

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**

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Disclosures

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- The individual author disclosures are listed in the manuscript.

Background

- Tissue plasminogen activator (tPA) is a proven intervention for acute ischemic stroke and the benefits of tPA are strongly time dependent.
- Because of the importance of rapid treatment, national guidelines recommend an arrival to treatment initiation (door-to-needle [DTN]) time of 60 minutes or less.
- However, patient characteristics, hospital factors, and outcomes associated with DTN times \leq 60 minutes have not been well studied.

Objectives

- The objectives of this study were to evaluate the presenting characteristics of acute ischemic stroke patients treated with intravenous tPA in whom a DTN time ≤ 60 minutes was achieved, patient and hospital characteristics associated with DTN times ≤ 60 minutes, temporal trends in timely thrombolytic care, and clinical outcomes.

Methods

- GWTG Stroke is an ongoing, voluntary, observational registry and a continuous performance improvement program for patients hospitalized with stroke or TIA.
- A web-based Patient Management Tool provides decision support at the point-of-care, on-demand reporting and patient education features (Outcome, Cambridge, MA).
- Patient data were abstracted by trained hospital personnel. These included demographics, medical history, initial CT findings, in-hospital treatment and events, discharge treatments, treatment contraindications, counseling, in-hospital mortality, and discharge destination.
- The eligibility of all acute stroke admissions was confirmed prior to chart abstraction.

Methods: Study Population

- 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. There were 2823 patients arriving to the hospital within 3 hours of symptom onset, but treated with tPA beyond 3 hours after symptom onset, who 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 time eligible, 25,504 (19.7%) were treated with intravenous tPA within 3 hours of symptom onset in 1082 hospitals.

Statistical Methods

- The Duke Clinical Research Institute (DCRI) served as the data analysis center
- Patient demographic and clinical variables and hospital-level characteristics were compared between patients with and without DTN time ≤ 60 minutes.
- Pearson Chi-square test and Wilcoxon rank-sum tests were used to compare the categorical and continuous variables.

Statistical Methods

- The relationships between patient/hospital characteristics and outcomes associated with DTN times ≤ 60 minutes were further examined using multivariable logistic regression models. To account for within-hospital clustering, generalized estimating equations (GEE) were used to generate both unadjusted and adjusted models.
- Temporal trends in DTN times ≤ 60 minutes by both calendar time and program time participating in GWTG-Stroke were evaluated.

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.
- Among patients arriving within 3 hours of onset and receiving intravenous tPA within 3 hours of last known well time, the mean DTN time for tPA administration was 79.3 ± 28.1 minutes and the median 78 minutes (25th-75th 60-98 minutes).
- There were 6790 (26.6%) patients with DTN times ≤ 60 minutes and 18,714 (73.4%) with DTN times >60 minutes.

Patient Characteristics

	DTN Times ≤60 Minutes N=6790	DTN Times >60 Minutes N=18,714	P value
Age, Years, Mean, (SD)	68.9 (14.5)	70.1 (14.8)	<0.0001
Sex, Female	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 EMS (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, Minutes, Median, (25 th -75 th)	60 (40-95)	49 (34-65)	<0.0001
NIHSS*, Median, (25 th 75 th)	12 (8-18)	12 (7-18)	0.1113
0-9	29.8%	30.9%	0.1111
10-14	20.2%	18.8%	
15-20	21.8%	19.2%	
21-42	13.0%	13.8%	
Not documented	15.2%	17.3%	

Patient Characteristics

	DTN Times ≤60 Minutes N=6790	DTN Times >60 Minutes N=18,714	P value
<i>Past Medical History</i>			
Atrial Fibrillation/Flutter	22.1%	25.0%	<0.0001
Prior Stroke/Transient Ischemic Attack	20.7%	25.1%	<0.0001
Coronary Artery Disease/Prior MI	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

Patient Characteristics

	DTN Times ≤60 Minutes N=6790	DTN Times >60 Minutes N=18,714	P value
<i>Hospital Diagnostics and Treatment Intervals</i>			
Time from Arrival to CT Scan, Minutes, Median, (25 th -75 th)	18 (11-26)	24 (15-36)	<0.0001
Door to CT Scan ≤ 25 Minutes	68.5%	53.0%	<0.0001
Time from Symptom Onset to tPA Treatment, Minutes, Median, (25 th -75 th)	110 (88-144)	145 (124-165)	<0.0001
DTN Time, Minutes, Mean (SD) Median (25 th -75 th)	46.0 (12.2) 49 (40-55)	91.4 (21.7) 88 (74-105)	<0.0001

Hospital Characteristics

	DTN Time ≤60 Minutes	DTN Time >60 Minutes	P value
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, (25 th -75 th)	400 (270-588)	380 (267-558)	0.0002
Hospital Type			
Non-Academic	33.5%	36.0%	0.0005
Academic	62.9%	60.9%	
TJC Primary Stroke Center	68.5%	65.9%	<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%	

Patient and Hospital Characteristics Associated with DTN ≤ 60 Minutes

Variables	Adjusted Odds Ratio	Lower 95% CI	Upper 95% CI	P-Value
Demographics				
Age, Per 10 Year Increase	0.92	0.90	0.95	<.0001
Sex, Female	0.87	0.81	0.93	0.0001
Race/Ethnicity (reference Non-Hispanic Whites)				
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
Admission Characteristics				
Arrival Mode Emergency Medical Services	1.10	0.97	1.23	0.1275
Arrival Time On Hours	1.27	1.18	1.37	<.0001
Symptom Onset to Arrival Times, Per 10 Minutes Increase	1.23	1.22	1.25	<.0001
NIHSS (Reference: 0-9)				
10-14	1.37	1.25	1.51	<.0001
15-20	1.58	1.44	1.73	<.0001
21-42	1.37	1.23	1.54	<.0001

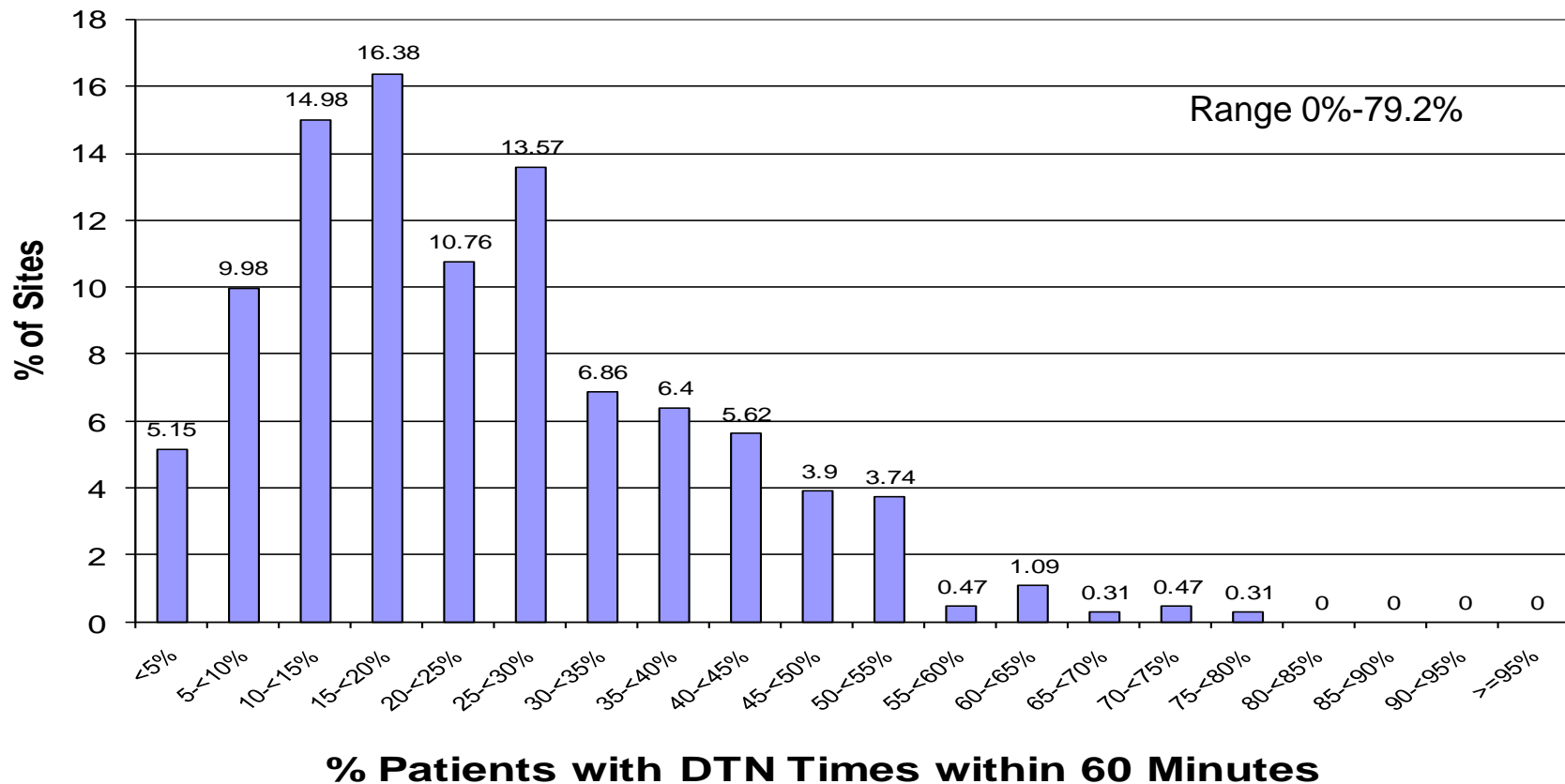
Patient and Hospital Characteristics Associated with DTN \leq 60 Minutes

Variables	Adjusted Odds Ratio	Lower 95% CI	Upper 95% CI	P-Value
Medical History				
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/Transient Ischemic Attack	0.81	0.74	0.88	<.0001

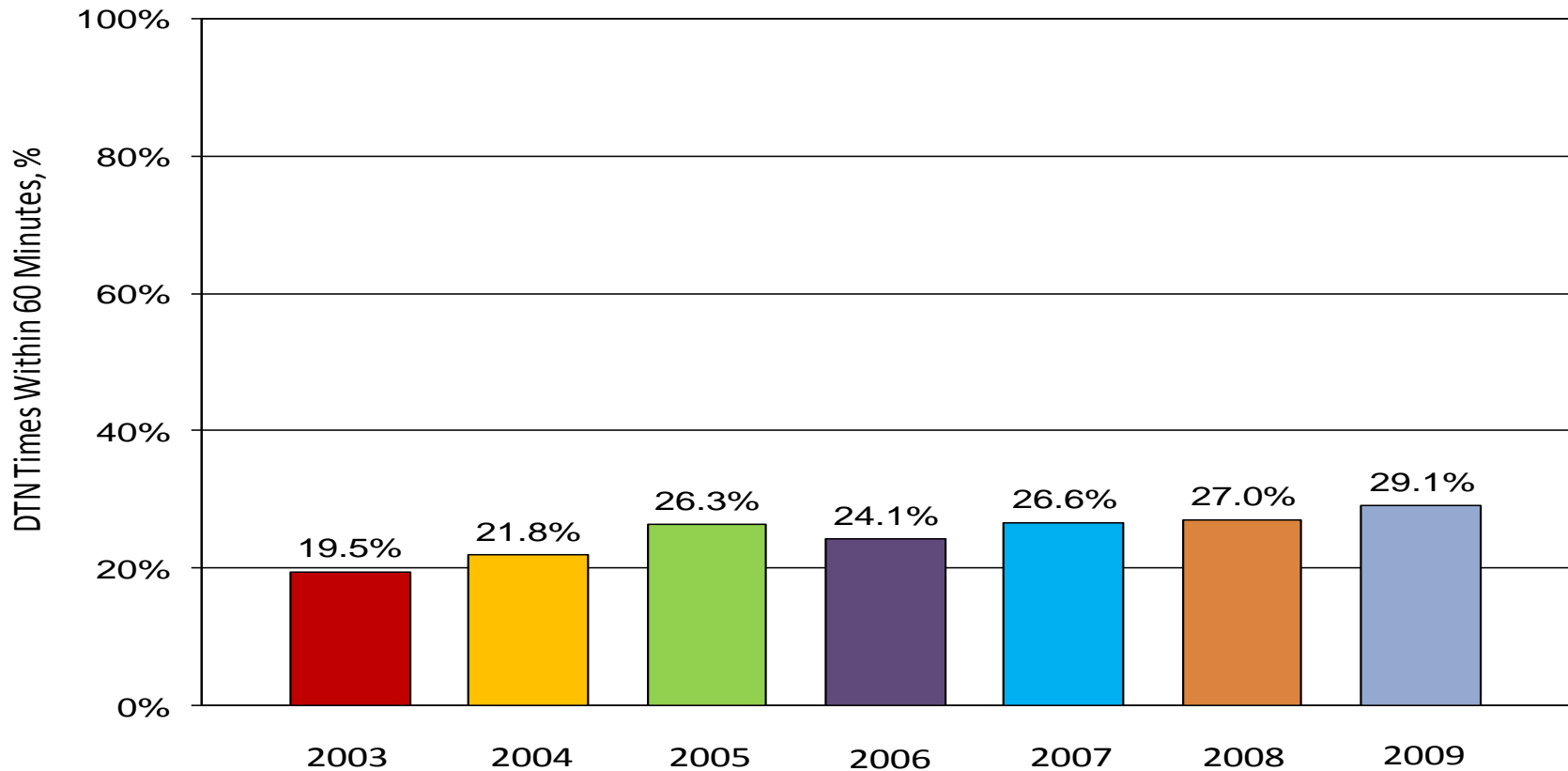
Patient and Hospital Characteristics Associated with DTN ≤ 60 Minutes

Variables	Adjusted Odds Ratio	Lower 95% CI	Upper 95% CI	P-Value
Hospital Characteristics				
The Joint Commission Primary Stroke Center	1.02	0.88	1.17	0.7903
Number of Hospital Beds, Per 200 Beds 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 Admits/Year (Reference ≤ 100)				
>100-300	0.86	0.74	1.00	0.0467
>300	0.53	0.38	0.75	0.0003
Intravenous tPA Patients/Year (Reference ≤ 10)				
>10-20	1.38	1.18	1.61	<.0001
>20	2.03	1.51	2.74	<.0001

Hospital Variation in the Proportion of Ischemic Stroke Patients with DTN Times ≤ 60 Minutes



Temporal Trends in the Proportion of Patients with DTN Times ≤ 60 Minutes 2003-2009



Clinical Outcomes by DTN Time in Acute Ischemic Stroke

	DTN Time ≤60 (N=6790)	DTN Time >60 (N=18,714)	P value
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, Days			0.2082
Median (25 th -75 th)	5 (3-8)	5 (3-8)	
Mean (SD)	7.0 (6.8)	7.0 (6.8)	
>4 Days	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 by DTN Time in Acute Ischemic Stroke

	DTN Time ≤60 Minutes (N=6790)	DTN Time >60 Minutes (N=18,714)	P value
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

* During the first 36 hours. LT = life threatening

Unadjusted and Adjusted Odds Ratios for Clinical Outcomes in Patients with DTN Time ≤ 60 Minutes Compared with Those with DTN Time >60 Minutes

Outcome	Unadjusted			Adjusted *		
	OR	95% CI	P-value	OR	95% CI	P-value
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 (≤ 4 Days)	1.00	0.93-1.07	0.9902	0.98	0.91-1.05	0.4982
Symptomatic	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

* Variables included in multivariable GEE models were age, sex, race, prior medical history of AF, stroke/TIA, CHD/MI, carotid stenosis, diabetes, PVD, hypertension, dyslipidemia, smoking, NIHSS (continuous), arrival mode (EMS vs other), arrival time on hours, hospital characteristics of geographic region, academic, PSC, bed size, annual number of strokes, annual number of tPA patients.

Multivariable Analysis of Association of DTN Time as a Continuous Variable with in-Hospital Mortality

After adjustment, every 15 minute reduction in DTN time was associated with 5% lower odds of in-hospital mortality

Adjusted OR 0.95, 95% CI 0.92-0.98, P=0.0007

* Variables included in multivariable GEE models were age, sex, race, prior medical history of AF, stroke/TIA, CHD/MI, carotid stenosis, diabetes, PVD, hypertension, dyslipidemia, smoking, NIHSS (continuous), arrival mode (EMS vs other), arrival time on hours, hospital characteristics of geographic region, academic, PSC, bed size, annual number of strokes, annual number of tPA patients.

Limitations

- Data were collected by medical chart review and are dependent upon the accuracy of documentation and abstraction.
- A number of additional variables that may be important in stroke prognosis or tPA complications were not captured in GWTG-Stroke and could not be adjusted for.
- Residual measured and unmeasured confounding variables may have influenced the findings.
- Post-discharge clinical outcomes, particularly modified Rankin score at 90 days were not collected and thus could not be analyzed.
- These findings may not apply to hospitals that differ in patient characteristics or care patterns from GWTG-Stroke Hospitals.
- These results may not extend to patients treated 3.0 to 4.5 hours after onset according to ECASS III criteria.

Conclusions

- Less than one-third of patients treated with intravenous tPA had DTN times ≤ 60 minutes.
- Patient factors most strongly associated with DTN times ≤ 60 minutes included younger age, male, white race, no prior stroke, arrival during regular hours, arrival times closer to 3 hours, and greater stroke severity. Hospital factors included greater annual volumes of tPA treated stroke patients, but not primary stroke center or teaching hospital status.
- There has been only modest improvement in the proportion of patients with DTN times ≤ 60 minutes over the past 6.5 years.
- Faster DTN times for tPA treated stroke patients was associated with lower risk adjusted in-hospital mortality and fewer complications.

Clinical Implications

- These findings support the need for a targeted initiative to improve the timeliness of intravenous tPA in acute ischemic stroke to maximize the clinical benefit.
- The ASA has recently launched the Target: Stroke initiative to increase the portion of patients with DTN times ≤ 60 minutes.