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Time to Anticoagulation Reversal and Outcomes After Intracerebral Hemorrhage

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IMPORTANCE Intracerebral hemorrhage (ICH) is the deadliest stroke subtype, and mortality rates are especially high in anticoagulation-associated ICH. Recently, specific anticoagulation reversal strategies have been developed, but it is not clear whether there is a time-dependent treatment effect for door-to-treatment (DTT) times in clinical practice.

OBJECTIVE To evaluate whether DTT time is associated with outcome among patients with anticoagulation-associated ICH treated with reversal interventions.

DESIGN, SETTING, AND PARTICIPANTS This cohort study used data from the American Heart Association Get With The Guidelines–Stroke quality improvement registry. Patients with ICH who presented within 24 hours of symptom onset across 465 US hospitals from 2015 to 2021 were included. Data were analyzed from January to September 2023.

EXPOSURES Anticoagulation-associated ICH.

MAIN OUTCOMES AND MEASURES DTT times and outcomes were analyzed using logistic regression modeling, adjusted for demographic, history, baseline, and hospital characteristics, with hospital-specific random intercepts to account for clustering by site. The primary outcome of interest was the composite inpatient mortality and discharge to hospice. Additional prespecified secondary outcomes, including functional outcome (discharge modified Rankin Scale score, ambulatory status, and discharge venue), were also examined.

RESULTS Of 9492 patients with anticoagulation-associated ICH and documented reversal intervention status, 4232 (44.6%) were female, and the median (IQR) age was 77 (68-84) years. A total of 7469 (78.7%) received reversal therapy, including 4616 of 5429 (85.0%) taking warfarin and 2856 of 4069 (70.2%) taking a non–vitamin K antagonist oral anticoagulant. For the 5224 patients taking a reversal intervention with documented workflow times, the median (IQR) onset-to-treatment time was 232 (142-482) minutes and the median (IQR) DTT time was 82 (58-117) minutes, with a DTT time of 60 minutes or less in 1449 (27.7%). A DTT time of 60 minutes or less was associated with decreased mortality and discharge to hospice (adjusted odds ratio, 0.82; 95% CI, 0.69-0.99) but no difference in functional outcome (ie, a modified Rankin Scale score of 0 to 3; adjusted odds ratio, 0.91; 95% CI, 0.67-1.24). Factors associated with a DTT time of 60 minutes or less included White race, higher systolic blood pressure, and lower stroke severity.

CONCLUSIONS AND RELEVANCE In US hospitals participating in Get With The Guidelines–Stroke, earlier anticoagulation reversal was associated with improved survival for patients with ICH. These findings support intensive efforts to accelerate evaluation and treatment for patients with this devastating form of stroke.

Supplemental content

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Intracerebral hemorrhage (ICH) is the deadliest stroke subtype.[1] ICH expansion is a well-established mediator of worse outcome, and serial neuroimaging studies show hematoma enlargement is more common and occurs more rapidly in the setting of anticoagulant-related ICH.[1] As a result, anticoagulation-associated ICH is associated with worse functional outcome and death compared with non–anticoagulation-associated ICH.[2] Fresh frozen plasma (FFP), prothrombin complex concentrate (PCC), and vitamin K are available treatment strategies for reversal in vitamin K antagonist (VKA)–related ICH. For direct thrombin inhibitor and newer factor Xa inhibitor oral anticoagulant medications, FFP and PCC have been frequently used, but specific reversal treatments, idarucizumab and andexanet alfa, became available in 2015 and 2018, respectively.[3,4]

Prior clinical trials of coagulopathy reversal have demonstrated a reduction in ICH expansion and improved clinical outcome.[5,6] However, there was not sufficient precision or power to establish the presence of a time-dependent effect. In an observational multicenter study, earlier (less than 4 hours after hospital arrival) reversal of VKA was associated with a significant reduction in ICH expansion and lower in-hospital mortality, but timing of reversal therapy was not assessed.[7]

ICH expansion often continues during the first hours after ictus in the prehospital and emergency department setting. In ischemic stroke, quality improvement interventions aimed at treating eligible patients faster were associated with substantial clinical outcome improvements[8]; a similar opportunity may exist in acute ICH. However, establishing the presence of a clinical outcome modification by time from hospital arrival to start of acute coagulopathy reversal treatment in ICH requires analysis from a large dataset of patients in routine clinical practice. In addition, prior ICH clinical trials have carefully selected patient populations, which may not readily generalize to broad practice environments.

To fill this scientific need, we analyzed the US nationwide American Heart Association (AHA) Get With The Guidelines (GWTG)–Stroke registry to determine the association of door-to-treatment (DTT) times for coagulopathy reversal and outcome in patients with anticoagulation-associated ICH.

Key Points

Question Is door-to-treatment time associated with improved outcomes in patients with anticoagulation-associated intracerebral hemorrhage receiving reversal interventions?

Findings In this cohort study including 9492 patients, a door-to-treatment time of 60 minutes or less was associated with lower mortality and hospice transfers. White race and stroke severity were associated with faster administration of reversal interventions.

Meaning This study highlights the importance of rapid treatment in improving survival and discharge to hospice for patients with anticoagulation-associated intracerebral hemorrhage, underscoring the need for efficient health care delivery in emergency settings.

Methods

Study Design and Data Source

The primary data resource was GWTG-Stroke. The AHA GWTG-Stroke registry is, to our knowledge, the largest national quality improvement registry for any cardiovascular disease state in the US, with more than half of all national stroke admissions entered into the database.[9] GWTG is administered using a web-based patient management tool by trained personnel at participating hospitals to obtain clinical data, education and decision support, and other support features aimed at continuous quality improvement. Details for data collection in the GWTG-Stroke registry as well as the validity and reliability of the data collection have been published previously.[10,11] Standardized data captured in the registry include patient demographic information, medical history, stroke onset time, arrival time, medications prior to admission, diagnostic tests (including brain imaging), treatment (including reversal intervention and treatment initiation time), and in-hospital outcomes. Severity was measured using the ICH score and National Institute of Health Stroke Scale (NIHSS) score.[12] Data on hospital-level characteristics were obtained from the American Hospital Association database.

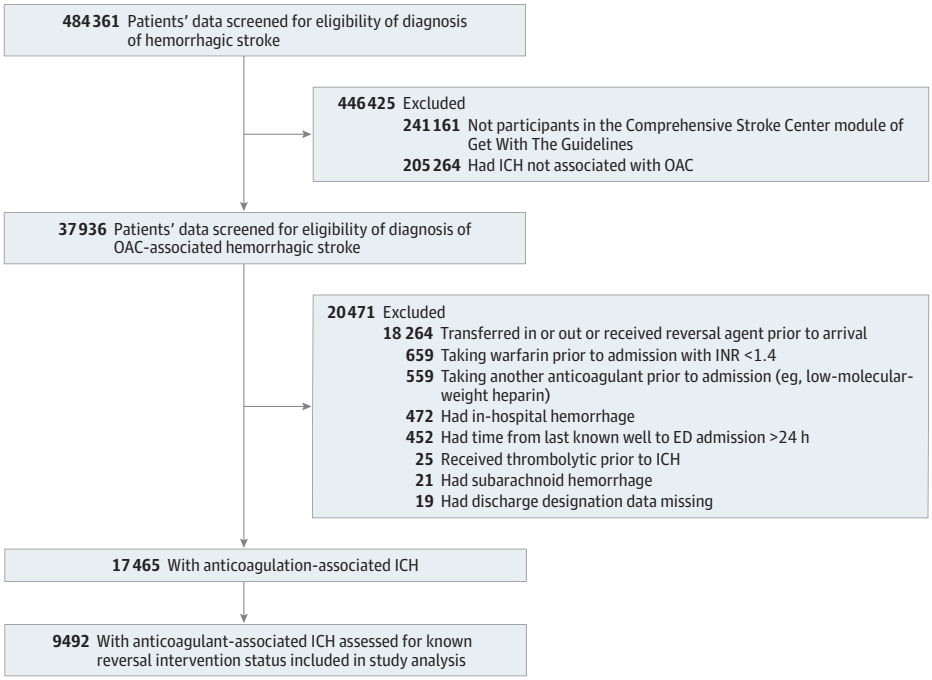
At the hospital level, either human research approval permitted patient enrollment without individual patient consent under the Common Rule or an exemption was authorized by the local institutional review board. The Duke Clinical Research Institute is the data analytics center for GWTG and maintains an agreement to analyze aggregate deidentified data for research. This study was approved by the Duke University Health System Institutional Review Board. Trained hospital personnel were instructed to ascertain patients admitted with the principal clinical diagnosis of nontraumatic ICH by prospective clinical identification, retrospective use of discharge codes, or a combination of these surveillance strategies.

Study Population

For this analysis, the patient population included direct-arriving patients with ICH treated with anticoagulant reversal treatment within 24 hours of symptom onset at participating GWTG Stroke hospitals between January 1, 2015, and December 31, 2021. Patients were either taking warfarin or non-VKA oral anticoagulants (NOACs) prior to their admission, defined as use in the prior week. Exclusion criteria included in-hospital ICH onset, transfer from another hospital, primary diagnosis of subarachnoid hemorrhage, taking both warfarin and NOACs, missing discharge destination, and, for patients taking warfarin, an international normalized ratio (INR) of 1.4 or less.

The primary exposure variable was DTT time, defined as time from hospital arrival to start of reversal agent administration. The lead analysis compared a DTT time of 60 minutes or less vs more than 60 minutes. DTT time was additionally analyzed as a continuous variable and in the 4 prespecified time windows of 0 to 60 minutes, 61 to 90 minutes, 91 to 120

Figure 1. Flow Diagram Showing Study Population Screening, Eligibility, and Inclusion



ED indicates emergency department; ICH, intracerebral hemorrhage; INR, international normalized ratio; OAC, oral anticoagulants.

minutes, and more than 120 minutes. Additional data collected regarding reversal therapy included class of anticoagulant (VKA vs NOAC); if NOAC use, specific agent (apixaban, dabigatran, edoxaban, or rivaroxaban); type of reversal agent (vitamin K, FFP, PCC), including factor Xa inhibitor reversal (andexanet-alfa) and thrombin IIa reversal (idarucizumab); time from onset (last known well) to treatment; and time from onset to arrival.

Outcome Measures

The primary outcome was an in-hospital outcome that combined in-patient mortality or discharge to hospice. Secondary outcomes were discharge modified Rankin Scale (mRS) score, ambulatory status at discharge (ambulatory without assistance, ambulatory with assistance, nonambulatory, or in-hospital death), discharge destination (home, inpatient rehabilitation facility, skilled nursing facility, hospice, or in-hospital death), and length of stay. The mRS score is a measure of disability commonly used in stroke and ranges from a score of 0 (no symptoms) to 6 (death).

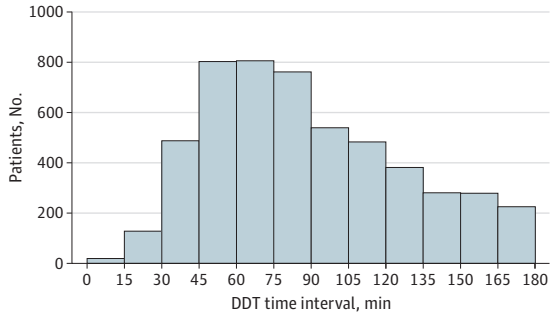
Statistical Analysis

Baseline patient demographic and hospital characteristics of the treating hospitals are described using proportions for continuous variables and medians and IQRs for continuous variables. Because of the large sample size, small differences could be statistically but not clinically significant. Therefore, absolute standardized differences (multiplied by 100) were calculated to compare the characteristics of patients; an absolute standardized difference greater than 10% was considered meaningful. Tests for differences between the ordinal DTT windows were performed using the Cochran-Mantel-Haenszel test for categorical variables and the Cochran-Mantel-Haenszel correlation test for continuous variables. This approach allows for assessment of whether there is a trend in patient or clinical characteristics across the DTT time categories. Histograms of the distribution of DTT times are shown.

Multivariable regression modeling was performed to investigate the association of reversal intervention with clinical outcome among patients with anticoagulation-associated ICH. The model used hospital-specific random intercepts to account for within-hospital and across-hospital variability. A logistic model was used for the binary outcomes, a cumulative logistic model for the ordinal mRS score outcome, and a negative binomial model with a log link for the overdispersed right-skewed length of stay outcome. Continuous variables were tested for linearity. As a nonlinear association between age and NIHSS score exists, an interaction term of these factors was also included.

Adjustment factors for the comparison of features of the reversal vs nonreversal groups were those factors that are expected to predict outcomes. They have been used in prior GWTG-Stroke analyses.[13-15] Patient-level demographic factors were age, sex, race and ethnicity, and insurance status. Self-reported race and ethnicity data were collected by admission staff, medical staff, or both, usually during registration. Medical history factors were atrial fibrillation/flutter or prosthetic heart valve, deep vein thrombosis or pulmonary embolism, prior stroke or transient ischemic attack, coronary artery disease or prior myocardial infarction, diabetes, hypertension, dyslipidemia, prior heart failure, kidney insufficiency, smok-

Figure 2. Distribution of Patients by 15-Minute Increments in Door-to-Treatment (DTT) Time Windows



ing, depression, obesity, pre-ICH antiplatelet use, and sleep apnea. Admission factors were arrival via emergency medical services (vs private vehicle), arrival off hours, NIHSS score, systolic blood pressure (SBP), and preadmission warfarin use. Hospital-level adjustment factors were region, teaching hospital status, number of beds, rolling-basis annual ICH stroke volume, mean annual number of anticoagulant-associated ICH reversal interventions, and The Joint Commission stroke center status. For supplementary analysis for NOAC and warfarin subgroups, continuous INR was included in the warfarin models. For the DTT time and outcome analysis, deep vein thrombosis, smoking history, sleep apnea, and arrival via emergency medical services were excluded from the models.

To identify those factors significantly associated with DTT times of 60 minutes or less, a multivariable logistic regression analysis was used to identify patient and hospital characteristics with rapid intervention. We fit a logistic random-effects model, accounting for within-site and across-site variability with hospital-specific random intercepts. Continuous variables were tested for linearity, and linear splines were applied as appropriate. Backward selection was used to identify the factors significantly associated with DTT times of 60 minutes or less, with a *P* value cutoff of .20 to remain in the model.

All statistical analyses were performed using SAS version 9.4 (SAS Institute). All *P* values are 2-sided, with values less than .05 considered statistically significant.

Results

Baseline Characteristics of the Study Population

From January 1, 2015, to December 31, 2021, 484 361 patients with primary ICH were admitted to 2447 hospitals participating in the AHA GWTG-Stroke registry. Patient flow through inclusion and exclusion criteria is shown in **Figure 1**. Among 17 465 direct-arriving patients with anticoagulation-associated ICH within 24 hours of last known well, 9492 had known reversal intervention status (documented use or nonuse of reversal agents). Of 9492 included patients with anticoagulation-associated ICH, 4232 (44.6%) were female, and the median (IQR) age was 77 (68-84) years. Patients received treatment across 465 GTWG-Stroke hospitals, and a total of 7469 (78.7%) received a reversal intervention. Reversal interventions were performed in 4616 of 5429 (85.0%) taking warfarin and 2856 of 4069 (70.2%) taking NOACs prior to the ICH (eTables 1 and 2 in Supplement 1). For the 5224 patients receiving a reversal intervention with documented workflow times, the median (IQR) onset-to-treatment time was 232 (142-482) minutes, and the median (IQR) DTT time was 82 (58-117) minutes (eTable 3 in Supplement 1).

Demographic, clinical, and hospital characteristics were generally similar between patients who received reversal interventions and those who did not (standardized difference less than 10%) (eTable 4 in Supplement 1). Patients receiving reversal interventions had higher median (IQR) SBPs (165 [144-188] mm Hg vs 157 [135-184] mm Hg; standardized difference, 18.1%) and were more likely to arrive via emergency medical services (6045 of 7469 [81.3%] vs 1489 of 2023 [74.9%]; standardized difference, 15.7%). Geographic variation was present, with reversal use highest in the Midwest (1485 of 1776 [83.6%]) and lowest in the South (2847 of 3739 [76.1%]) (standardized difference, 16.3%).

The distribution of DTT times is shown in **Figure 2**. Patient-level and hospital-level characteristics of patients in each of the 4 DTT time epochs is shown in **Table 1**, and multivariate characteristics associated with DTT times of 60 minutes or less shown in **Table 2**. Independent patient-level predictors of a DTT time of 60 minutes or less were non-Hispanic White race, history of atrial fibrillation, higher SBP, and milder neurologic deficit on the NIHSS (ie, NIHSS score of 5 or less). Independent hospital-level predictors were hospital region, being a teaching hospital, annual ICH volume, stroke certification status, and higher annual volume of reversal treatments. White patients were the most likely to present in each of the earlier time epochs (including 1140 of 3878 [29.4%] presenting within 60 minutes and 819 of 3878 [21.1%] presenting more than 120 minutes after ICH onset), while Black patients were the least likely to present in earlier time epochs (including 124 of 626 [19.8%] presenting within 60 minutes and 183 of 626 [29.2%] presenting more than 120 minutes after ICH onset). SBP monotonically declined over each of the time epochs (including a median [IQR] 172 [150-196] mm Hg at less than 60 minutes and 163 [141-186] mm Hg more than 120 minutes after ICH onset). NIHSS scores also monotonically declined (including a median [IQR] score of 15 [8-22] within 60 minutes and 7 [2-17] more than 120 minutes after ICH onset).

Primary Outcome

Use of a reversal agent was associated with reduced in-hospital mortality in both unadjusted (odds ratio [OR], 0.78; 95% CI, 0.70-0.87) and adjusted (adjusted OR, 0.74; 95% CI, 0.62-0.88) analyses. Similar estimates appeared for the subgroup taking anticoagulation before ICH onset (eg, those taking warfarin) (eTable 5 in Supplement 1). The mortality benefit was significant in patients with anticoagulation-associated ICH exposed to warfarin. Table 2 shows the results of the binary analysis within the reversal intervention group among patients who received treatment within and after 60 minutes. The adjusted analysis for mortality demon-

Table 1. Baseline Characteristics of Patients With Anticoagulation-Associated Intracerebral Hemorrhage (ICH) Who Received Reversal Therapy by Door-to-Treatment (DTT) Time

Characteristic	No. (%)					*P* value
		DTT time				
	Overall (N = 5224)	0-60 min (n = 1449)	61-90 min (n = 1573)	91-120 min (n = 1029)	>120 min (n = 1173)	
Demographic characteristics						
Age, median (IQR), y	77 (69-84)	77 (70-84)	77 (68-84)	77 (69-84)	77 (68-84)	.38
Sex						
Female	2245 (43.0)	612 (42.2)	672 (42.7)	443 (43.1)	518 (44.2)	.32
Male	2979 (57.0)	837 (57.8)	901 (57.3)	586 (56.9)	655 (55.8)	
Race and ethnicity[a]						
Asian	239 (4.6)	67 (4.6)	63 (4.0)	51 (5.0)	58 (4.9)	<.001
Black	626 (12.0)	124 (8.6)	178 (11.3)	141 (13.7)	183 (15.6)	
Hispanic (any race)	293 (5.6)	70 (4.8)	89 (5.7)	61 (5.9)	73 (6.2)	
White	3878 (74.2)	1140 (78.7)	1180 (75.0)	739 (71.8)	819 (69.8)	
Other race	188 (3.6)	48 (3.3)	63 (4.0)	37 (3.6)	40 (3.4)	
Clinical characteristics						
Insurance						
Private, VA, CHAMPUS, or other insurance	1824 (34.9)	484 (33.4)	541 (34.4)	367 (35.7)	432 (36.8)	.03
Medicaid	459 (8.8)	114 (7.9)	142 (9.0)	89 (8.6)	114 (9.7)	
Medicare	2423 (46.4)	716 (49.4)	732 (46.5)	470 (45.7)	505 (43.1)	
Self-pay or no insurance	76 (1.5)	22 (1.5)	26 (1.7)	13 (1.3)	15 (1.3)	
Medical history						
Atrial fibrillation or flutter	3698 (70.8)	1064 (73.4)	1112 (70.7)	723 (70.3)	799 (68.1)	.004
Prosthetic heart valve	440 (8.4)	117 (8.1)	118 (7.5)	93 (9.0)	112 (9.5)	.09
Prior stroke or TIA	1786 (34.2)	503 (34.7)	524 (33.3)	361 (35.1)	398 (33.9)	.91
DVT or PE	453 (8.7)	125 (8.6)	137 (8.7)	80 (7.8)	111 (9.5)	.66
CAD or prior MI	1615 (30.9)	436 (30.1)	460 (29.2)	314 (30.5)	405 (34.5)	.01
Carotid stenosis	150 (2.9)	46 (3.2)	38 (2.4)	33 (3.2)	33 (2.8)	.86
Diabetes	1664 (31.9)	441 (30.4)	482 (30.6)	340 (33.0)	401 (34.2)	.02
Peripheral vascular disease	328 (6.3)	87 (6.0)	88 (5.6)	72 (7.0)	81 (6.9)	.18
Hypertension	4397 (84.2)	1219 (84.1)	1322 (84.0)	871 (84.6)	985 (84.0)	.98
Dyslipidemia	2912 (55.7)	809 (55.8)	859 (54.6)	580 (56.4)	664 (56.6)	.52
Prior heart failure	1068 (20.4)	262 (18.1)	335 (21.3)	196 (19.0)	275 (23.4)	.005
Chronic kidney insufficiency	771 (14.8)	192 (13.3)	227 (14.4)	168 (16.3)	184 (15.7)	.04
Smoker	368 (7.0)	101 (7.0)	117 (7.4)	69 (6.7)	81 (6.9)	.78
Depression	731 (14.0)	188 (13.0)	206 (13.1)	162 (15.7)	175 (14.9)	.05
Obesity	1892 (36.2)	535 (36.9)	559 (35.5)	381 (37.0)	417 (35.5)	.65
Drug or alcohol use disorder	238 (4.6)	57 (3.9)	74 (4.7)	54 (5.2)	53 (4.5)	.36
Sleep apnea	563 (10.8)	167 (11.5)	146 (9.3)	116 (11.3)	134 (11.4)	.71
Anticoagulant use prior to admission						
Warfarin	3178 (60.8)	877 (60.5)	964 (61.3)	591 (57.4)	746 (63.6)	.38
Apixaban	1174 (22.5)	330 (22.8)	358 (22.8)	256 (24.9)	230 (19.6)	.16
Rivaroxaban	799 (15.3)	210 (14.5)	237 (15.1)	168 (16.3)	184 (15.7)	.28
Dabigatran	74 (1.4)	30 (2.1)	14 (0.9)	14 (1.4)	16 (1.4)	.23
Edoxaban	<11 (<0.2)[b]	<11 (<0.8)[b]	<11 (<0.7)[b]	<11 (<1.1)[b]	0	.46
Antiplatelet use prior to admission						
Aspirin	1621 (31.0)	436 (30.1)	481 (30.6)	323 (31.4)	381 (32.5)	.17
Clopidogrel	220 (4.2)	62 (4.3)	63 (4.0)	42 (4.1)	53 (4.5)	.76
Dual antiplatelet therapy	79 (1.5)	22 (1.5)	24 (1.5)	14 (1.4)	19 (1.6)	.93
Prasugrel	<11 (<0.2)[b]	<11 (<0.8)[b]	0	<11 (<1.1)[b]	0	.64
Ticagrelor	<11 (<0.2)[b]	0	<11 (<0.7)[b]	<11 (<1.3)[b]	<11 (<0.2)[b]	.20
Ticlopidine	0	0	0	0	0	
Clinical data at admission						
NIHSS score, median (IQR)	12 (5-21)	15 (8-22)	13 (6-22)	10 (4-22)	7 (2-17)	<.001

(continued)

Table 1. Baseline Characteristics of Patients With Anticoagulation-Associated Intracerebral Hemorrhage (ICH) Who Received Reversal Therapy by Door-to-Treatment (DTT) Time (continued)

Characteristic	No. (%)					P value
		DTT time				
	Overall (N = 5224)	0-60 min (n = 1449)	61-90 min (n = 1573)	91-120 min (n = 1029)	>120 min (n = 1173)	
NIHSS score group						
0-4	1068 (20.4)	167 (11.5)	249 (15.8)	260 (25.3)	392 (33.4)	<.001
5-9	767 (14.7)	229 (15.8)	255 (16.2)	142 (13.8)	141 (12.0)	
10-14	639 (12.2)	215 (14.8)	220 (14.0)	106 (10.3)	98 (8.4)	
15-20	743 (14.2)	290 (20.0)	226 (14.4)	116 (11.3)	111 (9.5)	
>20	1150 (22.0)	376 (25.9)	371 (23.6)	237 (23.0)	166 (14.2)	
ICH score, median (IQR)	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)	<.001
ICH score group						
0-1	1632 (31.2)	442 (30.5)	471 (29.9)	319 (31.0)	400 (34.1)	<.001
2-3	1705 (32.6)	520 (35.9)	534 (33.9)	333 (32.4)	318 (27.1)	
4-6	652 (12.5)	187 (12.9)	220 (14.0)	135 (13.1)	110 (9.4)	
Missing	1235 (23.6)	300 (20.7)	348 (22.1)	242 (23.5)	345 (29.4)	
SBP, mm Hg	168 (146-191)	172 (150-196)	169 (148-191)	167 (145-190)	163 (141-186)	<.001
INR, median (IQR)	2 (2-3)	2 (2-3)	2 (1-3)	2 (1-3)	2 (2-3)	.16
INR >1.4[c]	4151 (79.5)	1151 (79.4)	1240 (78.8)	795 (77.3)	965 (82.3)	.17
Arrival off hours[d]	2967 (56.8)	840 (58.0)	876 (55.7)	598 (58.1)	653 (55.7)	.45
Arrival via EMS	4486 (86.1)	1337 (92.6)	1414 (89.9)	841 (82.0)	894 (76.5)	<.001
Onset-to-arrival time, median (IQR), min	144.0 (64-388)	112.5 (59-284)	137.0 (62-367)	180.5 (74-486)	208.5 (79-540)	<.001
Onset-to-treatment time, median (IQR), min	232.0 (142-482)	159.0 (105-335)	213.5 (139-444)	286.0 (179-591)	354.0 (226-676)	<.001
≤120	660 (19.5)	463 (40.1)	186 (16.5)	<11 (<1.9)[b]	0	NA
121-240	1379 (40.7)	367 (31.8)	519 (46.0)	299 (49.5)	194 (38.4)	NA
241-360	588 (17.3)	138 (11.9)	186 (16.5)	124 (20.5)	140 (27.7)	NA
361-720	765 (22.6)	187 (16.2)	236 (20.9)	171 (28.3)	171 (33.9)	NA
Hospital characteristics						
Geographic region						
Northeast	1222 (23.4)	366 (25.3)	379 (24.1)	225 (21.9)	252 (21.5)	<.001
Midwest	1062 (20.3)	266 (18.4)	333 (21.2)	207 (20.1)	256 (21.8)	
South	1964 (37.6)	521 (36.0)	560 (35.6)	419 (40.7)	464 (39.6)	
West	976 (18.7)	296 (20.4)	301 (19.1)	178 (17.3)	201 (17.1)	
Rural location	<11 (<0.4)[b]	<11 (<0.8)[b]	<11 (<0.7)[b]	<11 (<1.1)[b]	<11 (<0.9)[b]	.77
Teaching hospital	4629 (89.8)	1302 (90.5)	1376 (88.5)	910 (90.5)	1041 (90.1)	.84
Beds, median (IQR), No.	528 (379-732)	537 (379-731)	524 (376-732)	520 (381-732)	524 (379-732)	.63
Annual ICH volume, median (IQR)	82.9 (62.4-128.0)	86.3 (66.8-133.5)	81.0 (62.7-128.0)	80.9 (60.6-127.1)	81.0 (58.0-127.1)	<.001
Annual anticoagulation-associated ICH reversal interventions, median (IQR)	6.1 (3.9-9.1)	7.0 (4.4-9.6)	6.1 (4.0-9.1)	5.9 (3.4-9.0)	5.6 (3.1-8.4)	<.001
Stroke center status						
Comprehensive stroke center	2984 (57.1)	860 (59.4)	907 (57.7)	573 (55.7)	644 (54.9)	<.001
Primary stroke center	1554 (29.7)	362 (25.0)	465 (29.6)	321 (31.2)	406 (34.6)	
Neither comprehensive nor primary stroke center	686 (13.1)	227 (15.7)	201 (12.8)	135 (13.1)	123 (10.5)	

Abbreviations: CAD, coronary artery disease; CHAMPUS, Civilian Health and Medical Program of the Uniformed Services; DVT, deep vein thrombosis; EMS, emergency medical services; INR, international normalized ratio; MI, myocardial infarction; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; PE, pulmonary embolism; SBP, systolic blood pressure; TIA, transient ischemic attack; VA, Veterans Affairs.

[a] Self-reported race and ethnicity data were collected by admission staff, medical staff, or both, usually during registration. The other race category included American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, multiracial, unknown, and other race.

[b] American Heart Association policy is to suppress cells with values of 10 or less.

[c] INR is captured quantitatively and qualitatively as INR greater than 1.4 This measure counts both types of data capture.

[d] Regular hours defined as 7 AM to 6 PM Monday through Friday, except for holidays.

strated adjusted ORs of 0.83 (95% CI, 0.69-1.00) and 0.82 (95% CI, 0.69-0.99) for in-patient mortality and the discharge to hospice composite, respectively. Directionally similar estimates appeared for the subgroup taking anticoagulation before ICH onset; however, the estimates did not reach statistical significance (eTable 6 in Supplement 1).

Table 2. Association of Door-to-Treatment (DTT) Time of 60 Minutes or Less vs More Than 60 Minutes With Clinical Outcomes

Outcome	No./total No. (%)		OR (95% CI)		Patients included in model, No.	
	DTT time ≤60 min	DTT time >60 min	Unadjusted	Adjusted	Unadjusted	Adjusted
In-hospital mortality	462/1449 (31.9)	1082/3775 (28.7)	1.15 (1.00-1.31)	0.83 (0.69-1.00)	5224	3453
In-hospital mortality or hospice discharge	668/1449 (46.1)	1556/3775 (41.2)	1.22 (1.08-1.38)	0.82 (0.69-0.99)	5224	3453
mRS score of 0-2 vs 3-6	66/1140 (5.8)	258/2907 (8.9)	0.63 (0.47-0.84)	1.04 (0.70-1.56)	4047	2737
mRS score of 0-3 vs 4-6	121/1140 (10.6)	484/2907 (16.6)	0.59 (0.47-0.73)	0.91 (0.67-1.24)	4047	2737
mRS score of 0-4 vs 5-6	387/1140 (33.9)	1168/2907 (40.2)	0.75 (0.65-0.88)	1.19 (0.96-1.48)	4047	2737
Ambulatory with or without assistance	384/966 (39.8)	1201/2443 (49.2)	0.66 (0.57-0.78)	1.13 (0.91-1.42)	3409	2358
Discharged home or to inpatient rehabilitation	449/1449 (31.0)	1381/3775 (36.6)	0.77 (0.68-0.88)	1.23 (1.02-1.49)	5224	3453

Abbreviations: mRS, modified Rankin Scale; OR, odds ratio.

Secondary Outcomes

With respect to multiple points of dichotomous analysis for the mRS, there was no significant association between DTT time and functional outcome (Table 2). With regard to discharge disposition, earlier reversal intervention was associated with the composite of discharge to home and inpatient rehabilitation (as well as the composite of discharge to home, inpatient rehabilitation, and skilled nursing facility). However, other favorable discharge dispositions, though directionally favorable, did not reach significance at other cut points (eTable 5 in Supplement 1). Results are shown by pre-ICH anticoagulation subgroup in eTable 6 in Supplement 1.

Factors associated with reversal intervention in the first 60 minutes after arrival appear in **Table 3**. White race, higher SBP, and lower stroke severity (NIHSS score of 5 or less) were all associated with faster time to reversal intervention.

Table 3. Factors Associated With a Door-to-Treatment Time of 60 Minutes or Less

Factor	Adjusted OR (95% CI)	*P* value
Race and ethnicity[a]		
Black	0.65 (0.49-0.85)	.003
White	1 [Reference]	
Other race	0.80 (0.63-1.02)	
Atrial fibrillation or prosthetic heart valve	1.13 (0.94-1.36)	.20
SBP per 5-mm Hg increase	1.02 (1.00-1.03)	.01
Onset-to-arrival time per 15-min increase	0.99 (0.99-0.99)	<.001
Admission NIHSS score		
≤5	1.24 (1.13-1.35)	<.001
6-15	0.85 (0.76-0.94)	
>15	0.94 (0.90-0.97)	
Geographic region		
Northeast	1 [Reference]	.23
South	0.99 (0.74-1.33)	
West	1.30 (0.92-1.83)	
Midwest	0.95 (0.68-1.31)	
Teaching hospital	1.39 (0.99-1.95)	.06
Annual ICH stroke volume per 10-patient increase		
≤120 Patients	1.01 (0.97-1.06)	.18
>120 Patients	0.96 (0.91-1.02)	
Mean annual number of reversals	1.05 (1.02-1.09)	.003
Stroke center status		
Comprehensive stroke center	0.88 (0.64-1.23)	.18
Primary stroke center	0.74 (0.53-1.04)	
Neither comprehensive nor primary stroke center	1 [Reference]	

Abbreviations: ICH, intracerebral hemorrhage; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SBP, systolic blood pressure.

[a] Self-reported race and ethnicity data were collected by admission staff, medical staff, or both, usually during registration. The other race category included American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, multiracial, unknown, and other race.

Discussion

In this analysis of more than 9000 patients with ICH while taking anticoagulants, 7469 (78.7%) received a coagulopathy reversal intervention in routine clinical practice. Importantly, in a cohort of more than 5000 patients for whom time of reversal administration was available, earlier administration of reversal intervention was associated with reduced in-hospital mortality or discharge to hospice as well as increased likelihood of discharge to home or inpatient rehabilitation.

These findings are consistent with and extend what is known about the pathophysiology of ICH expansion and neurological deterioration in anticoagulation-associated ICH and with prior research on reversal interventions in this patient population. While the biological basis for ICH expansion is complex, it is linked to coagulopathy, protracted in anticoagulation-associated ICH, and mediates neurological deterioration and death.[2,16] In a prior German multicenter observational study, warfarin reversal within 4 hours combined with blood pressure lowering was associated with decreased ICH expansion and lower in-hospital mortality.[7] However, this study evaluated less than 900 patients and did not evaluate anticoagulation reversal alone. Nevertheless, the German multicenter study observations are consistent with

other observational studies and the International Normalized Ratio Normalization in Coumadin Associated Intracerebral Haemorrhage (INCH) trial, which demonstrated that PCC was superior to FFP in quickly reversing INR and reducing ICH expansion.[5] The population of patients with anticoagulation-associated ICH receiving reversal intervention in the current study, which includes both warfarin-associated and NOAC-associated coagulopathy, is 5-fold as large as the German multicenter analysis and 100-fold larger than the sample of the INCH trial.

With regard to optimal timing, our analysis focused on DTT times because emergency department–based acute care is an established environment for time-dependent quality improvement in stroke.[8] Indeed, 2 recent studies in the UK and Eastern hemisphere incorporated warfarin reversal strategies into a quality improvement bundle intervention within 90 and 60 minutes, respectively.[6,17] In the present analysis, DTT times of less than 60 minutes most clearly demonstrated a time-dependent effect of coagulopathy reversal, but we cannot exclude an even greater effect with earlier initiation.

Further, it is possible that our results are conservative with regard to agent-specific reversal effects. NOACs are more effectively and rapidly reversed by agent-specific reversal interventions (eg, andexanet alfa or idarucizumab) than by 4-factor PCC or other approaches.[3,4] In the current analysis, a minority of patients with anticoagulation-associated ICH taking a NOAC received non-PCC agent-specific reversal interventions. If a NOAC-specific reversal agent were to result in improved hemostasis, the potential clinical impact may be even greater. These results should be confirmed in an adequately powered dataset that includes information regarding reversal agent type and appropriateness.

Our data also provided new findings regarding clinical practice patterns across the US at GWTG hospitals. Of those with documentation, less than 1 of 3 patients received a reversal intervention within 60 minutes of ICH onset. Black patients and those admitted to smaller hospitals with fewer overall ICH admissions were less likely to receive timely anticoagulation reversal. Patients with milder stroke severity, especially those with an NIHSS score less than 5, were also less likely to receive reversal interventions early, even though such patients may have more room for neurological deterioration and a larger opportunity to derive clinical benefit from OAC reversal. Current AHA ICH guidelines state that reversal interventions should be provided as soon as possible, without specifying a time target, whereas quality targets for tissue plasminogen activator DTT time aim for at least 60 minutes, with 45 minutes being better and 30 minutes being ideal.[18] Given that brain imaging is the same critical diagnostic step for ischemic stroke and anticoagulation-associated ICH, the data from this analysis support a time target that is consistent with the workflow already in place for patients with ischemic stroke.

Limitations

It is important to acknowledge potential limitations of the current analysis. First, the data reported from this quality improvement registry represent real-world data and are dependent on the accuracy and completeness of abstraction. The GWTG-Stroke registry has an established history of training abstractors, standardizing coding instructions, and implementing logic and code checks. Prior audits at the individual and state level have met established quality standards. Second, observational data such as these are susceptible to confounding by indication as well as unmeasured sources of confounding. The clear trend of decreasing NIHSS score with each time epoch in patients with anticoagulation-associated ICH suggests a potential for confounding by indication. Patients with more severe ICH are likely to be treated more aggressively and receive early reversal intervention. Although analyses were adjusted for this factor, residual confounding may remain. Missing data regarding reversal agent intervention status and timing of administration from the overall population may introduce the possibility of selection bias. Third, earlier reversal intervention may lead to improved survival but no difference in disability. On the other hand, good functional outcomes, as indexed by discharge to home or acute inpatient rehabilitation, were also associated with faster treatment.

In recent decades, substantial efforts in public education, marketing, and technological innovation have been undertaken to improve knowledge of stroke warning signs.[19,20] The aim of these efforts has been directed at early recognition, triage and treatment of time-sensitive interventions for stroke. Our results suggest that time is brain not only for ischemic stroke but also for ICH. Historically, care limitations and therapeutic nihilism characterized this patient population, but the current data, concordant with other reports, suggest that patients with anticoagulation-associated ICH may be a ripe population for quality improvement initiatives that target rapid administration of reversal interventions to achieve more robust and equitable survival.[21,22]

Conclusions

In the largest quality improvement stroke registry in the US, earlier administration of reversal interventions in anticoagulant-associated ICH was associated with reduced in-hospital mortality or discharge to hospice but no difference in functional outcomes. These findings support intensive efforts to accelerate evaluation and treatment for patients with this devastating form of stroke.

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