Time to Treatment With Intravenous Tissue Plasminogen Activator and Outcome From Acute Ischemic Stroke

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NTRAVENOUS (IV) TISSUE-TYPE PLAS-minogen activator (tPA) is a treatment of proven benefit for select patients with acute ischemic stroke as long as 4.5 hours after onset.[1,2] Available evidence suggests a strong influence of time to therapy on the magnitude of treatment benefit. In stroke animal models, time to reperfusion is a dominant determinant of final infarct volume.[3] In human patients, imaging studies show the volume of irreversibly injured tissue in acute cerebral ischemia expands rapidly over time, typically consuming 2 million additional neurons per minute until reperfusion is achieved.[4] Pooled data from IV tPA clinical trials indicate that therapeutic benefit of tPA is greatest when given very early after ischemic stroke

Importance Randomized clinical trials suggest the benefit of intravenous tissue-type plasminogen activator (tPA) in acute ischemic stroke is time dependent. However, modest sample sizes have limited characterization of the extent to which onset to treatment (OTT) time influences outcome; and the generalizability of findings to clinical practice is uncertain.

Objective To evaluate the degree to which OTT time is associated with outcome among patients with acute ischemic stroke treated with intraveneous tPA.

Design, Setting, and Patients Data were analyzed from 58 353 patients with acute ischemic stroke treated with tPA within 4.5 hours of symptom onset in 1395 hospitals participating in the Get With The Guidelines-Stroke Program, April 2003 to March 2012.

Main Outcomes and Measures Relationship between OTT time and in-hospital mortality, symptomatic intracranial hemorrhage, ambulatory status at discharge, and discharge destination.

Results Among the 58 353 tPA-treated patients, median age was 72 years, 50.3% were women, median OTT time was 144 minutes (interquartile range, 115-170), 9.3% (5404) had OTT time of 0 to 90 minutes, 77.2% (45 029) had OTT time of 91 to 180 minutes, and 13.6% (7920) had OTT time of 181 to 270 minutes. Median pretreatment National Institutes of Health Stroke Scale documented in 87.7% of patients was 11 (interquartile range, 6-17). Patient factors most strongly associated with shorter OTT included greater stroke severity (odds ratio [OR], 2.8; 95% CI, 2.5-3.1 per 5-point increase), arrival by ambulance (OR, 5.9; 95% CI, 4.5-7.3), and arrival during regular hours (OR, 4.6; 95% CI, 3.8-5.4). Overall, there were 5142 (8.8%) in-hospital deaths, 2873 (4.9%) patients had intracranial hemorrhage, 19 491 (33.4%) patients achieved independent ambulation at hospital discharge, and 22 541 (38.6%) patients were discharged to home. Faster OTT, in 15-minute increments, was associated with reduced in-hospital mortality (OR, 0.96; 95% CI, 0.95-0.98; $P < .001$), reduced symptomatic intracranial hemorrhage (OR, 0.96; 95% CI, 0.95-0.98; $P < .001$), increased achievement of independent ambulation at discharge (OR, 1.04; 95% CI, 1.03-1.05; $P < .001$), and increased discharge to home (OR, 1.03; 95% CI, 1.02-1.04; $P < .001$).

Conclusions and Relevance In a registry representing US clinical practice, earlier thrombolytic treatment was associated with reduced mortality and symptomatic intracranial hemorrhage, and higher rates of independent ambulation at discharge and discharge to home following acute ischemic stroke. These findings support intensive efforts to accelerate hospital presentation and thrombolytic treatment in patients with stroke.

JAMA. 2013;309(23):2480-2488   www.jama.com

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and declines throughout the first 4.5 hours after onset.[5,6]

The available trial data, however, have limitations in both precision and representativeness. The pooled tPA clinical trial data set is of moderate size (1850 tPA-treated patients from 8 trials), limiting precision in delineating the influence of time to treatment on magnitude of benefit.[5] The generalizability of clinical trial findings regarding time effects also needs to be confirmed in patients treated in routine clinical practice. Small observational studies of tPA in practice settings have been reported but were underpowered to interrogate time effects, with resulting variable results finding[7] or not finding[8,9] an independent effect of time to treatment on outcome after IV tPA.

To address the need for analysis of a large, practice-based data set, the US national Get With The Guidelines–Stroke (GWTG-Stroke) registry was analyzed to determine the association of time to treatment with outcomes from intravenous thrombolysis.

METHODS

GWTG–Stroke is a national registry launched by the American Heart Association and American Stroke Association to support continuous quality improvement of hospital systems of care for patients with stroke and transient ischemic attack (TIA).[10,11] Details of the design and conduct of the GWTG-Stroke Program have previously been described.[11] GWTG uses a web-based patient management tool (Outcome, Quintiles Company) to collect clinical data on consecutively admitted patients, to provide decision support, and to enable real-time online reporting features. After an initial pilot phase, the GWTG-Stroke Program was made available in April 2003 to any hospital in the United States.[10]

Data from hospitals that participated in the program any time between April 1, 2003, and April 1, 2012, were included in this analysis. Each participating hospital received either human research 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.

Outcome serves as the data collection and coordination center for GWTG. The Duke Clinical Research Institute was the data analysis center and it had an agreement to analyze the aggregate de-identified data for research purposes. The institutional review board of Duke University approved the study. Trained hospital personnel were instructed to ascertain consecutive patients admitted with the principal clinical diagnosis of acute stroke or TIA by prospective clinical identification, retrospective identification through the use of discharge codes, or a combination of both.

Patient data, including demographics, medical history, stroke onset time (last known well time), arrival time, in-hospital diagnostic studies, tPA treatment initiation time, tPA complications, other treatments and procedures, discharge treatments and counseling, in-hospital mortality, ambulatory status at discharge, and discharge destination were abstracted by trained hospital personnel. Stroke severity was measured by the National Institutes of Health Stroke Scale (NIHSS). Data on hospital-level characteristics (ie, bed size, academic or nonacademic status, annual stroke volume, and geographical region) were obtained from the American Hospital Association database. Whether the hospital had been certified by the Joint Commission as a primary stroke center and duration of participation in GWTG-Stroke were also determined. Admission staff, medical staff, or both recorded the patient's self-reported race/ethnicity, usually during registration. Prior studies have suggested differences in outcomes from acute ischemic stroke related to race/ethnicity.

Statistical Analysis

Patient demographic and clinical variables and hospital-level characteristics independently associated with onset to treatment (OTT) time analyzed as a continuous variable were identified with multivariable linear regression. Patient

demographic and clinical variables, hospital-level characteristics, and clinical outcomes were compared among patients treated in the 0 to 90-, 91 to 180-, and 181 to 270-minute OTT windows (time intervals selected because of their use in clinical trials and regulatory approvals). Percentages and mean standard deviations or median interquartile ranges (IQRs) were reported for categorical and continuous variables, respectively. The Pearson χ^2 test and Wilcoxon rank-sum tests were used to compare the categorical and continuous variables, respectively, between patients treated in the 3 OTT epochs.

The relationships between patient and hospital characteristics associated with OTT were further examined with multivariable logistic regression models. To account for within-hospital clustering, generalized estimating equations (GEEs) were used to generate both unadjusted and adjusted models. The variables used in the risk models were patient-level and hospital-level risk adjustors that were expected to be predictive of outcome, based on empirical analysis, prior literature, and clinical judgment.

Patient-level factors included age, race/ethnicity, sex, medical history (including atrial fibrillation, prosthetic heart valve, previous stroke or TIA, coronary heart disease or prior myocardial infarction, carotid stenosis, peripheral vascular disease, hypertension, dyslipidemia, diabetes, and current smoking), stroke severity (NIHSS), an age-by-NIHSS interaction term, arrival time during regular work hours (7 AM-PM Monday-Friday), arrival mode (ambulance, private vehicle), and select classes of vascular risk prevention medications prior to admission.

Hospital-level factors included hospital size, region, teaching status, rural location, certified primary stroke center status, average number of patients treated with tPA annually, and average number of annual stroke discharges. All variables were included in the predictive models without use of a stepwise or other formal variable selection process.

Figure 1. Distribution of Patients by 15-Minute Increment in Onset-to-Treatment Time Windows

Distribution of patients by OTT time intervals
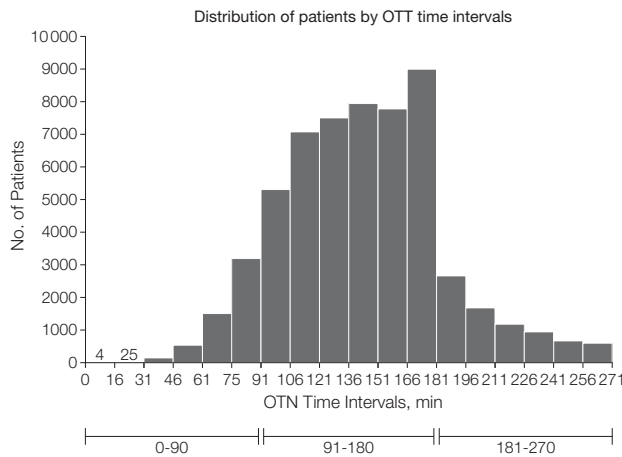
Both multivariable binary and ordinal logistic regression analyses were performed to explore the relationship between OTT and clinical outcome measures, including (1) in-hospital mortality, (2) discharge status (ordinal: home, acute rehabilitation, skilled nursing facility, or dead; and binary: home vs other), (3) and ambulatory status at discharge (ordinal: ambulatory without another person's assistance, ambulatory only with another person's assistance, nonambulatory, or dead; and binary: ambulatory without another person's assistance vs other). The relationships between OTT and the tPA complications of symptomatic intracranial hemorrhage within 36 hours, life-threatening or serious systemic hemorrhage within 36 hours, or any tPA complication within 36 hours were also analyzed. Data for select key variables were imputed as follows: sex (missing in 0.07%)—male; medical history (missing in 3.2%)—no; race/ethnicity (missing in 0.2%)—white; and arrival mode (missing in 5.7%)—emergency medical services. All P values were 2-sided and statistical significance was defined as P value of less than .05.

The associations of OTT as a continuous variable and outcomes were also analyzed by clinical subgroups of age (<70, ≥70), sex, race/ethnicity (non-Hispanic white, other), and pre-senting stroke severity (NIHSS 0-14, 15-42) with multiplicative interaction terms. P values for interaction were computed using WALD tests and analyzed with Bonferroni correction, with values of less than .013 considered significant.

For dichotomous outcomes, number needed to treat to benefit and number needed to treat to harm values were derived by dividing 100 by the absolute risk reduction. For ordinal outcomes, these values were derived using automated joint outcome table completion methods (automated random sampling and algorithmic). The methods were the same as described[12] except that table population occurred using only unidirectional changes in outcome, enabling fully automated calculation. Benefit per hundred and harm per hundred values were obtained by taking the inverse of number needed to treat to benefit and number needed to treat to harm values. All analyses were performed using SAS statistical software version 9.1 (SAS Institute Inc).

RESULTS

Between April 1, 2003, and March 31, 2012, data for 1 222 119 patients hospitalized with acute ischemic stroke were submitted to the registry by 1857 participating hospitals. For this analysis, we excluded data from sites with missing data on medical history in more than one-quarter of patients (43 sites, 34 287 patients), data from sites with fewer than 30 patients (166 sites, 1851 patients), cases with in-hospital onset of stroke (27 666 patients), and individuals treated with intra-arterial recanalization therapy (2622 patients) or experimental therapies (446). Of the remaining 1 154 247 patients from 1647 sites, 66 692 (5.8%) were treated with IV tPA. Of these, we further excluded patients with missing or imprecise onset, arrival, or treatment time data (3413); patients treated beyond 4.5 hours (1496) after onset of stroke; and patients with discharge destination data not indicative of functional status (3430) due to transfer to another acute hospital, leaving against medical advice, or missing.

The remaining 58 353 patients from 1395 sites treated after emergency department arrival with IV tPA within 4.5 hours of symptom onset, concordant with current national guideline recommendations,[1] constitute the study population. Among these patients (in whom median age was 72 years and 50.3% were women), the OTT time for IV tPA administration was mean (SD) 144 (41) minutes (median also 144 minutes; interquartile range [IQR], 115-170). There were 5404 (9.3%) patients with OTT time of 0 to 90 minutes (median, 80; IQR, 70-86), 45 029 (77.2%) with OTT time of 91 to 180 minutes (median, 140; IQR, 120-162), and 7920 (13.6%) with OTT time of 181 to 270 minutes (median, 208; IQR, 191-232). The distribution of OTT times is shown in **FIGURE 1**.

Patient-level and hospital-level characteristics of patients for each of the 3 time epochs are shown in **TABLE 1**. Patients with OTT times of 0 to 90 minutes were slightly more often men and slightly less often black. Patients with OTT times of 0 to 90 minutes were substantially more likely to arrive during regular hours (Monday-Friday, 7 AM-5 PM). Patients with later OTT times of 181 to 270 minutes were less likely to arrive by emergency medical service transport than patients treated earlier.

The pretreatment NIHSS was documented in 87.7% of patients. Among those patients, the mean (SD) NIHSS was highest in the 0 to 90-minute OTT group (13.2 [7.2]), intermediate in the 91 to 180-minute OTT group (12.5 [7.3]), and lowest in the 181 to 270-minute group (11.0 [7.3]).

Patient- and hospital-level factors independently associated with earlier OTT times are shown in TABLE 2. The most powerful characteristics indepen-

Table 1. Characteristics of Ischemic Stroke Patients With Onset-to-Treatment Times

	Onset to Treatment Times, min, %			P Value	Standardized Difference[a]	
	0-90 (n = 5404)	91-180 (n = 45 029)	181-270 (n = 7920)		0-90 vs 181-270	91-180 vs 181-270
Patient Characteristics						
Age, mean (SD), y	69.2 (14.7)	71.0 (14.8)	68.1 (15.0)	<.001	7.31	16.64
Female, sex	47.1	5.7	50.2	.006	6.17	1.02
Race/ethnicity						
White, non-Hispanic	71.9	73.9	70.9	<.001	2.18	6.69
Black	13.0	13.3	15.3	<.001	6.69	5.77
Hispanic	7.4	6.3	7.1	<.001	1.01	3.36
Other	7.7	6.5	6.7	<.001	4.25	0.53
Arrival on hours (vs off hours)[b]	52.7	46.4	43.0	<.001	19.4	6.81
Arrival by emergency medical services	78.7	81.3	71.4	<.001	16.9	23.54
NIHSS, median (IQR)	12.0 (7.0-18.0)	11.0 (6.0-18.0)	9.0 (5.0-16.0)	<.001	30.20	20.05
0-9	32.1	36.2	44.9	<.001	26.38	17.74
10-14	20.5	19.3	17.1	<.001	8.52	5.60
15-20	21.9	18.8	15.2	<.001	17.14	9.41
21-42	14.7	13.3	10.4	<.001	12.90	8.75
Not documented	10.8	12.5	12.4	<.001	4.70	0.48
Medical history						
Atrial fibrillation/flutter	21.6	23.6	18.2	<.001	8.75	13.32
Carotid stenosis	3.2	3.1	2.7	.04	3.31	2.75
Coronary artery disease/prior myocardial infarction	25.9	27.7	24.2	.001	3.79	7.90
Diabetes mellitus	22.4	25.5	26.8	<.001	10.12	3.05
Dyslipidemia	39.2	4.0	39.3	.80	0.13	1.59
Hypertension	72.6	75.0	72.9	.57	0.80	4.75
Prosthetic heart valve	1.1	1.2	1.3	.41	1.35	0.93
Peripheral vascular disease	3.4	3.7	3.7	.45	1.55	0.23
Smoker	19.4	18.8	20.4	.04	2.53	4.11
Previous stroke/transient ischemic attack	20.7	25.0	24.6	<.001	9.40	0.79
Length of stay, median, (IQR)	5 (3-7)	5 (3-8)	5 (3-7)	.02	2.04	1.61
Hospital Characteristics						
Annual volume of ischemic stroke admissions, median (IQR)	198 (139-304)	211 (146-312)	209 (141-307)	.48	3.55	3.29
Annual volume of tissue-type plasminogen activator administration, median (IQR)	16 (9-25)	15 (9-24)	15 (9-23)	<.001	7.05	0.59
Hospital size, median No. of beds (IQR)	360 (261-553)	380 (273-567)	384 (273-586)	<.001	7.74	1.45
The Joint Commission primary stroke center	53.7	55.8	53.6	.36	0.16	4.40
Academic hospital	54.0	58.1	56.3	.02	4.66	3.69
Rural location	2.7	2.7	3.2	.06	2.73	2.81
Hospital region						
West	24.2	2.6	20.1	<.001	9.88	1.37
South	30.7	34.7	35.9	<.001	11.01	2.41
Midwest	17.1	18.0	21.4	<.001	10.73	8.60
Northeast	28.0	26.7	22.7	<.001	12.24	9.32

Abbreviations: IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale.
[a] Calculated as the difference in means or proportions divided by a pooled estimate of the SD. A standardized difference greater than 10 is typically considered meaningful.
[b] On hours were 7 AM to 5 PM.

Table 2. Patient- and Hospital-Level Characteristics Independently Associated With Earlier Onset-to-Treatment Time Within the 0- to 270-Minute Time Period (Multivariable Analysis)[a]

Patient Characteristics	OTT Time, Mean (95% CI), min	Minutes Faster (95% CI)[b]	P Value
National Institutes of Health Stroke scale (per 5-point increase)		2.8 (2.5 to 3.1)	<.001
Arrival mode			
EMS	142.6 (142.2 to 143.0)	5.9 (4.5 to 7.3)	<.001
No EMS	151.1 (150.0 to 152.2)	0 [Reference]	
Arrival timeframe			
During on hours	141.5 (141.0 to 142.0)	4.6 (3.8 to 5.4)	<.001
During off hours	145.9 (145.4 to 146.4)	0 [Reference]	
Medical history			
Prior stroke/TIA	146.0 (145.3 to 146.7)	−3.0 (−2.1 to −3.9)	<.001
No prior stroke/TIA	143.2 (142.8 to 143.6)	0 [Reference]	
Diabetes	146.2 (145.5 to 146.9)	−1.8 (−0.4 to −3.1)	.009
No diabetes	143.1 (142.7 to 143.5)	0 [Reference]	
Peripheral vascular disease	146.0 (144.2 to 147.9)	−2.5 (−0.5 to −4.4)	.14
No peripheral vascular disease	143.8 (143.4 to 144.1)	0 [Reference]	
Carotid stenosis	142.5 (140.5 to 144.6)	2.4 (0.1 to 4.7)	.04
No carotid stenosis	143.9 (143.5 to 144.3)	0 [Reference]	
Taking diabetes medications prior to onset	146.5 (145.6 to 147.3)	−1.8 (−0.4 to −3.2)	.01
No diabetes medications prior to onset	143.3 (142.9 to 143.7)	0 [Reference]	
Female sex	144.4 (143.9 to 144.9)	−1.9 (−1.2 to −2.7)	.045
Male sex	143.3 (142.8 to 143.8)	0 [Reference]	
Age, per 5-y increase		−0.15 (−0.30 to 0.003)	.05
Hospital Characteristics			
Ischemic stroke admissions/year (per 50-cases increase)		−1.2 (−0.7 to −1.7)	<.001
IV tPA cases/year (per 5-cases increase)		1.6 (1.1 to 2.2)	<.001
Hospital region			.002
Northeast	142.7 (142.0 to 143.4)	0 [Reference]	
South	146.2 (145.4 to 147.0)	−3.1 (−1.2 to −5.0)	.001
Midwest	145.5 (144.9 to 146.1)	−3.2 (−1.2 to −5.4)	.003
West	140.4 (139.6 to 141.2)	0.3 (−2.0 to −0.3)	.79

Abbreviations: EMS, emergency medical services; IV, intravenous; TIA, transient ischemic attack; tPA, tissue-type plasminogen activator.
[a]Candidate variables not independently associated with early arrival: race/ethnicity; medical history of atrial fibrillation, coronary artery disease/prior myocardial infarction, carotid stenosis, dyslipidemia, hypertension, prosthetic heart valve, smoker, taking antithrombotics, antihypertensives at stroke onset, cholesterol reducers at stroke onset; teaching hospital; Joint Commission–certified primary stroke center; rural hospital; and hospital size.
[b]Values are the β coefficients from the generalized estimating equation linear regression model, which represent minutes. Negative values indicate that the factor is associated with slower arrival.

dently associated with earlier OTT were higher NIHSS score, arrival by emergency medical services, arrival during regular hours, absences of a history of prior stroke and TIA, a higher annual hospital volume of tPA cases, and a lower annual hospital volume of ischemic stroke admissions. Other factors independently associated with earlier OTT included male sex, absence of a history of diabetes or peripheral vascular disease, and location in the North-

east or Western regions of the United States. Race/ethnicity, hospital academic status, and hospital rural vs urban location were not independently associated with earlier OTT.

Overall, there were 5142 (8.8%) in-hospital deaths, 2873 (4.9%) patients had intracranial hemorrhage, 19 491 (33.4%) patients achieved independent ambulation at hospital discharge, and 22 541 (38.6%) patients were discharged to home.

TABLE 3 provides unadjusted and adjusted odds ratios (ORs) for the binary outcomes, with OTT as a continuous and as a categorical variable. More rapid tPA therapy was associated with reduced mortality, fewer symptomatic intracranial hemorrhages, more frequent independent ambulation at discharge, and more frequent discharge to home. For every 15-minute–faster interval of treatment, mortality was less likely to occur (OR, 0.96; 95% CI, 0.95-0.98), symptomatic intracranial hemorrhage was less likely to occur (OR, 0.96; 95% CI, 0.95-0.98), independence in ambulation at discharge was more likely to occur (OR, 1.04; 95% CI, 1.03-1.05), and discharge to home was more likely to occur (OR, 1.03; 95% CI, 1.02-1.04).

For patients treated in the first 90 minutes, compared with 181-270 minutes after onset, mortality was less likely to occur (OR, 0.74; 95% CI, 0.64-0.86), symptomatic intracranial hemorrhage was less likely to occur (OR, 0.72; 95% CI, 0.60-0.87), independence in ambulation at discharge was more likely to occur (OR, 1.51; 95% CI, 1.35-1.69), and discharge to home was more likely to occur (OR, 1.33; 95% CI, 1.20-1.46).

Similarly, outcomes across the entire ordinal range of ambulatory status at discharge and of discharge destination were independently linked to OTT (FIGURE 2; and eTable 1 available at www.jama.com). For every 15-minute–faster interval of treatment, better ambulation status at discharge was more likely to occur (OR, 1.04; 95% CI, 1.03-1.05). For every 15-minute–faster interval of treatment, discharge to a more independent destination environment was more likely to occur (OR, 1.03; 95% CI, 1.03-1.04). Improved ordinal outcomes with more timely treatment were also seen when OTT time was analyzed as 90-minute epochs.

In sensitivity analyses, these associations were robust when evaluated in the subset of patients from 2009-2012, in whom additional informa-

tion was collected on physiologic variables, including pretreatment blood pressure and serum glucose (n = 24 470, eTable 2). These associations were still present but attenuated in the sample of all tPA-treated patients (those with and without a documented NIHSS, n = 58 358), in which adjustment for baseline stroke severity could not be performed (eTable 3). The associations of shorter OTT times with improved outcomes were consistent across clinical subgroups of age, sex, race/ethnicity, and presenting stroke severity (eTable 4).

Table 3. Binary Clinical Outcomes in Patients With Documented National Institutes of Health Stroke Scale Scores With Onset-to-Treatment Times 0 to 90, 91 to 180, and 181 to 270 Minutes (n = 51 158)

	Outcome, No. of Patients (%)			Unadjusted OR (95% CI)				Adjusted OR (95% CI)			
	0-90 n=4818	91-180 n=39398	181-270 n=6942	OTT per 15-min Decrease	0-90 vs 91-180	0-90 vs 181-270	91-180 vs 181-270	OTT per 15-min Decrease	0-90 vs 91-180	0-90 vs 181-270	91-180 vs 181-270
In-hospital mortality	373 (7.7)	3425 (8.7)	558 (8.0)	1.00 (0.99-1.01)	0.90 (0.80-1.01)	0.97 (0.85-1.11)	1.08 (0.98-1.19)	0.96 (0.95-0.98)	0.86 (0.76-0.97)	0.74 (0.64-0.86)	0.86 (0.78-0.96)
P value				.58	.06	.68	.11	<.001	.02	.001	.005
tPA complications	463 (9.6)	4150 (10.5)	814 (11.7)	0.99 (0.98-1.00)	0.91 (0.83-1.01)	0.85 (0.75-0.96)	0.93 (0.85-1.01)	0.97 (0.96-0.98)	0.89 (0.79-1.00)	0.74 (0.64-0.86)	0.84 (0.76-0.92)
P value				.01	.08	.008	.09	<.001	.05	.001	.003
Symptomatic intracranial hemorrhage	193 (4.0)	1965 (5.0)	351 (5.1)	0.98 (0.97-0.99)	0.82 (0.71-0.95)	0.82 (0.69-0.97)	0.99 (0.89-1.12)	0.96 (0.95-0.98)	0.83 (0.71-0.97)	0.72 (0.60-0.87)	0.87 (0.76-0.99)
P value				.004	.01	.02	.93	<.001	.02	.005	.03
Serious systemic hemorrhage	40 (0.8)	432 (1.1)	79 (1.1)	0.98 (0.95-1.01)	0.76 (0.54-1.05)	0.73 (0.50-1.07)	0.96 (0.76-1.23)	0.96 (0.93-0.99)	0.79 (0.55-1.13)	0.66 (0.43-1.00)	0.83 (0.63-1.10)
P value				.17	.10	.11	.77	.02	.20	.05	.19
Ambulation independent at discharge	1706 (35.4)	13 132 (33.3)	2348 (33.8)	1.00 (0.99-1.01)	1.10 (1.03-1.17)	1.04 (0.95-1.13)	0.94 (0.89-1.00)	1.04 (1.03-1.05)	1.19 (1.10-1.29)	1.51 (1.35-1.69)	1.27 (1.18-1.38)
P value				.77	.005	.42	.05	<.001	<.001	<.001	<.001
Discharge home	1928 (40.0)	15 072 (38.3)	2907 (41.9)	0.99 (0.98-0.99)	1.05 (0.99-1.12)	0.92 (0.86-1.00)	0.88 (0.83-0.93)	1.03 (1.02-1.04)	1.09 (1.01-1.18)	1.33 (1.20-1.46)	1.21 (1.13-1.30)
P value				.005	.09	.04	<.001	<.001	.02	<.001	<.001

Abbreviations: OR, odds ratio; OTT, onset to treatment; tPA, tissue-type plasminogen activator.

Figure 2. Ordinal Outcomes for Onset-to-Treatment Time Windows for Ambulatory Status at Discharge and Discharge Destination, Adjusted for Baseline Covariates
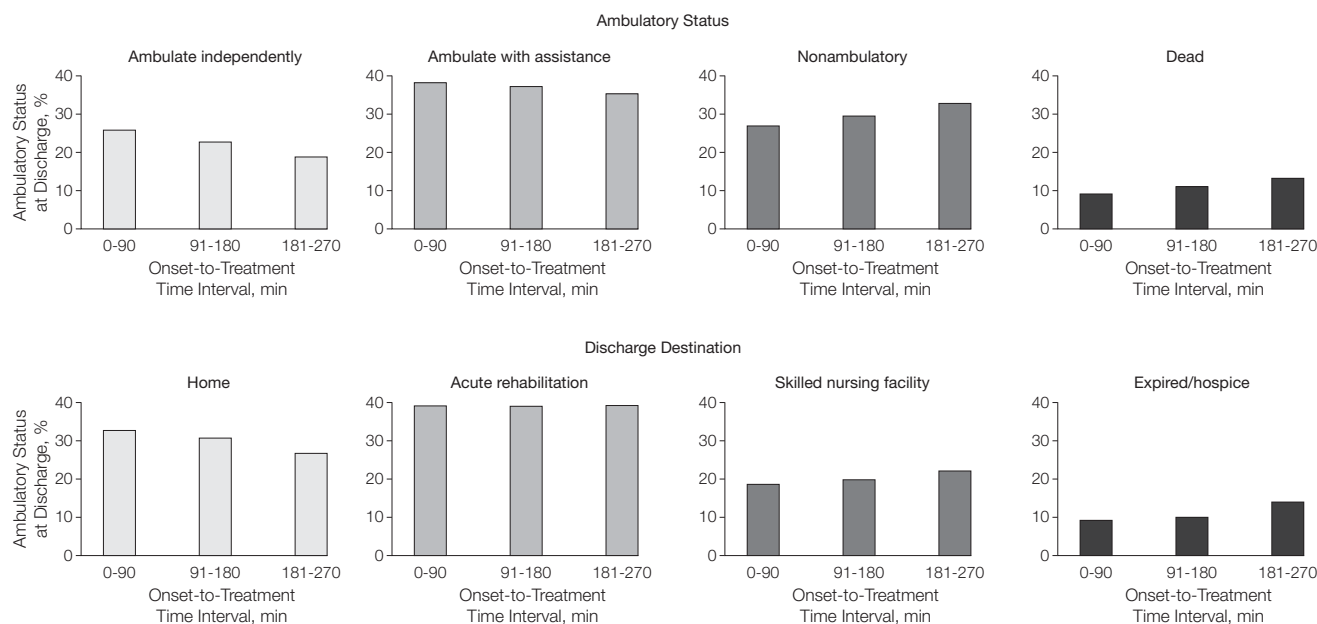
There were 5404 patients in the 0- to 90-minute time window, 45 029 in the 91- to 180-minute segment, and 7920 in the 181- to 270-minute time window. SNF indicates skilled nursing facility.

The number needed to treat and benefit per 1000 treated patients values for treatment in earlier vs later OTT epochs are shown in eTable 5. Among 1000 treated patients, every 15-minute–faster acceleration of treatment was associated with 18 more patients having improved ambulation at discharge (including 8 more having fully independent ambulation) and 13 more patients being discharged to a more independent environment (including 7 more being discharged to home) and 4 fewer patients dying prior to discharge.

DISCUSSION

In this study of more than 50 000 patients with acute ischemic stroke treated with IV thrombolysis in routine clinical practice there was an association of earlier treatment with outcome. Treatment started more rapidly after symptom onset was associated with reduced in-hospital mortality and symptomatic intracranial hemorrhage and increased achievement of independent ambulation by discharge and discharge to home.

These findings confirm and extend data regarding the relation between OTT time and good functional outcomes from formal clinical trials. The most recent analysis of pooled data from completed trials of IV tPA showed that earlier treatment is associated with greater magnitude of benefit.[5] However, the precision of estimates of time effects was limited by the modest sample size of 1850 patients treated with tPA, and the generalizability of the findings to conventional clinical practice among more diverse patients and hospitals was uncertain. The population of tPA-treated patients in the current study is more than 30 times larger than the pooled clinical trial sample and represents data from a more diverse set of hospitals, including more than one-quarter of all hospitals with an emergency department treating adults in the United States.

The magnitude of the association of OTT with improved functional outcomes after thrombolysis observed in this study is consonant with that in the formal clinical trials. In an analysis of the pooled IV tPA trial data set, for every 100 patients treated with IV therapy, with every 10-minute delay in the start of thrombolytic infusion within the 1- to 3-hour treatment time, 0.9 fewer patients had an improved final disability outcome.[13] Similarly, the current study found that for every 100 patients treated, for every 10-minute delay in patients treated within 4.5 hours of onset, 1.2 fewer had better ambulation at discharge and 0.8 fewer had a more independent discharge destination.

Our data also provide new findings regarding the relation between OTT with IV tPA and adverse outcomes from acute ischemic stroke. In the analysis of pooled clinical trial data, evidence of a relationship of earlier OTT and mortality was marginal, with a P value of .04 for OTT as a continuous variable and nonsignificant findings for the individual time epochs of 0 to 90, 91 to 180, and 181 to 270 minutes.[5] In the current larger study, the association of earlier OTT and reduced mortality was demonstrated more convincingly, both for OTT as a continuous variable ($P < .001$) and over each of the 90-minute treatment epochs. In the pooled clinical trial analysis, an interaction of OTT with large parenchymal hemorrhagic transformation was not detected.[5] With our larger sample size, we were able to identify that earlier OTT was clearly associated with a reduction in the occurrence of symptomatic intracranial hemorrhage. Our findings extend to the under 4.5-hour period those from the Safe Implementation of Treatments in Stroke registry of increased risk of symptomatic intracranial hemorrhage with tPA treatment beyond 4.5 hours.[14]

Our study also expands on prior studies of tPA in clinical practice that have analyzed OTT. These studies provided conflicting results, some reporting that OTT was independently related to outcomes[7] and some reporting that OTT was not.[8,9] These mixed findings likely reflect limits of study power because the sample sizes in prior practice reports were 200 to 900 patients, 2 orders of magnitude less than in the current study. With the much larger cohort in this study, we were able to detect an association of OTT that was sizeable in magnitude.

This analysis differs from the trial data set as well in considering time differences among IV tPA–treated patients rather than between IV tPA– and placebo-treated patients. Consequently, this study analyzes the temporal effect of delaying TPA treatment while the pooled analysis describes the temporal effect of foregoing TPA treatment. Considering the ORs for OTT as a continuous variable, every 15-minute acceleration in start of tPA after onset was associated with patients having a 4% greater odds of walking independently at discharge, a 3% greater odds of being discharged to home rather than an institution, a 4% lower odds of death before discharge, and a 4% lower odds of experiencing symptomatic hemorrhagic transformation of infarct. The current study reinforces and is consistent with findings from a prior analysis of the GWTG-Stroke population, demonstrating improved mortality and functional outcomes with accelerated "door-to-needle" times for initiation of IV tPA after hospital arrival.[15]

In this study, the association of OTT and clinical outcomes was greatest in analyses that included adjustment for baseline stroke severity, and was attenuated in analyses adjusted only for demographic and other variables. Since initial deficit severity is a dominant predictor of outcome from acute ischemic stroke, analyses controlling for presenting severity have substantially greater power to delineate relations between process of care variables such as OTT and outcome.[16] Stroke deficit severity is an important confounder of unadjusted analyses of OTT and outcome because it increases the likelihood of both earlier presentation and worse final outcome.

The findings from this study emphasize the importance of worldwide efforts to shorten onset to lytic treat-

ment times for acute ischemic stroke. Several interventions have been demonstrated to improve public knowledge of warning signs of a potential stroke in progress and readiness to activate the emergency medical system soon after onset including public service and paid media advertising[17]; dissemination of simple mnemonics such as the Face Arm Speech Test (FAST)[18]; education of school children[19]; and culturally appropriate, multifaceted interventions.[20]

Regional systems of stroke care accelerate treatment, in which prehospital personnel are trained to recognize stroke using validated screening tools, deliver patients at highest transport priority directly to certified stroke centers capable of delivering lytic therapy reliably and rapidly, and provide prearrival notification from the out-of-hospital setting to activate stroke teams and permit readying of computed tomographic or magnetic resonance imaging scanners for immediate use upon patient arrival.[21-23]

Multipronged quality improvement programs, such as the Target: Stroke initiative, have demonstrated success in accelerating the time from patient arrival at the hospital to start of lytic therapy, with components including written protocols for acute triage and patient flow; single call systems to activate all stroke team members; computed tomography or magnetic resonance imaging scanner clearance as soon as the center is made aware of an incoming patient; location of the computed tomography scanner in the emergency department; storage and rapid access to thrombolytic drugs in the emergency department; collaboration in developing treatment pathways among physicians, nurses, pharmacists, and technologists from emergency medicine, neurology, and radiology departments; and continuous data collection to drive iterative system improvement.[24-27]

Limitations

Several potential limitations should be considered in interpreting the results of this study. The data reported are dependent on the accuracy and completeness of abstraction from the medical record. To optimize data quality, the GWTG-Stroke Program includes detailed training of site chart abstractors, standardized case definitions and coding instructions, predefined logic and range checks on data fields at data entry, audit trails, and regular data quality reports for all sites.[11] Source documentation audits at the individual state and site levels have shown high data quality.[28] Participating hospitals are instructed to include all consecutive admissions for ischemic stroke. Although the potential exists for selection bias, comparison of entered patients with national Medicare data sets has confirmed the representativeness of the GWTG-Stroke population.[29] Physiologic determinants of outcome, including presenting blood pressure and serum glucose levels, were not analyzed in the main models but findings for OTT times and outcomes were similar in models confined to the 24 470 patients accrued after addition of these variables to the registry. Residual measured and unmeasured confounding variables may have influenced some or all of the findings. Finally, the outcomes reported in this study are short-term outcomes. No data on postdischarge stroke-related outcomes are currently collected in the GWTG-Stroke Program so the longer-term effect of OTT times on functional outcomes could not be directly investigated. However, studies have shown that functional status at time of acute hospital discharge, including ambulatory status and discharge destination, correlates strongly with long-term global disability outcomes at 3 months.[30,31]

CONCLUSIONS

In a registry representing national US clinical practice, earlier thrombolytic treatment of patients with acute ischemic stroke was associated with more frequent independent ambulation at discharge and discharge to home, and with reduced mortality and symptomatic intracranial hemorrhage. These findings support intensive efforts to accelerate patient presentation and to streamline regional and hospital systems of acute stroke care to compress OTT times.

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