Why are acute ischemic stroke patients not receiving IV tPA?
Results from a national registry

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ABSTRACT

Objective: To determine patient and hospital characteristics associated with not providing IV tissue plasminogen activator (tPA) to eligible patients with acute ischemic stroke (AIS) in clinical practice.

Methods: We performed a retrospective cohort study of patients with AIS arriving within 2 hours of onset to hospitals participating in Get With The Guidelines–Stroke without documented contraindications to IV tPA from April 2003 through December 2011, comparing those who received tPA to those who did not. Multivariable generalized estimating equation logistic regression modeling identified factors associated with not receiving tPA.

Results: Of 61,698 eligible patients with AIS presenting within 2 hours of onset (median age 73 years, 51% female, 74% non-Hispanic white, median NIH Stroke Scale score 11, interquartile range 6–18), 15,282 (25%) were not treated with tPA within 3 hours. Failure to give tPA decreased over time from 55% in 2003 to 2005 to 18% in 2010 to 2011 ($p < 0.0001$). After adjustment for all covariates, including stroke severity, factors associated with failure to treat included older age, female sex, nonwhite race, diabetes mellitus, prior stroke, atrial fibrillation, prosthetic heart valve, NIH Stroke Scale score <5, arrival off-hours and not via emergency medical services, longer onset-to-arrival and door-to-CT times, earlier calendar year, and arrival at rural, nonteaching, non–stroke center hospitals located in the South or Midwest.

Conclusions: Overall, about one-quarter of eligible patients with AIS presenting within 2 hours of stroke onset failed to receive tPA treatment. Thrombolysis has improved dramatically over time and is strongly associated with stroke center certification. Additionally, some groups, including older patients, milder strokes, women, and minorities, may be undertreated. *Neurology*® 2016;87:1565–1574

GLOSSARY

AIS = acute ischemic stroke; **CAD** = coronary artery disease; **EMS** = emergency medical services; **GWTG** = Get With The Guidelines; **IST3** = International Stroke Trial 3; **NIHSS** = NIH Stroke Scale; **TPA** = tissue plasminogen activator.

IV tissue plasminogen activator (tPA) has been demonstrated to improve outcome in select patients with acute ischemic stroke (AIS), and numerous guidelines have promoted its use in the United States.[1–6] As a result, IV tPA use has increased dramatically over the past decade, yet approximately one-third of potentially eligible patients are not receiving treatment.[7,8] The factors associated with not treating otherwise eligible patients have not been well characterized in a large, national registry reflective of recent clinical practice. We hypothesized that a number of specific patient and hospital factors will be associated with a lower likelihood of treatment with tPA, some of which may be modifiable, leading to improved treatment rates in the future.

Get With The Guidelines (GWTG)–Stroke is an ongoing, voluntary, national registry and quality-improvement initiative. Since its inception in 2003, >1,800 hospitals have entered >2.5 million patient records into the GWTG-Stroke database, and prior reports have demonstrated that the registry is representative of the US population hospitalized for AIS.[8–11] Appropriate and efficient use of IV tPA for AIS is a major objective of the GWTG-Stroke initiative, and sites are expected to provide the rationale for nontreatment from a prespecified list of potential contraindications and warnings. We sought to better understand the patient and hospital characteristics associated with not using IV tPA in otherwise eligible patients.

METHODS Within the GWTG-Stroke dataset, we identified all patients who presented within 2 hours of onset of ischemic stroke and had no documented contraindications to thrombolysis, and we then compared patient- and hospital-level factors for patients who received tPA to those who did not receive tPA. Several previous publications have provided detailed descriptions of the GWTG-Stroke program.[12,13] In brief, GWTG-Stroke is a national stroke quality-improvement program available to any hospital in the United States since the beginning in April 2003. Participating hospitals are instructed to collect deidentified patient-level data on clinical and demographic characteristics, diagnostic testing, treatments, the reason for not treating with tPA, adherence to quality measures, and in-hospital outcomes and discharge disposition in consecutive patients hospitalized with stroke. Trained hospital personnel identify patients admitted with stroke prospectively by clinical diagnosis or retrospectively using *International Classification of Diseases, Ninth Revision* discharge codes. The eligibility of each acute stroke is confirmed at chart review before abstraction, and the specificity of included patients and data accuracy have been demonstrated to be high.[14] After abstraction by trained personnel at each hospital, deidentified patient data are entered into the GWTG-Stroke database with the use of a web-based patient management tool (Outcome, A Quintiles Company, Cambridge, MA). Data elements abstracted include patient demographics, medical history and comorbidities, initial brain imaging findings, in-hospital treatment and events, discharge disposition, ambulatory status, and mortality.

Standard protocol approvals, registrations, and patient consents. All participating institutions were required to comply with local regulatory and privacy guidelines and to secure institutional review board approval if required. Because data were used primarily at the local site for quality improvement, sites were granted a waiver of informed consent under the common rule. The Duke Clinical Research Institute (Durham, NC) served as the data analysis center, and institutional review board approval was granted to analyze aggregate deidentified data for research purposes.

Data. The GWTG-Stroke dataset was queried to identify all patients admitted with AIS who arrived within 2 hours from the time they were last known well and had no documented contraindications to IV tPA. Over a period extending from April 2003 through December 2011, GWTG-Stroke enrolled 1,138,157 patients admitted with AIS to 1,783 hospitals. In 2009, the American Heart Association/American Stroke Association published a scientific advisory supporting the use of tPA within the 3- to 4.5-hour window, and GWTG-Stroke disseminated this information to participating hospitals and added a new quality measure to monitor patients who presented within 3.5 hours from the onset of stroke symptoms and were treated by 4.5 hours.[15] For this analysis, we excluded the 3,422 patients who arrived within 2 hours and were treated with tPA after 3 hours because we were interested in identifying factors associated with failure to treat, not delayed treatment. We also excluded patients with stroke occurring after hospital admission (26,008); patients treated with investigational use of thrombolytics (1,632); those with uncertain time of onset to arrival (598,611) or time of tPA treatment (527); those with time of onset to arrival >2 hours (304,898); patients treated with IV tPA at a non-GWTG hospital before transfer (16,973); patients treated at a site with <10 patients per year (809); and those with missing door-to-CT time, door-to-CT time beyond 2 hours, or door-to-CT-time after tPA treatment (7,558).

Statistical analyses. Descriptive statistics, including frequency numbers and percentages for categorical variables and medians with interquartile ranges describing the 25th and 75th percentiles for continuous variables, were generated. The relationships between individual patient and hospital characteristics and nontreatment with IV tPA were assessed in univariable analyses with the Pearson χ^2 test for categorical variables and Wilcoxon rank-sum test for continuous/ordinal variables. To determine independent factors associated with tPA nontreatment, we performed multivariable logistic regression modeling using a generalized estimating equation to account for hospital clustering. All hospital-level factors were analyzed at the patient level. Because the NIH Stroke Scale (NIHSS) score was missing in a large number of cases (23.9% overall), separate models were constructed with all patients (i.e., including those without NIHSS score) and in only those with NIHSS score documented, given its importance in quantifying stroke severity and predicting outcomes.[16] The functional form of continuous variables with tPA treatment was explored with restricted cubic spline plots. The models incorporated all the covariates described in table e-1 at Neurology.org. Patient variables other than NIHSS had <7% missing values and were imputed to the most common category. Models excluded observations with missing hospital characteristics (<2%). For the models that included NIHSS score, we used a categorical variable (0–4, 5–9, 10–14, 15–20, 21+). All hypothesis tests are 2 sided, with values of $p < 0.05$ considered statistically significant. All analyses were conducted by the GWTG-Stroke statistical analysis center at the Duke Clinical Research Institute (Durham, NC) with SAS software version 9.3 (SAS Institute, Cary, NC).

RESULTS Among the 177,719 patients who arrived within 2 hours of onset and met all other inclusion criteria, 116,021 (65%) had a documented contraindication to or warning for tPA use. As described in table 1, the most common documented reasons for not treating with tPA were mild or rapidly improving symptoms (51%); advanced age (7%); patient or family refusal (6%); CT findings of major infarct signs, intracerebral hemorrhage, or subarachnoid hemorrhage (6%); and platelets <100,000, partial thromboplastin time >40 seconds, international normalized ratio >1.7, or bleeding diathesis (5%). Patient or family refusal did not differ between teaching and nonteaching hospitals, rural and urban locations, hospital sizes,

Table 1	Documented contraindications and warnings for patients who arrived within 2 hours and did not receive IV tPA within 3 hours	
		Overall (N = 116,021), n (%)
Contraindications		
Any contraindications documented		34,564 (25.5)
SBP >185 mm Hg/DBP >110 mm Hg		4,857 (3.6)
Seizure		3,699 (2.7)
Surgery or major trauma <15 d		3,632 (2.7)
Head surgery/trauma/stroke <3 mo		5,182 (3.8)
History of ICH, brain aneurysm, tumor		3,419 (2.5)
Active internal bleeding <22 d		1,817 (1.3)
Platelets <100,000, PTT >40 s, INR >1.7, bleeding diathesis		7,229 (5.3)
Suspicion SAH		438 (0.3)
CT findings for ICH, SAH, infarct		7,497 (5.5)
Warnings		
Any warnings documented		92,957 (68.5)
Stroke too severe (NIHSS score >22)		5,047 (3.7)
Glucose <50 or >400 mmol/L		430 (0.3)
Left-sided heart thrombus		77 (0.1)
Increased risk of bleeding		3,512 (2.6)
Pregnancy		20 (0.01)
Advanced age		9,787 (7.2)
Rapid improvement or mild stroke		69,279 (51.4)
Life expectancy <1 y or severe comorbid illness		2,329 (1.7)
Patient or family refusal		8,500 (6.3)
Eligibility not clear		4,005 (3.0)
IV or intra-arterial tPA outside hospital		37 (0.03)
MI <3 mo		62 (0.05)

Abbreviations: DBP = diastolic blood pressure; ICH = intracerebral hemorrhage; INR = international normalized ratio; MI = myocardial infarction; PTT = partial thromboplastin time; SAH = subarachnoid hemorrhage; SBP = systolic blood pressure; tPA = tissue plasminogen activator.

with those treated with tPA, patients not treated with tPA were older, white, and female. They more often had vascular risk factors, including coronary artery disease (CAD), carotid stenosis, diabetes mellitus, hypertension, peripheral vascular disease, a prosthetic heart valve, and prior stroke/TIA, although they were less likely to have atrial fibrillation and to be a smoker. They arrived less frequently by emergency medical services (EMS), experienced a longer delay in door-to-CT time, and more often had an undocumented NIHSS score, and, when measured, their median NIHSS score was lower. Compared with those treated with tPA in the study period, patients not treated with tPA presented to hospitals that had a smaller number of beds, were less often teaching hospitals or Joint Commission–certified primary stroke centers, were more often in the South or Midwest, documented the NIHSS score less frequently overall, and had fewer annual ischemic stroke admissions.

After full adjustment for all covariates, there was no longer an association between white race and higher odds of not being treated; instead, black race and other race were associated with higher odds of not being treated (table 3). Additional patient-specific factors associated with nontreatment included older age, history of carotid stenosis, peripheral vascular disease, diabetes mellitus, CAD/myocardial infarction, stroke/TIA, and presence of a prosthetic heart valve. Method and timing of hospital arrival also were important, with patients with admission during an earlier calendar year, non-EMS arrival, arrival after work hours, or arrival at a longer duration after stroke onset (i.e., last known well time) having lower odds of receiving IV tPA. Several hospital characteristics were also independently associated with not providing tPA at the patient level. Hospitals that documented the NIHSS score less frequently in all patients, were not Joint Commission primary stroke centers or teaching hospitals, had lower annualized volumes of stroke patients, were located in the South or Midwest, or were located in rural locations were less likely to treat eligible patients with IV tPA. A sensitivity analysis using multiple imputation to account for missing data (excluding NIHSS score) found no meaningful differences in these results (table e-2).

Patients who had a documented NIHSS score had notable differences compared to those who did not have one documented (table e-3). When the model was confined to the 73.5% of patients in whom NIHSS score had been documented, women and patients with atrial fibrillation were less likely to receive IV tPA, and smaller hospital size was no longer significant. Table 4 presents the adjusted odds of being treated with tPA across strata of stroke severity. Compared to those with mild stroke (NIHSS score 0–4), patients with an NIHSS score ≥5 were more likely to

regions of the country, or average annual volumes of stroke patients ($p > 0.05$ for each).

There were 61,698 patients from 1,564 sites eligible for the GWTG-Stroke achievement measure of IV recombinant t-PA arrive by 2 hours with treatment by 3 hours (i.e., patients who had an onset-to-arrival time of ≤120 minutes and did not have any documented IV tPA contraindication or warning), of whom 15,282 (25%) did not receive tPA while the remaining 46,416 (75%) received tPA within 3 hours of onset. Nonuse of tPA among eligible patients decreased over time from 55% in 2003 to 2005 to 18% in 2010 to 2011 (figure).
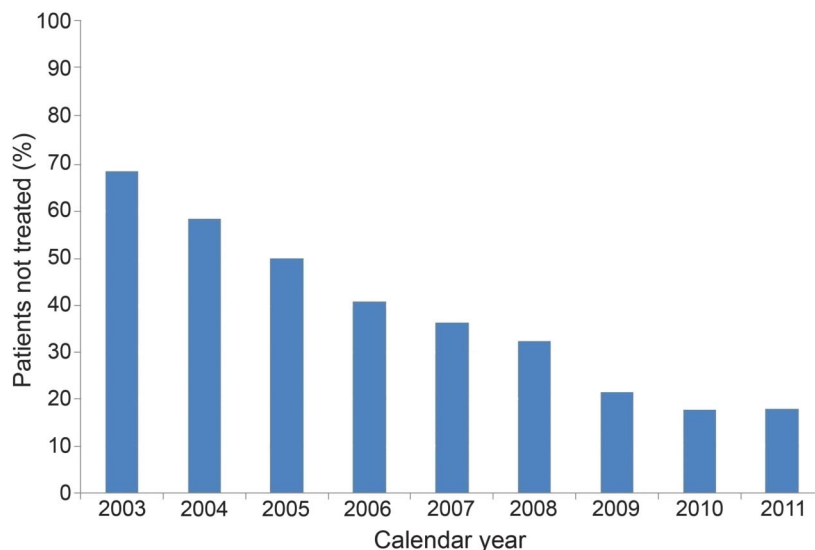
Table 2 presents the univariable analyses of patient and hospital characteristics of the cohort, overall and dichotomized by treatment with IV tPA. Compared

Figure Percentage of eligible acute ischemic stroke patients who did not receive IV tissue plasminogen activator, over time

receive treatment. Confining the analysis to patients with an NIHSS score ≥5 resulted in no meaningful changes to the findings (table e-4).

DISCUSSION As reported in prior studies, tPA treatment in GWTG-Stroke–participating hospitals has increased dramatically over time.[8,11] Nevertheless, even recently, up to 1 in 5 potentially eligible patients were not being treated. In this large cohort, several patient and hospital factors were independently associated with a lower likelihood of receiving IV tPA in eligible patients with AIS, many of which may be modifiable. As has been reported previously, treatment at a primary stroke center is one of the strongest predictors of tPA use.[17] Thus, to improve thrombolysis rates, continued development of systems of care for stroke should remain a high priority.

Underscoring a statement from the American Heart Association/American Stroke Association calling for an end to inequities in stroke care, we found that after adjustment for stroke severity, minorities and, to a lesser degree, women remained modestly more likely to not receive treatment when tPA eligible.[18] These findings are consistent with several prior publications including data from GWTG-Stroke.[19–26] Our current study includes more contemporary treatment data and more extensive adjustment for potential known confounders than many prior studies.

In addition to race and sex differences, we found that older patients were less likely to receive tPA treatment despite having no documented contraindication. Again, these findings are consistent with prior analyses.[27,28] A recent survey of neurologists reported that 4 of 5 were less likely to administer IV tPA to patients with dementia, and many were less likely to

treat patients from nursing homes, with more severe strokes, or >80 years of age.[29] Although the benefit to older patients has been uncertain in the past because many were excluded from the early IV tPA trials, the International Stroke Trial 3 (IST3) and recent meta-analyses have demonstrated no upper age limit for benefit of IV tPA.[30–33]

Several other patient factors were associated with less treatment, including carotid stenosis, peripheral vascular disease, diabetes mellitus, CAD/myocardial infarction, stroke/TIA, and presence of a prosthetic heart valve. These represent opportunities for more targeted education to patients with these risk factors on the need for rapid medical attention and available treatment when stroke symptoms occur. Consistent with prior publications, we found that arrival during off-hours, at later times within 2 hours, or via other modes of transport other than via EMS reduced the odds of treatment.[17,18] Multiple hospital characteristics were also independently associated with not receiving tPA, including failure to routinely document the NIHSS score, not being a Joint Commission primary stroke center or a teaching hospital, having a lower annual volume of stroke cases, and being located in the South or Midwest.

This analysis also contributes the description of the prespecified contraindications and warnings that excluded patients from treatment. By far the most common reason cited, reported in more than half of the patients, was mild or rapidly improving symptoms. Among patients without a documented reason for not receiving tPA, mild stroke symptoms, defined as NIHSS score <5, were strongly associated with a lower likelihood of being treated. Prior studies have found that this is the most common reason given for

Table 2 Univariate analysis of patient and hospital characteristics overall and dichotomized by IV tPA treatment

	Overall (N = 61,698)	No IV tPA (n = 15,282)	Yes IV tPA (n = 46,416)	p Value
Demographics				
Age, median (IQR), y	73 (60-82)	74 (62-83)	72 (60-82)	<0.0001
Age >85 y, %	15.6	17.1	15.2	<0.0001
Female sex, %	50.6	52.2	50.1	<0.0001
Race (0.14% missing), %				
Other	12.4	11.0	13.0	<0.0001
Black	13.0	12.5	13.1	
White	74.5	76.4	73.9	
Admission information				
Admissions by year				
2003	767	480	287	<0.0001
2004	1,409	757	652	
2005	3,283	1,425	1,858	
2006	5,632	2,023	3,609	
2007	7,340	2,385	4,955	
2008	9,075	2,583	6,492	
2009	10,451	1,976	8,475	
2010	11,759	1,815	9,944	
2011	11,982	1,838	10,144	
Arrival weekdays 7 AM-5 PM, %	51.2	49.4	51.8	<0.0001
Arrival via EMS, %	83.4	72.8	86.9	<0.0001
LKW to arrival median (IQR), min	53 (37-74)	61 (43-90)	50 (35-70)	<0.0001
Medical history (4.1% missing), %				
Atrial fibrillation/flutter	23.3	22.8	23.5	0.06
CAD/prior MI	28.1	30.9	27.2	<0.0001
Carotid stenosis	3.5	4.7	3.1	<0.0001
Diabetes mellitus	25.8	29.7	24.6	<0.0001
Dyslipidemia	39.4	39.4	39.4	0.90
Hypertension	75.1	78.0	74.2	<0.0001
Prosthetic heart valve	1.4	2.1	1.2	<0.0001
Peripheral vascular disease	4.0	5.3	3.6	<0.0001
Smoker	18.2	16.4	18.8	<0.0001
Previous stroke/TIA	27.0	35.9	24.1	<0.0001
BMI at admission, median (IQR) (27.8% missing), kg/m²	26.9 (23.6-31.1)	26.7 (23.3-30.8)	27.0 (23.7-31.2)	<0.0001
Prior antithrombotic use (8.7% missing), %	50.3	57.1	48.2	<0.0001
Diagnosis and evaluation				
First documented NIHSS score, median (IQR)	11 (6-18)	6 (2-13)	12 (7-18)	<0.0001
Missing NIHSS score, %	23.9	58.2	12.6	<0.0001
NIHSS score level, %				
21+	15.3	10.0	16.1	<0.0001
15-20	21.3	10.8	23.0	
10-14	20.8	12.9	22.0	
5-9	26.8	22.7	27.5	

Continued

Table 2	Continued			
	Overall (N = 61,698)	No IV tPA (n = 15,282)	Yes IV tPA (n = 46,416)	p Value
0–4	15.8	43.5	11.5	
Door to image, median (IQR) (1.6% missing), min	23 (14–37)	40 (23–65)	20 (13–30)	<0.0001
Door to image ≤25 min, %	56.7	29.8	65.1	<0.0001
Hospital characteristics				
Beds, median (IQR) (0.6% missing), n	375 (260–560)	333 (224–488)	397 (278–579)	<0.0001
Region, %				
West	20.6	17.0	21.8	<0.0001
South	34.3	39.0	32.8	
Midwest	18.8	22.8	17.4	
Northeast	26.3	21.1	28.0	
Teaching hospital (0.6% missing), %	61.1	50.8	64.5	<0.0001
TJC primary stroke center, %	49.6	36.4	53.9	<0.0001
Rural location (0.03% missing), %	3.6	7.5	2.3	<0.0001
Average annual ischemic cases, median (IQR), n	199 (136–302)	167 (99–257)	216 (146–314)	<0.0001
Average IV tPA-treated cases, median (IQR), %	14.0 (7.4–22.5)	8.2 (3.8–15.9)	16 (9.3–24.0)	<0.0001
NIHSS completed, median (IQR), %	50 (29–67)	43 (21–63)	51 (32–68)	<0.0001

Abbreviations: BMI = body mass index; CAD = coronary artery disease; EMS = emergency medical services; IQR = interquartile range; LKW = last known well; MI = myocardial infarction; NIHSS = NIH Stroke Scale; TJC = The Joint Commission; tPA = tissue plasminogen activator.
For each variable, there were no missing data if not stated otherwise.

not treating otherwise eligible patients with IV tPA, yet multiple cohorts have found that up to one-third of patients with mild stroke symptoms at presentation will have poor long-term outcomes.[34–37] Patients with mild stroke symptoms were largely excluded from prior randomized tPA trials until the IST3 randomized controlled trial of tPA up to 6 hours from symptom onset. Subgroup analysis suggested that patients with mild stroke did not appear to benefit from treatment, although a post hoc analysis restricted to treatment within 3 hours suggested a benefit, and the most recent meta-analysis of tPA studies, including IST3, suggests a potential benefit in mild stroke.[32,33,38] It is likely that patients with a low NIHSS score and clearly disabling symptoms such as a visual field deficit or isolated aphasia benefit from tPA. Uncertainty remains about the efficacy of tPA in mild stroke patients (i.e., those with low NIHSS scores and deficits that are not clearly disabling). Phase III trials are underway to test IV tPA in mild stroke patients in the United States (clinicaltrials.gov NCT02072226) and to test IV tenecteplase in patients with TIA or mild stroke with visualized intracranial occlusion in Canada (clinicaltrials.gov NCT02398656).

Many factors independently associated with lack of IV tPA use relate to the rapidity of the evaluation, including arrival via EMS, arrival during regular workday weekday hours, and time from onset to arrival. Thus, patient, family, and medical caregiver education about acute stroke symptoms, the importance of the use of EMS in this setting, and interventions that expedite the evaluation of potentially eligible stroke patients would likely increase treatment rates. A recent study showed that prehospital notification by EMS, taking the patients directly from the ambulance to the CT scanner, and initiating tPA in the CT suite led to a dramatic 42% reduction in door-to-needle times during regular workday hours.[39] In the past, treatment times in GWTG-Stroke have been below stated goals, and the Target: Stroke initiative was created to address this issue, resulting in shorter treatment times and clear improvements in survival, patients discharged home, and symptomatic intracerebral hemorrhage.[40]

The GWTG-Stroke registry is among the largest available datasets of hospitalized stroke patients in the world and represents a mix of academic and nonacademic hospitals of various sizes from all the regions of the United States. The GWTG-Stroke orientation and continuing education for participating centers emphasize the need to document why patients are not receiving treatment. It is representative of the Medicare fee-for-service population with ischemic stroke, and the specificity of included patients and

| Table 3 | Adjusted multivariable logistic regression for selected patient and hospital characteristics associated with nontreatment with IV tPA in acute ischemic stroke patients arriving within 2 hours of onset and without documented contraindications or warnings | | | | | | | |

	All patients				Only patients with NIHSS			
	OR	95% CI	Z	p Value	OR	95% CI	Z	p Value
Patient characteristics								
Age >70 y, per 5-y increase	1.08	1.06-1.10	8.82	<0.0001	1.13	1.11-1.16	10.30	<0.0001
Female (vs male)	0.99	0.95-1.04	0.38	0.70	1.08	1.02-1.15	2.64	0.008
Black race (vs white)	1.12	1.04-1.21	2.96	0.0031	1.26	1.14, 1.40	4.46	<0.0001
Other race (vs white)	1.09	1.01-1.17	2.15	0.0315	1.17	1.06-1.29	3.07	0.0022
Atrial fibrillation	1.00	0.95-1.05	0.07	0.95	1.15	1.07-1.23	3.85	0.0001
Prosthetic heart valve	1.66	1.42-1.94	6.29	<0.0001	1.77	1.40-2.23	4.84	<0.0001
CAD/prior MI	0.99	0.95-1.04	0.31	0.76	1.04	0.98-1.11	1.24	0.21
Carotid stenosis	1.12	1.00-1.26	2.02	0.04	1.04	0.88-1.21	0.43	0.6644
Diabetes mellitus	1.15	1.09-1.20	5.80	<0.0001	1.16	1.09-1.24	4.79	<0.0001
Dyslipidemia	0.93	0.89-0.98	2.87	0.004	0.91	0.86-0.97	2.79	0.005
Hypertension	1.03	0.98-1.08	1.10	0.27	1.00	0.93-1.07	0.08	0.94
PVD	1.18	1.07-1.30	3.34	0.0008	1.21	1.05-1.38	2.69	0.007
Smoker	0.95	0.89-1.00	1.81	0.07	0.96	0.88-1.03	1.11	0.27
Stroke/TIA	1.39	1.33-1.46	13.33	<0.0001	1.40	1.32-1.49	10.48	<0.0001
Antithrombotics	1.16	1.10-1.21	5.67	<0.0001	1.13	1.06-1.21	3.62	0.0003
Arrival characteristics								
Arrival during off-hours	1.12	1.07-1.17	5.14	<0.0001	1.12	1.06-1.19	4.09	<0.0001
Arrived via EMS	0.60	0.57-0.64	16.40	<0.0001	0.86	0.79-0.93	3.76	0.0002
Calendar time, per 1-y increase	0.71	0.69-0.73	25.37	<0.0001	0.69	0.67-0.71	23.22	<0.0001
Onset to arrival >45 min, per 10-min increase	1.21	1.20-1.23	32.01	<0.0001	1.21	1.19-1.23	23.85	<0.0001
Hospital characteristics								
Hospital size ≤700 beds, per 100-bed increase	0.91	0.86-0.98	2.71	0.0067	0.98	0.92-1.05	0.48	0.6313
Annual volume of patients with AIS ≤200, per 50-patient increase	0.74	0.68-0.80	7.43	<0.0001	0.72	0.65-0.79	6.93	<0.0001
Door to CT >25 min, per 10-min increase	1.54	1.51-1.57	44.90	<0.0001	1.41	1.38-1.44	31.37	<0.0001
Percent NIHSS completed, per 10% increase	0.92	0.89-0.94	5.86	<0.0001	1.07	1.04-1.11	3.97	0.0001
TJC primary stroke center	0.57	0.48-0.68	6.28	<0.0001	0.56	0.46-0.68	5.94	<0.0001
Teaching hospital	0.75	0.64-0.89	3.41	0.0007	0.79	0.65-0.96	2.40	0.02
Rural location	1.52	1.19-1.96	3.30	0.001	1.46	1.06-2.00	2.34	0.02
Midwest vs Northeast	2.33	1.85-2.94	7.22	<0.0001	2.06	1.59-2.66	5.50	<0.0001
South vs Northeast	2.25	1.82-2.77	7.61	<0.0001	2.38	1.89-2.99	7.38	<0.0001
West vs Northeast	1.33	1.05-1.67	2.41	0.0158	1.17	0.90-1.53	1.15	0.2485

Abbreviations: AIS = acute ischemic stroke; CAD = coronary artery disease; CI = confidence interval; EMS = emergency medical services; MI = myocardial infarction; NIHSS = NIH Stroke Scale; OR = odds ratio; PVD = peripheral vascular disease; TJC = The Joint Commission; tPA = tissue plasminogen activator.
Data are shown for models incorporating all patients and restricted to those with NIHSS documented.
Adjusted model above includes patient demographics (age, sex, race, medical history, atrial fibrillation, diabetes mellitus, dyslipidemia, prior stroke/TIA, prosthetic valve, smoker, CAD/MI, carotid stenosis, PVD, hypertension), arrival characteristics (on-off hours, by EMS, onset to arrival time, calendar time), and hospital variables (percent NIHSS completed, primary stroke center status, teaching status, annual ischemic case volume, geographic region, bed size per 100 beds).

data accuracy have been demonstrated to be high.[10,14] However, there are important limitations to this study. First, it is possible that increases in tPA treatment rates may reflect improved documentation of contraindications over time. However, documentation of the rationale for nontreatment with tPA has been a key data point of GWTG-Stroke since its inception, and a prior analysis reported that the percentage of patients with documented contraindications has remained static over time while treatment rates have risen dramatically.[41] A related

Table 4 Adjusted odds of not being treated with IV tPA among eligible acute ischemic stroke patients, stratified by stroke severity, compared to those with mild stroke (NIHSS score 0–4)

NIHSS Score	OR (95% CI)	p Value
0–4	1.0 (Reference)	
5–9	0.26 (0.23–0.28)	<0.0001
10–14	0.19 (0.17–0.21)	<0.0001
15–20	0.16 (0.14–0.18)	<0.0001
21–40	0.19 (0.16–0.21)	<0.0001

Abbreviations: CI = confidence interval; NIHSS = NIH Stroke Scale; OR = odds ratio; tPA = tissue plasminogen activator.
Eligibility determined by failure to document a contraindication or warning.
Adjusted model above includes patient demographics (age, sex, race, medical history, atrial fibrillation, diabetes mellitus, dyslipidemia, prior stroke/TIA, prosthetic valve, smoker, coronary artery disease/myocardial infarction, carotid stenosis, peripheral vascular disease, hypertension), arrival characteristics (on-off hours, by emergency medical services, onset to arrival time, calendar time), and hospital variables (percent NIHSS completed, primary stroke center status, teaching status, annual ischemic case volume, geographic region, bed size per 100 beds).

concern is that some factors associated with not treating with IV tPA were in fact associated with failure to document that specific contraindication to treatment. In addition, the effect of time factors may have been underestimated, given that we focused on the GWTG-Stroke quality measure and included only patients who presented within 2 hours of stroke onset. Similarly, we excluded patients who were treated beyond 3 hours of onset because we were focusing on failure to treat. Delays in treatment are a very important topic that we did not assess. In addition, the assignment of race/ethnicity in hospitals may underestimate nonwhite or Hispanic populations and is often not based on interrogation of the patient during emergency visits. Our findings regarding mild stroke defined by low NIHSS score should be interpreted with caution, given the large number of untreated patients missing these data. The data from GWTG-Stroke depend on the accuracy and completeness of clinical documentation, and there are limited data addressing the reliability and data quality in GWTG-Stroke. Finally, residual measured and unmeasured confounding variables may have influenced the findings.

Although tPA rates have increased over the past decade, about one-quarter of eligible patients are not receiving treatment. To improve treatment rates, patients with stroke risk factors and their families should be educated about potential stroke symptoms and encouraged to call EMS if stroke is suspected. Continued efforts to develop stroke systems of care and establish stroke centers, to implement standardized protocols for stroke recognition by EMS dispatchers and providers, and to accelerate triage in emergency departments with an emphasis on rapid brain imaging may also improve treatment rates and timing. Older patients, women, and nonwhites, as well as patients with milder strokes, may be undertreated. Additional studies should be taken to address this potential disparity in care for patients with AIS.

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