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# Temporal Trends in Patient Characteristics and Treatment With Intravenous Thrombolysis Among Acute Ischemic Stroke Patients at Get With the Guidelines–Stroke Hospitals

Lee H. Schwamm, MD; Syed F. Ali, MD; Mathew J. Reeves, PhD; Eric E. Smith, MD, MPH; Jeffrey L. Saver, MD; Steven Messe, MD; Deepak L. Bhatt, MD; Maria V. Grau-Sepulveda, MD, MPH; Eric D. Peterson, MD; Gregg C. Fonarow, MD

**Background**—Substantial efforts over the past decade have increased rates of intravenous tissue plasminogen activator (tPA) use in the United States. We sought to determine changes in patient characteristics and rates of tPA use over time among hospitalized acute ischemic stroke (AIS) patients.

**Methods and Results**—We analyzed all AIS patients (n=1 093 895) and those arriving  $\leq 2$  hours and treated with tPA  $\leq 3$  hours after onset (n=50 798) from 2003 to 2011 in the American Heart Association's Get with the Guideline–Stroke (GWTG–Stroke). Categorical data were analyzed by Pearson  $\chi^2$  and continuous data by Wilcoxon test. Intravenous tPA use  $\leq 3$  hours after onset increased from 4.0% to 7.0% in all AIS admissions and 42.6% to 77.0% in AIS patients arriving  $\leq 2$  hours and fully eligible for tPA ( $P < 0.001$ ). In univariate analysis, tPA use increased over time, especially in those aged  $> 85$  years, nonwhite, and with milder strokes (National Institutes of Health Stroke Scale 0–4). Door-to-image time (median 24 versus 20 minutes) and door-to-tPA time (median 81 versus 72 minutes) also improved, with  $\approx 65\%$  of tPA-treated patients getting brain imaging  $\leq 25$  minutes after arrival. Multivariable analysis showed that with each additional calendar year, the odds that an eligible patient would receive tPA increased by 1.37-fold, adjusting for other covariates.

**Conclusions**—The frequency of IV tPA use among all AIS patients, regardless of contraindications, nearly doubled from 2003 to 2011. Treatment with tPA has expanded to include more patients with mild deficits, nonwhite race/ethnicity, and oldest old age. (*Circ Cardiovasc Qual Outcomes*. 2013;6:543–549.)

**Key Words:** cerebrovascular disorders ■ ischemic attack, transient ■ thrombolysis, therapeutic

An estimated 795 000 Americans experience a stroke each year, with  $\approx 610 000$  of these being first events and 185 000 recurrent episodes.<sup>1</sup> Stroke is the fourth leading cause of mortality and accounted for 1 in every 18 deaths in the United States in 2007.<sup>1</sup> With improvements in prevention and acute treatment, between 1997 and 2007, the annual per capita stroke death rate decreased by 34.3%, and the annual number of actual strokes decreased by 18.8%.<sup>1</sup> The use of intravenous recombinant tissue plasminogen activator (tPA), which was approved in 1996 for the treatment of acute ischemic stroke (AIS),<sup>2</sup> has played an essential role in reducing morbidity and disability after stroke.

Although tPA improves clinical outcomes and has a Class I recommendation in national guidelines, many patients with AIS arrive at the hospital within 3 hours of stroke onset without documented contraindications who still do not receive tPA.<sup>1</sup> Substantial efforts by professional societies, state

and federal government agencies, and national patient support organizations have led to increased tPA use in eligible patients.<sup>3</sup> Participation over the past decade by almost 2000 hospitals in quality improvement registries like the American Heart Association's Get With the Guideline–Stroke (GWTG–Stroke) has resulted in increased access to acute stroke care and administration of tPA.<sup>4</sup>

Although previous studies do suggest overall increases in tPA-treated patients, little is known about the changes over the past decade regarding which patients are or are not receiving intravenous tPA in the United States. We sought to analyze temporal trends in tPA treatment among AIS patients and identify changes in demographic and clinical characteristics over the 9-year period since GWTG–Stroke implementation in 2003.

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## WHAT IS KNOWN

- The use of intravenous recombinant tissue plasminogen activator (tPA), which was approved in 1996 for the treatment of acute ischemic stroke, has played an essential role in reducing morbidity and disability after stroke.
- Participation over the past decade by almost 2000 hospitals in quality improvement registries like the American Heart Association's Get with the Guide-line–Stroke has resulted in increased access to acute stroke care and administration of intravenous tPA.

## WHAT THE STUDY ADDS

- In this large cohort of ischemic stroke patients, we found that absolute rates of intravenous tPA use nearly doubled over the past decade among all patients arriving within 2 hours of stroke symptom onset.
- Treatment with intravenous tPA has expanded to include more stroke patients with milder deficits, non-white race ethnicity, and in those of very advanced age.
- Nevertheless, there is still substantial undertreatment of acute stroke patients with intravenous tPA, and major improvements may require increased public awareness, regionalization of stroke care, and increased use of telemedicine.

## Methods

### GWTG Program Design, Case Identification, and Data Abstraction

GWTG–Stroke is an ongoing voluntary, continuous registry and performance improvement initiative. A detailed description of the program has been previously reported.<sup>4</sup> Sites collect and enter deidentified patient-level data on clinical and demographic characteristics, diagnostic testing, treatments, adherence to quality measures, and in-hospital outcomes in patients hospitalized with stroke. GWTG–Stroke launched in April 2003 as a national stroke quality improvement program available to any hospital in the United States. Hospitals have continued to join over the past decade.

GWTG–Stroke includes a patient management platform that provides real-time decision support, logic checks and smart form controls to enhance data accuracy, and real-time online reporting features. Trained hospital personnel ascertain consecutive patients admitted with stroke by either prospective clinical identification, retrospective identification using International Classification of Diseases (ICD)-9 discharge codes, or a combination. Prospective identification includes regular surveillance of emergency department records (ie, presenting symptoms and chief complaints), ward census logs, or neurological consultations. The eligibility of each acute stroke is confirmed at chart review before abstraction. After abstraction by trained personnel at hospital, deidentified patient data are entered into the GWTG–Stroke database using 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 treatment and counseling, mortality, and discharge destination.<sup>3,4</sup>

All participating institutions were required to comply with local regulatory and privacy guidelines and, if required, to secure institutional review board approval. Because data were used primarily at the local site for quality improvement, sites were granted a waiver of informed consent under the common rule. Outcome, A Quintiles Company served as the registry coordinating center. 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.

### Patient Population

The primary objective of the study was to evaluate the changes in the patterns of use of intravenous thrombolysis over the 9-year period from April 2003 to December 2011. We report data on the following 3 cohorts—all AIS patients, patients arriving within 2 hours of onset without documented contraindications for tPA treatment, and patients arriving within 2 hours of onset and actually treated with IV tPA within 3 hours of onset. Patients treated after 3 hours and those who received additional treatment with intra-arterial reperfusion or experimental therapies were not included in the treated population. We restricted the tPA-eligible and treated population to those patients who arrived within the first 2 hours after last known well, and who received tPA within the first 3 hours, because this is the nationally recognized performance measure of tPA use and the primary tPA measure in GWTG–Stroke. Because the extended use of tPA up to 4.5 hours was recommended only after 2009, we did not include these subjects in our treated patient analysis. Eligible patients were those who presented with AIS, had no documented contraindications to tPA use, and did not receive experimental thrombolytic treatment, intra-arterial tPA, or intravenous tPA at an outside hospital. Data were collected on demographics, medical history, initial National Institutes of Health Stroke Scale (NIHSS) score, time intervals related to symptom onset, hospital arrival, brain imaging, and tPA treatment.

### Statistical Analysis

Patient demographics and clinical variables were analyzed for each of the 3 patient cohorts. Temporal trends were only explored for the cohort treated with intravenous tPA within 3 hours of onset by calendar year from 2003 through 2011. Percentages were used for categorical variables and medians with interquartile ranges for continuous variables. Statistical test for the time trends were assessed using  $\chi^2$  rank-based group means score statistics for categorical variables (equivalent to Kruskal-Wallis test) and  $\chi^2$  rank correlation statistics for continuous/ordinal variables (equivalent to Wilcoxon rank sum tests).

Regression models were also generated and odds ratios computed for tPA use as an outcome with calendar year of admission and number of years in program as independent variables. A final model with tPA administration as outcome and both calendar year and time in program as independent variables was also analyzed to assess the effect of year of participation while controlling for secular trends. Logistic regression models with Generalized Estimating Equation method were used to account for within-hospital clustering and compute odds ratios (ORs) for year increase since beginning of the study (April 2003) and change of calendar year of admission (2003–2011) for AIS patients presenting within 2 hours and treated by 3 hours. We developed 2 models, one without NIHSS and the other with NIHSS to calculate adjusted ORs (the high rate of missing values reduces the sample size considerably when NIHSS is included, but results are similar). Other parameters included were demographics (age, sex, race), medical comorbidities (atrial fibrillation, prosthetic valve, coronary artery disease/prior myocardial infarction, carotid stenosis, diabetes mellitus, peripheral vascular disease, hypertension, smoking, dyslipidemia, prior stroke/transient ischemic attack), use of emergency medical services (EMS), time intervals from onset to emergency department, imaging and treatment, and hospital characteristics (bed size, region, rural, academic, average annual ischemic cases, percent with NIHSS completed, primary stroke center status). All probability values are 2 sided, with values of  $P < 0.05$  considered statistically significant. All analyses were conducted by the statistical division of the Duke Clinical Research Institute using SAS software version 9.1.3 (SAS Institute, Cary, NC).

## Results

From April 2003 through December 2011, we identified 1093895 patients admitted for ischemic stroke entered into

GWTCG–Stroke from 1683 participating hospitals. Of all AIS patients, 240 424/1 093 895 (22.0%) presented to 1652 hospitals within 2 hours of last known well. Among these 75 115/240 424 (31.2%) were fully eligible for tPA treatment. Within the eligible patients (n=75 115), who should otherwise have been treated with tPA according to the medical record information, 50 798 (67.6%) received intravenous tPA. Increases in the rates of administration of tPA over time were observed for all cohorts of patients evaluated. From 2003–2005 to 2010–2011, intravenous tPA use within 3 hours of onset increased among all acute ischemic stroke patients (4.0% versus 7.0%,  $P<0.001$ ) and among eligible patients arriving within 2 hours (42.6% versus 77.0%,  $P<0.001$ ; Figure).

Patient characteristics are shown in Table 1 for the three cohorts. Age and sex distributions were similar across the cohorts. Atrial fibrillation was more common in the tPA-eligible and tPA-treated patients as compared with all AIS patients. History of hypertension and diabetes mellitus was less common in the tPA-eligible and tPA-treated patients compared with all AIS patients. Other vascular risk factors were similar among the 3 groups. Of all AIS patients, 52.9% were brought to the hospital by EMS, whereas 77.5% of tPA-eligible and 81.8% of tPA-treated patients used EMS. Median initial NIHSS was substantially higher in the tPA-eligible and tPA-treated groups compared with all AIS patients. As expected, tPA-eligible and tPA-treated patients had lower time intervals for last known well to hospital arrival and from door to initial imaging (in sensitivity analysis, similar findings were observed in the population of all patients treated with IV tPA within 3 hours of onset, regardless of arrival before or after 2 hours after onset; Table I in the online-only Data Supplement).

In univariate analysis, tPA use changed over time across most of the patient characteristics measured, with a pattern of expanding the treated population into a broader range (Table 2). The proportion of patients receiving tPA aged >85 years increased from 10.5% of treated patients in 2003–2005 to 16.4% in 2010–2011 ( $P<0.001$ ). Also, the sex distribution of tPA use changed slightly, with the proportion of tPA use among women increasing from 48.6% to 51.0%. The population receiving tPA also became more diverse, with nonwhites accounting for 21.1% of tPA use in 2003 to 2005 but 28.9% in 2010 to 2011 ( $P<0.001$ ). The prevalence of atrial fibrillation, hypertension, coronary

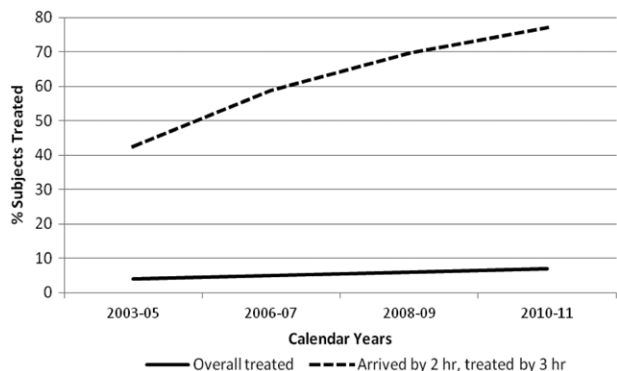
**Table 1. Demographics, Clinical Characteristics, and Care of All Acute Ischemic Stroke (AIS) Patients, Those tPA-Eligible Patients Arriving Within 2 Hours of Last Known Well, and the Subset of Those Eligible Patients Treated With tPA Within 3 Hours Over the 9-Year Period From 2003 to 2011**

Patients Characteristics	All AIS patients (n=1 093 895)	Eligible 2-Hour AIS Patients (n=75 115)	AIS 2-Hour Patients Treated With tPA (n=50 798)
<b>Demographics</b>			
Age, y (median [IQR])	73 (61–82)	73 (60–82)	72 (60–82)
Age >85	16.6%	15.4%	15.0%
Male sex	47.8%	49.1%	49.8%
<b>Race</b>			
White	71.6%	73.9%	73.6%
Black	15.8%	13.3%	13.3%
Others	12.6%	12.8%	13.1%
<b>Ethnicity</b>			
Hispanic	5.8%	6.2%	6.4%
<b>Medical history</b>			
Atrial fibrillation	18.4%	22.9%	23.4%
Hypertension	77.4%	75.3%	74.3%
CAD/previous MI	27.3%	28.1%	27.3%
Carotid stenosis	4.4%	3.5%	3.1%
Diabetes mellitus	32.3%	26.4%	24.6%
Dyslipidemia	40.8%	39.3%	39.3%
Smoking	19.3%	18.1%	18.9%
EMS from home	52.9%	77.5%	81.8%
NIHSS, median (IQR)	4 (2–11)	11 (6–17)	12 (7–18)
<b>NIHSS levels</b>			
21+	4.3%	11.0%	13.9%
15–20	4.7%	15.3%	19.9%
10–14	5.6%	15.1%	19.2%
0–9	37.7%	32.1%	34.0%
Missing	47.8%	26.5%	13.0%
Door to image time, min [median (IQR)]	58 (29–109)	25 (15–41)	21 (13–31)
Door to image time ≤25 min	16.7%	49.2%	60.9%
LKW to arrival, min [median (IQR)]	191 (67–540)	55 (37–76)	50 (35–70)

Eligible patients are those without documented reasons for nontreatment with tPA. CAD indicates coronary artery disease; IV, intravenous; IQR, interquartile range; LKW, last known well; MI, myocardial infarction; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack; and tPA, tissue plasminogen activator.

disease, and smoking decreased over time, whereas diabetes mellitus and dyslipidemia increased and previous stroke/TIA stayed the same. Average pretreatment stroke severity declined over time, with the median NIHSS decreasing, and the proportion of patients with mild strokes (NIHSS 0–4) almost doubling (7.3% versus 13.4%,  $P<0.0001$ ).

Among resource utilization and timeliness of care, the proportion of tPA-treated patients who activated EMS to get to the hospital was >85% at baseline and remained so over the study period (Table 3). The median time in minutes from the



**Figure.** Rates of IV-tPA use within 3 hours of onset over time, in all ischemic stroke cases regardless of time of arrival or any tPA contraindications (solid line) and among fully tPA-eligible AIS patients arriving ≤2 hours (dashed line).

**Table 2. Univariate Analysis of Temporal Trends in Demographics, Clinical Characteristics of Ischemic Stroke Patients Presenting Within 2 Hours and Receiving tPA Within 3 Hours**

Patients Characteristics	2003–05 (n=3006)	2006–07 (n=9320)	2008–09 (n=16571)	2010–11 (n=21901)	P Value
Demographics					
Age, y (median [IQR])	72 (60–80)	72 (59–81)	73 (60–82)	73 (60–82)	<0.001
Age >85	10.5%	12.6%	15.5%	16.4%	<0.001
Male sex	51.4%	51.4%	49.8%	49.0%	<0.001
Race					
White	78.9%	76.7%	74.3%	71.1%	<0.001
Black	11.3%	12.2%	12.7%	14.4%	
Others	9.8%	11.1%	13.0%	14.5%	
Ethnicity					
Hispanic	3.0%	4.8%	6.4%	7.6%	<0.001
Medical history					
Atrial fibrillation	24.1%	25.7%	23.1%	22.8%	<0.001
Hypertension	76.9%	78.1%	74.0%	72.8%	<0.001
CAD/previous MI	29.7%	29.6%	27.7%	25.7%	<0.001
Carotid stenosis	4.3%	3.4%	3.0%	2.9%	0.0011
Diabetes mellitus	23.1%	24.5%	24.3%	25.1%	0.0196
Dyslipidemia	36.8%	39.4%	38.5%	40.3%	0.0004
Smoking	21.5%	22.5%	18.6%	17.4%	<0.001
NIHSS [median (IQR)]	12 (8–18)	12 (7–18)	12 (7–18)	11 (6–18)	<0.001
NIHSS levels*					
21+	15.9%	16.4%	16.5%	15.6%	
15–20	25.0%	23.8%	23.4%	21.5%	
10–14	24.4%	23.3%	22.4%	21.0%	
5–9	27.4%	26.7%	26.7%	28.5%	
0–4	7.3%	9.8%	10.6%	13.4%	
Rates of missing NIHSS	25.1%	19.7%	12.8%	8.6%	<0.001

CAD indicates coronary artery disease; IV, intravenous; IQR, interquartile range; LKW, last known well; MI, myocardial infarction; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack; and tPA, tissue plasminogen activator.

\*Temporal trends in NIHSS levels in patients with known NIHSS (n=2253 in 2003–2005; 7487 in 2006–2007; 14 455 in 2008–2009; and 20 014 in 2010–2011).

time of last known well to hospital arrival increased slightly in patients receiving intravenous tPA (47 versus 50;  $P<0.001$ ). Hospital-based processes showed improvement over the study period. The median door-to-image time in minutes improved during the study (24 versus 20;  $P<0.001$ ) as did the percentage of patients with a door-to-image time  $\leq 25$  minutes (53.6% versus 64.8%;  $P<0.001$ ). Despite the stagnant use of EMS and

onset to arrival times, the last known well-to-needle and door-to-needle times both improved significantly from 2003 to 2005 to 2010 to 2011 by about 7 and 9 minutes, respectively.

Finally, to assess the impact of time on the rates of treatment, multivariable Generalized Estimating Equation regression models were constructed that included all clinical variables plus calendar year. An adjusted OR of 1.38 per calendar year (95%

**Table 3. Temporal Trends in Timeliness of Care Delivery of Ischemic Stroke Patients Presenting Within 2 Hours and Receiving Intravenous tPA Within 3 Hours on Univariate Analyses**

Patients Characteristics	2003–2005 (n=3006)	2006–2007 (n=9320)	2008–2009 (n=16571)	2010–2011 (n=21 901)	P Value
Use of EMS from home	86.9%	87.4%	86.6%	85.5%	<0.001
door-to-image time, minutes, median (IQR)	24 (15–36)	22 (14–33)	21 (14–32)	20 (13–29)	<0.001
door-to-image time $\leq 25$ min	53.7%	57.4%	59.1%	64.8%	<0.001
LKW to hospital arrival, minutes, median (IQR)	47 (33–65)	50 (35–69)	50 (35–70)	50 (35–70)	<0.001
LKW to IV tPA time, minutes, median (IQR)	137 (115–160)	138 (115–160)	135 (110–160)	130 (106–155)	<0.001
Door to IV tPA time, minutes, median (IQR)	81 (63–102)	80 (62–100)	77 (60–97)	72 (56–92)	<0.001

EMS indicates emergency medical services; IV, intravenous; IQR, interquartile range; LKW, last known well; and tPA, tissue plasminogen activator.

confidence interval [CI], 1.35–1.41;  $P < 0.0001$ ;  $n = 45\,656$ ) was calculated for the increase in tPA administration among fully eligible ischemic stroke patients over each of the 9 calendar years. To explore what proportion of this might have been due solely to temporal trends in the United States outside the program, as compared with program-specific effects related to quality improvement efforts within GWTG–Stroke, a model term for years participating in GWTG–Stroke was added to the model in addition to calendar year. In this model, both year of participation in the program (adjusted OR, 1.05; 95% CI, 1.02–1.07;  $P < 0.001$ ) and calendar year (adjusted OR, 1.38; 95% CI, 1.35 to 1.41;  $P < 0.001$ ) were associated with increasing odds of tPA use per year, suggesting that both secular trends and program-specific effects contributed to the rising tPA use.

Because NIHSS is not documented in the medical record in a moderate number of tPA-eligible (26.5%) or tPA-treated (13.0%) patients, NIHSS was not included in the main multivariable model. A sensitivity analysis that included the NIHSS in the multivariable model ( $n = 39\,814$ ) showed a similar relationship between increasing calendar year and the odds of tPA use in eligible patients (OR, 1.32 per year; 95% CI 1.29–1.35;  $P < 0.0001$ ).

## Discussion

This study is among the first and largest to date to describe the temporal trends of the past decade in intravenous tPA use in patients with AIS in a clinically derived dataset from a sizeable cohort of US hospitals nationwide. GWTG–Stroke is the largest registry of hospitalized stroke patients and represents a mix of academic and nonacademic, small- and large-sized hospitals from all the regions of the country and has been shown to be representative of the Medicare fee-for-service population with ischemic stroke.<sup>5–9</sup>

In this large cohort of ischemic stroke patients, we found that absolute rates of tPA use within 3 hours of onset among all patients with ischemic stroke nearly doubled from 4.0% in 2003–2005 to 7.0% in 2010–2011. This substantial improvement is attributable in part to a decade of national efforts in stroke quality improvement targeting hospital-based processes.<sup>10</sup> Similar increases in the rate of intravenous tPA use have been reported in US Paul Coverdell National Acute Stroke Registry,<sup>7,9</sup> the National Hospital Discharge Survey,<sup>11</sup> and the population-based Cincinnati-Kentucky region.<sup>8</sup>

Our data suggest a shift in the population of patients treated with intravenous tPA by hospital-based providers. One pattern was toward treating those with milder strokes and fewer selected vascular risk factors. Although the proportion of most vascular risk factors decreased, dyslipidemia and diabetes mellitus increased. Initially after tPA approval there was criticism from some quarters that given the real risk of brain hemorrhage, it was unwise to treat patients with mild stroke syndromes because of their perceived more benign outcomes and good recovery<sup>9</sup> and that vascular imaging was needed to exclude these and other high-risk patients or nonresponders from treatment. Over time, these fears have proven to be unfounded, and evidence suggests that these patients who are too good to treat in fact can have worse than expected outcomes.<sup>12</sup> Overall, there is increasing interest in the concept of treating patients with milder symptoms or rapid improvement.

A different trend is the increased proportion of very old patients receiving tPA. Again, we can only speculate as to the cause, but this may be attributable to increasing confidence in the benefit to harm ratio of tPA and the lack of evidence of excess harm in those of advanced age.<sup>13</sup> We have previously shown that the improvements in the rates of eligible patients treated is not solely a consequence of more aggressive documentation of reasons for nontreatment but is based on actual increased rates of use.<sup>13</sup> Our current study corroborates that finding and shows that there has been a consistent year by year increase in use.

In our dataset, a total of 22.0% of patients presented within 3 hour of last known well, the theoretical limit for tPA use before 2009. This is similar to the percentage reported by other regional or national registries. In a prospective, multi-center, hospital-based registry of acute stroke patients in urban China, 25% of patients arrived within 3 hours and 37% within 6 hours after symptom onset.<sup>14</sup> In the California Acute Stroke Pilot Registry, 23.5% arrived at the emergency department within 3 hours of symptom onset.<sup>15</sup> The Coverdell Registry reported <18.5% of stroke patients arrived at the emergency department within 2 hours of symptom onset in 2005–2006.<sup>7</sup> Other studies have found that ≈15% to 32% of patients presenting with ischemic stroke arrive within 3 hours of symptom onset.<sup>16–20</sup> A recent publication by Tong et al<sup>5</sup> in a similar GWTG–Stroke cohort described this finding in detail. We observed that the time of symptom onset to arrival increased from 47 minutes to 50 minutes. EMS systems cannot reliably deliver patients much faster than ≈45 minutes from onset of symptoms. The increase to 50 minutes observed in our study transport times among treated patients may reflect an increase in the use of EMS in more rural areas with longer transport times, not deterioration in EMS performance. Similarly, the longer time intervals from onset to arrival might be a reflection of hospitals speeding up their processes so that they are able to treat a greater proportion of late arriving patients.

Finally, we observed steady and substantial improvements in hospital-based processes of care, as measured by timeliness of imaging and therapeutics and increased use of tPA.<sup>21</sup> Median time from door to brain imaging decreased by 11 minutes over the study period, and the overall median time to imaging in the eligible 2 hours arrival cohort was 25 minutes. By 2010 to 2011, 64.8% of patients were imaged within 25 minutes of hospital arrival, which compares favorably with rates of improvement reported in the literature and likely enabled greater numbers of patients to be treated with tPA. The Coverdell registry reported a median time interval to initial imaging of ≈72 minutes for all patients and 42 minutes for the patients who arrived within 2 hours of symptoms onset.<sup>7</sup> A recent GWTG publication by Kelly et al describes the temporal trends in the timeliness of imaging acquisition in a similar timeframe from 2003 to 2009, and our data from the last 2 years demonstrate continued improvement in the trend of rapid imaging.<sup>22</sup> To further facilitate and accelerate these changes, the American Heart Association launched the Target: Stroke initiative in 2010 to assist hospitals in focusing their efforts to improve the proportion of patients receiving tPA within 60 minutes of hospital arrival, and thereby improve health outcomes for their patients.<sup>23</sup>

Implementation of quality improvement registries like GWTG–Stroke, coupled with national initiatives such as the Joint Commission Primary Stroke Center program and the Coverdell registry, have helped participating hospitals continue to enhance their performance.<sup>24</sup> These accreditation and registry programs have reached a receptive audience within hospital emergency departments and stroke teams. Unfortunately, far too few patients with acute ischemic stroke receive tPA despite these demonstrated increases in utilization. A variety of factors contribute to this. Major improvements may require a multi-pronged approach that includes (1) increased public awareness of stroke symptoms and the benefits of using the emergency medical response system,<sup>21</sup> (2) regionalization of acute stroke care to ensure a tiered system of response that gets patients rapidly to the center most appropriate to their needs,<sup>25</sup> (3) increased use of telemedicine to support community and rural hospitals to become acute stroke-ready hospitals,<sup>26</sup> and (4) changes in healthcare reimbursement that promote effective and coordinated stroke systems of care.

### Limitations

The data used were collected by medical chart review and are dependent on the accuracy of documentation and abstraction. Some patients may have had contraindications to tPA that were present but not documented, whereas other patients may have had contraindications documented that should not have precluded tPA use. Residual measured and unmeasured confounding may have influenced the findings, especially as it relates to stroke subtype and initial stroke severity. Because of the large sample size, some results may be statistically significant but not clinically meaningful, and therefore results have been placed into the appropriate context to mitigate this effect. The difference in rates may, in part, be influenced by rolling in and dropping out of hospitals with varying treatment rates over time. The GWTG–Stroke program is voluntary, and the hospitals that participate are more likely to be larger teaching hospitals with a strong interest in stroke and quality improvement. However, the population in GWTG–Stroke is similar in makeup to the Medicare Fee for Service population and is broadly representative.<sup>7</sup> Hospitals are instructed to include all consecutive ischemic stroke admissions; however, because these processes are not audited, the potential exists for selection bias at the site level. Because there are a substantial number of cases with missing NIHSS values, we cannot be certain that the change in the median NIHSS over time reflects a reduction in overall stroke severity. However, with only 13% of missing NIHSS among the patients treated with tPA, it is likely that this trend of treating milder strokes is valid.

### Conclusion

In conclusion, the frequency of intravenous tPA use among all AIS patients, regardless of contraindications, and among eligible patients without contraindications arriving within 2 hours nearly doubled from 2003 to 2011. Treatment with tPA has expanded to include more stroke patients with milder deficits, nonwhite race ethnicity, and in those of very advanced age. Nevertheless, there is still substantial undertreatment of AIS with tPA.

### Disclosures

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