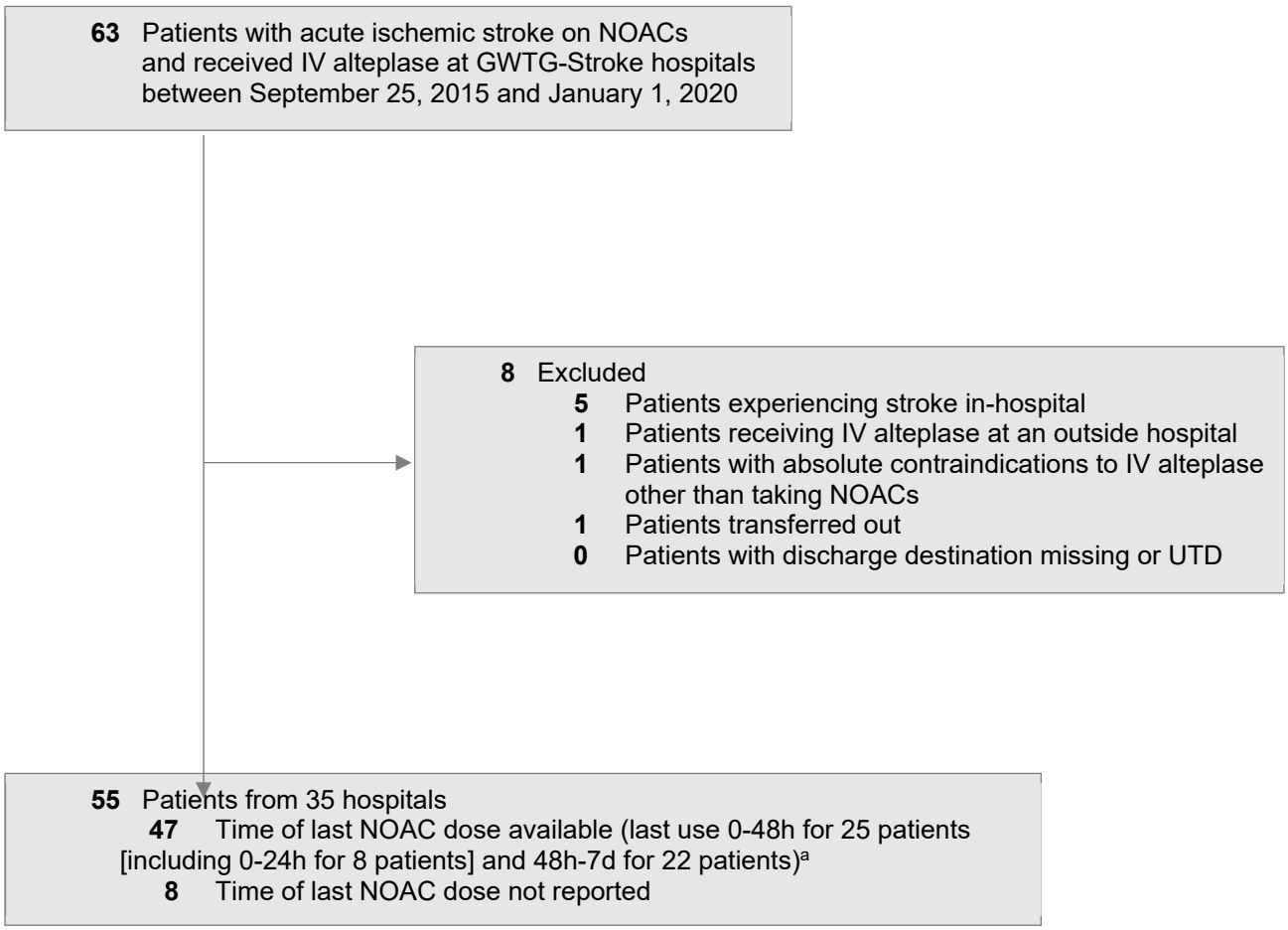
Supplementary Online Content

Kam W, Holmes DN, Hernandez AF, et al. Association of recent use of non–vitamin K antagonist oral anticoagulants with intracranial hemorrhage among patients with acute ischemic stroke treated with alteplase. *JAMA*. Published online February 10, 2022. doi:10.1001/jama.2022.0948

This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure. Study Population in the ARAMIS Registry



Abbreviations: ARAMIS, Addressing Real-world Anticoagulant Management Issues in Stroke; GWTG-Stroke, Get With The Guidelines-Stroke; IV, intravenous; NOAC, non-vitamin K antagonist oral anticoagulant; UTD, unable to determine.

[a] The reported date and time that the patient last took their anticoagulant medication was used to generate the time epochs; however, if the exact date and time was not available, the response to the question “Did patient stop anticoagulant medication >2 days prior to stroke onset?” was alternatively used to define the <48 hours and >48 hours time epochs.

eMethods. Propensity Score Overlap Weighting

The study used overlap weighing that has been previously described in JAMA Guide to Statistics and Methods: Overlap Weighting: A Propensity Score Method That Mimics Attributes of a Randomized Clinical Trial.

"Overlap weighting assigns weights to each patient that are proportional to the probability of that patient belonging to the opposite treatment group. Specifically, treated patients are weighted by the probability of not receiving treatment (1 – propensity score) and untreated patients are weighted by the probability of receiving the treatment (propensity score). These weights are smaller for extreme PS values so that outliers who are nearly always treated (PS near 1) or never treated (PS near 0) do not dominate results. These outliers contribute relatively less to the result, while patients whose characteristics are compatible with either treatment contribute relatively more. Overlap weighting leads to exact balance on the mean of every measured covariate when the PS is estimated by a logistic regression" (Thomas et al. 2020).

Li F, Morgan KL, Zaslavsky AM. Balancing covariates via propensity score weighting. *J Am Stat Assoc*. 2018;113(521):390-400. doi:10.1080/01621459.2016.1260466

Thomas LE, Li F, Pencina MJ. Overlap Weighting: A Propensity Score Method That Mimics Attributes of a Randomized Clinical Trial. *JAMA*. 2020;323(23):2417-2418. doi:10.1001/jama.2020.7819

eTable 1. Brain Imaging Results

	Taking NOACs (n=2207)	Not taking AC (n=160831)	*P* Value
Positive finding on brain imaging of parenchymal hematoma, SAH, and or IVH following IV alteplase among hospitals reporting comprehensive stroke center data elements	90 (4.1%)	5699 (3.5%)	.68
Results of positive brain image			
PH2	15 (0.7%)	1060 (0.7%)	.80
IVH	12 (0.5%)	740 (0.5%)	.80
SAH	27 (1.2%)	1532 (1.0%)	.43
RIH	5 (0.2%)	291 (0.2%)	.77
Not documented	21 (1.0%)	1224 (0.8%)	.56
Other positive finding not listed above	36 (1.6%)	2271 (1.4%)	.78

Abbreviations: AC, anticoagulant; IV, intravenous; IVH, intraventricular hemorrhage; NOAC, non-vitamin K antagonist oral anticoagulant; PH2, parenchymal hematoma type 2; RIH, remote site of intraparenchymal hemorrhage outside the area of infarction; SAH, subarachnoid hemorrhage.

eTable 2. Associations between NOAC Treatment and Post-Thrombolytic Outcomes by Receipt of Endovascular Therapy (interaction *P* values)

Outcome	*P* Value
Symptomatic intracranial hemorrhage <36 h	.29
Life-threatening/serious systemic hemorrhage <36 h	.13
Any alteplase complication[a]	.11
In-hospital mortality	.95
In-hospital mortality or discharge to hospice	.79
Independent ambulation at discharge	.85
Discharge mRS 0-2	.45
Discharge mRS 0-1	.94
Discharge to home	.12
Discharge to hospice	.54
Discharge to inpatient rehabilitation facility	.24
Discharge to skilled nursing facility	.39
Length of stay (>4 days)	.58

Abbreviations: mRS, modified Rankin Scale; NOAC, non-vitamin K antagonist oral anticoagulant.
[a] Any alteplase complication includes symptomatic intracranial hemorrhage <36 h, life-threatening/serious systemic hemorrhage <36 h, or other serious complications (those that require additional medical interventions or prolonged length of stay).

eTable 3. Baseline Patient and Hospital Characteristics of Patients Taking NOACs and Treated with Alteplase by ARAMIS and GWTG-Stroke Registries

	ARAMIS NOAC (n=55)	GWTG NOAC (n=2152)	Absolute standardized difference[a]
Demographics			
Age, median (IQR), y	74 (66-81)	75 (64-82)	6.7
Sex, n (%)			5.4
Male	31 (56.4)	1155 (53.7)	
Female	24 (43.6)	997 (46.3)	
Race and ethnicity, n (%)			
Asian	3 (5.5)	73 (3.4)	10.0
Hispanic	4 (7.3)	192 (8.9)	6.1
Non-Hispanic Black	8 (14.5)	334 (15.5)	2.7
Non-Hispanic White	37 (67.3)	1451 (67.4)	0.3
Other[b]	3 (5.5)	102 (4.7)	3.3
Health insurance status, n (%)			
Medicare	22/52 (42.3)	1060/2048 (51.8)	19.0
Private	26/52 (50.0)	719/2048 (35.1)	30.5
Medicaid	4/52 (7.7)	218/2048 (10.6)	10.2
Self pay/no insurance	0/52 (0.0)	43/2048 (2.1)	20.7
Not documented	0/52 (0.0)	8/2048 (0.4)	8.9
Year of stroke admission, n (%)			
2015	1 (1.8)	200 (9.3)	33.1
2016	10 (18.2)	330 (15.3)	7.6
2017	11 (20.0)	408 (19.0)	2.6
2018	16 (29.1)	531 (24.7)	10.0
2019	17 (30.9)	600 (27.9)	6.7
2020	0 (0.0)	83 (3.9)	28.3
Medical history, n (%)			
Atrial fibrillation/flutter	44 (80.0)	1570 (73.0)	16.7
CAD/prior MI	18 (32.7)	606 (28.2)	9.9
Heart failure	12 (21.8)	409 (19.0)	7.0
Prior stroke	15 (27.3)	613 (28.5)	2.7
Prior TIA	6 (10.9)	208 (9.7)	4.1
Prosthetic heart valve	0 (0.0)	21 (1.0)	14.0
Carotid stenosis	2 (3.6)	56 (2.6)	6.0
Diabetes mellitus	22 (40.0)	697 (32.4)	15.9
Peripheral vascular disease	1 (1.8)	74 (3.4)	10.1
Hypertension	46 (83.6)	1707 (79.3)	11.1
Smoker	4 (7.3)	238 (11.1)	13.2
Dyslipidemia	32 (58.2)	1067 (49.6)	17.3
Chronic kidney disease	6 (10.9)	163 (7.6)	11.5
Medications prior to admission, n (%)			
Any antiplatelets	18 (32.7)	751 (34.9)	4.6
Single antiplatelet	18 (32.7)	689 (32.0)	1.5
Aspirin	16 (29.1)	675 (31.4)	5.0
Clopidogrel	1 (1.8)	131 (6.1)	22.0
Ticagrelor	1 (1.8)	1 (0.0)	18.5
Prasugrel	0 (0.0)	3 (0.1)	5.3
Aspirin/dipyridamole	0 (0.0)	1 (0.0)	3.1

	ARAMIS NOAC (n=55)	GWTG NOAC (n=2152)	Absolute standardized difference[a]
Dual antiplatelet	0 (0.0)	61 (2.8)	24.2
Antihypertensives	42 (76.4)	1518 (70.5)	13.2
Cholesterol-reducers	31 (56.4)	1331 (61.8)	11.2
Diabetic medications	10 (18.2)	461 (21.4)	8.1
Patient information			
NIHSS, median (IQR)	9 (5-15)	10 (5-17)	13.3
Ambulatory status prior to admission, n (%)			
Able to ambulate independently	44/45 (97.8)	1446/1553 (93.1)	22.5
With assistance from person	1/45 (2.2)	65/1553 (4.2)	11.2
Unable to ambulate	0/45 (0.0)	42/1553 (2.7)	23.6
Ambulatory status at admission, n (%)			
Able to ambulate independently	12/37 (32.4)	324/1207 (26.8)	12.3
With assistance from person	9/37 (24.3)	326/1207 (27.0)	6.2
Unable to ambulate	16/37 (43.2)	557/1207 (46.1)	5.8
Arrival by EMS, n (%)	38 (69.1)	1708 (79.4)	23.7
Arrival during off-hours, n (%)	37 (67.3)	1148 (53.3)	28.8
BMI, median (IQR), kg/m^2	27.0 (24.6-33.8)	28.1 (24.3-33.2)	7.8
SBP, median (IQR), mm Hg	152 (142-168)	154 (136-173)	3.6
DBP, median (IQR), mm Hg	91 (75-97)	87 (75-100)	6.5
Heart rate, median (IQR), beats/min	79 (70-98)	82 (70-96)	2.3
Blood glucose, median (IQR), mg/dL	124 (106-153)	122 (103-153)	9.9
INR, median (IQR)	1.1 (1.0-1.2)	1.1 (1.0-1.2)	29.1
Serum creatinine, median (IQR), mg/dL	1.1 (0.9-1.3)	1.0 (0.8-1.3)	0.2
Treatment characteristics			
Onset-to-needle time, median (IQR), min	143 (90-181)	121 (89-167)	18.1
Door-to-needle time, median (IQR), min	55 (34-80)	51 (37-69)	1.9
Onset-to-arrival time, median (IQR), min	80.5 (45.0-116.0)	62.0 (40.0-101.0)	21.0
Received EVT, n (%)	12 (21.8%)	403 (18.7%)	7.7
Presence of large vessel occlusion, n (%)[c]	16/38 (42.1%)	516/1176 (43.9%)	3.6
Site of occlusion, n (%)[c]			
Middle cerebral artery	13/16 (81.3)	429/516 (83.1)	4.9
Internal carotid artery	2/16 (12.5)	67/516 (13.0)	1.5
Other cerebral artery branch	2/16 (12.5)	39/516 (7.6)	16.5
Basilar artery	0/16 (0.0)	16/516 (3.1)	25.3
Vertebral artery	0/16 (0.0)	9/516 (1.7)	18.8
Hospital characteristics			
Number of beds, median (IQR)	513 (381-650)	409 (276-620)	10.5
Annual ischemic stroke volume, median (IQR)	558 (287-704)	368 (232-558)	41.4
Annual IV thrombolytic cases, median (IQR)	66 (39-85)	51 (29-81)	26.5
Academic hospital, n (%)	49 (89.1)	1614 (75.0)	37.4
Stroke center status, n (%)			
Comprehensive Stroke Center (CSC)	27 (49.1)	251 (11.7)	89.1
Primary Stroke Center (PSC)	19 (34.5)	1143 (53.1)	38.1
Neither CSC or PSC	9 (16.4)	758 (35.2)	44.2
Geographic region, n (%)			
South	17 (30.9)	993 (46.1)	31.7
West	19 (34.5)	484 (22.5)	26.9
Northeast	7 (12.7)	366 (17.0)	12.1
Midwest	12 (21.8)	309 (14.4)	19.5

	ARAMIS NOAC (n=55)	GWTG NOAC (n=2152)	Absolute standardized difference[a]
Rural location, n (%)	0 (0.0)	41 (1.9)	19.7

Abbreviations: AC, anticoagulant; ARAMIS, Addressing Real-world Anticoagulant Management Issues in Stroke; BMI, body mass index; CAD, coronary artery disease; DBP, diastolic blood pressure; EMS, Emergency Medical Services; EVT, endovascular therapy; GWTG-Stroke, Get With The Guidelines-Stroke; INR, international normalized ratio; IQR, interquartile range; IV, intravenous; MI, myocardial infarction; NIHSS, National Institutes of Health Stroke Scale; NOAC, non-vitamin K antagonist oral anticoagulant; SBP, systolic blood pressure; TIA, transient ischemic attack.

[a] The absolute standardized difference is calculated as the difference in means or proportions divided by a pooled estimate of the standard deviation and multiplied by 100.

[b] Other includes American Indian/Alaska Native, Native Hawaiian or Pacific Islander, multiracial, or any other non-Black or non-White race categories.

[c] Not available in the GWTG-Stroke registry until 2019.

eTable 4. Baseline Patient and Hospital Characteristics of Patients Taking NOACs Who Are Eligible for Intravenous Alteplase, Stratified by Treatment Status

	NOAC rt-PA (n=2207)	NOAC no rt-PA (n=22977)	Absolute standardized difference[a]
Demographics			
Age, median (IQR), y	75 (64-82)	77 (68-85)	19.8
Sex, n (%)			
Male	1186 (53.7)	11509 (50.1)	7.3
Female	1021 (46.3)	11468 (49.9)	
Race and ethnicity, n (%)			
Asian	76/2207 (3.4)	581/22973 (2.5)	5.4
Hispanic	196/2207 (8.9)	1367/22973 (6.0)	11.2
Non-Hispanic Black	342/2207 (15.5)	2924/22973 (12.7)	8.0
Non-Hispanic White	1488/2207 (67.4)	17275/22973 (75.2)	17.3
Other[b]	105/2207 (4.8)	826/22973 (3.6)	5.8
Health insurance status, n (%)			
Medicare	1082/2100 (51.5)	11763/22258 (52.8)	2.7
Private	745/2100 (35.5)	8433/22258 (37.9)	5.0
Medicaid	222/2100 (10.6)	1719/22258 (7.7)	9.9
Self pay/no insurance	43/2100 (2.0)	287/22258 (1.3)	5.9
Not documented	8/2100 (0.4)	56/22258 (0.3)	2.3
Year of stroke admission, n (%)			
2015	201 (9.1)	1990 (8.7)	1.6
2016	340 (15.4)	3194 (13.9)	4.3
2017	419 (19.0)	4314 (18.8)	0.5
2018	547 (24.8)	5527 (24.1)	1.7
2019	617 (28.0)	6956 (30.3)	5.1
2020	83 (3.8)	996 (4.3)	2.9
Medical history, n (%)			
Atrial fibrillation/flutter	1614 (73.1)	17110 (74.5)	3.0
CAD/prior MI	624 (28.3)	7393 (32.2)	8.5
Heart failure	421 (19.1)	4639 (20.2)	2.8
Prior stroke	628 (28.5)	8837 (38.5)	21.3
Prior TIA	214 (9.7)	3236 (14.1)	13.6
Prosthetic heart valve	21 (1.0)	446 (1.9)	8.3
Carotid stenosis	58 (2.6)	997 (4.3)	9.3
Diabetes mellitus	719 (32.6)	7654 (33.3)	1.6
Peripheral vascular disease	75 (3.4)	1520 (6.6)	14.8
Hypertension	1753 (79.4)	18631 (81.1)	4.2
Smoker	242 (11.0)	2181 (9.5)	4.9
Dyslipidemia	1099 (49.8)	12626 (55.0)	10.3
Chronic kidney disease	169 (7.7)	2556 (11.1)	11.9
Medications prior to admission, n (%)			
Any antiplatelets	769 (34.8)	7200 (31.3)	7.5
Single antiplatelet	707 (32.0)	6723 (29.3)	6.0

	NOAC rt-PA (n=2207)	NOAC no rt-PA (n=22977)	Absolute standardized difference[a]
Aspirin	691 (31.3)	6344 (27.6)	8.1
Clopidogrel	132 (6.0)	1214 (5.3)	3.0
Ticagrelor	2 (0.1)	40 (0.2)	2.3
Prasugrel	3 (0.1)	4 (0.0)	4.3
Aspirin/dipyridamole	1 (0.0)	27 (0.1)	2.5
Dual antiplatelet	61 (2.8)	462 (2.0)	4.9
Antihypertensives	1560 (70.7)	16424 (71.5)	1.8
Cholesterol-reducers	1362 (61.7)	14171 (61.7)	0.1
Diabetic medications	471 (21.3)	5089 (22.1)	2.0
Patient information			
NIHSS, median (IQR)	10 (5-17)	5 (2-13)	43.3
Ambulatory status prior to admission, n (%)			
Able to ambulate independently	1490/1598 (93.2)	14575/16540 (88.1)	17.7
With assistance from person	66/1598 (4.1)	1272/16540 (7.7)	15.1
Unable to ambulate	42/1598 (2.6)	693/16540 (4.2)	8.6
Ambulatory status at admission, n (%)			
Able to ambulate independently	336/1244 (27.0)	4604/12645 (36.4)	20.3
With assistance from person	335/1244 (26.9)	3798/12645 (30.0)	6.9
Unable to ambulate	573/1244 (46.1)	4243/12645 (33.6)	25.8
Arrival by EMS, n (%)	1746 (79.1)	15942 (69.4)	22.4
Arrival during off-hours, n (%)	1185 (53.7)	12511 (54.5)	1.5
BMI, median (IQR), kg/m^2	28.1 (24.3-33.3)	27.7 (24.1-32.3)	11.0
SBP, median (IQR), mm Hg	154 (136-173)	151 (133-171)	9.6
DBP, median (IQR), mm Hg	88 (75-100)	83 (72-95)	20.9
Heart rate, median (IQR), beats/min	82 (70-96)	80 (69-93)	10.3
Blood glucose, median (IQR), mg/dL	122 (103-153)	121 (103-154)	0.3
INR, median (IQR)	1.1 (1.0-1.2)	1.2 (1.1-1.3)	60.5
Serum creatinine, median (IQR), mg/dL	1.0 (0.8-1.3)	1.0 (0.8-1.3)	0.8
Treatment characteristics			
Onset-to-needle time, median (IQR), min	122 (89-168)		.
Door-to-needle time, median (IQR), min	51 (37-69)		.
Onset-to-arrival time, median (IQR), min	62 (40-102)	78 (47-132)	31.0
Received EVT, n (%)	415 (18.8)	2910 (12.7)	16.9
Presence of large vessel occlusion, n (%)[c]	532/1214 (43.8)	4120/12271 (33.6)	21.2
Site of occlusion, n (%)[c]			
Middle cerebral artery	442/532 (83.1)	3125/4113 (76.0)	17.7
Internal carotid artery	69/532 (13.0)	737/4113 (17.9)	13.7
Other cerebral artery branch	41/532 (7.7)	391/4113 (9.5)	6.4
Basilar artery	16/532 (3.0)	140/4113 (3.4)	2.3
Vertebral artery	9/532 (1.7)	126/4113 (3.1)	9.0
Hospital characteristics			
Number of beds, median (IQR)	411 (278-620)	376 (244-585)	10.3
Annual ischemic stroke volume, median (IQR)	368 (232-563)	336 (203-545)	7.4
Annual IV thrombolytic cases, median (IQR)	51 (30-82)	40 (20-67)	29.3
Academic hospital, n (%)	1663 (75.4)	16935 (73.7)	3.8

	NOAC rt-PA (n=2207)	NOAC no rt-PA (n=22977)	Absolute standardized difference[a]
Stroke center status, n (%)			
Comprehensive Stroke Center (CSC)	278 (12.6)	2761 (12.0)	1.8
Primary Stroke Center (PSC)	1162 (52.7)	12099 (52.7)	0.01
Neither CSC or PSC	767 (34.8)	8117 (35.3)	1.2
Geographic region, n (%)			
South	1010 (45.8)	9444 (41.1)	9.4
West	503 (22.8)	4164 (18.1)	11.6
Northeast	373 (16.9)	5383 (23.4)	16.3
Midwest	321 (14.5)	3986 (17.3)	7.7
Rural location, n (%)	41 (1.9)	812 (3.5)	10.4

Abbreviations: AC, anticoagulant; BMI, body mass index; CAD, coronary artery disease; DBP, diastolic blood pressure; EMS, Emergency Medical Services; EVT, endovascular therapy; INR, international normalized ratio; IQR, interquartile range; IV, intravenous; MI, myocardial infarction; NIHSS, National Institutes of Health Stroke Scale; NOAC, non-vitamin K antagonist oral anticoagulant; rt-PA, recombinant tissue-type plasminogen activator; SBP, systolic blood pressure; TIA, transient ischemic attack.

[a] The absolute standardized difference is calculated as the difference in means or proportions divided by a pooled estimate of the standard deviation and multiplied by 100.

[b] Other includes American Indian/Alaska Native, Native Hawaiian or Pacific Islander, multiracial, or any other non-Black or non-White race categories.

[c] Not available in the GWTG-Stroke registry until 2019.