

Times From Symptom Onset to Hospital Arrival in the Get With The Guidelines–Stroke Program 2002 to 2009

Temporal Trends and Implications

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Background and Purpose—Time from symptom onset to hospital arrival is the most important factor in determining eligibility for intravenous tissue-type plasminogen activator. We used data from a large contemporary nationwide study to determine temporal trends in the proportions of patients arriving within time windows for potential acute ischemic stroke therapies.

Methods—Trends in symptom onset to hospital arrival time (“onset-to-door time”) for patients with acute ischemic stroke in the Get With The Guidelines–Stroke (GWTG–Stroke) program were analyzed between 2003 and 2009. Factors associated with early onset-to-door time (≤ 2 hours) were also examined.

Results—Between April 2003 and March 2009, 1287 hospitals submitted data on 413 147 patients with acute ischemic stroke of whom 194 352 (47.0%) had a specific onset time documented. Among all 413 147 patients, onset-to-door time was documented as ≤ 2 hours in 20.6%, ≤ 3 hours in 25.1%, ≤ 3.5 hours in 26.8%, and ≤ 8 hours in 35.8%. Early arrival within 2 hours was significantly associated with emergency medical services transport ($P < 0.0001$). There was no substantial change in onset-to-door time over the 6-year study period. Expansion of the tissue-type plasminogen activator treatment window from 3 to 4.5 hours (allowing 60 minutes for provision of tissue-type plasminogen activator) increases the pool of potentially eligible patients by 6.3% (30.1% relative increase).

Conclusions—More than one fourth of patients with ischemic stroke arrive within the time window for tissue-type plasminogen activator therapy; however, this percentage has remained unchanged over recent years. Further efforts are needed to increase the portion of patients with acute ischemic stroke presenting within the time window for acute interventions. (*Stroke*. 2012;43:1912–1917.)

Key Words: ischemic stroke ■ epidemiology ■ thrombolysis

Eligibility for acute ischemic stroke interventions depends on the time from symptom onset to hospital arrival. Although many studies have reported that only a minority of patients arrive early enough to be considered for acute therapy, most of these studies describe the experience of specific centers or regional networks over a limited time period.^{1,2} Few studies have documented temporal trends in onset to hospital arrival times for patients with acute stroke.

The large nationwide Get With The Guidelines–Stroke (GWTG–Stroke) program provides a unique opportunity to analyze time trends in onset to arrival over recent years and to identify factors related to early arrival to the hospital. Because there may have been increasing public awareness of

stroke symptoms based on public education campaigns,^{3–5} we hypothesized that a greater proportion of patients with ischemic stroke would arrive at earlier times in more recent years, within time windows in which intravenous or endovascular acute stroke therapies could be considered.

Methods

The design and conduct of the GWTG–Stroke program have been previously described.^{6,7} Briefly, GWTG uses a web-based patient management tool (Outcome Services, Inc, Cambridge, MA) to collect clinical data, provide decision support, and real-time online reporting features. Each participating hospital received human research approval from their Institutional Review Board. Outcome

Received November 12, 2011; final revision received February 15, 2012; accepted February 27, 2012.

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Louis Caplan, MD, was the Guest Editor for this paper.

The online-only Data Supplement is available with this article at <http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.111.644963/-DC1>.

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Stroke is available at <http://stroke.ahajournals.org>

DOI: 10.1161/STROKEAHA.111.644963

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.

Case Identification and Data Abstraction

Deidentified patient data from consecutive stroke admissions were abstracted from the medical records using the patient management tool, including demographics, medical history, time of symptom onset and hospital arrival, mortality, and discharge destination. Before January 2008, the time of symptom onset was recorded as the witnessed time or as the time the patient was last known to be well if the stroke onset was not witnessed along with the source of the information (patient or other informant). In the absence of information on the exact time, chart abstractors were allowed to record an approximate time of onset if supported by chart documentation; for the purpose of this analysis, these approximate times were treated as missing exact onset times. After January 2008, the data collection tool was simplified and stroke onset times were recorded as the time the patient was last known to be well and the time that symptom onset was discovered, approximate times were no longer allowed, and the source of information (patient versus witness) was no longer recorded. The onset-to-door time (OTD) was defined as the time of emergency department arrival minus the stroke onset time. Data on hospital-level characteristics (bed size, academic or nonacademic status, annual volume of stroke discharges, and geographical region) were derived from information provided by the American Hospital Association.

Patient Population

Between April 2003 and March 2009, 516 236 acute ischemic stroke emergency department admissions were recorded in GWTG-Stroke. Of these 86 247 (16.7%) were excluded because they were transferred from another hospital. Another 11 946 with unknown date or time of hospital arrival (2.3%) and 4896 (0.9%) who had negative OTD (either because of coding error or because stroke symptoms began in the emergency department after arrival) were also excluded. Thus, there were 413 147 patients from 1287 hospitals who were included in the analysis. When analyzing the patient and hospital characteristics associated with earlier arrival, we restricted the analysis population to 182 092 of 414 540 patients (44.1%) from 1266 hospitals who had documented symptom onset within 24 hours, like in similar studies.⁸

Statistical Analysis

Yearly trends over time in OTD were tabulated and graphed according to the following categories: OTD ≤ 2 hours, OTD > 2 to 3 hours, OTD > 3 to 4.5 hours, OTD > 4.5 to 6 hours, OTD > 6 to 24 hours, OTD > 24 hours, and unknown date or time of onset (including missing onset time but same day arrival, missing onset time but documented day of arrival ≥ 1 before to the day of presentation, and missing both onset time and day of arrival). Continuous variables were compared by χ^2 rank-based group means score statistics. Categorical variables were compared by χ^2 rank-based group means score statistics. Predictors of early arrival (≤ 2 hours) were identified using multivariable logistic regression using the generalized estimating equation method to account for clustering of patients by hospital. All patient and hospital-level variables were included in the initial model and then backward selection was used to eliminate nonsignificant variables with $P > 0.10$. Data on National Institutes of Health Stroke Scale (NIHSS) were missing in $> 40\%$; therefore, NIHSS was not included in the models. The rate of missing data for other variables was $< 4\%$ and was imputed as the most common category, except that patients with missing hospital characteristic data were excluded from the models. The adjusted relationship between calendar year and OTD ≤ 2 hours was determined in a model that included all patients with ischemic stroke, including those with undocumented times. To determine patient characteristics associated with earlier arrival, patients with OTD ≤ 2 hours were compared with patients with OTD 2 to 24 hours.

Statistical analyses were performed using SAS Version 9.2 software (SAS Institute, Cary, NC).

Results

OTD Among All Patients With Ischemic Stroke

There were 413 147 patients with ischemic stroke admitted to participating hospitals between April 2003 and March 2009. Median age was 73 years (interquartile range, 61–82 years) and 47.5% were male. The median bed size of the admitting hospital was 365 beds (interquartile range, 256–530 beds), 58.0% were teaching hospitals, 95.9% were in an urban location, and 69.2% participated in GWTG-Stroke for at least 2 years. The geographical distribution of the patients was 17.5% from the West region, 37.6% from the South region, 18.9% from the Midwest region, and 26.0% from the North-east region.

Overall, among the 413 147 patients, 20.6% presented ≤ 2 hours, 4.5% presented at 2 to 3 hours, 4.6% presented at 3 to 4.5 hours, 6.1% presented at 4.5 to 8 hours, 8.3% presented at 8 to 24 hours, 3.0% presented > 24 hours, and 53.0% did not have exact time of onset documented. Therefore, expansion of the tissue-type plasminogen activator time window when expressed on the basis of the “practical” time window of 2 hours to 3.5 hours, allowing the guideline-recommended maximum of 60 minutes to initiate intravenous tissue-type plasminogen activator,⁹ increased the portion of potentially eligible patients from 20.6% to 26.9% (a 6.3% absolute increase or 30.1% relative increase).

More than half of patients did not have exact times of onset documented (218 795 of 413 147 [53.0%]), usually because the day of symptom onset was recorded but not the exact time of day (171 995 of 218 795 [78.6%]). The characteristics of patients with documented onset-to-arrival times compared with undocumented times are shown in online-only Data

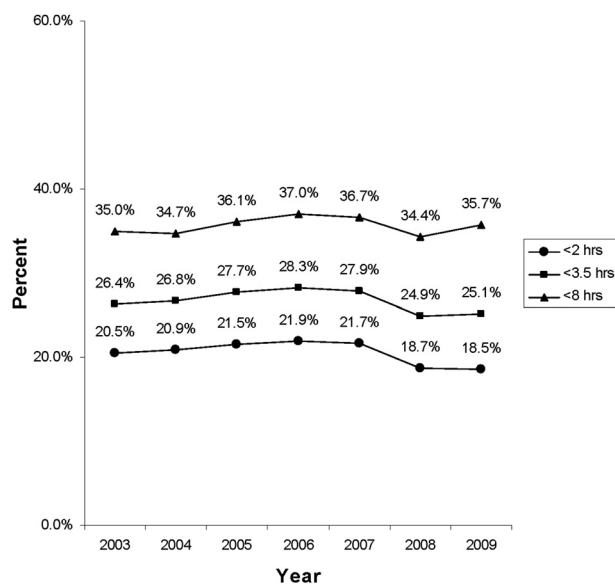


Figure. Percent of patients arriving ≤ 2 hours, ≤ 3.5 hours, or ≤ 8 hours as a proportion of all ischemic stroke patient admissions (with or without documented time of onset) in 2003 ($n=10\ 480$), 2004 ($n=21\ 035$), 2005 ($n=48\ 011$), 2006 ($n=81\ 725$), 2007 ($n=106\ 031$), 2008 ($n=128\ 979$), and 2009 ($n=16\ 866$).

Table 1. Characteristics of Patients According to Onset-to-Door Time Categories Among Patients With Documented Time of Arrival ≤ 24 h After Symptom Onset

Characteristic	Onset-to-Door Time				P Value
	0–2 h (n=85 284)	>2–3.5 h (n=25 642)	>3.5–6 h (n=24 924)	>6–24 h (n=46 242)	
Demographic					
Age, y	74 [62, 83]	74 [62, 83]	73 [61, 82]	72 [59, 81]	<0.001
Female sex	50.8	51.9	51.3	50.3	0.39
Race					
White	76.9	75.6	73.9	71.3	<0.001
Black	12.2	12.9	14.7	16.5	
Hispanic (any race)	4.9	5.0	4.7	5.4	
Other	6.0	6.4	6.8	6.8	
Arrival mode					
Emergency medical services	77.5	66.5	62.3	55.5	<0.001
Private transport	22.5	33.5	37.7	44.5	
Medical history					
Atrial fibrillation	24.5	21.3	18.8	16.7	<0.001
Previous stroke or TIA	32.8	34.0	32.6	30.0	<0.001
Coronary artery disease	30.8	30.0	28.7	27.0	<0.001
Diabetes mellitus	26.6	30.0	32.0	33.4	<0.001
Hypertension	78.1	79.5	79.8	80.2	<0.001
Smoker	17.9	18.8	20.5	23.5	<0.001
Dyslipidemia	39.7	40.0	41.2	40.3	0.004
NIHSS					
NIHSS	7 [3, 15]	5 [2, 11]	5 [2, 10]	4 [2, 9]	<0.001
NIHSS not documented	38.4	46.6	49.6	50.4	<0.001
Outcomes					
Length of stay	4 [3, 7]	4 [3, 6]	4 [3, 6]	4 [3, 6]	<0.001
Discharge outcome					
Died	6.8	5.2	4.6	4.4	<0.001
Hospice	3.9	3.2	3.0	2.6	
Left against medical advice	0.5	0.5	0.4	0.6	
Transfer to acute care facility	4.0	3.0	2.7	2.3	
Rehabilitation	21.3	21.2	23.8	24.5	
Skilled nursing facility	17.2	18.1	18.1	17.0	
Home	46.3	48.9	47.3	48.6	
Onset time					
Weekday onset	51.6	55.3	52.8	36.0	<0.001
Symptom onset time					
6 AM–noon	33.3	39.7	39.3	25.6	<0.001
Noon–6 PM	36.1	33.7	31.7	21.1	
6 PM–midnight	24.9	18.5	14.9	34.7	
Midnight–6 AM	5.7	8.2	14.0	18.6	
Hospital characteristics					
No. of stroke discharges					0.13
0–100	8.8	8.4	8.4	9.1	
101–300	55.0	54.2	54.7	54.4	
301+	36.2	37.4	36.9	36.6	
No. of beds	365 [256, 527]	375 [262, 546]	374 [262, 5573]	378 [262, 561]	<0.001

(Continued)

Table 1. Continued

Characteristic	Onset-to-Door Time				P Value
	0–2 h (n=85 284)	>2–3.5 h (n=25 642)	>3.5–6 h (n=24 924)	>6–24 h (n=46 242)	
Region					<0.001
West	19.6	18.4	18.3	18.9	
South	36.0	36.1	35.6	35.3	
Midwest	18.3	19.1	20.2	20.2	
Northeast	26.2	26.4	25.9	25.6	
Academic hospital	58.9	60.9	61.6	62.6	<0.001
Rural location	3.2	3.2	3.0	3.2	0.50

Values are percentages or medians [25th, 75th percentiles].

TIA indicates transient ischemic attack; NIHSS, National Institutes of Health Stroke Scale score.

Supplement Table I. Because of the large size of the database, all comparisons were statistically significant but not necessarily clinically meaningful; however, patients with unknown or undocumented onset-to-arrival times were more likely to have less severe strokes, to arrive by private transport rather than by emergency medical services (EMS), to be black, and to have a history of atrial fibrillation and diabetes mellitus. There were no major changes in the rate of missing or undocumented times from 2003 to 2009; yearly rates ranged from 49.1% to 56.0%.

OTD Trends Over Time

Among all patients with ischemic stroke, including those with undocumented times, there was no significant trend toward an increase in the documented proportion of early arriving patients over time and even a slight decrease in the number of early arriving patients in 2008 and 2009 (Figure). The proportion of acute ischemic strokes transported by EMS was essentially the same from 2003 to 2008 (57.3%–56.7%) but was somewhat lower in 2009 (51.4%; $P<0.001$). After adjustment for other characteristics, including EMS transport, increasing calendar year was associated with a slight decrease in the adjusted odds of arriving ≤ 2 hours (OR, 0.96 per calendar year; 95% CI, 0.95–0.97). This association was essentially the same (OR, 0.96; 95% CI, 0.95–0.98) in a subgroup analysis restricted to 478 hospitals (contributing 281 750 patients) with continuous participation between 2003 and 2009. Despite the lack of increase in patients arriving within 2 hours, the overall rate of intravenous tissue-type plasminogen activator use increased from 3.6% of all patients with ischemic stroke in 2003% to 6.6% in 2009 ($P<0.001$).

Characteristics of Earlier Arrival Among Patients With Documented Onset Times ≤ 24 Hours

The characteristics of 182 092 patients with acute ischemic stroke and documented OTD ≤ 24 hours, according to 4 OTD categories, are shown in Table 1. Earlier arrival was strongly associated with transport by EMS (77.5% ≤ 2 hours OTD versus 55.5% 6–24 hours OTD; $P<0.001$). Early arrival patients were also significantly more likely to be older, white, have a history of atrial fibrillation/flutter, coronary artery disease, and were less likely to have diabetes or to be smokers

($P<0.001$). Among the 55.9% of patients with documented NIHSS scores, median NIHSS was higher in patients with shorter OTD (median, 7 in ≤ 2 hours OTD versus median 4 in 6–24 hours OTD; $P<0.001$). Early arrival patients were more likely to present during morning or afternoon hours and on weekdays compared with weekends ($P<0.001$).

Results of the multivariable-adjusted logistic regression analysis of predictors of OTD ≤ 2 hours, among patients with documented time of onset ≤ 24 hours, are shown in Table 2. Because of the size of the database, some factors associated with OTD ≤ 2 hours were statistically significant but had small effects. Factors associated with OTD ≤ 2 hours included white race, arrival by EMS, history of atrial fibrillation or flutter, and onset during weekday regular hours. Conversely, factors associated with decreased likelihood of OTD ≤ 2 hours included increasing age, increasing calendar time, and history of diabetes or smoking. Patients in the Midwest region and patients presenting to academic teaching hospitals were less likely to arrive ≤ 2 hours. Arrival by EMS was the factor that was most strongly associated with early arrival (OR, 2.28; 95% CI, 2.22–2.35). The independent predictors of early arrival were similar when the model was rerun among all patients with ischemic stroke ($n=413\ 147$), with the sole exception was that previous stroke or transient ischemic attack was no longer associated with ≤ 2 hours presentation.

Discussion

The main finding of this study is that the proportion of early arriving patients with ischemic stroke has not increased significantly from 2003 to 2009. Factors associated with shorter times from symptom onset to hospital presentation include arrival by EMS, younger age, male sex, white race, and history of atrial fibrillation. Overall $>20\%$ of patients with ischemic stroke had ≤ 2 hours OTD and $>25\%$ OTD ≤ 3.5 hours, showing that expansion of the intravenous tissue-type plasminogen activator time window from 3 to 4.5 hours increases the relative proportion of potentially eligible patients by approximately 30%, allowing 60 minutes for provision for tissue-type plasminogen activator. These results are consistent with prior studies showing a substantial percentage of patients with ischemic stroke arrive ≤ 3 hours after symptom onset.^{10–15}

Table 2. Factors Associated With OTD \leq 2 h (Versus OTD 2–24 h) in Multivariable Analysis

Variable	OR	95% Confidence Limits		P Value
		Lower	Upper	
Calendar year (per 1-y increase)	0.93	0.91	0.94	<0.001
Age (per 10-y increase)	0.93	0.92	0.94	<0.001
Female sex	0.97	0.95	0.99	0.002
Race (white versus nonwhite)	1.11	1.08	1.15	<0.001
Arrival by emergency medical services	2.28	2.22	2.35	<0.001
Weekday onset regular hours*	1.3	1.27	1.33	<0.001
Atrial fibrillation	1.29	1.26	1.33	<0.001
Previous stroke/TIA	1.03	1.01	1.06	0.004
Coronary artery disease	1.09	1.07	1.12	<0.001
Diabetes mellitus	0.77	0.75	0.79	<0.001
Peripheral vascular disease	0.95	0.9	0.99	0.03
Hypertension	0.91	0.89	0.93	<0.001
Smoking	0.79	0.77	0.81	<0.001
Dyslipidemia	1.03	1.01	1.05	0.004
Academic hospital	0.90	0.86	0.94	<0.001
Region				
Northeast (reference)
Midwest	0.94	0.88	1.00	0.03
South	1.02	0.97	1.08	
West	0.99	0.93	1.05	
No. of beds (per 100 increase)	0.98	0.97	0.99	<0.001

OTD indicates onset-to-door time; TIA, transient ischemic attack.

*Defined as onset during Monday to Friday, 6 AM to 6 PM.

Adjusted analyses showed a slight decrease in the number of patients arriving \leq 2 hours over time due to a slight decrease in documented early arrival times beginning in 2008 (Figure). This decrease in 2008 may be related to a change in how stroke onset time information was captured in the database (“Methods”). Stroke onset time information is complex and there are no uniform standards for how to capture it.¹⁶ Regardless of the cause of the decline in early arrival in 2008, it is clear that there has been no increase in the proportion of early arriving patients based on the stable proportions of early arriving patients from 2003 to 2008 and from 2008 to 2009 (Figure). This lack of improvement is unlikely to be related to differences in patient characteristics over time or changes in the GWTG-Stroke hospital population related to hospital entry or dropout in the program, because the lack of improvement was still seen in models controlling for patient and hospital characteristics and in a sensitivity analysis restricted to core hospitals that participated in the program for all 6 years (2003–2009). Also, during the study period, there was little change in the proportion of subjects with documented exact onset times versus missing onset times. Because our patient sample was hospital-based, not population-based, it is possible that the lack of increase in the proportion of early arrivers could

reflect an increase in the absolute number of patients presenting at later times rather than a lack of increase in the absolute number of patients presenting at earlier times. This could happen if, for example, increased public awareness of stroke led patients with milder stroke with longer duration symptoms to present to the hospital instead of their doctor’s office. Previous studies suggest that up to \geq 15% of strokes may present as an outpatient to the doctor’s office rather than the emergency room.^{17,18} Prospective epidemiological studies with active surveillance of stroke incidence in the outpatient and inpatient setting will be needed to address this possibility.

A previous population-based study showed a slight increase in patients arriving \leq 3 hours between 1993 and 1999 (23%–26%),¹⁹ but a subsequent multicenter study of 909 patients found no increase in the proportion of patients arriving \leq 2 hours between 2001 and 2004.⁸ We have extended these findings to a more contemporary time period with substantially more hospitals and patients and also find no increase in the number of early arriving patients.

A large number of patients had undocumented times of onset, usually because the day of onset was recorded but not the exact time in patients who arrived too late for reperfusion therapies. In some cases, the time and date may have been missing because reliable witnesses were not available. A similarly high rate of undocumented time of onset (57%) was seen in the Paul Coverdell National Acute Stroke Registry.²⁰ It is possible that the number of early arriving patients could be somewhat underestimated because of undocumented times. Nonetheless, our data are consistent with other studies that show that a large percentage of patients are ineligible for acute therapy based on time criteria alone.¹⁴

Arrival by EMS was strongly associated with greater likelihood of early arrival, an effect that has also been seen in prior studies,^{10,21,22} emphasizing the importance of emergency transportation. It is likely that the association between EMS transport and earlier arrival was partly driven by a relationship between higher stroke severity and the likelihood of calling for EMS. Early arriving patients had higher NIHSS in the univariate analysis (Table 1), but the high rate of missing NIHSS information (>50%) prevented us from adjusting for NIHSS in the multivariable model and thus we were unable to directly test whether stroke severity confounded the relationship between EMS transport and early arrival. Older age was associated with increased likelihood of early arrival in univariate analysis, but after multivariable adjustment, the effect was reversed such that older age was associated with lower likelihood of early arrival, as also suggested by a previous study.⁸ We could not determine whether patient living circumstances or knowledge of stroke symptoms were associated with the time from symptom onset to arrival, because there is limited information on prehospital characteristics in the GWTG-Stroke database. It is possible that some of the patient characteristics associated with later presentation (Table 2) are proxies for other characteristics such as lack of awareness of stroke signs that are the true determinants of delays in presentation. Future prospective studies are needed to explore barriers to timely activation of EMS and rapid transport to stroke centers.

This study has limitations similar to other large registries. The data provided by the sites were not independently audited or validated, although participating hospitals are instructed to include all patients with ischemic stroke. Data are dependent on the accuracy and completeness of the individual hospital data abstraction and original chart documentation. The NIHSS was missing in many patients, reflecting inconsistent use of the score in routine clinical practice. Because GWTG centers are voluntarily participating in a stroke quality improvement program and have different characteristics from US acute care hospitals as a whole, these findings may not be entirely representative. However, OTD is more likely to be influenced by prehospital factors than hospital characteristics and the GWTG-Stroke patient demographics are similar to the overall US ischemic stroke population.²³

Conclusions

Our analysis shows that there is substantial room for reducing the time from symptom onset to arrival in acute ischemic stroke. Slightly more than one fourth of patients arrives within 3.5 hours and could be treated by 4.5 hours given a door-to-needle time of ≤ 60 minutes. To increase the size of this time-eligible population will require additional efforts. Previous studies show that public education campaigns can reduce presentation times to the hospital.⁵ A public awareness campaign of nationwide scope may be needed that should include education to activate emergency medical systems when acute stroke symptoms are suspected.

Sources of Funding

The Get With The Guidelines[®]-Stroke (GWTG-Stroke) program is provided by the American Heart Association/American Stroke Association. The GWTG-Stroke program is currently supported in part by a charitable contribution from Bristol-Myers Squibb/Sanofi Pharmaceutical Partnership and the American Heart Association Pharmaceutical Roundtable. GWTG-Stroke has been funded in the past through support from Boehringer-Ingelheim and Merck.

Disclosures

Dr Reeves, Dr Hernandez, Dr Fonarow, Dr Schwamm, and Dr Smith have served as unpaid volunteers on American Heart Association GWTG committees. Dr Hernandez, Dr Olson, and Ms Zhao are employees of the Duke Clinical Research Center, which is contracted as the data analysis center for the GWTG program.

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