Stroke

ORIGINAL CONTRIBUTION

Intracerebral Hemorrhage Outcomes After Reversal of Subtherapeutic Warfarin: Analysis of Data From GWTG-Stroke

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BACKGROUND: Current guidelines recommend reversal of warfarin anticoagulation in intracranial hemorrhages. The benefit of reversing subtherapeutic warfarin anticoagulation in acute spontaneous intracerebral hemorrhage is uncertain.

METHODS: An observational cohort from the entire Get With The Guidelines Stroke registry between January 2015 and January 2022 was used to determine the association of reversal with outcomes for subtherapeutic anticoagulation (international normalized ratio, 1.5–1.9). Inclusion required current warfarin use. Exclusions included thrombolytics, direct oral anticoagulants, transferring out, or leaving against medical advice. The prespecified primary outcome was the modified Rankin Scale (mRS) score of 0 to 3 at discharge. Logistic regression was used to assess the association between reversal and the mRS score of 0 to 3. Propensity scores with overlap weighting were used to control treatment selection bias. Information on the dose and timing of reversal agents was unknown.

RESULTS: Initial cohort 239 681 patients, 18 419 on warfarin. Excluded were 15 712 with an international normalized ratio ≤1.5, ≥1.9, or missing, and 701 missing mRS. Final cohort 1868 (mean age 73, 42% female). Reversal occurred in 894 (47.9%). Primary outcome occurred in 188/894 (21.0%) versus 225/974 (23.1%) with reversal versus without (adjusted odds ratio, 0.80 [95% CI, 0.63–1.005]). Ordinal analysis showed higher odds of mRS score of 0 to 4 versus 5 to 6 (52.7% versus 42.5% [adjusted odds ratio, 1.21 [1.001–1.48]). Outcomes not requiring mRS were analyzed among 2569 patients. Mortality or discharge to hospice was lower 30.6% versus 41.5% (adjusted odds ratio, 0.75 [95% CI, 0.63–0.89]). Hospital length of stay was longer (median, 6 versus 4 days; adjusted risk ratio, 1.25 [95% CI, 1.13–1.37]). There was no difference in venous thromboembolism (2.9% versus 2.3%; adjusted odds ratio, 1.47 [0.88–2.46]).

CONCLUSIONS: Reversal of subtherapeutic warfarin with acute spontaneous intracerebral hemorrhage and international normalized ratio 1.5 to 1.9 was not associated with improvement in functional outcome based on discharge mRS score of 0 to 3 versus 4 to 6. Patients receiving reversal agents had 25% lower odds of dying in hospital or being discharged to hospice, but had a longer hospital stay. This exploratory data has limitations inherent to not being a randomized controlled trial.

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

Key Words: anticoagulation reversal ■ cerebral hemorrhage ■ hemorrhagic stroke ■ intracranial hemorrhage ■ warfarin

Intracerebral hemorrhage (ICH) is a highly morbid condition. The primary neurological injury occurs at the time of the bleeding event. Patients with subsequent neurological deterioration have worse long-term outcomes.[1,2] Hematoma expansion is a major cause of neurological deterioration within the first 24 hours[3,4] followed

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ORIGINAL CONTRIBUTION

Nonstandard Abbreviations and Acronyms

DVT	deep venous thrombosis
FUNC	functional outcome in patients with primary intracerebral hemorrhage score
GWTG	Get With The Guidelines
ICH	intracerebral hemorrhage
INR	international normalized ratio
LOS	length of stay
mRS	modified Rankin Scale
PE	pulmonary embolus

by cerebral edema formation in the first 72 hours,[1] both are related to the total intracranial hematoma volume. Two interventions are widely used to limit hematoma expansion and the subsequent total burden of disease[4,5] and disability[6]: correction of any coagulopathy[7–9] and reduction of elevated blood pressure.[6,10–14]

Recent guidelines are available for intracranial hemorrhage and recommend reversal of vitamin K antagonists when patients are fully anticoagulated with an international normalized ratio (INR) >2.0.[15–17] ICH constitutes a large proportion of these patients. However, some patients present with less than full anticoagulation (INR, 1.5–1.9). In this population, the benefit or harm of administering reversal agents has not been investigated. The expectation of benefit is not obvious for several reasons: the magnitude of the effect of the primary injury may outweigh any benefit of reversal, the effect of reversal on INR may diminish when values are closer to normal, and there may be increased thrombotic complications or volume overload when administering agents to reverse anticoagulation. For example, the reversal of antiplatelet agents in the PATCH trial resulted in increased mortality and disability, although the reasons for this finding are unclear.[18] The ANNEXA-I trial had increased thrombotic events,[19] including ischemic stroke, and the INCH trial also documented thrombotic complications.[20] Lastly, the significance of subtherapeutic INR is uncertain since the vitamin K-dependent factor (II, VII, IX, X) activities do not decrease below 50% of normal activity until INR is >1.5.[21]

There is clinical equipoise whether to provide reversal for subtherapeutic warfarin anticoagulation in patients with ICH. The aim of this investigation was to determine whether reversal is associated with functional outcome, mortality, or thrombotic events in patients taking warfarin who have ICH and incomplete anticoagulation (INR, 1.5–1.9).

METHODS

Study Design

This observational cohort study analyzes data from the GWTG-Stroke (Get With The Guidelines Stroke) registry[22] between January 1, 2015, and January 4, 2022. Statistical analysis was performed in March through May 2022.

The Duke Clinical Research Institute served as the data analysis center and has an agreement to analyze the aggregate de-identified data for research purposes. The institutional review board at Duke University Health approved this study. Each participating hospital received either human research approval to enroll cases without individual patient consent under the common rule or a waiver of authorization and exemption from subsequent review by its institutional review board. The GWTG-Stroke data belongs to the American Heart Association. The data supporting this article may be requested through GWTG. We followed the Strengthening the Reporting of Observational Studies in Epidemiology[23] reporting guidelines as a guide.

Study Population

Inclusion Criteria

Patients were included if admitted on or after January 1, 2015, through January 4, 2022, for ICH to a hospital reporting on the comprehensive stroke center form. ICH is one of 6 discrete final diagnoses for cases included in the GWTG-Stroke registry. Cases due to trauma and underlying vascular malformations are excluded by registry guidelines. The reporting hospitals must be fully participating (hospital-level medical history completion rate >75%). Patients must have been on warfarin with an INR of 1.5 to 1.9 at admission. INR was rounded to 2 significant figures before applying the inclusion criterion.

Exclusion Criteria

The following exclusions were applied: direct oral anticoagulant before admission, patients transferred out of the reporting hospital, patients who left against medical advice, patients for whom a thrombolytic was given, and patients with missing data for gender, INR, modified Rankin Scale (mRS) at discharge, or warfarin use. The absence of a recorded gender was used to screen for incomplete records and is consistent with other GWTG-Stroke analyses. There were no specific analyses based on sex or gender. Please refer to Figure 1 for an explanation of how the patient cohorts were determined.

Exposure

The primary exposure was whether patients were treated with reversal agents for subtherapeutic anticoagulation.

Primary Outcome

Dichotomized mRS at discharge was used as the primary outcome. The mRS is an ordinal score of disability and dependence after stroke on a scale of 0 (no effect) to 6 (death). Dichotomization of mRS is sometimes performed at 0 to 3 versus 4 to 6 for studies in highly morbid neurological conditions, such as ICH or severe stroke.[24–26]

Secondary Outcomes

In-hospital mortality was combined with discharge to hospice as a secondary outcome. Patients with documented comfort measures only were counted as an event for this composite outcome of in-hospital mortality or discharge to hospice. Other secondary aims included discharge mRS on an ordinal scale (0,

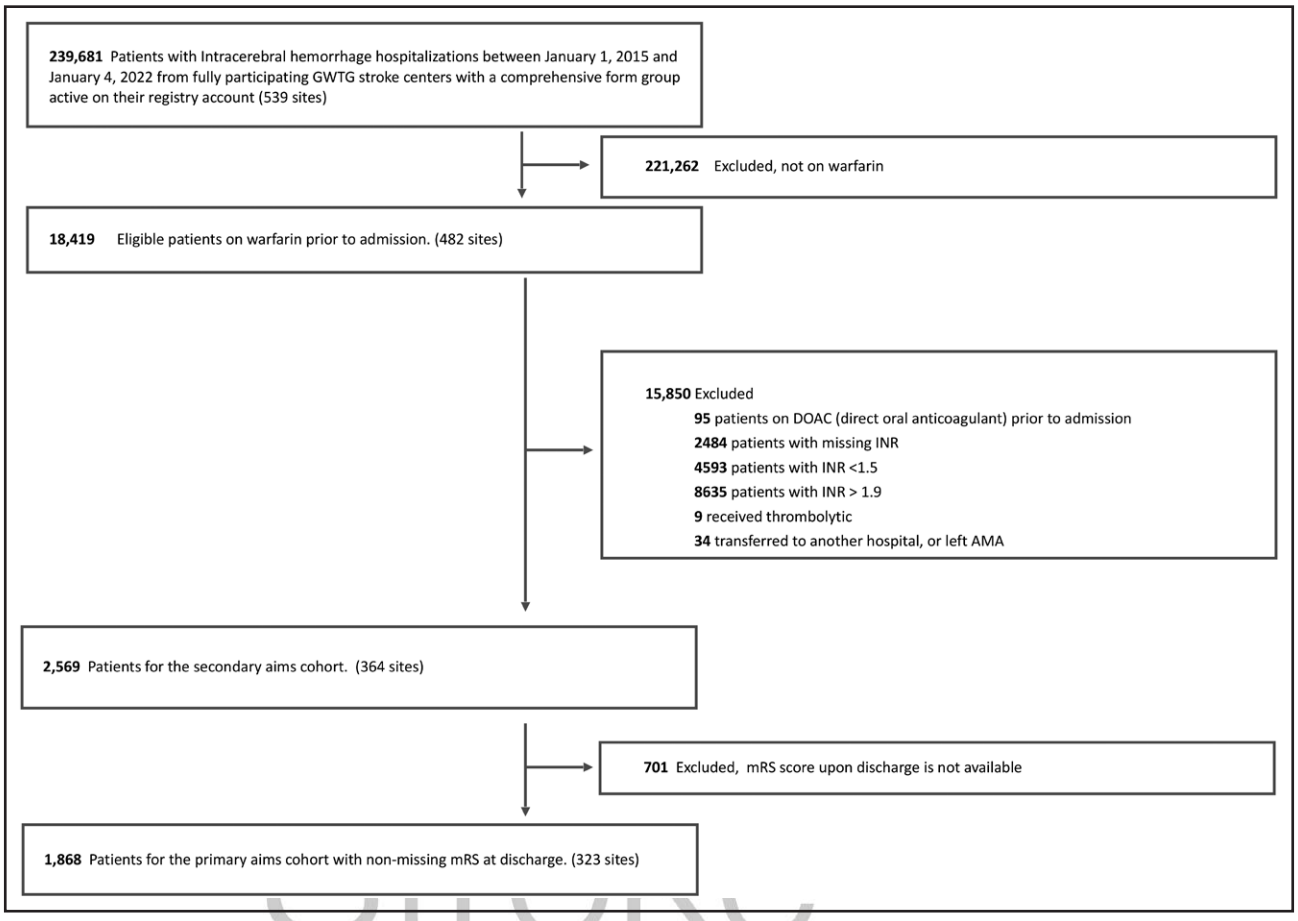

Figure 1. Study cohort flow chart.
This figure is a visual representation of study participants from the GWTG-Stroke study (Get With The Guidelines–Stroke) population and includes the breakdown of how the study population was refined based upon predetermined exclusion criteria. AMA indicates against medical advice; INR, international normalized ratio; and mRS, modified Rankin Scale.

1, 2, 3, 4, 5–6), hospital length of stay (LOS), hospital LOS of those that survived to discharge, discharge disposition (home, hospice/death, skilled nursing, rehab), and ambulation status at discharge (fully ambulatory versus all other states) among those who were fully ambulatory prestroke. Deep vein thrombosis (DVT) and pulmonary embolism (PE) are counted as thrombotic complications but are limited to inpatient events. All measures were counted at the time of discharge. To determine any influence of disease severity, we tested for interaction between ICH score (0–1, 2–3, 4–6, and unknown) and the effect of reversal agents on discharge mRS as both dichotomized (0–3 versus 4–6) and ordinal values (0, 1, 2, 3, 4, 5–6), the composite outcome of in-hospital mortality or discharge to hospice, and ambulatory status at discharge among those who were fully ambulatory prestroke.

Handling of Missing Data

Patients were excluded if missing data for INR, mRS at discharge, or warfarin usage. Variables for medical history elements that had missing values were interpreted as the condition was not present. Hospital characteristics were not imputed. Model covariates with large proportions of missing values (25% or more) were excluded from the analysis. For variables with fewer than 25% missing values, multiple imputation was used with the full conditional specification method. Purely descriptive data not used in models were not imputed. Missing values for anticoagulant reversal were assumed to mean no reversal was given. Missing values in documented DVT/PE were assumed to mean that the complication did not occur. By selection of the cohort, there were no missing values in the primary cohort for age, sex, and INR value. The missingness of data for functional outcome in patients with primary ICH (FUNC) score (93.0%), time from onset to arrival (51.8%), and prestroke mRS (78.9%) led to those prespecified covariates being removed from the list of variables for the propensity score model. ICH score and initial National Institutes of Health Stroke Scale were categorized, and missing values were designated as unknown. Please see the supplement for Table S1 for a missingness inventory of covariates.

Unable to be Obtained

Some possible predictors of outcome after ICH were not contained within the data set and thus were not incorporated into the models. These include imaging-derived information, such as baseline ICH volume, ICH expansion, midline shift, presence of intraventricular extension, and baseline presence of leukoariosis. Long-term outcomes were not present in the data set.

Statistical Analysis

Propensity scores were created using multivariable logistic regression with reversal of anticoagulation as the dependent variable and with following as covariates: age, gender, race/ethnicity, hypertension, diabetes, heart failure, coronary artery disease/MI, prior ischemic stroke, renal insufficiency, atrial fibrillation, smoking, alcohol/drug abuse, sleep apnea, antiplatelet medications, antihypertensive medications, arrival via emergency medical services, arrival during off-hours, admission Glasgow coma scale, ICH score, National Institutes of Health Stroke Scale, body mass index, weakness/paresis, altered level of consciousness, aphasia, systolic blood pressure, diastolic blood pressure, heart rate, INR, creatinine, hospital region, annual ICH stroke volume, and joint commission status as primary or comprehensive stroke center. Three propensity models were created: 1 with 1868 patients for whom the discharge mRS was known, 1 for 2569 patients for secondary outcomes not requiring mRS, and 1 for sensitivity analysis with INR ≤1.4 in place of initiation of anticoagulation. Each set of propensity scores was used to create a set of overlap weights.

The association between reversal of anticoagulation and discharge mRS score of 0 to 3 was assessed using logistic regression. Similarly, logistic regression was used to test associations between reversal and the composite of death or discharge to hospice, development of DVT/PE, the 4 binary variables for discharge disposition, and being fully ambulatory at discharge. For the association between reversal and mRS score as an ordinal variable, a cumulative logistic regression model was fit that did not assume proportional odds. For LOS, a negative binomial regression model was fit. Overlap weights were used to account for potential confounding.

As overlap weights produce exact balance on the mean when estimated using logistic regression, all covariates were balanced after weighting by the scores estimated in that population. Some secondary outcomes analyzed a subgroup of patients (LOS among those who survived to discharge and were fully ambulatory at discharge, among those fully ambulatory prestroke). As the propensity scores were not reestimated in these subgroups, balance was reassessed. Glasgow Coma Scale, ICH score, and initial National Institutes of Health Stroke Scale were found to have residual imbalance. Of these imbalances, the Glasgow coma scale for the LOS among survivors model had the largest postweighting standardized mean difference at −0.19. The models for these outcomes accounted for that by further adjusting for these variables.

Please refer to Table 1 for a comparison of the treated and untreated groups in the primary aims cohort. Patient and hospital characteristics were described by whether a reversal agent was administered during hospitalization. Continuous variables were summarized using mean (SD), median (25th percentile–75th percentile), and range. Categorical variables are presented as n/N (percentage). All percentages were calculated out of the number of patients with nonmissing data for that variable.

Subjects were weighted in proportion to the probability that they belonged to the opposite group (overlap weighting) for all models. The propensity score model for the primary aim and mRS-related secondary aims was modeled using the 1868 patients with nonmissing mRS. The propensity score model for the non-mRS secondary aims used 2569 patients (patients with and without discharge mRS available). Both propensity score models used the same list of covariates. For the primary aim, we determined the association between reversal of anticoagulation and discharge mRS score of 0 to 3 using logistic regression. When considering mRS as an ordinal variable, the proportional odds assumption was tested and found to have been violated. Therefore, a nonproportional odds cumulative logistic regression model was fit. The model generated 5 odds ratios comparing better versus worse mRS (eg, mRS score of 0 versus 1–6, 0–1 versus 2–6,... 0–4 versus 5–6) and allowed assessment of the impact of warfarin reversal across the spectrum of categories, similar to fitting a separate logistic regression model for each level of comparison but this was accomplished in a unified framework. Logistic regression was used to model the composite of in-hospital mortality or discharge to hospice, development of DVT or PE, the 4 binary variables for discharge disposition, and ambulation status at discharge among those who were fully ambulatory prestroke. A negative binomial regression model was fit for the LOS. All statistical analyses were performed in SAS 9.4, and figures were made in R 4.1.3.

Sensitivity Analysis for the Primary Aim

As a sensitivity analysis, we refit the propensity model using INR ≤1.4 after reversal in place of reversal itself. A similar logistic regression model as the primary aim was refit using these new weights and changing the independent variable.

Interaction With ICH Score

We tested an interaction between reversal and ICH score (0–1, 2–3, 4–6, and unknown) to determine whether the effect on mRS at discharge, combined in-hospital mortality and discharge-to-hospice, and ambulatory status at discharge among those who were fully ambulatory prestroke varied by disease severity.

RESULTS

The starting cohort of ICHs was 239 681 patients before applying inclusion criteria, such as requiring current warfarin use, subtherapeutic INR, known mRS, not on direct oral anticoagulant, not receiving thrombolytic, and not leaving against medical advice. The patient and hospital characteristics for the 1868 patients in the primary aim cohort are shown in Table 1. There were 974 (52%) patients who were not given a reversal agent and 894 (48%) who received a reversal agent.

The mean age was 73 years, 42% were female, and 75% of patients identified as white. The observed mean body mass index was on the threshold of obesity at 29.6 kg/m^2, but 22% of patients were missing body mass index (Table S1 for more details on missingness rates). Medicare and private insurance were the most common payors at 47% and 42%, respectively. Just under 10% of patients were on Medicaid. Hypertension was the most common comorbidity (82%), followed by atrial fibrillation/flutter (66%), and then dyslipidemia (50%). As such,

Table 1. Patient and Hospital Characteristics Between Those Exposed to a Reversal Agent Versus Not Exposed–Primary Aim Cohort

	Primary aim cohort (N=1868), N (%)	Without reversal (N=974), N (%)	Reversal agent used (N=894), N (%)
Age, mean (SD), y	73.2 (12.7)	72.9 (13.3)	73.6 (12.0)
Female gender (%)	777 (41.6)	429 (44.0)	348 (38.9)
Race/ethnicity			
White	1392 (74.5)	739 (75.9)	653 (73.0)
Black	239 (12.8)	122 (12.5)	117 (13.1)
Hispanic (any race)	92 (4.9)	37 (3.8)	55 (6.2)
Asian	50 (2.7)	26 (2.7)	24 (2.7)
Other (includes unable to determine)	95 (5.1)	50 (5.1)	45 (5.0)
BMI, mean (SD)	29.6 (7.9)	29.6 (8.1)	29.5 (7.6)
N (missing)	1460 (408)	724 (250)	736 (158)
Insurance type, N/total N (%)			
Private/VA/champus/other insurance	585/1401 (41.8)	295/739 (39.9)	290/662 (43.8)
Medicaid	129/1401 (9.2)	71/739 (9.6)	58/662 (8.8)
Medicare	657/1401 (46.9)	357/739 (48.3)	300/662 (45.3)
Self pay/no insurance	26/1401 (1.9)	14/739 (1.9)	12/662 (1.8)
Not documented	4/1401 (0.3)	2/739 (0.3)	2/662 (0.3)
Past medical history			
Hypertension	1538 (82.3)	801 (82.2)	737 (82.4)
Dyslipidemia	938 (50.2)	494 (50.7)	444 (49.7)
Diabetes	654 (35.0)	360 (37.0)	294 (32.9)
Heart failure	412 (22.1)	231 (23.7)	181 (20.2)
CAD/prior MI	643 (34.4)	329 (33.8)	314 (35.1)
Previous ischemic stroke	126 (6.7)	59 (6.1)	67 (7.5)
Chronic renal insufficiency	305 (16.3)	164 (16.8)	141 (15.8)
Atrial fibrillation/flutter	1226 (65.6)	628 (64.5)	598 (66.9)
Carotid stenosis	39 (2.1)	19 (2.0)	20 (2.2)
Obesity/overweight	600 (32.1)	311 (31.9)	289 (32.3)
Smoker	181 (9.7)	105 (10.8)	76 (8.5)
Drugs/alcohol abuse	99 (5.3)	58 (6.0)	41 (4.6)
Peripheral vascular disease	109 (5.8)	59 (6.1)	50 (5.6)
Sleep apnea	205 (11.0)	114 (11.7)	91 (10.2)
Depression	230 (12.3)	111 (11.4)	119 (13.3)
Prestroke mRS			
mRS score of 0, 1, or 2	322 (17.2)	155 (15.9)	167 (18.7)
mRS score of 3, 4, or 5	72 (3.9)	41 (4.2)	31 (3.5)
mRS score not documented	1474 (78.9)	778 (79.9)	696 (77.9)
Medications before admission, N/total N (%)			
Antiplatelet	716/1868 (38.3)	368/974 (37.8)	348/894 (38.9)
Antihypertensive	1401/1732 (80.9)	712/896 (79.5)	689/836 (82.4)
Cholesterol reducer	1055/1866 (56.5)	543/973 (55.8)	512/893 (57.3)
Diabetic medication	473/1705 (27.7)	242/879 (27.5)	231/826 (28.0)
Admission information			
Ambulatory status before admission			
Able to ambulate independently (no help from another person) with or without device	1214 (74.6)	596 (70.4)	618 (79.0)
With assistance (from person)	76 (4.7)	46 (5.4)	30 (3.8)

(*Continued*)

Table 1. Continued

	Primary aim cohort (N=1868), N (%)	Without reversal (N=974), N (%)	Reversal agent used (N=894), N (%)
Unable to ambulate	65 (4.0)	29 (3.4)	36 (4.6)
Not documented	273 (16.8)	175 (20.7)	98 (12.5)
Glasgow coma scale, median (25th–75th)	14.0 (7.0–15.0)	13.0 (6.0–15.0)	14.0 (9.5–15.0)
Weakness/paresis	784 (42.0)	374 (38.4)	410 (45.9)
Altered level of consciousness	677 (36.2)	386 (39.6)	291 (32.6)
Aphasia/language disturbance	557 (29.8)	274 (28.1)	283 (31.7)
ICH score			
0–1	586 (31.4)	258 (26.5)	328 (36.7)
2–3	506 (27.1)	220 (22.6)	286 (32.0)
4–6	188 (10.1)	113 (11.6)	75 (8.4)
Unknown	588 (31.5)	383 (39.3)	205 (22.9)
FUNC score, median (25th–75th)	3.0 (1.0–8.0)	3.0 (1.0–5.0)	6.0 (2.0–8.0)
N (missing)	131 (1737)	57 (917)	74 (820)
Systolic blood pressure, mean (SD), mm Hg	153.9 (31.6)	150.8 (31.7)	156.9 (31.3)
Diastolic blood pressure, mean (SD), mm Hg	83.7 (19.8)	82.6 (19.5)	84.9 (19.9)
Heart rate, mean (SD), bpm	83.6 (20.1)	84.3 (20.7)	82.9 (19.4)
Fasting blood glucose, median (25th–75th), mg/dL	135.0 (110.0–176.0)	138.0 (111.0–182.0)	131.0 (109.0–171.0)
INR, mean (SD)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)
Creatinine, median (25th–75th), mg/dL	1.0 (0.8–1.4)	1.0 (0.8–1.4)	1.0 (0.8–1.4)
Arrival information			
Off-hour arrival (regular hour: 7 AM-6 PM, M-F, nonholiday)	1171 (62.7)	607 (62.3)	564 (63.1)
Ambulatory status on admission, N/total N (%)			
Able to ambulate independently (no help from another person) with or without device	181/1510 (12.0)	90/785 (11.5)	91/725 (12.6)
With assistance (from person)	210/1510 (13.9)	92/785 (11.7)	118/725 (16.3)
Unable to ambulate	706/1510 (46.8)	367/785 (46.8)	339/725 (46.8)
Not documented	413/1510 (27.4)	236/785 (30.1)	177/725 (24.4)
Arrived via EMS	539/1836 (29.4)	226/954 (23.7)	313/882 (35.5)
Transferred in from another hospital	1149 (61.5)	662 (68.0)	487 (54.5)
Initial NIHSS			
Low (0–4)	478 (25.6)	238 (24.4)	240 (26.8)
Medium (5–15)	366 (19.6)	153 (15.7)	213 (23.8)
High (16+)	459 (24.6)	256 (26.3)	203 (22.7)
Unknown	565 (30.2)	327 (33.6)	238 (26.6)
Time from onset to arrival, median (25th–75th), min	332.0 (165.0–680.0)	390.0 (200.0–743.0)	286.5 (135.0–618.0)
Hospital characteristics			
Annual volume of ICH stroke admissions, median (25th–75th)	108.1 (70.5–144.8)	110.1 (70.7–145.5)	100.8 (70.4–141.5)
Number of beds in hospital, median (25th–75th)	571.0 (421.0–755.0)	571.0 (421.0–755.0)	571.0 (409.0–776.0)
Rural location	3 (0.2)	0 (0.0)	3 (0.3)
Academic hospital	1484 (84.6)	782 (84.7)	702 (84.5)
Region			
Northeast	516 (27.6)	262 (26.9)	254 (28.4)
Midwest	439 (23.5)	234 (24.0)	205 (22.9)
South	695 (37.2)	372 (38.2)	323 (36.1)
West	218 (11.7)	106 (10.9)	112 (12.5)
Annual volume of IV tPAs	48.5 (23.6)	47.9 (22.6)	49.2 (24.6)

(*Continued*)

Table 1. Continued

	Primary aim cohort (N=1868), N (%)	Without reversal (N=974), N (%)	Reversal agent used (N=894), N (%)
TJC stroke center status			
Neither CSC nor PSC	158 (8.5)	80 (8.2)	78 (8.7)
CSC	1318 (70.6)	660 (67.8)	658 (73.6)
PSC	392 (21.0)	234 (24.0)	158 (17.7)

BMI indicates body mass index; CAD, coronary artery disease; CSC, comprehensive stroke center; EMS, emergency medical services; FUNC, functional outcome in patients with primary intracerebral hemorrhage score; ICH, intracerebral haemorrhage; INR, international normalized ratio; MI, myocardial infarction; mRS, modified Rankin scale; NIHSS, NIH stroke scale; PSC, primary stroke center; TJC, The Joint Commission on accreditation of hospitals; and tPA, tissue-type plasminogen activator.

81% of patients were on an antihypertensive, and 57% were on a cholesterol reducer before admission.

The primary outcome was discharge mRS score of 0 to 3 after reversal of subtherapeutic warfarin anticoagulation for patients with acute ICH. Event rates and adjusted effect sizes are reported in Table 2. The distribution of mRS at discharge by reversal agent is shown in Figure 2. A similar proportion of patients at discharge had an mRS score of 0 to 3 with reversal or without reversal (21.0% versus 23.1%, respectively; adjusted odds ratio, 0.80 [95% CI, 0.63–1.005]). The sensitivity analysis of INR ≤1.4 after reversal showed similar results for the primary outcome (adjusted odds ratio, 0.82 [95% CI, 0.63–1.06]). When considering mRS as an ordinal outcome, the model estimated the odds cumulatively of having a given level of mRS or better by combining that level of mRS with all lower mRS values. The cumulative odds model was used because the proportional odds assumption was violated for the ordinal mRS model. Receiving a reversal agent was associated with 21% higher odds of having an mRS score of 0 to 4 versus 5 to 6 at discharge (95% CI, 1.001–1.48).

Patient and hospital characteristics for the 2569 patients in the secondary aims cohort for outcomes not requiring mRS are displayed in Table S2 in the Supplemental Appendix. There were 1351 (53%) patients who were not given a reversal agent and 1218 (47%) who were. Characteristics were similar to the primary aim cohort.

Patients receiving a reversal agent had 25% lower odds of dying in the hospital or being discharged to hospice (95% CI, 0.63–0.89) after weighting. LOS was longer for patients who received a reversal agent, both among all patients (median, 6 days versus 4 days) and just those who survived to discharge (median, 7 days versus 6 days). Receiving reversal was associated with 21% lower odds of being discharged to home (95% CI, 0.65–0.97) and 33% higher odds of being discharged to skilled nursing (95% CI, 1.08–1.65). Patients who received a reversal agent did not have significantly different odds of developing DVT/PE. There was also not a significant difference in the odds of being fully ambulatory at discharge among those who were fully ambulatory prestroke. Outcomes not requiring mRS using the secondary aims cohort are displayed in Table 3. See Table S3 for mRS of those discharged to home.

Outcome by ICH Score

We were unable to assess mRS and ambulation status at discharge stratified by ICH score as originally

Table 2. Association Between Reversal Agent Use and Outcomes

	Overall (N=1868), N (%)	No reversal agent used (N=974), N (%)	Reversal agent used (N=894), N (%)	Unadjusted effect size (95% CI)	Adjusted effect size (95% CI)
Primary					
mRS at discharge (0–3 vs 4–6)	413 (22.1)	225 (23.1)	188 (21.0)	0.89 (0.71–1.10)*	0.80 (0.63–1.00)*
Secondary					
mRS at discharge (ordinal)					
0	81 (4.3)	48 (4.9)	33 (3.7)	0.73 (0.48–1.15)*	0.66 (0.41–1.07)*
1	90 (4.8)	45 (4.6)	45 (5.0)	0.90 (0.66–1.24)*	0.87 (0.62–1.22)*
2	92 (4.9)	56 (5.7)	36 (4.0)	0.81 (0.62–1.05)*	0.77 (0.58–1.02)*
3	150 (8.0)	76 (7.8)	74 (8.3)	0.89 (0.71–1.08)*	0.80 (0.63–1.00)*
4	472 (25.3)	189 (19.4)	283 (31.7)	1.51 (1.25–1.80)*	1.21 (1.00–1.48)*
5–6	983 (52.6)	560 (57.5)	423 (47.3)	…	…

Propensity score overlap weighting based on the likelihood of belonging to the other group was used to adjust the effect sizes. mRS indicates modified Rankin scale.

*Odds ratio.

†Risk ratio.

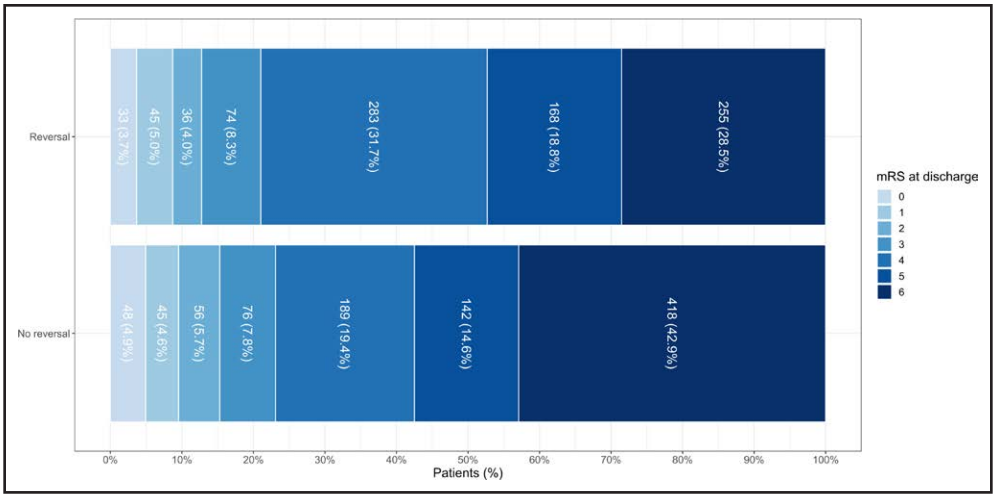

Figure 2. Distribution of modified Rankin scale (mRS) at discharge by receipt of a reversal agent for the primary cohort.
The distribution of mRS at discharge by whether a reversal agent was given is shown in Figure 2A. When considering mRS as an ordinal variable, we used a nonproportional odds cumulative logistic regression model. The model estimated consecutively the odds of having each level of mRS or better by comparing the combination of patients at that level of mRS combined with all lower mRS values. That is, 0 vs 1 to 6, 0 to 1 vs 2 to 6, etc. Receiving a reversal agent was associated with 21% increased odds of mRS score of 0 to 4 vs 5 to 6 at discharge (95% CI, 1.001–1.48).

planned due to low events in certain subgroups. There were no unreversed patients with an ICH score of 4 to 6 who had a 0 to 3 mRS score at discharge. Most of those patients died in the hospital. Similarly, there were no unreversed patients with an ICH score of 4 to 6 who were fully ambulatory at discharge. Even among those who received a reversal agent and had an ICH score of 4 to 6, only 2/46 (4.3%) were fully ambulatory at discharge.

Among those with a high (4–6) ICH score, patients who received a reversal agent had 80% lower odds (95% CI, 0.08–0.51) of dying in the hospital or being discharged to hospice. Among those with a low (0–1) or medium (2–3) ICH score, reversal was not associated with in-hospital mortality or discharge to hospice after weighting. Among those with an unknown ICH score, patients who received a reversal agent had lower odds of dying in the hospital or being discharged to hospice (adjusted odds ratio, 0.62 [95% CI, 0.46–0.85]), but it is difficult to know who these patients are or why they are missing an ICH Score.

Full results for any association between reversal agent use and outcomes by ICH score can be found in Table S4.

Table 3. Association Between Reversal Agent Use and Outcomes

	Overall (N=2569), N (%)	No reversal agent used (N=1351), N (%)	Reversal agent used (N=1218), N (%)	Unadjusted effect size (95% CI)	Adjusted effect size (95% CI)
In-hospital mortality or discharge to hospice, N/total N (%)	930/2563 (36.3)	558/1346 (41.5)	372/1217 (30.6)	0.62 (0.53–0.73)*	0.75 (0.63–0.89)*
Development of DVT or PE, N/total N (%)	66/2569 (2.6)	31/1351 (2.3)	35/1218 (2.9)	1.26 (0.77–2.06)*	1.47 (0.88–2.46)*
Length of stay among all patients, median (25th–75th), d	5 (3–10)	4 (2–9)	6 (4–12)	1.34 (1.23–1.46)†	1.25 (1.13–1.37)†
Length of stay among those that survived to discharge, median (25th–75th), d	6 (4–12)	6 (3–10)	7 (4–13)	1.23 (1.12–1.34)†	1.17 (1.07–1.28)†‡
Home, N/total N (%)	516/2563 (20.1)	292/1346 (21.7)	224/1217 (18.4)	0.81 (0.67–0.99)*	0.79 (0.65–0.97)*
Hospice/death, N/total N (%)	930/2563 (36.3)	558/1346 (41.5)	372/1217 (30.6)	0.62 (0.53–0.73)*	0.75 (0.63–0.89)*
Skilled nursing, N/total N (%)	467/2563 (18.2)	211/1346 (15.7)	256/1217 (21.0)	1.43 (1.17–1.75)*	1.33 (1.08–1.65)*
Rehab, N/total N (%)	557/2563 (21.7)	254/1346 (18.9)	303/1217 (24.9)	1.43 (1.18–1.72)*	1.20 (0.98–1.47)*
Fully ambulatory at discharge among those fully ambulatory preevent, N/total N (%)	432/1638 (26.4)	237/824 (28.8)	195/814 (24.0)	0.78 (0.63–0.97)*	0.83 (0.64–1.07)*‡

Propensity score overlap weighting based on the likelihood of belonging to the other group was used to adjust the effect sizes. DVT indicates deep venous thrombosis; GCS, Glasgow coma scale; ICH, intracerebral haemorrhage; NIHSS, National Institutes of Health Stroke Scale; and PE, pulmonary embolus.

*Odds ratio.

†Risk ratio.

‡Model included GCS, ICH score, and NIHSS due to imbalance between treatment arms in the subgroup after weighting.

Prevalence of Withdrawal of Life-Sustaining Treatments

Among the patients who died, a lower proportion of those with reversal were classified as receiving comfort measures only, 203/255 (79.6%) versus 373/418 (89.2%).

DISCUSSION

Reversal of subtherapeutic warfarin anticoagulation after acute spontaneous ICH was not associated with improved short-term functional outcomes based on an expected predetermined threshold for highly morbid neurological illness. The primary outcome of mRS score of 3 or lower at the time of discharge was chosen and would detect benefit in patients who avoided severe disability due to acute spontaneous ICH. Disability and death are common with ICH. Early good outcomes may avoid needing a prolonged recovery period with this illness. Even with patients with severe disability at the time of discharge after ICH, there is a normal trajectory of recovery that is different from a successfully treated ischemic stroke that must be appreciated.[27–30] In a reanalysis of the CLEAR-III and MISTIE-III cohorts, the potential for slow recovery over time was well demonstrated.[27] In the subgroup of CLEAR-III patients who had an mRS score of 4 to 5 at 30 days, by 6 months 38% had improved to mRS score of 3 or better, and at 1 year 45% had improved to mRS score of 3 or better. Similarly, in the MISTIE-III subgroup of patients who were mRS score of 4 to 5 at 30 days, by 6 months 36% of those had improved to mRS score of 3 or better whereas 10% had died, and by 1 year 41% had improved mRS score of 3 or better whereas 14% had died. An mRS score of 4 represents moderately severe disability, characterized by patients being unable to walk without assistance and unable to attend to their own bodily needs without assistance. It is at an mRS score of 4 that we see an association with subtherapeutic warfarin reversal and outcome. The apparent shift in functional outcome from death to disability is reminiscent of the effect of other treatments in highly morbid neurological disease, such as decompressive hemicraniectomy for traumatic brain injury, decompression of massive ischemic stroke, and surgical treatment of ICH, albeit those outcomes were on a longer horizon (Figure 2).

In this study, fewer patients with warfarin reversal had combined in-hospital mortality or discharge to hospice (30.6% versus 41.5%). Compared with those without reversal, the greatest effect is in highly morbid patients. Patients with a high (4–6) ICH score who received a reversal agent had 80% lower odds (95% CI, 0.08–0.51) of dying in the hospital or being discharged to hospice. Reversal was associated with increased odds of discharge to a nursing facility, decreased odds of discharge to home, decreased odds of being discharged to hospice, and increased LOS.

The GWTG-Stroke registry does not report data on hematoma expansion, so it cannot be determined whether the association between reversal and survival was related to the actual lessening of the hematoma expansion. The reversal is believed to have been effective in changing the INR based on the sensitivity analysis, where there was only 22% crossover of reversed patients to not having corrected INR. A subgroup analysis would be able to determine if the reversed patients who did not achieve corrected INR contributed to the disability or death in that cohort of reversed patients. The specific outcomes of those who failed to be reversed are not known, and the specific timing and type of reversal agent are not known.

Because of the observational nature of this study, we cannot exclude the possibility that the results may have been affected by residual or unmeasured confounding, even though propensity weighting was used to control for confounding as best as possible. As previously mentioned, some factors potentially influencing ICH outcome were not included in the propensity weighting models due to their absence from the data set. These include, but are not limited to, leukoaraiosis, hematoma volume, and intraventricular extension.[27] One potential source of confounding could be the differential use of limitation of care orders or early withdrawal of care. It is possible that patients who received reversal were more likely to receive future life-sustaining care of all kinds. There were imbalances between the reversed and nonreversed groups that suggest that the reversed and nonreversed patients may have been treated with different intensities; however, that evidence is weak. Treating physicians and families may have opted not to treat the more severe cases as aggressively.

The ICH score is a measure of severity in intracranial hemorrhage; the ICH score was unknown in 31.5% of patients, making any inference from the ICH scores speculative, but the ICH scores were higher among the unreversed patients. Similarly, the FUNC score is designed as a predictor of functional recovery after ICH. The FUNC score was worse in the unreversed patients in whom it was known; however, the FUNC score was only recorded in 7% of patients.

The time to reversal is an important potential confounder.[31] The time from door to reversal was known in only 86% (N=1044) of patients, although the number of patients with known time from symptom onset to reversal time was only 47% (N=567). The median time from door to reversal was 133 minutes (Table S5). Among the subset of 482 patients who presented within 6 hours of last known well, the propensity model and model for the primary end point were refit. Similar to the full cohort, there was not a significant difference in the mRS score of 0 to 3 between the treated and untreated groups (Table S6). There was probably some intrinsic partial correction in the propensity score weighting, as

the models included elements that would affect the time to presentation: the models include stroke center type and arrival by emergency medical services in the overlap weighting. The comprehensive stroke centers were more likely to receive referral patients who may not have received reversal before transportation. The time elapsed is greater for patients transferred from other hospitals than for patients arriving directly by emergency medical services. To some degree, the patients with subtherapeutic INR may represent patients who already have a greater time since the onset of injury to presentation.

The question addressed in this study is an important one, as there is an increasing appreciation of the potential risks of reversal of anticoagulation. Although we did not demonstrate any difference in thrombotic complications, the results of the ICH trial and the ANNEXA-I trial did raise justifiable concern for increased thrombotic complications. In the INCH trial, 5/27 patients in the PCC arm experienced DVT or PE. In the ANNEXA-I trial, 5.6% of patients in the usual care arm (85.5% of whom received PCC) developed thrombotic complications, and in the andexanet alfa arm, 10.3% of patients had thrombotic complications. The rates of thrombotic complications in these studies may be higher because an randomized controlled trial is able to prospectively collect this information. In addition, the thrombotic complications may have occurred later, with more thrombotic complications occurring after 12 days and up to 90 days in the INCH trial, and with assessments continuing up to 30 days with the ANNEXA-I trial.

There appears to be clinical equipoise given the similar proportions of patients who were treated or not treated. Although the use of vitamin K antagonists has decreased over time, there remain several subgroups of patients in whom vitamin K antagonists are preferred over direct oral anticoagulants, including patients with metallic heart valves, ventricular assist devices, severe renal disease, antiphospholipid antibody syndrome, and gastrointestinal malignancies. Therefore, managing vitamin K antagonist-associated ICH will remain an important part of clinical practice for the foreseeable future. Of the patients who present with vitamin K antagonist-associated ICH, ≈25% have INR <2.[32] This analysis provides the clinician with information, albeit not from a controlled trial, on the potential benefits and risks of reversing INR in the subset with INR 1.5 to 1.9.

Reversal of subtherapeutic INR appears safe with few thrombotic complications. Reversal is associated with lower mortality and with survival at higher disability mRS than was expected. The effects seen in this data suggest that a randomized controlled trial would be helpful to explore the potential mortality benefit, the potential functional outcome difference, and the potential risk of harm associated with reversal. The functional outcome at discharge is not a long enough assessment to determine full recovery potential for an randomized controlled trial, but can be hypothesis-generating from this study.

LIMITATIONS

This study uses data that was abstracted for nonresearch purposes, and analysis is only possible for the existing data. Important covariates, such as time from onset to arrival, FUNC score, and prestroke mRS, were missing to the degree that they were not included in the models. Baseline mRS before the event was not documented in 79% of patients. The mRS as an outcome at the time of discharge is a meaningful, yet imperfect, outcome.[30] An outcome at a time of fuller recovery would be preferable, but harder to obtain without greater loss to follow-up in a quality control database. An alternative would be prospective data collection or for an observational study to use projections of long-term outcomes derived from a smaller data set of 6-month recovery.[29] There is an additional data layer of the GWTG-Stroke database, which will be available for future studies, which was not available for the current analysis, but is an exciting area for future developments.

Selection bias is inherent in this observational cohort. The outcomes here may be affected by uncontrolled effects of physicians' decisions to treat and family decisions regarding withdrawal of life-sustaining treatment. However, without specific information regarding end-of-life decision-making, any inference about decision-making is tentative. The final determination of the meaningfulness of an outcome is best interpreted by the patients and families themselves. Satisfaction scores for the patients and families are unknown. Thus, the absence of patient-reported outcomes remains a shortcoming.

CONCLUSIONS

This study detected an association between the combined outcome of fewer hospital deaths or discharges to hospice with reversal of subtherapeutic warfarin anticoagulation for acute ICH. There was not a significant difference in functional outcome at the time of discharge. The absence of a statistically significant difference in functional outcome at this early stage should not be construed as justification for withholding reversal of anticoagulation. No harm was detected from the reversal of anticoagulation. This study serves as justification for a randomized controlled trial to further explore both the risk of harm of reversal and the long-term functional outcomes after reversal.

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Supplemental Material

Tables S1–S6
STROBE Checklist

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