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Outcomes After Endovascular Thrombectomy With or Without Alteplase in Routine Clinical Practice

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IMPORTANCE The effectiveness and safety of intravenous alteplase given before or concurrently with endovascular thrombectomy (EVT) is uncertain. Randomized clinical trials suggest there is little difference in outcomes but with only modest precision and insufficient power to analyze uncommon outcomes including symptomatic intracranial hemorrhage (sICH).

OBJECTIVE To determine whether 8 prespecified outcomes are different in patients with acute ischemic stroke treated in routine clinical practice with EVT with alteplase compared with patients treated with EVT alone without alteplase. It was hypothesized that alteplase would be associated with higher risk of sICH.

DESIGN, SETTING, AND PARTICIPANTS This was an observational cohort study conducted from February 1, 2019, to June 30, 2020, that included adult patients with acute ischemic stroke treated with EVT within 6 hours of time last known well, after excluding patients without information on discharge destination and patients with in-hospital stroke. Participants were recruited from Get With The Guidelines–Stroke, a large nationwide registry of patients with acute ischemic stroke from 555 hospitals in the US.

EXPOSURES Intravenous alteplase or no alteplase.

MAIN OUTCOMES AND MEASURES Prespecified outcomes were discharge destination, independent ambulation at discharge, modified Rankin score at discharge, discharge mortality, cerebral reperfusion according to modified Thrombolysis in Cerebral Infarction grade, and sICH.

RESULTS There were 15 832 patients treated with EVT (median [IQR] age, 72.0 [61.0-82.0] years; 7932 women [50.1%]); 10 548 (66.7%) received alteplase and 5284 (33.4%) did not. Patients treated with alteplase were younger, arrived via Emergency Medical Services sooner, were less likely to have certain comorbidities, including atrial fibrillation, hypertension, and diabetes, but had similar National Institutes of Health Stroke Severity (NIHSS) scores. Compared with patients who did not receive alteplase treatment, patients treated with alteplase were less likely to die (11.1% [1173 of 10 548 patients] vs 13.9% [734 of 5284 patients]; adjusted odds ratio [aOR] 0.83; 95% CI, 0.77-0.89; $P < .001$), more likely to have no major disability based on modified Rankin scale of 2 or less at discharge (28.5% [2415 of 8490 patients] vs 20.7% [894 of 4322 patients]; aOR, 1.36; 95% CI, 1.28-1.45; $P < .001$), and to have better reperfusion based on modified Thrombolysis in Cerebral Infarction grade 2b or greater (90.9% [8474 of 9318 patients] vs 88.0% [4140 of 4705 patients]; aOR, 1.39; 95% CI, 1.28-1.50; $P < .001$). However, alteplase treatment was associated with higher risk of sICH (6.5% [685 of 10 530 patients] vs 5.3% [279 of 5249 patients]; OR, 1.28; 95% CI, 1.16-1.42; $P < .001$).

CONCLUSIONS AND RELEVANCE In this observational cohort study of patients treated with EVT, intravenous alteplase treatment was associated with better in-hospital survival and functional outcomes but higher sICH risk after adjusting for other covariates.

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Supplemental content

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For patients with large vessel occlusion who are eligible for endovascular thrombectomy (EVT) and intravenous alteplase, current guidelines recommend that they receive both.[1-3] The initial pivotal randomized trials of EVT included the use of intravenous alteplase in both the treatment and control groups, if the patient was eligible, because use of alteplase was previously established as the standard of care.

More recently, the benefit of using alteplase in patients who are eligible for EVT and initially present to a thrombectomy-capable center has been questioned. Alteplase may increase the risk of bleeding and is unlikely to achieve recanalization before EVT in patients who can be treated with EVT without delay.[4] Furthermore, it may increase the risk of thrombus fragmentation with distal embolization of multiple smaller fragments, increasing the technical challenge of performing thrombectomy.[5] Six randomized clinical trials have compared EVT with altepase with EVT without alteplase, finding small differences without evidence for the superiority of either approach.[6-11] Pooled analysis of the first 4 trials found a nonsignificant approximate 1% increase in favorable modified Rankin scale (mRS) score at 90 days for EVT without alteplase,[12,13] whereas conversely the last 2 trials,[10,11] currently published in abstract form only, found a nonsignificant decrease in favorable mRS for EVT without alteplase. The most recent meta-analysis of all 6 trials found that using EVT without alteplase resulted in worse disability outcomes at 90 days, but this difference was not statistically significant.[14] There were fewer symptomatic intracranial hemorrhage (sICH) when using EVT without alteplase. Based on these data, the European Stroke Organization–European Society for Minimally Invasive Neurological Therapy (ESO-ESMINT) recommended, based on moderate-quality evidence, that alteplase continue to be used in eligible patients undergoing EVT.[14] However, it is not known whether outcomes in routine clinical practice are similar to those in the trials, which were primarily conducted in large, high-performing centers.

The objective of this analysis was to compare outcomes of discharge mortality, discharge destination, discharge ambulation status, and sICH in patients treated with EVT with alteplase with outcomes of patients treated with EVT without alteplase in the large, national, Get With The Guidelines-Stroke (GWTG-Stroke) registry.

Key Points

Question In patients with acute ischemic stroke attributable to large vessel occlusion, does combining endovascular thrombectomy (EVT) with alteplase result in better outcomes than using EVT alone?

Findings In this cohort study of 15 832 patients, compared with EVT without alteplase, treatment with EVT with alteplase was associated with greater likelihood of discharge to home, independent ambulation at discharge, and lower mortality, but higher risk of symptomatic intracranial hemorrhage.

Meaning Results suggest that combining alteplase with EVT in routine clinical practice was associated with less disability and mortality, with similar effect sizes as in recent randomized clinical trials, but that these improvements come with a significant increased risk for symptomatic intracranial hemorrhage.

Methods

Source Population

GWTG-Stroke is a nationwide registry maintained by the American Heart Association and American Stroke Association to support continuous quality improvement of care for patients with stroke and transient ischemic attack. Details of the program design have been previously published.[15] GWTG-Stroke uses a web-based patient management tool to collect clinical data on consecutively admitted patients. Hospitals received either approval to enroll patients without individual patient consent under the Common Rule or a waiver of authorization and exemption from subsequent review by their institutional review board. The institutional review board of the data analysis center at Duke University approved the study. Duke Clinical Research Institute serves as the data analysis center and has an agreement to analyze the aggregate deidentified data for research purposes. This study followed Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Patients were selected who presented to a participating hospital with acute ischemic stroke between February 1, 2019, and June 31, 2020, and underwent EVT within 6 hours from last known well. We excluded patients who did not have complete information on discharge destination from the acute care hospital, one of the study end points, either because they were transferred to another acute care hospital, left against medical advice, or had missing discharge information. We also excluded patients with missing information on intravenous alteplase administration or who had experienced an in-hospital stroke.

Race and ethnicity were collected to characterize the study population and for adjustment as a covariate in the multivariable models. Reporting of race and ethnicity is required by the American Heart Association, and we followed American Heart Association guidelines for describing and analyzing race and ethnicity. Race and ethnicity were self-reported and recorded in the database by the investigators. Racial categories were based on National Institutes of Health policy and included Asian, Black, White, and other. Ethnicity was categorized, independent of race, as Hispanic or non-Hispanic. For the purpose of analysis, race and ethnicity were combined and reported as Asian, Black, Hispanic (any race), White (non-Hispanic), and other, which included unable to determine. Race or ethnicity information was missing in 2 patients.

Measurements

Data were extracted from the medical record. The abstracted data in GWTG-Stroke have been validated and found to have high accuracy with the data recorded in the medical record.[16] Abstracted data included age, race and ethnicity, sex, medical history, certain preadmission medications (including antiplatelet and anticoagulant drugs), mode of arrival (emergency medical services [EMS] or private transport), arrival

during regular workday hours (Monday to Friday 7 AM to 5 PM) or off hours, National Institutes of Health Stroke Scale (NIHSS) score, times of last known well, treatment with EVT (arterial puncture) or intravenous alteplase, and arrival times to the hospital. Reasons for not treating with alteplase were captured according to prespecified categories. Thrombus location was defined as proximal if the occlusion was in the internal carotid artery, M1 (sphenoidal or horizontal) segment of the middle cerebral artery (MCA), vertebral artery, or basilar artery, and distal if the occlusion was in the M2 (insular), M3 (opercular), or M4 (cortical) branches of the MCA, the anterior cerebral artery, or the posterior cerebral artery.

The exposure of interest was treatment with intravenous alteplase at either the receiving EVT hospital or the referring hospital. A sensitivity analysis was performed confined to patients arriving directly to the EVT hospital. The clinical outcomes included in-hospital death, independent ambulation status at discharge, discharge to home, and sICH within 36 hours after EVT. sICH was defined as neurologic worsening attributed to ICH verified by computed tomography or magnetic resonance imaging within 36 hours of EVT or alteplase. Life-threatening systemic bleeding and other serious bleeding complications were also recorded. The modified Rankin scale (mRS) was assigned at discharge. Final perfusion status after EVT was captured using a modified version of the Thrombolysis in Cerebral Infarction (TICI) scale,[17] where grade 2a was defined as filling less than half of the previously occluded target artery ischemic territory, 2b as filling more than half but not all of the target artery ischemic territory, and grade 3 as complete reperfusion. Successful reperfusion was defined as grade 2b or 3.

Statistical Analysis

Baseline patient characteristics and clinical factors were compared between patients treated with EVT with and without intravenous alteplase. Categorical variables were summarized by frequencies with percentages and compared using Pearson χ^2 test. Continuous variables were summarized by the median (IQR) and compared using Wilcoxon rank sum test. To aid comparisons between groups, we calculated absolute standardized differences for continuous and categorical variables to enable relative differences to be assessed on the same scale.[18] We considered standardized differences of greater than 10% to indicate a potentially clinically relevant imbalance between the groups.[19] Reasons why patients did not receive intravenous alteplase were tabulated.

Multivariable logistic regression analysis was performed to assess the association of intravenous alteplase with each outcome. Ordinal logistic regression was used to estimate the association of alteplase with a 1-point shift in mRS and TICI grade. Because, as expected, there were significant differences in clinical characteristics of treatment groups, the outcome models were adjusted via inverse probability weighting of the propensity to be treated with alteplase in addition to EVT. The propensity weights were determined using a multivariable logistic model with random intercepts with adjustment for age, sex, race and ethnicity, atrial fibrillation or flutter, prior stroke, prior coronary stenosis, diabetes type 1 or type 2, peripheral vascular disease, hypertension, dyslipidemia, smoking, prior heart failure, kidney insufficiency, prior medication (antiplatelet, anticoagulant, antihypertensive, cholesterol reducers), arrival via EMS, arrival during regular business hours vs off hours, admission NIHSS score, time from onset to EVT time, and hospital characteristic (region, teaching hospital, number of beds, annual stroke volume, annual intravenous alteplase volume, annual EVT volume, rural location, and The Joint Commission Primary Stroke Center status). The model estimates are shown in eTable 1 in the Supplement. The outcome model included only treatment and the inverse weights. This model was a logistic random-effects model to account for within- and across-site variability with hospital-specific random intercepts. Sensitivity analyses were performed, restricted to patients arriving less than 3 hours, less than 4.5 hours, and patients not taking anticoagulants before the stroke.

Missing medical history, preadmission antihypertensive medications, and arrival by EMS were imputed to no, and hospital characteristics were complete and were not imputed. Other model covariates were multiply imputed before entering into models using multiple imputation methods with 10 data sets. Outcome variables were not imputed. SAS software, version 9.4 (SAS Institute Inc) was used for all statistical analyses. All *P* values were 2-sided, and statistical significance was defined as a *P* value < .05.

Results

Of 540 427 patients with ischemic stroke admitted to hospitals participating in GWTG-Stroke between February 1, 2019, and June 31, 2020, there were 16 357 patients from 561 sites who underwent EVT within 6 hours from time last known well. After excluding patients without information on discharge destination (n = 498; 6 sites) and patients with in-hospital stroke (n = 27), there were 15 832 patients (median [IQR] age, 72.0 [61.0-82.0] years; 7932 women [50.1%]; 7900 men [49.9%]) from 555 sites for analysis. A total of 10 548 patients (66.7%) received alteplase and 5284 patients (33.4%) did not. Patients with the following races and ethnicities were included: 494 Asian (3.1%), 2366 non-Hispanic Black (14.9%), 1257 Hispanic (7.9%), 10 682 non-Hispanic White (67.5%), and 1041 other race and ethnicity (6.6%). Other race and ethnicity included American Indian or Alaska Native, Native Hawaiian or Pacific Islander, or unable to determine. Information on intravenous alteplase administration was present for all patients. Rates of missingness of baseline patient characteristic data were low (<5%) except for preadmission antihypertensives (1707 of 15 832 [10.8%]) and thrombus location (2691 of 15 832 [17.0%]) (eTable 2 in the Supplement). Data on ambulation at discharge were missing in 671 of 15 832 patients (4.2%), on mRS in 3201 of 15 832 patients (20.2%), on TICI in 1809 of 15 832 patients (11.4%), and on hemorrhagic complications (including sICH and life-threatening or serious systemic hemorrhage) in 53 of 15 832 patients (0.3%); patients with missing data for outcomes were excluded from models of those outcomes.

Patients who received alteplase with EVT treatment were younger with a median age of 70 (IQR, 59.0-81.0) years com-

pared with 74 (IQR, 63.0-83.0) years among patients who were treated with EVT without alteplase (**Table 1**). Compared with patients with EVT who were not treated with alteplase, patients treated with alteplase had a lower rate of atrial fibrillation or flutter (2608 of 10 528 [24.8%] vs 2687 of 5277 [50.9%]), prior stroke (1771 of 10 528 [5.8%] vs 1679 of 5277 [31.8%]), and prior heart failure (1298 of 10 528 [12.3%] vs 965 of 5277 [18.3%]). As expected, very few patients who received both EVT and alteplase were taking anticoagulants (709 of 10 548 [6.7%]), compared with almost half of patients who received EVT only (2310 of 5284 [43.7%]). Patients treated with alteplase had a shorter median time from last known well to arrival at the hospital than those who were not treated with alteplase: 101 (IQR, 50-183) minutes vs 124 (IQR, 55-208) minutes. NIHSS score results were similar; median NIHSS score was 16.0 (IQR, 11.0-21.0) in patients treated with alteplase compared with 17.0 (IQR, 11.0-22.0) in patients not treated with alteplase. The proportion of patients transferred in for EVT was similar. Of the patients treated with alteplase, 64.8% of patients (6835 of 10 548) received it at the same hospital that provided EVT whereas 35.2% of patients (3713 of 10 548) received it at another hospital before transfer to the EVT-capable hospital. Time from EVT hospital arrival to EVT did not differ between the groups. Median time from last known well to EVT was longer in patients treated without alteplase (207 [IQR, 151-278] minutes vs 193 [IQR, 146-255] minutes).

The most common reason that intravenous alteplase was not administered was bleeding diathesis (1749 of 4326 patients [40.4%] who arrived within 4.5 hours and had recorded reasons for not treating; this includes patients taking warfarin with international normalized ratio >1.7 and patients taking non-vitamin K oral anticoagulants) (**Table 2**). Other common reasons included arrival outside the window for thrombolysis (1146 of 4326 [26.5%]), recent surgery (471 of 4326 [10.9%]), history of intracranial hemorrhage or bleeding-prone intracranial lesion (285 of 4326 [6.6%]), recent major surgery or trauma (183 of 4326 [4.2%]), and recent gastrointestinal or urinary tract hemorrhage (115 of 4326 [2.7%]).

Patients with EVT who were treated with intravenous alteplase had lower rates of in-hospital mortality (1173 of 10 548 [11.1%] vs 734 of 5284 [13.9%]), and more were discharged home (3629 of 10 548 [34.4%] vs 1455 of 5284 [27.5%]), could ambulate independently at discharge (3909 of 10 108 [38.7%] vs 1537 of 5053 [30.4%]), had low mRS at discharge (mRS 0-1: 1727 of 8490 [20.3%] vs 596 of 4322 [13.8%]; mRS 0-2: 2415 of 8490 [28.5%] vs 894 of 4322 [20.7%]), and had high TICI reperfusion grades (≥2b, 8474 of 9318 [90.9%] vs 4140 of 4705 [88.0%]) (**Table 3**). The distribution of mRS at discharge is shown in the **Figure**. Patients treated with alteplase had higher rates of sICH (685 of 10 530 [6.5%] vs 279 of 5249 [5.3%]) but not other life-threatening (106 of 10 530 [1.0%] vs 58 of 5249 [1.1%]) or other serious bleeding complications (541 of 10 530 [5.1%] vs 236 of 5249 [4.5%]).

Unadjusted and multivariable-adjusted odds ratios (aORs) for outcomes are shown in **Table 4**. After adjustment, EVT with alteplase was associated with lower mortality (aOR, 0.83; 95% CI, 0.77-0.89; $P < .001$), home discharge destination (aOR, 1.29; 95% CI, 1.23-1.36; $P < .001$), greater likelihood to have no major disability based on modified Rankin scale of 2 or less at discharge (aOR, 1.36; 95% CI, 1.28-1.44; $P < .001$), and to be able to ambulate at discharge (aOR, 1.33; 95% CI, 1.26-1.40; $P < .001$) but higher risk of sICH (aOR, 1.28; 95% CI, 1.16-1.42; $P < .001$) and life-threatening bleeding complications (aOR, 1.15; 95% CI, 1.03-1.28; $P = .02$). EVT with alteplase was associated with higher likelihood of successful reperfusion, based on modified Thrombolysis in Cerebral Infarction grade 2b or greater (aOR, 1.39; 95% CI, 1.28-1.50; $P < .001$). Results were similar when analyzing only direct-arriving patients, excluding those transferred for EVT (Table 4). Results were also similar in sensitivity analyses excluding patients arriving after 3 hours (eTable 3 in the Supplement), arriving after 4.5 hours (eTable 4 in the Supplement), and receiving anticoagulants (eTable 5 in the Supplement).

Discussion

In this large retrospective cohort study of a nationwide stroke registry, we found that treatment of EVT with alteplase was associated with greater likelihood of discharge outcomes of survival, discharge to home, being ambulatory, and having less global disability, compared with treatment of EVT without alteplase. EVT with alteplase was associated with higher TICI grade reperfusion, suggesting that the addition of alteplase may have enhanced reperfusion either by beginning to recanalize the vessel before EVT began or by lysing distal thrombus fragments. However, EVT with alteplase was associated with a higher risk of sICH (OR, 1.28; 95% CI, 1.16-1.42). Although the data from this study must be interpreted cautiously because the use of alteplase was not randomized, and therefore, the results are vulnerable to confounding, the direction of the effects was the same as those seen in a recent meta-analysis of 6 randomized clinical trials by ESO-ESMINT.[14] This meta-analysis showed that using alteplase was associated with less mortality and lower 90-day mRS but higher odds of sICH, although only the association with sICH was statistically significant.[14] Our findings from routine clinical practice support the ESO-ESMINT recommendations that alteplase should continue to be used in eligible patients undergoing EVT.

In contrast to the findings from this registry, the pooled data from the clinical trials did not show statistically significant benefits in patients treated with EVT and alteplase compared with patients treated with EVT without alteplase. In the trials, differences in mortality and disability were small. Pooled results from the first 4 trials slightly favored EVT without alteplase with a nonsignificant 1% absolute risk difference,[12,13] but in the next 2 trials, patients with EVT without alteplase fared nonsignificantly worse than patients with EVT and alteplase.[10,11] Meta-analyses of the randomized clinical trials found that using alteplase resulted in nonsignificant improvements in 90-day disability but caused more sICH, and the increase in sICH was statistically significant in the largest meta-analysis.[14] Prior observational studies have not provided clear results. A systematic review of 9 observational studies with 2797 patients found that the quality of evidence was low because of heterogeneity in treatment protocols and reporting.[20] The second largest observational study (after the current

Table 1. Characteristics of Patients Treated With EVT With and Without Intravenous Alteplase

Characteristic	No. (%)			Absolute standard difference, %
	Overall (N = 15 832)	EVT with alteplase (n = 10 548)	EVT without alteplase (n = 5284)	
Baseline demographics				
Age, median (IQR), y	72.0 (61.0-82.0)	70.0 (59.0-81.0)	74.0 (63.0-83.0)	21.62
Female sex	7932 (50.1)	5175 (49.1)	2757 (52.2)	6.23
Male sex	7900 (49.9)	5373 (50.9)	2527 (47.8)	
Race and ethnicity				
Asian	484 (3.1)	319 (3.0)	165 (3.1)	3.83
Non-Hispanic Black	2366 (14.9)	1594 (15.1)	772 (14.6)	
Hispanic	1257 (7.9)	849 (8.1)	408 (7.7)	
Non-Hispanic White	10 682 (67.5)	7065 (67.0)	3617 (68.5)	
Other[a]	1041 (6.6)	719 (6.8)	322 (6.1)	
Medical history				
AF/flutter	5295 (33.5)	2608 (24.8)	2687 (50.9)	55.98
Prior stroke or TIA	3450 (21.8)	1771 (16.8)	1679 (31.8)	35.50
Prior CAD	3609 (22.8)	2212 (21.0)	1397 (26.5)	12.87
Diabetes type 1 or 2	4066 (25.7)	2625 (24.9)	1441 (27.3)	5.41
Prior heart failure	2263 (14.3)	1298 (12.3)	965 (18.3)	16.60
Hypertension	11 433 (72.3)	7414 (70.4)	4019 (76.1)	13.00
Dyslipidemia	7343 (46.5)	4705 (44.7)	2638 (50.0)	10.63
Chronic renal insufficiency	1340 (8.5)	798 (7.6)	542 (10.3)	9.45
Smoker	2617 (16.6)	1823 (17.3)	794 (15.1)	6.17
Preadmission medications				
Antiplatelet	5668 (35.8)	3839 (36.4)	1829 (34.6)	15.84
Anticoagulant	3019 (19.1)	709 (6.7)	2310 (43.7)	109.34
Antihypertensive	8917 (56.3)	5550 (52.6)	3367 (63.7)	25.76
Cholesterol reducing	6739 (42.6)	4079 (38.7)	2660 (50.4)	23.61
Stroke characteristics				
Arrival via EMS	9539 (60.3)	6378 (60.5)	3161 (59.8)	1.29
Transferred for EVT	5482 (34.6)	3658 (34.7)	1824 (34.5)	0.32
Arrival off hours[b]	8805 (55.6)	5957 (56.5)	2848 (53.9)	5.18
NIHSS score, median (IQR)	16.0 (11.0-22.0)	16.0 (11.0-21.0)	17.0 (11.0-22.0)	2.93
Last known well to EVT, median (IQR), min	198 (148-262)	193 (146-255)	207 (151-278)	23.54
Thrombus location				
ICA	1926 (14.4)	1278 (14.3)	648 (14.7)	4.84
MCA M1[c]	6566 (49.3)	4376 (49.1)	2190 (49.5)	
MCA M2	2642 (19.8)	1799 (20.2)	843 (19.1)	
MCA M3 or M4	246 (1.8)	174 (2.0)	72 (1.6)	
MCA not otherwise specified	58 (0.4)	654 (7.3)	321 (7.3)	
ACA	95 (0.7)	61 (0.7)	34 (0.8)	
Posterior	823 (6.2)	528 (5.9)	295 (6.7)	
Other	58 (0.4)	38 (0.4)	20 (0.5)	
Hospital characteristics				
Region				
Northeast	3138 (19.8)	2047 (19.4)	1091 (20.6)	5.94
Midwest	3316 (20.9)	2269 (21.5)	1047 (19.8)	
South	6295 (39.8)	4137 (39.2)	2158 (40.8)	
West	3083 (19.5)	2095 (19.9)	988 (18.7)	

(continued)

Table 1. Characteristics of Patients Treated With EVT With and Without Intravenous Alteplase (continued)

Characteristic	No. (%)			Absolute standard difference, %
	Overall (N = 15 832)	EVT with alteplase (n = 10 548)	EVT without alteplase (n = 5284)	
No. of beds	531 (370-711)	531 (367-717)	531 (374-708)	2.95
Rural location	69 (0.4)	40 (0.4)	29 (0.5)	2.50
Academic/teaching hospital	14 055 (90.0)	9375 (90.1)	4680 (89.8)	1.00
Annual ischemic stroke volume	357.5 (255.7-507.6)	355.9 (255.3-507.6)	360.5 (258.2-514.2)	1.59
Annual intravenous alteplase volume	60.0 (42.0-87.0)	60.0 (42.0-88.0)	58.0 (41.0-85.0)	6.66
Annual EVT volume	68.0 (44.0-104.0)	68.0 (44.0-103.0)	69.0 (45.0-104.5)	5.68
Stroke Center status				
Comprehensive Stroke Center	3931 (24.8)	2687 (25.5)	1244 (23.5)	5.01
Primary Stroke Center	7871 (49.7)	5167 (49.0)	2704 (51.2)	
Neither	4030 (25.5)	2694 (25.5)	1336 (25.3)	

Abbreviations: ACA, anterior cerebral artery; AF, atrial fibrillation; CAD, coronary artery disease; EMS, emergency medical services, EVT, endovascular thrombectomy; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale.

[a] Other race and ethnicity includes unable to be determined.

[b] Off hours were defined as any time other than 7 AM to 6 PM Monday to Friday.

[c] M1 to M4 represent segments of the MCA; M1 is the sphenoidal or horizontal segment; M2 is the insular segment; M3 is the opercular segment; M4 is the cortical segment.

study), from the Safe Implementation of Treatment in Stroke-International Stroke Thrombectomy Register, included 6350 patients and found that, similar to our study, EVT with alteplase was associated with lower mortality and lower disability.[21] The risk of sICH was nonsignificantly increased in EVT with alteplase but not when restricted to patients arriving within 4.5 hours.[21] However, their propensity-matched analysis included relatively few sICH events compared with our study (126 vs 964 events).[21]

Reasons for the differing results between our registry-based study and the pooled trial data should be considered. Foremost, our registry results come from an observational study without randomization and the groups had imbalances in multiple known confounding factors. Patients treated with EVT without alteplase were older, more likely to have atrial fibrillation, and had longer times to hospital arrival, all of which are associated with worse prognosis. However, NIHSS score was only slightly higher. Although we used advanced statistical modeling to control for the propensity to receive alteplase, our results may nonetheless be affected by residual confounding favoring the EVT with alteplase group as they had better prognostic characteristics. On the other hand, we may have underestimated the benefits of alteplase if some patients who received alteplase before transfer improved en route, such that they no longer required EVT on arrival to the comprehensive stroke center. It is also possible that patients who receive intravenous alteplase before transfer may develop a symptomatic ICH before EVT, and they also would not have been captured in this analysis. Other potential reasons may lie in the patient populations studied. Patients in the GWTG-Stroke registry were comparable in terms of age, sex, and stroke severity to the trial participants, many of whom were of East Asian race and ethnicity, but were more likely to have atrial fibrillation, diabetes type 1 or type 2, and hypertension, and less likely to be smokers.[12] To reflect routine clinical practice, we included patients who underwent EVT for occlusions in the posterior circulation, anterior cerebral artery, and distal MCA branches. Importantly, the clinical trials were done at high-volume, experienced centers with immediate access to either alteplase or EVT or both, whereas in GWTG-Stroke, many of the patients were transferred after receiving alteplase at a primary stroke center. It is possible that alteplase may be more effective when it is given before transfer or in other scenarios where there will be a delay in starting EVT (eg, if the interventional team or angiography suite are not immediately available), because alteplase will be given more "dwell time" to act before starting EVT. That said, our results were unchanged when we restricted the analysis to patients who first presented to the hospital where they received EVT, excluding the transferred patients.

Table 2. Most Common Patient-Related Reasons[a] for Not Treating With Intravenous Alteplase

Reason	Overall, No. (%)
Total No.	4326
Arrived outside the thrombolysis window	1146 (26.5)
Bleeding diathesis (including anticoagulant use)	1749 (40.4)
Care team unable to determine eligibility	353 (8.2)
Recent surgery, trauma, or prior stroke in previous 3 mo	471 (10.9)
History of intracranial hemorrhage, neoplasm, or arteriovenous malformation	285 (6.6)
Major surgery or serious trauma within previous 14 d	183 (4.2)
Elevated blood pressure despite treatment	71 (1.6)
Gastrointestinal or urinary tract hemorrhage within previous 21 d	115 (2.7)
Active internal bleeding	101 (2.3)

[a] Reasons for not treating with intravenous alteplase were provided for 4326 of 5284 patients (81.8%). Other prespecified categories, selected 1.5% of the time or less, included multilobar infarction, arterial puncture at a noncompressible site within 7 days, blood glucose concentration less than 50 mg/dL, pregnancy, patient or family declination, stroke severity too mild, rapidly improved stroke symptoms, stroke too severe, recent myocardial infarction, advanced age, and seizure at onset. If there were multiple reasons for not treating, sites were allowed to select more than one reason.

Limitations

The main limitation of this study was the lack of a randomized comparison group. Another limitation was the lack of postdischarge 90-day outcomes. However, discharge disability status and ambulation have been shown to correlate

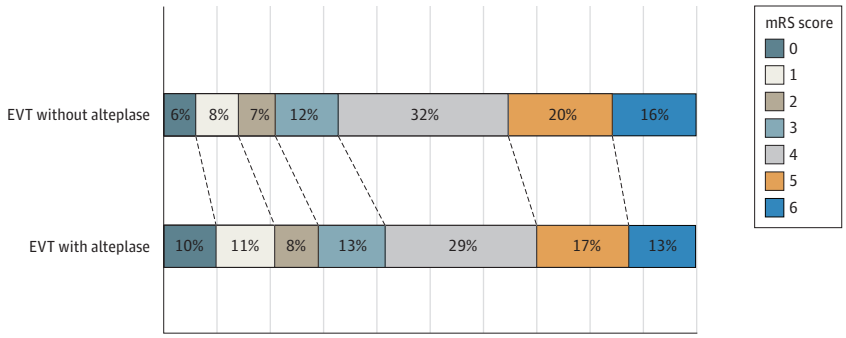
Table 3. Outcomes in Patients Treated With EVT With Intravenous Alteplase Compared With EVT Without Intravenous Alteplase

Characteristic	No. (%) Overall (N = 15 832)	EVT with alteplase (n = 10 548)	EVT without alteplase (n = 5284)	*P* value
In-hospital mortality	1907 (12.0)	1173 (11.1)	734 (13.9)	<.001
Discharge destination				
Home	5084 (32.1)	3629 (34.4)	1455 (27.5)	<.001
Hospice	1299 (8.2)	765 (7.3)	534 (10.1)	
Skilled nursing facility	2489 (15.7)	1555 (14.7)	934 (17.7)	
Inpatient rehab facility	4673 (29.5)	3171 (30.1)	1502 (28.4)	
mRS ≤1	2323 (18.1)	1727 (20.3)	596 (13.8)	<.001
mRS ≤2	3309 (25.8)	2415 (28.5)	894 (20.7)	<.001
Ambulatory at discharge	5446 (35.9)	3909 (38.7)	1537 (30.4)	<.001
TICI grade[a]				
Grade 0	560 (4.0)	328 (3.5)	232 (4.9)	<.001
Grade 1	177 (1.3)	107 (1.2)	70 (1.5)	
Grade 2a	672 (4.8)	409 (4.4)	263 (5.6)	
Grade 2b	4825 (34.4)	3274 (35.1)	1551 (33.0)	
Grade 3	7789 (55.5)	5200 (55.8)	2589 (55.0)	
TICI grade ≥2b	12 614 (90.0)	8474 (90.9)	4140 (88.0)	<.001
Bleeding complications				
sICH	964 (6.1)	685 (6.5)	279 (5.3)	.003
Life-threatening	164 (1.0)	106 (1.0)	58 (1.1)	.57
Other serious bleeding	777 (4.9)	541 (5.1)	236 (4.5)	.08

Abbreviations: EVT, endovascular thrombectomy; mRS, modified Rankin scale; sICH, symptomatic intracranial hemorrhage; TICI, thrombolysis in cerebral infarction.

[a] TICI grade represents degrees of reperfusion of the territory of the previously occluded target artery; 0: no filling; 1: minimal flow past the occlusion but no reperfusion; 2a: filling less than half of the previously occluded target artery ischemic territory, 2b: filling more than half but not all; 3: complete reperfusion.

Figure. Distribution of Modified Rankin Scale (mRS) Scores in Patients With Endovascular Thrombectomy (EVT) Without Intravenous Alteplase and EVT With Intravenous Alteplase



well with 90-day outcomes[22]; therefore, predictors of disability status at discharge are likely to predict variation in disability at 90 days as well, even though some degree of stroke recovery is expected. We did not study outcomes in patients treated with tenecteplase before EVT. The evidence for use of tenecteplase in place of alteplase is still moderate,[1,23] and it is not labeled by the US Food and Drug Administration for use in acute ischemic stroke. However, a small, randomized trial concluded that it was superior to alteplase when used before EVT.[24] Information on Alberta Stroke Programme Early Computed Tomography Score (ASPECTS) and results of perfusion imaging are not collected by GWTG; therefore, we were unable to analyze whether they influenced the decision to give alteplase or not.

Current guidelines recommend alteplase for all eligible patients including patients in whom EVT is planned. Intravenous thrombolysis may even obviate the need for EVT by lysing the thrombus before arrival at the angiography suite. When EVT is unsuccessful at achieving full perfusion, intravenous thrombolysis may recanalize residual occluded arteries.[25] However, our data support findings from the trials that using alteplase comes at the cost of a modestly increased risk of sICH. Therefore, given the relatively small and nonsignificant differences in disability outcomes in the trials, it would be reasonable to individualize patient treatment to avoid use of alteplase in patients at higher risk for sICH, if EVT is immediately available on-site.

Conclusions

The findings from this observational cohort study complement the results from randomized clinical trials by suggest-

Table 4. Unadjusted and Adjusted Outcomes in Patients Treated With EVT With Intravenous Alteplase Compared With EVT Without Intravenous Alteplase

Outcome	OR (95% CI)		
	Unadjusted	Adjusted	Adjusted excluding transfers
In-hospital mortality	0.77 (0.70-0.85)	0.83 (0.77-0.89)	0.84 (0.77-0.92)
Discharge destination			
Home	1.41 (1.31-1.51)	1.29 (1.23-1.36)	1.37 (1.29-1.46)
To IRF	1.07 (0.99-1.15)	0.98 (0.93-1.03)	0.96 (0.89-1.02)
To SNF	0.80 (0.73-0.88)	0.93 (0.87-0.99)	0.82 (0.76-0.89)
To hospice	0.69 (0.61-0.77)	0.79 (0.73-0.86)	0.83 (0.75-0.92)
Disability			
Lower discharge mRS score (mRS shift)[a]	1.39 (1.30-1.49)	1.10 (1.07-1.13)	1.15 (1.11-1.20)
Discharge mRS ≤1	1.61 (1.45-1.79)	1.42 (1.33-1.53)	1.62 (1.49-1.77)
Discharge mRS ≤2	1.53 (1.39-1.67)	1.36 (1.29-1.44)	1.56 (1.44-1.69)
Ambulate independently at discharge	1.46 (1.36-1.58)	1.33 (1.26-1.40)	1.45 (1.36-1.55)
Reperfusion			
Lower TICI posttreatment reperfusion grade	0.91 (0.85-0.97)	0.80 (0.78-0.83)	0.77 (0.74-0.80)
TICI posttreatment reperfusion score ≥2b	1.41 (1.26-1.58)	1.39 (1.28-1.50)	1.40 (1.27-1.55)
Bleeding			
sICH	1.23 (1.06-1.42)	1.28 (1.16-1.42)	1.37 (1.20-1.56)
Life-threatening	1.11 (0.94-1.30)	1.15 (1.03-1.28)	1.07 (0.92-1.23)
Any serious (life-threatening or other)	1.07 (0.92-1.24)	1.08 (0.97-1.19)	1.06 (0.93-1.20)

Abbreviations: EVT, endovascular thrombectomy; IRF, inpatient rehabilitation facility; mRS, modified Rankin scale; OR, odds ratio; SNF, skilled nursing facility; TICI, thrombolysis in cerebral infarction.

[a] Odds of 1-point decrease in mRS.

ing that although alteplase treatment probably increases the risk of sICH after EVT in routine clinical practice, this does not translate to worsening in discharge disability or mortality. Alteplase or other thrombolytics may still have an important role in patients undergoing EVT for large vessel occlusion, particularly in patients where a delay in accessing the angiography suite is anticipated, such as when transfer to an EVT-capable site is required or when personnel are off-site. To fully define the role of alteplase or other lytics (eg, tenecteplase) in combination with EVT, more data from randomized clinical trials will be needed to narrow the margin of noninferiority or to prove superiority.

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primarily for research, data sharing agreements require an application process for other researchers to access the data. Interested researchers can submit proposals to utilize Get With The Guidelines for research purposes, including for validation purposes. Proposals can be submitted at http://www.heart.org/qualityresearch. Additional information regarding the statistical analysis plan and analytic code may also be available from DCRI upon request.

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