compared baseline characteristics between NOACs patients treated with rt-PA versus those who were otherwise eligible but did not receive rt-PA in the GWTG-Stroke registry during the same study period. We considered a patient eligible if he or she presented within 3.5 hours after symptom onset (eligible for 0- to 4.5-hour treatment window) and had no other contraindications, with the exception of NOAC use before stroke.

All P values are 2-sided, with <0.05 considered statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC) and Stata Statistical Software, Version 14 (Statacorp, College Station, TX). The Institutional Review Board of Duke University approved the study.

RESULTS

Among 42 887 patients who had ischemic stroke treated with intravenous rt-PA, 251 were receiving NOACs (87 dabigatran, 129 rivaroxaban, and 35 apixaban), 1500 were on warfarin with an INR <1.7, and 41 136 were not receiving any anticoagulation before stroke. Tables 1 and 2 display demographic, clinical, and hospital characteristics according to prestroke anticoagulation use. In comparison with nonanticoagulated patients, patients receiving NOACs and warfarin were older (median age, 74, 79, and 71 years for NOACs, warfarin, and no anticoagulation, respectively), had a higher prevalence of cardiovascular risk factors, including atrial fibrillation, previous stroke/transient ischemic attack, coronary artery disease, heart failure, and hypertension (all P<0.001). The initial NIHSS scores were significantly higher in patients receiving NOACs (median [25th–75th percentile], 12 [6–18]) and warfarin (13 [7–19]) than no anticoagulation (9 [5–15]). The baseline INR levels at admission were slightly higher in NOACs (median 1.1 [1.0–1.2]) and warfarin-treated patients (1.2 [1.1–1.4]) than in nonanticoagulated patients. Although INR is not a sensitive test for NOACs, the relatively low INR values likely suggested that warfarin and NOAC patients were not sufficiently anticoagulated at the time of hospital admission. Although time from symptom onset to arrival was relatively similar across 3 groups, patients on NOACs (median, 65 [50–88] minutes) or warfarin (69 [54–91]) experienced a slight delay in terms of door-to-needle time in comparison with nonanticoagulated patients (61 [47–83]). Baseline characteristics after propensity score matching are shown in online-only Data Supplement Tables I and II.

Primary and Secondary Outcomes

Overall, 1672 patients (3.9%) developed sICH after intravenous rt-PA administration (Table 3). Unadjusted rates of sICH were numerically higher in NOACs and warfarin than in patients not on any anticoagulant (4.8%, 4.9%, and 3.9%, respectively, P=0.11). However, after adjusting for potential confounders, neither NOACs (adjusted odds ratio [OR], 0.92; 95% confidence interval [CI], 0.51–1.65) or warfarin (adjusted OR, 0.85; 95% CI, 0.66–1.10) were significantly associated with sICH risk. Indeed, the adjusted ORs changed direction, suggesting that observed higher rates might be due to greater risk profiles such as age, stroke severity, and comorbidities in NOACs and warfarin cohorts. Patients on NOACs had the lowest unadjusted rates of life-threatening or serious systemic hemorrhage (0.4%) and any rt-PA complications (6.8%), although none of these differences were statistically significant after adjustment.

The unadjusted in-hospital mortality rates were higher in NOAC- (9.2%) and warfarin-treated patients (11.3%) in comparison with patients not receiving anticoagulants (6.3%, P<0.001, Table 3). However, neither NOACs (adjusted OR, 0.93; 95% CI, 0.59–1.48) nor warfarin (adjusted OR, 1.05; 95% CI, 0.87–1.26) were associated with excess mortality risk after adjustment.

Table 1. Demographics, Medical History, and Hospital Characteristics According to Anticoagulation Therapy Before Stroke

Variable	NOACs n=251	Warfarin with INR<1.7 n=1500	No Oral Anticoagulant n=41 136	*P* Value
Demographics				
Age, median (p25-p75), y	74 (66–82)	79 (68–86)	71 (59–82)	<0.001
Women, n (%)	129 (51.4)	839 (55.9)	20 591 (50.1)	<0.001
Race/ethnicity, n (%)				0.41
White	183 (72.9)	1056 (70.5)	29 081 (70.8)	
Black	36 (14.3)	225 (15.0)	6241 (15.2)	
Asian	24 (9.6)	115 (7.7)	3072 (7.5)	
Hispanic	6 (2.4)	41 (2.7)	1129 (2.7)	
Other	2 (0.8)	61 (4.1)	1568 (3.8)	
History of, n (%)				
Atrial fibrillation/flutter	196 (78.1)	1159 (77.3)	7430 (18.1)	<0.001
Prosthetic heart valve	4 (1.6)	90 (6.0)	370 (0.9)	<0.001
Previous stroke/TIA	77 (30.7)	540 (36.0)	10 533 (25.6)	<0.001
Carotid stenosis	7 (2.8)	41 (2.7)	1067 (2.6)	0.93
CAD/MI	79 (31.5)	505 (33.7)	9705 (23.6)	<0.001
Heart failure	38 (15.1)	356 (23.7)	3601 (8.8)	<0.001
Hypertension	198 (78.9)	1217 (81.1)	30 106 (73.2)	<0.001
Dyslipidemia	106 (42.2)	721 (48.1)	17 916 (43.6)	0.002
Peripheral vascular disease	8 (3.2)	97 (6.5)	1478 (3.6)	<0.001
Diabetes mellitus	64 (25.5)	457 (30.5)	11 211 (27.3)	0.02
Smoker	19 (7.6)	147 (9.8)	7339 (17.8)	<0.001
Hospital characteristics				
Number of beds, median (p25-p75)	370 (273–555)	400 (286–595)	389 (264–584)	0.14
Annual ischemic stroke volume, median (p25-p75)	230 (147–337)	224 (157–337)	224 (155–347)	0.86
Annual IV rt-PA cases, median (p25-p75)	20 (11–37)	22 (13–31)	21 (13–31)	0.57
Hospital type, academic, n (%)	151 (60.4)	894 (61.7)	24 569 (61.5)	0.93
Joint Commission Primary Stroke Center, n (%)	104 (41.4)	718 (47.9)	19 831 (48.2)	0.10
Rural hospital, n (%)	2 (0.8)	50 (3.3)	1350 (3.3)	0.09

CAD indicates coronary artery disease; INR, international normalized ratio; IV rt-PA, intravenous recombinant tissue-type plasminogen activator; MI, myocardial infarction; NOACs, non–vitamin K antagonist oral anticoagulants; p25-p75, percentiles; and TIA, transient ischemic attack.

Similarly, there were no statistically significant differences in discharge to hospice, skilled nursing facility, and inpatient rehabilitation facility across the 3 cohorts. In comparison with no anticoagulation, patients receiving NOACs were more likely to be discharged home (42.2% versus 47.1%; unadjusted OR, 0.82; 95% CI, 0.64–1.06; adjusted OR, 1.38; 95% CI, 1.03–1.86) and ambulate independently at hospital discharge (46.1% versus 49.3%; unadjusted OR, 0.88; 95% CI, 0.68–1.14; adjusted OR, 1.44; 95% CI, 1.06–1.94). In the subset of patients (58%, 24 832/42 887) who had mRS measured at discharge, the adjusted ORs for good outcomes (mRS, 0–1; adjusted OR, 1.23; 95% CI, 0.81–1.85 or mRS, 0–2; adjusted OR, 1.08; 95% CI, 0.73–1.60) in patients receiving NOACs in comparison with patients not receiving anticoagulants were higher but were not statistically significant. The characteristics of patients with or without a documented mRS score at discharge are shown in the online-only Data Supplement Table III.

Primary and secondary outcome measures after propensity score matching are shown in Table 4. There was no statistically significant difference in sICH, life-threatening or serious systemic hemorrhage, any rt-PA complications, in-hospital mortality, discharge destination, and functional outcomes across 3 groups.

Table 2. Clinical Characteristics According to Anticoagulation Therapy Before Stroke

Variable	NOACs n=251	Warfarin With INR<1.7 n=1500	No Oral Anticoagulant n=41 136	*P* Value
Medications before admission, n (%)				
Anticoagulant	251 (100.0)	1500 (100.0)	–	–
Warfarin	–	1500 (100.0)	–	–
Dabigatran	87 (34.7)	–	–	–
Rivaroxaban	129 (51.4)	–	–	–
Apixaban	35 (13.9)	–	–	–
Antiplatelet	76 (30.3)	407 (27.1)	19 677 (47.8)	<0.001
Aspirin only	60 (23.9)	337 (22.5)	14 660 (35.6)	
Aspirin/clopidogrel	8 (3.2)	25 (1.7)	2374 (5.8)	
Aspirin/dipyridamole	0 (0.0)	2 (0.1)	394 (1.0)	
Clopidogrel only	8 (3.2)	33 (2.2)	1998 (4.9)	
Others	0 (0.0)	10 (0.7)	251 (0.6)	
No antiplatelet	175 (69.7)	1093 (72.9)	21 459 (52.2)	
Antihypertensive	189 (84.8)	1270 (86.7)	23 232 (65.3)	<0.001
Cholesterol reducer	143 (57.0)	831 (55.4)	17 252 (41.9)	<0.001
Diabetic medication	49 (22.2)	357 (24.6)	7197 (20.7)	0.002
Arrival by EMS, n (%)	205 (84.4)	1326 (89.0)	31 913 (80.6)	<0.001
Off-hour presentation,* n (%)	124 (49.4)	728 (48.5)	19 875 (48.3)	0.93
NIHSS, median (p25-p75)	12 (6–18)	13 (7–19)	9 (5–15)	<0.001
Time from symptom onset to arrival, median (p25-p75), min	60 (37–90)	56 (37–85)	60 (40–94)	<0.001
Door-to-needle time, median (p25-p75), min	65 (50–88)	69 (54–91)	61 (47–83)	<0.001
Heart rate, median (p25-p75), bpm	82 (70–98)	81 (70–96)	80 (70–92)	<0.001
Systolic blood pressure, median (p25-p75), mm Hg	155 (136–172)	153 (136–173)	155 (138–176)	0.009
Diastolic blood pressure, median (p25-p75), mm Hg	85 (74–100)	85 (74–98)	84 (73–96)	0.02
Creatinine, median (p25-p75), mg/dL	1.0 (0.9–1.2)	1.0 (0.8–1.3)	1.0 (0.8–1.2)	<0.001
Blood glucose, median (p25-p75), mg/dL	119 (102–149)	122 (104–152)	118 (102–149)	0.005
Body mass index, median (p25-p75)	29.0 (24.3–33.5)	27.0 (23.6–32.0)	27.4 (24.0–31.9)	0.03
INR, median (p25-p75)	1.1 (1.0–1.2)	1.2 (1.1–1.4)	1.0 (1.0–1.1)	<0.001

EMS indicates emergency medical services; INR, international normalized ratio; NIHSS, National Institutes of Health Stroke Scale; NOACs, non–vitamin K antagonist oral anticoagulants; and p25-p75, percentiles.

*Off-hour presentation, presentation anytime outside of 7 AM to 6 PM on weekdays.

Potential Treatment Selection in Intravenous rt-PA

We identified 318 NOAC patients who arrived within 3.5 hours after symptom onset without any other contraindications and did not receive rt-PA in the GWTG-Stroke Registry during the same period and compared with 251 NOAC patients treated with rt-PA (online-only Data Supplement Tables IV and V). NOAC patients treated with rt-PA were slightly younger (median, 74 versus 77 years), had fewer comorbidities, and were more likely to receive care at experienced centers (median annual ischemic stroke volume, 230 versus 189; annual rt-PA volume, 20 versus 14) in comparison with NOAC patients who arrived within the rt-PA time window but were not treated. However, patients treated with rt-PA tended to arrive significantly earlier (median time from symptom onset to arrival 60 versus 103 minutes) and present with more severe stroke (median NIHSS 12 versus 4) than those who did not receive rt-PA. There were no significant differences in terms of NOAC agents or prestroke antiplatelet therapy between 2 groups.

DISCUSSION

In this nationwide contemporary registry of patients with acute ischemic stroke, we found that use of intravenous

Table 3. Primary and Secondary Outcomes According to Anticoagulation Therapy Before Stroke

	No. Events/Total No. of Patients (%)			Adjusted OR* NOACs vs No (95% CI)	Adjusted OR* Warfarin vs No (95% CI)
	NOACs (n=251)	Warfarin With INR<1.7 (n=1500)	No Oral Anticoagulant (n=41 136)		
Primary outcomes					
Symptomatic intracranial hemorrhage <36 h	12/251 (4.8)	73/1500 (4.9)	1587/41 136 (3.9)	0.92 (0.51–1.65)	0.85 (0.66–1.10)
Life-threatening or serious systemic hemorrhage <36 h	1/251 (0.4)	14/1500 (0.9)	347/41 136 (0.8)	0.38 (0.05–2.71)	0.78 (0.45–1.37)
Any rt-PA complication†	17/251 (6.8)	152/1500 (10.1)	3140/41 136 (7.6)	0.64 (0.39–1.05)	0.90 (0.75–1.08)
Secondary outcomes					
In-hospital mortality	23/251 (9.2)	170/1500 (11.3)	2612/41 136 (6.3)	0.93 (0.59–1.48)	1.05 (0.87–1.26)
Discharge to home	106/251 (42.2)	451/1500 (30.1)	19 365/41 136 (47.1)	1.38 (1.03–1.86)	0.90 (0.78–1.03)
Discharge to hospice	19/251 (7.6)	136/1500 (9.1)	2150/41 136 (5.2)	0.97 (0.59–1.61)	0.94 (0.76–1.15)
Discharge to skilling nursing facility	34/251 (13.5)	302/1500 (20.1)	6120/41 126 (14.9)	0.71 (0.49–1.03)	0.99 (0.87–1.14)
Discharge inpatient rehabilitation facility	63/251 (25.1)	396/1500 (26.4)	10 214/41 126 (24.8)	0.98 (0.73–1.32)	1.10 (0.97–1.25)
Able to ambulate independently at discharge‡	107/232 (46.1)	467/1404 (33.3)	17 806/36 126 (49.3)	1.43 (1.06–1.94)	0.99 (0.87–1.14)
Modified Rankin Scale at discharge‡					
mRS 0–1	37/154 (24.0)	164/925 (17.7)	6951/23 753 (29.3)	1.23 (0.81–1.85)	1.09 (0.89–1.33)
mRS 0–2	48/154 (31.2)	239/925 (25.8)	9292/23 753 (39.1)	1.08 (0.73–1.60)	1.15 (0.96–1.38)

CI indicates confidence interval; EMS, emergency medical services; INR, international normalized ratio; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NOACs, non–vitamin K antagonist oral anticoagulants; OR, odds ratio; rt-PA, recombinant tissue-type plasminogen activator; and TIA, transient ischemic attack.

*Adjustment for patient-level characteristics including age, sex, race, systolic blood pressure, blood glucose, baseline NIHSS, door-to-needle time, medical history of atrial fibrillation/flutter, prior stroke/TIA, coronary artery disease/myocardial infarction, heart failure, carotid stenosis, hypertension, dyslipidemia, diabetes mellitus, peripheral vascular disease, smoking status, EMS arrival, on/off hour presentation, preadmission antiplatelet use, and hospital-level characteristics including bed size, academic status, primary stroke center, annual ischemic stroke volume, annual rt-PA volume, hospital region, and rural location.

†Any rt-PA complication including symptomatic intracranial hemorrhage <36 h, life-threatening or serious systemic hemorrhage <36 h, or other serious complications.

‡Missing data excluded.

rt-PA among patients receiving NOACs before stroke appeared to be reasonably well tolerated without prohibitive risks for adverse events. Although the unadjusted rates of sICH were numerically higher, NOACs were used in patients with higher clinical risk profiles and more severe strokes. After adjustment for these baseline clinical factors, NOAC use before stroke was not associated with an increased risk of sICH or in-hospital mortality relative to those not on oral anticoagulants. In contrast, patients receiving NOACs had better adjusted outcomes in terms of discharge home and ambulatory status at discharge than those not on any oral anticoagulant before stroke. Collectively, these preliminary experiences suggest that giving intravenous rt-PA to selected patients who were receiving NOACs before stroke is not associated with markedly elevated risks and must be weighed against the risk of prolonged morbidity from stroke if rt-PA is withheld.

Our study is among the first, and the largest to date, to report the outcomes of NOAC patients treated with intravenous rt-PA. While these data are reassuring that those treated did not have significantly increased risk of bleeding complications, we caution that these data are limited to only 251 cases and a very small number of events of sICH. In addition, we did not have information on the timing of last NOAC dose, coagulation parameters such as prothrombin time, activated partial thromboplastin time, thrombin time, dilute thrombin time, ecarin clotting time, or antifactor Xa assay, and whether or not nonspecific reversal strategies may have been applied before rt-PA administration. Therefore, we cannot exclude the possibility that recent NOAC users or those with elevated or residual anticoagulation effects could be at higher risk.

Table 4. Primary and Secondary Outcomes After Propensity Score Matching

	No. Events/Total No. of Patients (%)			Odds Ratio NOACs vs No (95% CI)	Odds Ratio Warfarin vs No (95% CI)
	NOACs (n=245)	Warfarin with INR<1.7 (n=245)	No Oral Anticoagulant (n=245)		
Primary outcomes					
Symptomatic intracranial hemorrhage <36 h	12/245 (4.9)	12/245 (4.9)	15/245 (6.1)	0.79 (0.36–1.72)	0.79 (0.36–1.72)
Life-threatening or serious systemic hemorrhage <36 h	1/245 (0.4)	1/245 (0.4)	1/245 (0.4)	1.00 (0.06–16.1)	1.00 (0.06–16.1)
Any rt-PA complication*	16/245 (6.5)	23/245 (9.4)	24/245 (9.8)	0.64 (0.33–1.24)	0.95 (0.53–1.74)
Secondary outcomes					
In-hospital mortality	23/245 (9.4)	21/245 (8.6)	24/245 (9.8)	0.95 (0.52–1.74)	0.86 (0.47–1.60)
Discharge to home	101/245 (41.2)	88/245 (35.9)	86/245 (35.1)	1.30 (0.90–1.87)	1.04 (0.72–1.50)
Discharge to hospice	19/245 (7.8)	26/245 (10.6)	24/245 (9.8)	0.77 (0.41–1.45)	1.09 (0.61–1.96)
Discharge to skilling nursing facility	34/245 (13.9)	43/245 (17.6)	45/245 (18.4)	0.72 (0.44–1.16)	0.95 (0.60–1.50)
Discharge inpatient rehabilitation facility	62/245 (25.3)	61/245 (24.9)	59/245 (24.8)	1.07 (0.71–1.61)	1.05 (0.69–1.58)
Able to ambulate independently at discharge†	102/226 (45.1)	80/225 (35.6)	89/225 (39.6)	1.26 (0.86–1.83)	0.84 (0.58–1.24)
Modified Rankin Scale at discharge†					
mRS 0–1	34/149 (22.8)	23/151 (15.2)	38/143 (26.6)	0.82 (0.48–1.39)	0.50 (0.28–0.89)
mRS 0–2	44/149 (29.5)	44/151 (29.1)	47/143 (32.9)	0.86 (0.52–1.41)	0.84 (0.51–1.38)

CI indicates confidence interval; INR, international normalized ratio; mRS, modified Rankin Scale; NOACs, non–vitamin K antagonist oral anticoagulants; and rt-PA, recombinant tissue-type plasminogen activator.

*Any rt-PA complication includes symptomatic intracranial hemorrhage <36 h, life-threatening or serious systemic hemorrhage <36 h, or other serious complications.

†Missing data excluded.

NOACs are important alternatives to vitamin K antagonist in patients with atrial fibrillation. Although the incidence of stroke can be largely reduced by NOACs, the rapid adoption of NOACs in clinical practice poses new problems once the patient develops an ischemic stroke. NOACs act directly on thrombin or factor X in the coagulation cascade. These drugs may impact stroke thrombolysis in terms of risk of major bleeding complications. However, use of intravenous rt-PA in these patients has not been well studied. All major rt-PA trials were conducted in the era before any NOACs became available. Despite the lack of data from clinical trials, intravenous rt-PA in NOACs has been used in community practice, albeit largely limited to case reports. Of 74 NOAC patients receiving intravenous rt-PA in the literature, the overall sICH rate was 5.4% (4/74), which appeared comparable to rates of sICH in nonselective patient populations outside randomized clinical trials (5.2%).[44] Of these 4 sICHs, one patient might have stopped dabigatran for a prostate biopsy. It remained unclear whether the hemorrhagic transformation in this patient was attributable to dabigatran or other risk factors.[16]

Nevertheless, observations from case report or case series must be considered with caution because of small sample size, potential treatment selection bias, and publication bias. Indeed, the current AHA/ASA guidelines, solely on the basis of expert opinion, consider that rt-PA is contraindicated in patients taking NOACs, unless time since last intake is >48 hours or sensitive laboratory tests are normal.[6,35] It is interesting to note that very few cases reported so far had the last intake of NOACs >24 hours.[22,28,34] On the basis of the elimination half-lives of dabigatran (12–14 hours), rivaroxaban (5–9 hours), and apixaban (12 hours), normal coagulation may be expected 24 hours after last intake (eg, 2 half-lives) in patients with normal renal function.

Our study represents the largest clinical experience of intravenous rt-PA in patients receiving NOAC before stroke. Among 42 887 patients with ischemic stroke treated with intravenous rt-PA, 251 were receiving NOACs and 1500 were receiving warfarin with INR<1.7 before stroke onset. Although the unadjusted incidences of sICH were ≈0.9% higher in NOACs and 1.0% higher in warfarin in comparison with no anticoagulation, these

findings appear to be ascribed to the differences in risk profiles, most notably, age, NIHSS, and comorbid illness. After adjusting for all these factors in the multivariable analysis, neither NOACs (adjusted OR, 0.92; 95% CI, 0.51–1.65) nor warfarin were significantly associated with sICH (adjusted OR, 0.85; 95%, CI 0.66–1.10). Similarly, there were no statistically significant differences in outcomes after propensity score matching analysis. On the basis of these data, intravenous rt-PA in the background of NOACs appeared to be a reasonable clinical option for consideration in selected patients at experienced centers. It should be noted that, although NOAC patients have numerically more sICH, our study was not adequately powered to detect <1% difference, despite being the largest cohort available so far. Nevertheless, it is reassuring that adjusted ORs changed directions toward lower odds of sICH. The observed incidences of life-threatening or serious systemic hemorrhage and any rt-PA complications were numerically lower in NOAC than in nonanticoagulated patients even before the adjustment.

Our finding of no statistically significant differences in bleeding complications might seem surprising. A potential explanation is the low anticoagulant activity at the time of thrombolysis. Although we do not have data on NOAC plasma concentration or other coagulation parameters in the registry, evaluation of INR in warfarin-treated patients may provide an insight. The median INR of warfarin-treated patients were 1.2 in our study, 1.2 in a separate GWTG-Stroke cohort,[39] and 1.3 in the European SITS registry,[34] suggesting these patients were not sufficiently anticoagulated at all. Indeed, this may have been the major reason why patients had an ischemic stroke despite receiving NOACs or warfarin treatment. Therefore, NOAC anticoagulant effect might be minimal at stroke onset, which could have favored the absence of bleeding complications.

Our study should be interpreted in the context of the following limitations. First, this was a retrospective observational analysis with unblinded use of NOAC, warfarin, and antiplatelet agents. The use of rt-PA was likely based on patient and clinician factors that are difficult to assess, and likely to be different among those on NOACs, warfarin, or nonanticoagulated patients. Although we adjusted for measured factors in the model and performed propensity score analysis, treatment selection and unmeasured confounding may bias outcomes comparisons. However, we found that patients on NOACs had more risk factors in terms of advanced age, higher prevalence of vascular risk profiles, and more severe stroke than those not receiving oral anticoagulation before stroke. Furthermore, among NOAC patients potentially eligible for rt-PA, more patients were not treated than were treated with rt-PA, which mostly appears to be attributable to avoidance of treatment in patients with milder stroke severity or those who arrive late, the same as we see in unanticoagulated patients. Therefore, selection bias might be more likely to be against NOAC patients treated with rt-PA. Second, NIHSS score, a critical determinant of stroke outcomes, was missing in 2.1% of our cohort. Although we performed multiple imputations to fill in missing data with plausible values, this method might have introduced bias if missing was not at random.

Third, GWTG-Stroke does not collect exact time on the last intake of medication. As a result, we are unable to determine the relationship between bleeding risk and timing of last dose. It is possible that the risk of sICH could be higher than our reported risk in patients who took the last dose quite recently (within the last 24 hours), whereas, conversely, the risk might be much lower in patients who had missed several days of doses. Nevertheless, it appears that most rt-PA–treated NOAC patients that were reported in the literature had the last dose within 24 ho urs.[7–10,13–15,17,19–21,23–27,29–34] Fourth, besides baseline INR, other laboratory tests such prothrombin time, activated partial thromboplastin time, thrombin time, dilute thrombin time, ecarin clotting time, and antifactor Xa assay are not currently collected in the GWTG-Stroke Registry. Although warfarin-treated patients were excluded if there was prolongation of INR, we were unable to assess the coagulation level in NOAC-treated patients. In addition, patients might have received NOAC reversal treatment before rt-PA administration.[45] However, there was no NOAC-specific reversal agent commercially available during our study period, and nonspecific reversal treatments such as prothrombin complex concentrates were not collected in the registry. Future study should evaluate the safety and efficacy of NOAC reversal treatment in the setting of rt-PA for ischemic stroke and how these patients are treated if tPA complications occur. To address these limitations, we recently launched a new prospective substudy within GWTG-Stroke, with the objective of systematically collecting data on last intake of NOACs, coagulation test results, and postdischarge outcomes (URL: ClinicalTrials.gov. Unique identifier: NCT02478177).[46] These data will help us to better understand the clinical circumstance guiding treatment selection and identify optimal strategies to care for these complex but increasingly common clinical challenges.

Fifth, computed tomography or MRI scans were interpreted locally and not centrally adjudicated. The GWTG-Stroke Registry does not have the actual brain images for review. Therefore, we cannot determine the hemorrhage type according to the commonly used ECASS (European Cooperative Acute Stroke Study) grading system. Sixth, the GWTG-Stroke is an inpatient registry. We were unable to report long-term functional outcomes such as mRS at 90 days. Seventh, although hospitals are required to report consecutive ischemic stroke cases in the registry, regardless of whether or not tPA or other treatment was given, we cannot exclude the possibility of selective inclusion or exclusion of some patients. However, previous

study has shown that ischemic stroke admissions in the GWTG-Stroke are generally representative of the national ischemic stroke population at least among those with Medicare fee-for-service coverage.[47] Last, GWTG-Stroke is a voluntary program. Hospitals participated on their level of interest in quality improvement in stroke care and their capacity to fulfill the requirements. Therefore, these results might not be extrapolated to patients treated in non–GWTG-Stroke hospitals or in other countries.

In summary, the current study represents the largest clinical experience of stroke thrombolysis in patients receiving NOACs before stroke. Although the unadjusted sICH rate was numerically higher, the use of intravenous rt-PA in NOAC patients, selected by their treating physician, was not associated with statistically significant increased sICH risk. However, our observations must be considered as preliminary because of the absence of coagulation parameters, timing of the last NOACs intake, and whether or not nonspecific reversal strategies may have been applied. Although experience with rt-PA in patients with ischemic stroke on a NOAC is relatively limited, these initial findings suggest that intravenous rt-PA appears to be well tolerated without prohibitive risks for adverse events among selected NOAC-treated patients.

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FOOTNOTES

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Use of Intravenous Recombinant Tissue Plasminogen Activator in Patients With Acute Ischemic Stroke Who Take Non–Vitamin K Antagonist Oral Anticoagulants Before Stroke

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SUPPLEMENTAL MATERIAL

Supplemental Table 1. Demographics, Medical History and Hospital Characteristics after Propensity Score Matching

Variable	NOACs N=245	Warfarin with INR<1.7 N=245	No oral anticoagulant N=245	p-value
Demographics				
Age, median (p25-p75), y	74 (66, 82)	75 (63, 85)	74 (62, 84)	0.87
Women, N (%)	128 (52.2)	138 (56.3)	117 (47.8)	0.16
Race/ethnicity, N (%)				0.17
White	178 (72.7)	169 (69.0)	178 (72.7)	
Black	35 (14.3)	46 (18.8)	29 (11.8)	
Asian	24 (9.8)	17 (6.9)	21 (8.6)	
Hispanic	6 (2.4)	8 (3.3)	7 (2.9)	
Other	2 (0.8)	5 (2.0)	10 (4.1)	
History of, N (%)				
Atrial fibrillation/flutter	191 (78.0)	182 (74.3)	192 (78.4)	0.50
Prosthetic heart valve	4 (1.6)	16 (6.5)	5 (2.0)	0.004
Previous stroke/TIA	76 (31.0)	67 (27.3)	76 (31.0)	0.59
Carotid stenosis	7 (2.9)	4 (1.6)	14 (5.7)	0.04
CAD/MI	76 (31.0)	58 (23.7)	62 (25.3)	0.15
Heart failure	37 (15.1)	43 (17.6)	27 (11.0)	0.12
Hypertension	193 (78.8)	195 (79.6)	184 (75.1)	0.44
Dyslipidaemia	103 (42.0)	94 (38.4)	100 (40.8)	0.70
Peripheral vascular disease	8 (3.3)	8 (3.3)	9 (3.7)	0.96
Diabetes mellitus	63 (25.7)	64 (26.1)	62 (25.3)	0.98
Smoker	19 (7.8)	10 (4.1)	10 (4.1)	0.11
Hospital characteristics				
Number of beds, median (p25-p75)	376 (273-560)	407 (276-610)	379 (250-561)	0.43

Annual ischemic stroke volume, median (p25-p75)	227 (147-349)	217 (144-350)	222 (149-319)	0.85
Annual IV rt-PA cases, median p25-p75)	20 (11-36)	21 (12-30)	21 (13-31)	0.91
Hospital type, academic, N (%)	150 (61.2)	159 (64.9)	139 (56.7)	0.18
Joint Commission primary stroke center, N (%)	104 (42.4)	97 (39.6)	91 (37.1)	0.49
Rural hospital, N (%)	2 (0.8)	3 (1.2)	3 (2.2)	0.88

Abbreviations: CAD, coronary artery disease; IV rt-PA, intravenous tissue plasminogen activator; MI, myocardial infarction; NOACs, non-vitamin K antagonist oral anticoagulants; p25-p75, percentiles; SD, standard deviation; TIA, transient ischaemic attack

Supplemental Table 2. Clinical Characteristics after Propensity Score Matching

Variable	NOACs N=245	Warfarin with INR<1.7 N=245	No oral anticoagulant N=245	p-value
Medications prior to admission, N (%)				
Anticoagulant	245 (100.0)	245 (100.0)	-	-
Warfarin	-	245 (100.0)	-	-
Dabigatran	84 (34.3)	-	-	-
Rivaroxaban	127 (51.8)	-	-	-
Apixaban	34 (13.9)	-	-	-
Antiplatelet	73 (29.8)	70 (28.6)	81 (33.1)	0.55
Aspirin only	58 (23.7)	59 (24.1)	63 (25.7)	
Aspirin/clopidogrel	7 (2.9)	4 (1.6)	9 (3.7)	
Aspirin/dipyridamole	0 (0.0)	0 (0.0)	2 (0.8)	
Clopidogrel only	8 (3.3)	7 (2.9)	6 (2.4)	
Others	0 (0.0)	10 (0.7)	1 (0.4)	
No antiplatelet	172 (70.2)	175 (71.4)	164 (66.9)	
Antihypertensive	184 (84.8)	197 (82.8)	148 (68.8)	<0.001
Cholesterol-reducer	140 (57.1)	122 (49.8)	102 (41.6)	0.003
Diabetic medication	48 (22.3)	50 (21.2)	43 (20.4)	0.89
Arrival by EMS, N (%)	204 (83.3)	210 (85.7)	202 (82.4)	0.59
Off-hour presentation*, N (%)	119 (48.6)	110 (44.9)	121 (49.4)	0.57
NIHSS, median (p25-p75)	12 (6, 18)	13 (7, 19)	9 (5, 15)	<0.001
Time from symptom onset to arrival, median (p25-p75), min	60 (37-90)	59 (37-90)	58 (38-86)	0.80
Door-to-needle time, median (p25-p75), min	65 (50-88)	67 (52-87)	59 (47-81)	0.03
Heart rate, median (p25-p75), bpm	82 (70-98)	85 (74-97)	82 (71-98)	0.41
Systolic blood pressure, median (p25-p75), mmHg	155 (136-172)	157 (139-177)	151 (134-169)	0.20

Diastolic blood pressure, median (p25-p75), mmHg	85 (74-100)	87 (76-98)	83 (71-95)	0.08
Creatinine, median (p25-p75), mg/dL	1.0 (0.9-1.2)	1.0 (0.9-1.2)	1.0 (0.8-1.2)	0.14
Blood glucose, median (p25-p75), mg/dL	120 (103-149)	123 (103-150)	120 (104-145)	0.84
Body mass index, median (p25-p75),	28.7 (24.3-33.1)	27.7 (24.0-33.5)	26.9 (24.1-30.9)	0.28
International normalized ratio (INR), median (p25-p75)	1.1 (1.0-1.2)	1.2 (1.1-1.4)	1.0 (1.0-1.1)	<0.001

Abbreviations: NIHSS, National Institutes of Health Stroke Scale; NOACs, non-vitamin K antagonist oral anticoagulants; p25-p75, percentiles;

*Off-hour presentation, presentation anytime outside of 7am to 6pm on weekdays

Supplemental Table 3. Characteristics of Patients with or without Documented modified Rankin Scale (mRS) at Discharge

Variable	Patients with mRS N=24,832	Patients without mRS N=18,055	p-value
Demographics			
Age, median (p25-p75), y	72 (60-83)	70 (59-81)	<0.001
Women, N (%)	12,459 (50.2)	9100 (50.4)	0.64
Race/ethnicity, N (%)			<0.001
White	17,430 (70.2)	12,890 (71.5)	
Black	3,781 (15.2)	2,721 (15.1)	
Asian	1,873 (7.5)	1,338 (7.4)	
Hispanic	754 (3.0)	422 (2.3)	
Other	986 (4.0)	645 (3.6)	
History of , N (%)			
Atrial fibrillation/flutter	5254 (21.2)	3531 (19.6)	<0.001
Prosthetic heart valve	285 (1.1)	179 (1.0)	0.12
Previous stroke/transient ischaemic attack	6,483 (26.1)	4,667 (25.9)	0.56
Carotid stenosis	672 (2.7)	443 (2.5)	0.11
Coronary artery disease/myocardial infarction	5959 (24.0)	4330 (24.0)	>0.99
Heart failure	2,306 (9.3)	1,689 (9.4)	0.80
Hypertension	18,372 (74.0)	13,149 (72.9)	0.009
Dyslipidaemia	10,933 (44.0)	7,810 (43.3)	0.12
Peripheral vascular disease	914 (3.7)	669 (3.7)	0.89
Diabetes mellitus	6,742 (27.2)	4,990 (27.7)	0.25
Smoker	4,130 (16.6)	3,375 (18.7)	<0.001
Medications prior to admission, N (%)			
Anticoagulant	1,079 (4.3)	672 (3.7)	<0.001
Warfarin	925 (3.7)	575 (3.2)	

Dabigatran	57 (0.2)	30 (0.2)	
Rivaroxaban	85 (0.3)	44 (0.2)	
Apixaban	12 (0.0)	23 (0.1)	
Antiplatelet	11,638 (46.9)	8522 (47.2)	0.29
Aspirin only	8712 (35.1)	6345 (35.1)	
Aspirin/clopidogrel	1373 (5.5)	1,034 (5.7)	
Aspirin/dipyridamole	215 (0.9)	181 (1.0)	
Clopidogrel only	1206 (4.9)	833 (4.6)	
Others	16 (0.1)	18 (0.1)	
Antihypertensive	14,927 (67.0)	9764 (65.1)	<0.001
Cholesterol-reducer	10,461 (42.1)	7765 (43.0)	0.07
Diabetic medication	4,504 (20.6)	3,099 (21.3)	0.15
Arrival by EMS, N (%)	19,806 (81.8)	13,638 (79.6)	<0.001
Off-hour presentation*, N (%)	12,061 (48.6)	8,666 (48.0)	0.24
National Institutes of Health Stroke Scale, median (p25-p75)	9 (5-16)	9 (5-15)	<0.001
Time from symptom onset to arrival, median (p25-p75), min	60 (40-94)	60 (39-92)	<0.001
Door-to-needle time, median (p25-p75), min	60 (46-81)	64 (50-86)	<0.001
Heart rate, median (p25-p75), bpm	80 (69-92)	80 (70-92)	0.82
Systolic blood pressure, median (p25-p75), mmHg	155 (138-176)	155 (138-176)	0.40
Diastolic blood pressure, median (p25-p75), mmHg	84 (73-96)	84 (73-96)	0.59
Creatinine, median (p25-p75), mg/dL	1.0 (0.8-1.2)	1.0 (0.8-1.2)	0.64
Blood glucose, median (p25-p75), mg/dL	119 (102, 149)	118 (101, 148)	0.01
Body mass index, median (p25-p75)	27.3 (23.9-31.6)	27.6 (24.1-32.3)	<0.001
International normalized ratio (INR), median (p25-p75)	1.0 (1.0-1.1)	1.0 (1.0-1.1)	0.003

Abbreviation: p25-p75, percentiles. *Off-hour presentation, presentation anytime outside of 7am to 6pm on weekdays

Supplemental Table 4. Risk Profiles of Eligible NOACs Patients With vs. Without Intravenous rt-PA

Variable	rt-PA Yes n=251	rt-PA No N=318	p-value
Demographics			
Age, median (p25-p75), y	74 (66-82)	77 (68-85)	0.01
Women, N (%)	129 (51.4)	187 (58.8)	0.08
Race/ethnicity, N (%)			0.08
White	183 (72.9)	247 (78.7)	
Black	36 (14.3)	35 (11.1)	
Asian	24 (9.6)	17 (5.4)	
Hispanic	6 (2.4)	6 (1.9)	
Other	2 (0.8)	9 (2.9)	
History of, N (%)			
Atrial fibrillation/flutter	196 (78.1)	239 (75.9)	0.53
Prosthetic heart valve	4 (1.6)	4 (1.3)	0.75
Previous stroke/transient ischaemic attack	77 (30.7)	157 (49.8)	<0.001
Carotid stenosis	7 (2.8)	13 (4.1)	0.39
Coronary artery disease/myocardial infarction	79 (31.5)	113 (35.9)	0.27
Heart failure	38 (15.1)	63 (20.0)	0.13
Hypertension	198 (78.9)	253 (80.3)	0.67
Dyslipidaemia	106 (42.2)	156 (49.5)	0.08
Peripheral vascular disease	8 (3.2)	22 (7.0)	0.05
Diabetes mellitus	64 (25.5)	115 (36.5)	0.005
Smoker	19 (7.6)	32 (10.2)	0.29
Medications prior to admission, N (%)			
Anticoagulant			0.82
Dabigatran	87 (34.7)	113 (35.5)	
Rivaroxaban	129 (51.4)	156 (49.1)	
Apixaban	35 (13.9)	49 (15.4)	

Antiplatelet	76 (30.3)	101 (31.8)	0.70
Aspirin only	60 (23.9)	85 (26.7)	
Aspirin/clopidogrel	8 (3.2)	5 (1.6)	
Aspirin/dipyridamole	0 (0.0)	1 (0.3)	
Clopidogrel only	8 (3.2)	10 (3.1)	
Antihypertensive	189 (84.8)	237 (87.5)	0.39
Cholesterol-reducer	143 (57.0)	183 (57.7)	0.86
Diabetic medication	49 (22.2)	75 (29.4)	0.07
Arrival by EMS, N (%)	205 (84.4)	223 (71.9)	<0.001
Off-hour presentation*, N (%)	124 (49.4)	161 (50.6)	0.77
National Institutes of Health Stroke Scale, median (p25-p75)	12 (6-18)	4 (1-10)	<0.001
Time from symptom onset to arrival, median (p25-p75), min	60 (37-90)	103 (57-145)	<0.001
Heart rate, median (p25-p75), bpm	82 (70-98)	83 (70-96)	0.80
Systolic blood pressure, median (p25-p75), mmHg	155 (136-172)	150 (133-169)	0.20
Diastolic blood pressure, median (p25-p75), mmHg	85 (74-100)	80 (68-93)	0.001
Creatinine, median (p25-p75), mg/dL	1.0 (0.9-1.2)	1.0 (0.9-1.4)	0.32
Blood glucose, median (p25-p75), mg/dL	119 (102-149)	124 (102-171)	0.15
Body mass index, median (p25-p75)	29.0 (24.3-33.5)	25.9 (22.8-30.5)	0.002
International normalized ratio (INR), median (p25-p75)	1.1 (1.0-1.2)	1.2 (1.0-1.4)	<0.001
Hospital characteristics			
Number of beds, median (p25-p75)	370 (273-555)	341 (227-471)	<0.001
Annual ischemic stroke volume, median (p25-p75)	230 (147-337)	189 (126-285)	0.001
Annual IV rt-PA volume, median (p25-p75)	20 (11-37)	14 (7-24)	<0.001
Hospital type, academic, N (%)	151 (60.4)	157 (51.3)	0.03
Joint Commission Primary Stroke Center, N (%)	104 (41.4)	123 (38.7)	0.51

Rural hospital, N (%)	2 (0.8)	26 (8.2)	<0.001

Abbreviation: IV rt-PA, intravenous tissue plasminogen activator; NOACs, non-vitamin K antagonist oral anticoagulant; p25-p75, percentile

*Off-hour presentation, presentation anytime outside of 7am to 6pm on weekdays

Supplemental Table 5. In-hospital Outcomes of Eligible NOACs Patients Treated with Intravenous rt-PA vs. Not

In-hospital outcomes	rt-PA Yes n=251	rt-PA No N=318
Symptomatic intracranial hemorrhage <36 hours	12 (4.8)	-
Life-threatening or serious systemic hemorrhage <36 hours	1 (0.4)	-
Any rt-PA complication*	17 (6.8)	-
In-hospital mortality	23 (9.2)	24 (7.6)
Discharge to home	106 (42.2)	133 (41.8)
Discharge to hospice	19 (7.6)	24 (7.6)
Discharge to skilling nursing facility	34 (13.5)	77 (24.2)
Discharge inpatient rehabilitation facility	63 (25.1)	52 (16.4)
Able to ambulate independently at discharge†	107 (46.1)	118 (43.5)
Modified Rankin Scale at discharge†		
mRS 0-1	37 (24.0)	34 (22.2)
mRS 0-2	48 (31.2)	46 (30.1)

Abbreviation: IV rt-PA, intravenous tissue plasminogen activator; NOACs, non-vitamin K antagonist oral anticoagulant

*Only collected for rt-PA treated patients

† Missing data excluded