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# Timeliness of Tissue-Type Plasminogen Activator Therapy in Acute Ischemic Stroke

## Patient Characteristics, Hospital Factors, and Outcomes Associated With Door-to-Needle Times Within 60 Minutes

Gregg C. Fonarow, MD; Eric E. Smith, MD, MPH; Jeffrey L. Saver, MD; Mathew J. Reeves, PhD; Deepak L. Bhatt, MD, MPH; Maria V. Grau-Sepulveda, MD, MPH; DaiWai M. Olson, PhD, RN; Adrian F. Hernandez, MD, MHS; Eric D. Peterson, MD, MPH; Lee H. Schwamm, MD

**Background**—The benefits of intravenous tissue-type plasminogen activator (tPA) in acute ischemic stroke are time dependent, and guidelines recommend an arrival to treatment initiation (door-to-needle) time of  $\leq 60$  minutes.

**Methods and Results**—Data from acute ischemic stroke patients treated with tPA within 3 hours of symptom onset in 1082 hospitals participating in the Get With the Guidelines—Stroke Program from April 1, 2003, to September 30, 2009 were studied to determine frequency, patient and hospital characteristics, and temporal trends in patients treated with door-to-needle times  $\leq 60$  minutes. Among 25 504 ischemic stroke patients treated with tPA, door-to-needle time was  $\leq 60$  minutes in only 6790 (26.6%). Patient factors most strongly associated with door-to-needle time  $\leq 60$  minutes were younger age, male gender, white race, or no prior stroke. Hospital factors associated with  $\leq 60$  minute door-to-needle time included greater annual volumes of tPA-treated stroke patients. The proportion of patients with door-to-needle times  $\leq 60$  minutes varied widely by hospital (0% to 79.2%) and increased from 19.5% in 2003 to 29.1% in 2009 ( $P < 0.0001$ ). Despite similar stroke severity, in-hospital mortality was lower (adjusted odds ratio, 0.78; 95% confidence interval, 0.69 to 0.90;  $P < 0.0003$ ) and symptomatic intracranial hemorrhage was less frequent (4.7% versus 5.6%;  $P < 0.0017$ ) for patients with door-to-needle times  $\leq 60$  minutes compared with patients with door-to-needle times  $> 60$  minutes.

**Conclusions**—Fewer than one-third of patients treated with intravenous tPA had door-to-needle times  $\leq 60$  minutes, with only modest improvement over the past 6.5 years. These findings support the need for a targeted initiative to improve the timeliness of reperfusion in acute ischemic stroke. (*Circulation*. 2011;123:750-758.)

**Key Words:** hospital performance ■ mortality ■ registries ■ stroke ■ thrombolytics

Tissue-type plasminogen activator (tPA) is a proven intervention for acute ischemic stroke patients.<sup>1,2</sup> The benefit of intravenous tPA in acute ischemic stroke is strongly time dependent. Analysis of pooled data from 6 large randomized tPA trials showed greater neurological improvement at 90 days with earlier tPA treatment.<sup>3</sup> The therapeutic benefit of tPA is greatest when given early after ischemic stroke onset and declines over 3 to 4.5 hours.<sup>3-6</sup> Because of the importance of rapid treatment, national guidelines recommend that hospitals complete the clinical and imaging evaluation of acute ischemic stroke patients and initiate intravenous tPA

therapy within 60 minutes of patient arrival in those without contraindications.<sup>2,7-9</sup>

### Clinical Perspective on p 758

Despite the proven benefits, guidelines recommendations, and explicit goals for timely administration of intravenous tPA, the frequency, patient and hospital characteristics, temporal trends, and outcomes of ischemic stroke with door-to-needle times  $\leq 60$  minutes have not been well studied in the United States or elsewhere. To address this need, the Get With the Guidelines—Stroke (GWTG-Stroke) national regis-

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try was analyzed to determine the presenting characteristics of acute ischemic stroke patients treated with intravenous tPA within 3 hours of symptom onset in whom a door-to-needle time  $\leq 60$  minutes was achieved, patient and hospital characteristics associated with door-to-needle time  $\leq 60$  minutes, hospital-level variation in door-to-needle times, in-hospital clinical outcomes, and temporal trends in timely thrombolytic care.

## Methods

The American Heart Association and American Stroke Association (AHA/ASA) launched the GWTG-Stroke initiative focused on the redesign of hospital systems of care to improve the quality of care for patients with stroke and transient ischemic attack (TIA).<sup>10,11</sup> Details of the design and conduct of the GWTG-Stroke program have previously been described.<sup>11</sup> GWTG uses a Web-based patient management tool (Outcome Sciences, Inc, Cambridge, MA) 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.<sup>10</sup> Data from hospitals that participated in the program any time between April 1, 2003, and September 31, 2009, were included in this analysis. Each participating hospital received either human research approval to enroll cases without individual patient consent under the common rule or a waiver of authorization and exemption from subsequent review by their institutional review board. Outcome Sciences, Inc serves as the data collection and coordination center for GWTG. The Duke Clinical Research Institute serves as the data analysis center and has an agreement to analyze the aggregate deidentified data for research purposes.

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. Methods used for the prospective clinical identification of cases involved regular review of a combination of data sources, including emergency department admission logs, ward census logs, intensive care unit logs, and neurology service consultations. Methods used for the retrospective clinical identification of cases included regular surveillance of discharge codes, specifically *International Classification of Disease*, ninth revision, codes 433.xx, 434.xx, and 436 for ischemic stroke. The eligibility of all acute stroke admissions was confirmed before chart abstraction.<sup>11</sup>

Patient data, including demographics, medical history, onset time of stroke symptoms (recorded as last known well time), arrival time, in-hospital diagnostic studies, treatments and procedures, discharge treatments and counseling, tPA treatment initiation time, tPA complications, in-hospital mortality, and discharge destination, were abstracted by trained hospital personnel. Stroke severity was indexed by the National Institutes of Health Stroke Scale (NIHSS). The NIHSS is an ordinal categorical scale designed to quantify abnormalities on the neurological examination caused by acute stroke. The 11 individual elements of the scale include measures of language, visual abnormalities, motor weakness, sensory loss, and ataxia. The total score ranges from 0 to 42 points (lower scores represent less severe deficits). The absence of neurological examination findings are scored 0, mild examination findings typically not warranting thrombolysis are usually scored 1 to 5, and very severe deficits from middle cerebral artery or basilar artery occlusion are typically scored  $\geq 20$ .<sup>1,2</sup> All patient data were deidentified before submission. 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.<sup>12</sup> 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.

Between April 1, 2003, and September 30, 2009, 595 172 acute ischemic stroke admissions were submitted by 1259 participating hospitals. We excluded 465 269 patients who did not present within

3 hours symptom onset (defined as last known well time). There were 2823 patients arriving to the hospital within 3 hours of symptom onset but treated with intravenous tPA beyond 3 hours after symptom onset; they were excluded. There were 472 patients treated with experimental thrombolytic therapy who were also excluded. Of the 129 431 ischemic stroke cases presenting during the study period and potentially eligible, 25 504 (19.7%) were treated with intravenous tPA within 3 hours of symptom onset in 1082 hospitals. These 25 504 patients treated with intravenous tPA within 3 hours of symptom onset, concordant with national guideline recommendations throughout the study period,<sup>2</sup> constitute the study population. The characteristics of the patient cohorts included and excluded from the study are shown in Table I in the online-only Data Supplement.

## Statistical Analysis

Patient demographic and clinical variables, hospital-level characteristics, and clinical outcomes were compared between patients with and without door-to-needle time  $\leq 60$  minutes. Percentages and mean  $\pm$  SDs were reported for categorical and continuous variables, respectively. The Pearson  $\chi^2$  test and Wilcoxon rank-sum tests were used to compare the categorical and continuous variables, respectively, between patients with door-to-needle times  $\leq 60$  and  $> 60$  minutes. The relationships between patient and hospital characteristics associated with door-to-needle time  $\leq 60$  minutes 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 adjusted models included the following prespecified potential confounders: age, race, sex, medical history (including atrial fibrillation, prosthetic heart valve, previous stroke/TIA, coronary heart disease or prior myocardial infarction, carotid stenosis, peripheral vascular disease, hypertension, dyslipidemia, and current smoking), stroke severity (NIHSS), arrival time during regular work hours (7 AM to 5 PM Monday through Friday), arrival mode (ambulance, private vehicle), onset-to-arrival time, hospital size, region, teaching status, certified primary stroke center status, average number of patients treated with tPA annually, and average number of annual stroke discharges from each hospital. Similar multivariable logistic regression analyses were performed to explore the relationship between door-to-needle times  $\leq 60$  minutes compared with door-to-needle times  $> 60$  minutes for other binary clinical outcome measures (ie, in-hospital mortality, discharge status [home versus other], discharge status [home or acute rehabilitation versus other], ambulatory without assistance, hospital length of stay  $\leq 4$  days). The relationships between door-to-needle time  $\leq 60$  minutes 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 in GEE models. We included the same set of prespecified potential confounders in all of these outcomes-based models. Missing values were imputed as follows: sex, male; medical history, no; race, white; and arrival mode, emergency medical services. Finally, we explored temporal trends in door-to-needle times  $\leq 60$  minutes by both calendar time and program time participating in GWTG-Stroke. *P* values were based on  $\chi^2$  1-*df* rank correlation statistics. GEE logistic regression models were also developed to determine temporal trends in door-to-needle times  $\leq 60$  minutes with adjustment for patient and hospital characteristics. Statistical significance was defined as  $P \leq 0.05$ . All statistical analyses were performed with SAS version 9.1 software (SAS Institute, Cary, NC).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

## Results

During the 6.5-year study time period, 25 504 acute ischemic stroke patients were treated with tPA within 3 hours of symptom onset at 1082 hospital sites. These 25 504 cases represented 19.6% of all ischemic stroke patients ( $n = 129\,903$ ) who arrived at the emergency department

within 3 hours of onset (last known well time) and 4.3% of all ischemic stroke patients registered in the GWTG-Stroke Program ( $n=595\ 172$ ). Among patients arriving within 3 hours of onset and receiving intravenous tPA within 3 hours of last known well time, the mean door-to-needle time for intravenous tPA administration was  $79.3\pm 28.1$  minutes and the median was 78 minutes (25th to 75th percentile, 60 to 98 minutes). There were 6790 (26.6%) patients with door-to-needle times  $\leq 60$  minutes and 18 714 (73.4%) with door-to-needle times  $> 60$  minutes.

Table 1 shows the characteristics of patients with door-to-needle times  $\leq 60$  minutes compared with those with door-to-needle times  $> 60$  minutes. Patients with door-to-needle times  $\leq 60$  minutes were slightly younger and more often male compared with patients with door-to-needle times  $> 60$  minutes. Patients whose door-to-needle times were  $\leq 60$  minutes were more likely to arrive during on-hours (Monday through Friday, 7 AM to 5 PM) and by emergency medical service transport. Among those patients in whom NIHSS was documented ( $n=21\ 227$ , 83.4%), severity was similar among patients with door-to-needle times  $> 60$  and  $\leq 60$  minutes (median NIHSS, 12 for both). Notably, patients with door-to-needle times  $\leq 60$  minutes were more likely to arrive later after stroke symptom onset; among those patients receiving tPA within 60 minutes of arrival, the median time from onset to arrival was 60 minutes compared with 49 minutes for those with door-to-needle times  $> 60$  minutes ( $P<0.0001$ ).

The hospital characteristics of patients with door-to-needle times  $\leq 60$  minutes and those with door-to-needle times  $> 60$  minutes are shown in Table 2. Treatment within 60 minutes of arrival occurred more often at hospitals with higher annual volume of tPA-treated ischemic stroke patients and larger hospitals. There was considerable variation among hospitals in the proportion of ischemic stroke patients with door-to-needle times  $\leq 60$  minutes. When the analysis was confined to the 641 hospitals that had at least 10 patients who were treated with intravenous tPA within 3 hours of symptom onset, door-to-needle times  $\leq 60$  minutes varied widely with a median rate of 21.1% (25th to 75th percentile, 13.0% to 33.3%) and range of 0% to 79.2%. Among hospitals with at least 10 patients treated with tPA within 3 hours of symptom onset, the proportion of patients in whom door-to-needle times  $\leq 60$  minutes were achieved was 0% to  $< 20\%$  at 290 hospitals (45.2%), 21% to  $< 40\%$  at 242 (37.8%), 40% to  $< 60\%$  at 95 (14.8%), and 60% to  $< 80\%$  at 14 (2.2%). Only 6.7% of hospitals achieved door-to-needle times  $\leq 60$  minutes in  $\geq 50\%$  of patients.

Patient and hospital factors independently associated with door-to-needle time  $\leq 60$  minutes are shown in Table 3. The most powerful patient characteristics independently associated with door-to-needle time  $\leq 60$  minutes were more severe neurological deficits, arrival on-hours rather than off-hours, and longer onset-to-arrival times. Other patient factors independently associated with decreased odds of door-to-needle times  $\leq 60$  minutes included older age, female sex, black race, and medical history of atrial fibrillation, diabetes mellitus, and prior stroke/TIA. Hospital factors independently associated with increasing odds of door-to-needle time  $\leq 60$  minutes included higher number of patients treated with

intravenous tPA annually and lower annual number of stroke admissions. Hospital size, academic or nonacademic status, primary stroke center certification, and geographic region were not independently associated with door-to-needle times within 60 minutes.

From 2003 to 2009, the proportion of patients with a door-to-needle time  $\leq 60$  minutes increased modestly over time, from 19.5% in 2003 to 29.1% in 2009, with a trend line showing an increase of  $\approx 1.6\%/y$ . There was also an unadjusted relationship between the achievement of door-to-needle times  $\leq 60$  minutes and the duration of hospital participation in the GWTG-Stroke Program. The proportion of patients with door-to-needle times  $\leq 60$  minutes increased from 21.1% at the program baseline to 32.4% in year 6 or more of program participation. In multivariable GEE models, each successive calendar year was associated with a modest increased odds of door-to-needle times  $\leq 60$  minutes (adjusted odds ratio [OR], 1.09; 95% confidence interval [CI], 1.04 to 1.14;  $P=0.0004$ ). In contrast, after adjustment for calendar year and other variables, each successive GWTG-Stroke Program year was not associated with shorter door-to-needle times (adjusted OR, 1.01; 95% CI, 0.97 to 1.05;  $P=0.63$ ). Door-to-needle time was also analyzed as a continuous variable. From 2003 to 2009, the median door-to-needle time decreased from 85 to 75 minutes ( $P<0.0001$ ), with a trend line showing a decrease of  $\approx 1.6$  min/y. In multivariable GEE models, each successive calendar year was associated with a 1.7% improvement (95% CI, 1.0 to 2.5) in decrease in door-to-needle times ( $\approx 1.6$ -minute decrease per year).

Differences were observed in certain clinical outcomes between patients with door-to-needle times  $\leq 60$  minutes and those with door-to-needle times  $> 60$  minutes. The crude (unadjusted) in-hospital case fatality rate was lower in patients with door-to-needle times  $\leq 60$  minutes compared with those with door-to-needle times  $> 60$  minutes (8.6% versus 10.4%;  $P<0.0001$ ; Table 4). Patients with door-to-needle times  $\leq 60$  minutes had similar ambulatory status at discharge but were slightly more often discharged to home or short-term rehabilitation (71.7% versus 69.0%;  $P=0.0146$ ; Table 4). Hospital lengths of stay were similar in the 2 groups. The intravenous tPA complication rates were lower among patients treated in a more timely fashion. The rates of intracranial hemorrhage within 36 hours were lower in the patients with door-to-needle times  $\leq 60$  minutes compared with those with door-to-needle times  $> 60$  minutes (4.7% versus 5.6%;  $P=0.002$ ); overall tPA complications rates were also lower (Table 4). Adjusting for potential confounding variables, including stroke severity, and accounting for the correlation of data within hospitals demonstrate that patients with door-to-needle times  $\leq 60$  minutes had lower odds of in-hospital mortality (adjusted OR, 0.78; 95% CI, 0.69 to 0.90;  $P<0.0003$ ; Table 5). The results were similar when the models were constructed with the complete cohort of patients, including those with NIHSS not documented. In multivariable GEE models analyzing the relationship of door-to-needle time as a continuous variable to in-hospital mortality, every 15-minute reduction in door-to-needle time was associated with a 5% lower odds of mortality (adjusted OR, 0.95; 95%

**Table 1. Characteristics of Ischemic Stroke Patients With Door-to-Needle Times  $\leq 60$  Minutes Compared With Those With Door-to-Needle Times  $> 60$  Minutes**

	Door-to-Needle Time $\leq 60$ min	Door-to-Needle Time $> 60$ min	<i>P</i>
n	6790	18 714	
Patient-level characteristics			
Age, mean (SD), y	68.9 (14.5)	70.1 (14.8)	<0.0001
<46, %	6.5	6.6	<0.0001
46–65, %	33.1	28.7	
66–85, %	48.4	50.7	
>85, %	12.0	14.0	
Female sex, %	46.0	50.3	<0.0001
Race-ethnicity, %			
White, non-Hispanic	77.0	75.7	0.0115
Black	10.9	12.7	
Asian	2.0	2.1	
Hispanic	5.4	5.3	
Arrival by emergency medical services (vs private transport), %	85.9	84.2	<0.0001
Arrival on-hours (vs off-hours), %	50.7	45.5	<0.0001
Time from symptom onset to arrival, median (25th–75th percentile), min	60 (40–95)	49 (34–65)	<0.0001
NIHSS, median (25th–75th percentile), %*			
0–9	29.8	30.9	0.1113
10–14	20.2	18.8	
15–20	21.8	19.2	
21–42	13.0	13.8	
Not documented	15.2	17.3	
Atrial fibrillation/flutter, %	22.1	25.0	<0.0001
Prior stroke/TIA, %	20.7	25.1	<0.0001
Coronary artery disease/prior myocardial infarction, %	27.7	29.5	0.0099
Carotid stenosis, %	3.2	3.3	0.7782
Peripheral vascular disease, %	3.2	3.8	0.0367
Prosthetic heart valve, %	1.1	1.4	0.0588
Diabetes mellitus, %	23.5	24.5	0.1032
Hypertension, %	75.0	76.5	0.0168
Smoker, %	22.8	20.1	<0.0001
Dyslipidemia, %	38.0	39.0	0.1444
Hospital diagnostics and treatment intervals			
Time from arrival to CT scan, median (25th–75th percentile), min	18 (11–26)	24 (15–36)	<0.0001
Door to CT scan $\leq 25$ min, %	68.5	53.0	<0.0001
Time from symptom onset to tPA treatment, median (25th–75th percentile), min	110 (88–144)	145 (124–165)	<0.0001
Door-to-needle time, mean (SD), min	46.0 (12.2)	91.4 (21.7)	<0.0001
Median (25th–75th percentile), min	49 (40–55)	88 (74–105)	

CT indicates computerized tomography.

\*NIHSS values were recorded in 21 277 patients. Sex was missing in 0.07%, race/ethnicity in 0.17%, medical history in 2.08%, and arrival mode in 2.68%.

CI, 0.92 to 0.98;  $P=0.0007$ ). There were no significant differences in the risk-adjusted odds for discharge home, ambulatory status, and length of stay  $\leq 4$  days. Multivariable GEE analyses revealed an adjusted OR of 0.88 (95% CI, 0.75

to 1.02;  $P=0.09$ ) for the tPA complication of intracranial hemorrhage for patients with door-to-needle times  $\leq 60$  minutes compared with those with door-to-needle times  $> 60$  minutes.

**Table 2. Hospital Characteristics of Ischemic Stroke Patients With Door-to-Needle Times  $\leq 60$  Minutes Compared With Those With Door-to-Needle Times  $> 60$  Minutes**

Hospital-Level Characteristics	Door-to-Needle Time $\leq 60$ min	Door-to-Needle Time $> 60$ min	<i>P</i>
n	6790	18 714	
Annual volume of ischemic stroke admissions, %			
301+	15.6	14.7	0.0003
101–300	64.5	63.2	
0–100	19.8	22.1	
Annual volume of tPA administration, %			
20+	23.5	15.4	$< 0.0001$
11–20	34.8	32.3	
0–10	41.7	52.4	
Hospital size, beds, median (25th–75th percentile)	400 (270–588)	380 (267–558)	0.0002
Hospital type, %			
Nonacademic	33.5	36.0	0.0005
Academic	62.9	60.9	
TJC primary stroke center, %	68.5	65.9	$< 0.0001$
Time in GWTG-Stroke, median (25th–75th percentile), mo	30 (15–45)	27 (15–42)	$< 0.0001$
Hospital region, %			
West	21.8	21.0	$< 0.0001$
South	30.9	33.0	
Midwest	17.0	18.3	
Northeast	30.4	27.7	

TJC indicates The Joint Commission. Bed size was missing in 4.11%, and academic status was missing in 3.20%.

## Discussion

Despite the proven benefits of timely administration of tPA for acute ischemic stroke and national goals, our analysis demonstrates that a minority of patients treated with intravenous tPA receive this therapy within 60 minutes of arrival. Older patients, black patients, women, and those with less severe strokes or arriving during off-hours were particularly less likely to receive timely care. Additionally, hospitals with less experience in providing tPA to ischemic stroke patients were less likely to provide thrombolytic therapy within 60 minutes. This study is also important in finding only modest improvements in the timely administration of tPA over calendar time or duration of program participation. Given the slow progress in achieving faster door-to-needle times and the large remaining “gap,” we believe that these data support the need for a collaborative national campaign to improve timely treatment with intravenous tPA.

Data supporting the benefits of timely intravenous tPA on acute ischemic stroke outcomes in the setting of clinical trials are clear.<sup>1–6</sup> Time to treatment with intravenous tPA is an important determinant of 90-day and 1-year functional outcomes in acute ischemic stroke. In a pooled analysis of 6 randomized placebo-controlled trials of intravenous tPA

**Table 3. Patient- and Hospital-Level Characteristics Associated With Door-to-Needle Time  $\leq 60$  Minutes**

Variables	Adjusted OR	Lower 95% CI	Upper 95% CI	<i>P</i>
<b>Demographics</b>				
Age, per 10-y increase	0.92	0.90	0.95	$< 0.0001$
Sex, female	0.87	0.81	0.93	0.0001
Race/ethnicity (reference non-Hispanic white)				
Black	0.80	0.71	0.89	0.0001
Hispanic	0.96	0.82	1.13	0.6598
Other	0.98	0.83	1.15	0.7916
<b>Admission characteristics</b>				
Arrival mode, emergency medical services	1.10	0.97	1.23	0.1275
Arrival time, on-hours	1.27	1.18	1.37	$< 0.0001$
Symptom-onset-to-arrival times, per 10-min increase	1.23	1.22	1.25	$< 0.0001$
NIHSS (reference: 0–9)				
10–14	1.37	1.25	1.51	$< 0.0001$
15–20	1.58	1.44	1.73	$< 0.0001$
21–42	1.37	1.23	1.54	$< 0.0001$
<b>Medical history</b>				
Atrial fibrillation	0.89	0.81	0.97	0.0077
Prosthetic heart valve	0.75	0.55	1.00	0.0539
Coronary artery disease/prior myocardial infarction	0.95	0.86	1.04	0.2313
Carotid stenosis	1.01	0.84	1.22	0.9225
Diabetes mellitus	0.89	0.83	0.97	0.0051
Peripheral vascular disease	0.89	0.73	1.08	0.2444
Hypertension	1.01	0.94	1.08	0.8625
Smoker	1.00	0.92	1.10	0.9637
Dyslipidemia	1.01	0.94	1.09	0.7223
Stroke/TIA	0.81	0.74	0.88	$< 0.0001$
<b>Hospital characteristics</b>				
The Joint Commission primary stroke center	1.02	0.88	1.17	0.7903
No. of hospital beds, per 200-bed increase	0.96	0.91	1.01	0.1260
Academic hospital	1.01	0.89	1.15	0.8233
Hospital region (reference: Northeast)				
Midwest	1.05	0.88	1.25	0.5826
South	0.97	0.83	1.14	0.7273
West	0.89	0.74	1.07	0.2237
Ischemic stroke admissions per year (reference: $\leq 100$ )				
$> 100$ –300	0.86	0.74	1.00	0.0467
$> 300$	0.53	0.38	0.75	0.0003
Intravenous tPA patients per year (reference: $\leq 10$ )				
$> 10$ –20	1.38	1.18	1.61	$< 0.0001$
$> 20$	2.03	1.51	2.74	$< 0.0001$

The table reflects multivariable modeling performed with 20 358 patients with full data available, including NIHSS. No major differences (apart from NIHSS) were observed when the model was constructed using the more complete cohort of patients ( $n = 24\ 385$ ) without recorded NIHSS. The findings were also similar when hospital characteristics of annual ischemic stroke admissions and annual tPA patients treated were analyzed as continuous variables and interaction terms were included in the model.

**Table 4. Clinical Outcomes of Ischemic Stroke Patients With Door-to-Needle Times  $\leq$ 60 Minutes Compared With Those With Door-to-Needle Times  $>$ 60 Minutes**

Hospital Events and Discharge Status	Door-to-Needle Time $\leq$ 60 min	Door-to-Needle Time $>$ 60 min	<i>P</i>
n	6790	18 714	
In-hospital mortality, %*	8.6	10.4	$<0.0001$
Discharge destination, %			$<0.0001$
Home	37.3	37.3	
Rehabilitation	34.4	31.7	
Skilled nursing facility	17.8	18.8	
Hospice	4.1	4.9	
Transfer out	5.3	6.4	
Against medical advice/other	0.5	0.5	
Length of stay†			0.2082
Median (25th–75th percentile), d	5 (3–8)	5 (3–8)	
Mean (SD), d	7.0 (6.8)	7.0 (6.8)	
$>$ 4 d, %	53.9	56.5	0.4457
Ambulatory status, %*			0.7519
Able	40.2	39.6	
With assistance	29.8	30.1	
Not able	22.0	22.5	
Not documented	2.0	2.0	
tPA complications, %*			
Any	8.0	9.0	0.0065
Symptomatic intracranial hemorrhage	4.7	5.6	0.0017
LT or serious systemic hemorrhage	1.2	1.5	0.0932
Other complication	1.2	1.0	0.0900

LT indicates life-threatening.

\*Excludes patients who transferred out.

†Excludes transfer-in and -out patients.

treatment started within 360 minutes of onset of stroke in 2775 patients, the odds of a favorable 3-month outcome increased as onset to treatment decreased.<sup>3</sup> Odds for improved functional outcomes were 2.8 (95% CI, 1.8 to 4.5) for 0 to 90 minutes, 1.6 (95% CI, 1.1 to 2.2) for 91 to 180 minutes, 1.4 (95% CI, 1.1 to 1.9) for 181 to 270 minutes, and 1.2 (95% CI, 0.9 to 1.5) for 271 to 360 minutes. This pooled analysis demonstrates that the sooner intravenous tPA is given to stroke patients, the greater the benefit is, especially if started within 90 minutes of symptom onset. In another analysis, for every 100 patients treated with intravenous therapy, with every 10-minute delay in the start of thrombolytic infusion within the 1- to 3-hour treatment time period, 1 fewer patient had an improved disability outcome.<sup>6</sup>

Results from clinical trials have encouraged multiple organizations to set targets for timely initiation of thrombolytic therapy after hospital arrival. A National Institute of Neurological Disorders and Stroke (NINDS) national symposium on the rapid identification and treatment of acute stroke recommended a door-to-needle target time of 60 minutes.<sup>7</sup>

AHA/ASA guidelines recommend that target for completion of initial evaluation and treatment start with tPA should be within 1 hour of the patient's arrival in the emergency department.<sup>2,9</sup> The Brain Attack Coalition's target for primary stroke centers is to achieve a door-to-needle time within 60 minutes in  $\geq$ 80% of patients.<sup>8</sup>

Among hospitals participating in GWTG-Stroke, the speed of initiation of tPA treatment after hospital arrival was frequently below the recommended national target of a door-to-needle time  $\leq$ 60 minutes. During the overall study period, only one quarter of patients with acute ischemic stroke treated with tPA within 3 hours of symptom onset had door-to-needle times within 60 minutes, and the overall median door-to-needle time for the entire cohort of patients was 78 minutes. Other studies have also shown relatively prolonged door-to-needle times in patients treated with tPA for acute ischemic stroke. The Standard Treatment With Alteplase to Reverse Stroke (STARS) multicenter tPA study of 57 academic and community centers in the United States found a median door-to-needle time of 96 minutes.<sup>13</sup> In contrast, other studies have reported more rapid reperfusion therapy times. In the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) observational study conducted in 285 centers and 6483 patients in the European Union, there was a mean door-to-needle time of 68 minutes.<sup>14</sup> In the 2 NINDS tPA trials, the median door-to-needle time was 64 minutes despite the need to obtain research informed consent by virtue of trial participation.<sup>1</sup> Select centers have reported mean door-to-needle times well below 60 minutes, including 50 minutes in Cologne, Germany, and 38 minutes in Bergen, Norway.<sup>15,16</sup> Many of these are dedicated stroke centers that benefit from regionalization of acute stroke care.

In the GWTG-Stroke data set, the most powerful independent determinants of door-to-needle times  $\leq$ 60 minutes were greater severity of stroke deficits on the NIHSS and higher annual hospital volume of tPA patients. Certain patient characteristics and comorbid conditions like diabetes mellitus and atrial fibrillation were independently associated with less timely administration of thrombolytic therapy. It is of concern that older patients, women, and black patients were less likely to receive timely administration of tPA. It is also notable that the symptom-onset-to-arrival times were shorter in patients with door-to-needle times  $>$ 60 minutes, suggesting that hospitals were taking a more relaxed approach to the administration of tPA in earlier-arriving patients. Encouraging in our study were observations that achievement of door-to-needle times within 60 minutes was highest at hospitals with a larger annual volumes of intravenous tPA and that certain centers were able to achieve door-to-needle times  $\leq$ 60 minutes in the majority of patients. The number of hospitals with greater experience administering tPA is likely to increase in coming years owing to the regionalization of emergency stroke care in the United States with direct routing of patients to designated stroke centers and the emergence into practice of a generation of treatment-oriented emergency physicians, stroke neurologists, and dedicated inpatient neurohospitalists.<sup>17</sup> The finding that the length of time participating in the GWTG-Stroke Program and The Joint Commission primary stroke center certification were not

**Table 5. Unadjusted and Adjusted ORs for Clinical Outcomes in Patients With Door-to-Needle Times  $\leq 60$  Minutes Compared With Those With Door-to-Needle Times  $> 60$  Minutes**

Outcome	Unadjusted			Adjusted*		
	OR	95% CI	P	OR	95% CI	P
Mortality	0.78	0.69–0.88	0.0001	0.78	0.69–0.90	0.0003
Discharge home	0.96	0.90–1.04	0.3331	0.98	0.91–1.07	0.7130
Discharge home or acute rehabilitation	1.10	1.02–1.19	0.0146	1.07	0.98–1.17	0.1277
Ambulatory at discharge	1.01	0.94–1.09	0.8085	1.03	0.95–1.13	0.4848
Length of stay ( $\leq 4$ d)	1.00	0.93–1.07	0.9902	0.98	0.91–1.05	0.4982
Symptomatic ICH	0.84	0.73–0.97	0.0182	0.88	0.75–1.02	0.0886
Systemic hemorrhage	0.82	0.61–1.11	0.2046	0.81	0.59–1.13	0.2171
Any tPA complication	0.90	0.81–1.00	0.0455	0.91	0.81–1.02	0.1148

ICH indicates intracranial hemorrhage.

\*Variables included in multivariable models were sex, race, prior medical history of atrial fibrillation, stroke/TIA, coronary heart disease or myocardial infarction, carotid stenosis, diabetes mellitus, peripheral vascular disease, hypertension, dyslipidemia, smoking, NIHSS (continuous), arrival mode, arrival time on-/off-hours, onset-to-door time (continuous), hospital characteristics of geographic region, academic, primary stroke center, bed size, and annual number of strokes. No major differences were observed when the models were constructed using the more complete cohort of patients ( $n=24\ 284$ ) with or without recorded NIHSS.

independently associated with an increase in the proportion of patients with door-to-needle times  $\leq 60$  minutes of arrival demonstrates the need to expand the focus of GWTG beyond efforts to increase tPA use among eligible patients. To this end, attention should turn to revising aspects of the GWTG-Stroke toolkit, intervention strategies, and recognition system to better highlight the importance of this door-to-needle target and to provide best practice strategies for its achievement.

Successful efforts to accelerate door-to-needle times in acute ischemic stroke have previously been reported.<sup>16–21</sup> These include prearrival notification by emergency medical service providers; 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 physician, nurses, pharmacists, and technologists from emergency medicine, neurology, and radiology; and continuous data collection to drive iterative system improvement.<sup>16–21</sup> It is also recommended that stroke programs continually evaluate their performance using quality improvement methods to ensure that eligible patients are evaluated and treated in a timely manner.<sup>9</sup>

Although there may be concerns that attempting to achieve shorter door-to-needle times may lead to rushed assessments, dosing errors, and greater likelihood of complications,<sup>17</sup> there was no evidence in this study of worse in-hospital outcomes or increased bleeding complications from tPA for patients with door-to-needle times  $\leq 60$  minutes compared with those with door-to-needle times  $> 60$  minutes. In-hospital mortality was lower among those patients treated in a more timely fashion, even after extensive risk adjustment. Lower mortality has not previously been reported with more timely tPA therapy within the first 3 hours after stroke onset, so this finding should be interpreted cautiously and should be repli-

cated in independent data sets. This finding is, however, consonant with meta-analysis data indicating that late thrombolytic therapy beyond 3 hours after onset increases mortality and earlier thrombolytic therapy within 3 hours does not.<sup>22,23</sup> Importantly, the rate of symptomatic intracerebral hemorrhage in tPA-treated patients with door-to-needle times within 60 minutes was 4.7%, lower than the 5.6% rate of reported in patients with door-to-needle times  $> 60$  minutes. These rates may also compare favorably with those observed in the NINDS trial (6.4%) and other phase IV studies.<sup>1</sup> These findings suggest that more rapid reperfusion therapy can be achieved without compromising short-term clinical outcomes.

This study identifies substantial opportunities nationally for improvement in the speed of tPA therapy initiation in acute ischemic stroke patients. Once patients with ischemic stroke have arrived at the hospital, it is incumbent on the hospital to perform rapid diagnostic evaluation/imaging and, in eligible patients without contraindications, to promptly initiate intravenous tPA therapy.<sup>5,9</sup> It is important to acknowledge that a door-to-needle time  $\leq 60$  minutes may not be appropriate or achievable in all ischemic stroke patients, particularly those with unstable hemodynamics, respiratory compromise, or challenging clinical presentations. Nevertheless, these findings suggest that there is a critical need for a targeted campaign tailored to increase the portion of patients with door-to-needle times  $\leq 60$  minutes such as the recently launched ASA Target: Stroke initiative.

### Limitations

A number of potential limitations should be considered in interpreting the results of this study. Hospitals participating in GWTG-Stroke are self-selected and tend to be larger teaching institutions and have an interest in stroke quality improvement.<sup>10,11</sup> They also may have better-organized stroke systems of care than nonparticipating hospitals. As such, it is likely that other US hospitals would have a smaller portion of patients with door-to-needle time  $\leq 60$  minutes than those



observed in this study. These 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, pre-defined logic and range checks on data fields at data entry, audit trails, and regular data quality reports for all sites.<sup>11</sup> Limited source documentation audits at the individual state and site levels have shown high data quality. Participating hospitals are instructed to include all consecutive admissions for ischemic stroke. However, because these processes are not audited, the potential exists for selection bias. Although we investigated the influence of multiple patient- and hospital-level factors on door-to-needle time  $\leq 60$  minutes, a number of additional factors that may be important in timely reperfusion were not captured in GWTG-Stroke and could not be analyzed. These include prehospital notification by emergency medical service, existence of a regional stroke system of care with routing of stroke patients directly to designated stroke centers, use of stroke pathways, availability of stroke neurologists, location of computed tomography or magnetic resonance imaging scanners in the emergency department, and timely feedback of performance.<sup>17</sup> A number of factors that influence in-hospital clinical outcomes or complications of tPA such as blood pressure control, adherence to dosing protocols, and early use of antiplatelet therapy were not collected or adjusted for.<sup>2</sup> NIHSS was not documented in 16.6% of patients, although findings for door-to-needle times and outcomes were similar in models with and without NIHSS. Residual measured and unmeasured confounding variables may have influenced some or all of the findings. As a result of the large sample size, some small differences in absolute terms are still highly statistically significant. Finally, no data on postdischarge stroke-related outcomes are currently collected in the GWTG-Stroke Program, so the longer-term impact of door-to-needle times within 60 minutes on functional outcomes could not be determined.

## Conclusions

Among hospitals participating in GWTG-Stroke, target door-to-needle times  $\leq 60$  minutes are achieved in only 26.6% of acute ischemic stroke patients treated within 3 hours of symptom onset. Furthermore, over the past 6.5 years, there has been only modest improvement in the proportion of patients in whom this time-related goal was achieved. A number of patient and hospital characteristics were associated with door-to-needle times  $\leq 60$  minutes. Although door-to-needle times vary substantially by hospital, certain hospitals participating in GWTG-Stroke achieve door-to-needle times  $\leq 60$  minutes in the majority of patients treated with intravenous tPA. Short-term clinical outcomes were not compromised in those patients receiving timelier reperfusion therapy. These findings lend support for a targeted initiative to shorten door-to-needle times in acute ischemic stroke to maximize the clinical benefit.

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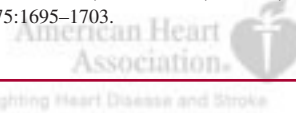
## Disclosures

Dr Fonarow receives research support from the National Institutes of Health; served as a consultant to Pfizer, Merck, Schering Plough, Bristol Myers Squibb, and Sanofi-Aventis; received honoraria from Pfizer, Merck, Schering Plough, Bristol Myers Squibb, and Sanofi-Aventis; and is an employee of the University of California, which holds a patent on retriever devices for stroke. Dr Fonarow had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr Smith serves as a member of the GWTG Science Subcommittee; receives research support from the NIH (NINDS R01 NS062028), Canadian Stroke Network, Canadian Institutes of Health Research, and Heart and Stroke Foundation of Canada; and has served on an advisory board for Genentech. Dr Saver serves as a member of the GWTG Science Subcommittee and as a scientific consultant regarding trial design and conduct to CoAxia, Concentric Medical, Talacris, Ferrer, Photothera, Brainsgate, Sygnis, and Ev3; received lecture honoraria from Ferrer; and is an employee of the University of California, which holds a patent on retriever devices for stroke. Dr Reeves receives salary support from the Michigan Stroke Registry and serves as a member of the AHA's GWTG Quality Improvement Subcommittee. Dr Bhatt receives research support from AstraZeneca, Bristol-Myers Squibb, Eisai, Sanofi Aventis, and The Medicines Co. Dr Grau-Sepulveda is a member of the Duke Clinical Research Institute, which serves as the AHA GWTG data coordinating center. Drs Olson and Hernandez are members of the Duke Clinical Research Institute, which serves as the AHA GWTG Data Coordinating Center. Dr Hernandez is a recipient of an AHA Pharmaceutical Roundtable grant (0675060N); has received a research grant from Johnson & Johnson; and has received honorarium from AstraZeneca and Amgen. Dr Peterson has received research grants from Lilly, Johnson & Johnson, and Bristol-Myers Squibb, Sanofi-Aventis, and Merck-Schering Plough partnership. Dr Peterson serves as principal investigator of the Data Analytic Center for AHAs GWTG. Dr Schwamm serves as chair of the AHA GWTG Steering Committee; serves as a consultant to the Research Triangle Institute and to the Massachusetts Department of Public Health; and serves on the Steering Committee for Lundbeck's DIAS4 clinical trial.

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### CLINICAL PERSPECTIVE

Tissue-type plasminogen activator (tPA) is a proven intervention for acute ischemic stroke patients. The benefits of intravenous tPA in acute ischemic stroke are time dependent, and guidelines recommend an arrival to treatment initiation (door-to-needle) time of  $\leq 60$  minutes. Despite the proven benefits, guidelines recommendations, and explicit goals for timely administration of tPA, the frequency, patient and hospital characteristics, temporal trends, and outcomes of ischemic stroke with door-to-needle times  $\leq 60$  minutes have not been well studied. Data from 25 504 acute ischemic stroke patients treated with tPA within 3 hours of symptom onset from 2003 to 2009 in 1082 hospitals participating in the Get With the Guidelines–Stroke Program were analyzed to determine frequency, patient and hospital characteristics, and temporal trends in patients treated with door-to-needle times  $\leq 60$  minutes. Only 26.6% of tPA-treated patients had a door-to-needle time  $\leq 60$  minutes. Patient factors most strongly associated with door-to-needle time  $\leq 60$  minutes were younger age, male gender, white race, and no prior stroke. Hospital factors associated with  $\leq 60$ -minute door-to-needle times included greater annual volumes of tPA-treated stroke patients. The proportion of patients with door-to-needle times  $\leq 60$  minutes varied widely by hospital and increased modestly from 19.5% in 2003 to 29.1% in 2009. Despite similar stroke severity, in-hospital mortality was lower and symptomatic intracranial hemorrhage was less frequent for patients with door-to-needle times  $\leq 60$  minutes compared with patients with door-to-needle times  $> 60$  minutes. These findings support the need for a targeted initiative to improve the timeliness of reperfusion in acute ischemic stroke.

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SUPPLEMENTAL MATERIAL

Timeliness of Tissue Plasminogen Activator Therapy in Acute Ischemic Stroke: Patient Characteristics, Hospital Factors, and Outcomes Associated with Door-to-Needle Times within 60 Minutes

**Table I: Characteristics of Ischemic Stroke Patients Arriving within 3 Hours of Symptom Onset and Treated with tPA within 3 Hours of Symptoms Onset, Ischemic Stroke Patients Arriving within 3 Hours of Symptom Onset and not Treated with tPA or Treated Beyond 3 Hours, and Ischemic Stroke Patients Not Arriving within 3 Hours**

	Arriving within 3 Hours of Symptom Onset and Treated with tPA within 3 hours of Onset (Study Population)	Arriving within 3 Hours of Symptom Onset and Not Treated with tPA or Treated Beyond 3 Hours* (Excluded)	Arriving after 3 Hours of Symptom Onset† (Excluded)
N	25,504	103,927	465,269
<i>Patient Level Characteristics</i>			
Age, Years, Mean, (SD)	69.7 (14.7)	72.2 (14.5)	70.7 (14.6)
<46	6.6%	5.0%	5.5%
46-65	29.9%	25.1%	29.1%
66-85	50.1%	51.4%	49.7%
>85	13.4%	18.5%	15.7%
Sex, Female	49.3%	52.2%	52.7%
Race-Ethnicity			
White, Non-Hispanic	76.2%	77.2%	72.5%
Black	12.2%	12.1%	15.8%
Other	6.3%	6.0%	6.7%
Hispanic	5.6%	4.8%	5.1%
Arrival by Emergency Medical Services (vs Private Transport)	87.3%	73.1%	56.3%
Arrival On Hours (vs. Off Hours)	46.9%	46.3%	46.9%
Time from Symptom Onset to Arrival, Minutes, Median, (25 <sup>th</sup> -75 <sup>th</sup> )	50 (35-71)	73 (46-120)	623 (348-926)
NIHSS, Median, (25 <sup>th</sup> 75 <sup>th</sup> )	12 (7-18)	5 (2-12)	4 (2-10)
0-9	30.6%	39.2%	30.9%
10-14	19.2%	6.3%	4.2%
15-20	19.9%	5.5%	3.3%
21-42	13.5%	5.8%	2.9%
Not documented	16.8%	43.3%	58.7%
Atrial Fibrillation/Flutter	24.2%	24.1%	17.5%
Prior Stroke/Transient Ischemic Attack	24.0%	35.3%	32.3%
Coronary Artery Disease/Prior Myocardial Infarction	29.0%	30.8%	28.3%
Carotid Stenosis	3.2%	4.6%	4.8%
Peripheral Vascular Disease	3.6%	5.2%	5.4%

Prosthetic Heart Valve	1.4%	2.1%	1.5%
Diabetes Mellitus	24.3%	27.8%	33.4%
Hypertension	76.1%	78.1%	79.1%
Smoker	20.8%	16.6%	20.7%
Dyslipidemia	38.7%	40.0%	39.3%

\*There were 2823 patients arriving within 3 hours of symptom onset and treated with tPA beyond 3 hours

†There were 1490 patients arriving after 3 hours of symptom onset and treated with tPA