Original Investigation

Door-to-Needle Times for Tissue Plasminogen Activator Administration and Clinical Outcomes in Acute Ischemic Stroke Before and After a Quality Improvement Initiative

Gregg C. Fonarow, MD; Xin Zhao, MS; Eric E. Smith, MD, MPH; Jeffrey L. Saver, MD; Mathew J. Reeves, PhD; Deepak L. Bhatt, MD, MPH; Ying Xian, MD, PhD; Adrian F. Hernandez, MD, MHS; Eric D. Peterson, MD, MPH; Lee H. Schwamm, MD

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IMPORTANCE The benefits of intravenous tissue plasminogen activator (tPA) in patients with acute ischemic stroke (AIS) are time dependent and guidelines recommend a door-to-needle (DTN) time of 60 minutes or less. However, studies have found that less than 30% of US patients are treated within this time window. Target: Stroke was designed as a national quality improvement initiative to improve DTN times for tPA administration in patients with AIS.

OBJECTIVES To evaluate DTN times for tPA administration and the proportion of patients with times of 60 minutes or less before and after initiation of a quality improvement initiative and to determine whether potential improvements in DTN times were associated with improvements in clinical outcomes.

DESIGN, SETTING, AND PATIENTS The Target: Stroke initiative disseminated 10 care strategies to achieve faster DTN times for tPA administration, provided clinical decision support tools, facilitated hospital participation, and encouraged sharing of best practices. This study included 71 169 patients with AIS treated with tPA (27 319 during the preintervention period from April 2003-December 2009 and 43 850 during the postintervention period from January 2010-September 2013) from 1030 Get With The Guidelines—Stroke participating hospitals (52.8% of total).

MAIN OUTCOMES AND MEASURES The DTN times for tPA administration of 60 minutes or less and in-hospital risk-adjusted mortality, symptomatic intracranial hemorrhage, ambulatory status at discharge, and discharge destination.

RESULTS Measures of DTN time for tPA administration improved significantly during the postintervention period compared with the preintervention period as did clinical outcomes.

	Study Period		Adjusted Odds Ratio (95% CI)	*P* Value
	Preintervention (n = 27 319)	Postintervention (n = 43 850)		
tPA DTN time, median (IQR), min	77 (60-98)	67 (51-87)		< .001
tPA DTN time ≤ 60 min, % (95% CI)	26.5 (26.0-27.1)	41.3 (40.8-41.7)		< .001
End of each period	29.6 (27.8-31.5)	53.3 (51.5-55.2)		< .001
Improvement in tPA DTN time ≤ 60 min, % per year (95% CI)	1.36 (1.04-1.67)	6.20 (5.58-6.78)		< .001
In-hospital all-cause mortality, %	9.93	8.25	0.89 (0.83-0.94)	< .001
Discharge to home, %	37.6	42.7	1.14 (1.09-1.19)	< .001
Independent ambulatory status, %	42.2	45.4	1.03 (0.97-1.10)	.31
Symptomatic intracranial hemorrhage within 36 h, %	5.68	4.68	0.83 (0.76-0.91)	< .001

CONCLUSIONS AND RELEVANCE Implementation of a national quality improvement initiative was associated with improved timeliness of tPA administration following AIS on a national scale, and this improvement was associated with lower in-hospital mortality and intracranial hemorrhage, along with an increase in the percentage of patients discharged home.

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Author Affiliations: Division of Cardiology, University of California, Los Angeles (Fonarow); Duke Clinical Research Center, Durham, North Carolina (Zhao, Xian, Hernandez, Peterson); Department of Clinical Neurosciences, Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta, Canada (Smith); Department of Neurology, University of California, Los Angeles (Saver); Department of Epidemiology, Michigan State University, East Lansing (Reeves); Brigham and Women's Hospital Heart and Vascular Center and Harvard Medical School, Boston, Massachusetts (Bhatt); Department of Neurology, Massachusetts General Hospital, Boston, Massachusetts (Schwamm).

Corresponding Author: Gregg C. Fonarow, MD, Ahmanson-UCLA Cardiomyopathy Center, Ronald Reagan UCLA Medical Center, 10833 LeConte Ave, Room 47-123 CHS, Los Angeles, CA 90095 (gfonarow@mednet.ucla.edu).

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Intravenous tissue plasminogen activator (tPA) reduces long-term disability when administered early to eligible patients with acute ischemic stroke.[1-3] These benefits, however, are highly time dependent.[4-6] Earlier intravenous tPA administration is also associated with lower risks for complications, including symptomatic intracranial hemorrhage.[7,8] Because of the importance of rapid treatment, national guidelines recommend that hospitals complete the evaluation of patients with acute ischemic stroke and initiate intravenous tPA therapy within 60 minutes of patient arrival in eligible patients.[1,9-11] However, prior studies demonstrate that less than one-third of patients presenting with acute ischemic stroke in the United States were treated within the guideline-recommended door-to-needle time for tPA administration and this measure had improved minimally over time.[8,12]

Target: Stroke, a national quality improvement initiative organized by the American Heart Association/American Stroke Association (AHA/ASA), was launched in January 2010 to address this shortfall in providing timely acute ischemic stroke care.[13] To evaluate the principle results of the quality improvement initiative, we analyzed the temporal trends in door-to-needle times for tPA administration and determined the proportion of patients with times of 60 minutes or less before and after initiation of the program. In addition, we evaluated whether any potential improvements in door-to-needle times for tPA administration were associated with improvements in clinical outcomes, including in-hospital all-cause mortality, discharge destination, ambulatory status, symptomatic intracranial hemorrhage within 36 hours after receiving tPA, and overall tPA complications.

Methods

Design and Implementation of Target: Stroke

Target: Stroke was initiated by the AHA/ASA together with other partner organizations in January 2010 as previously described.[13] This collaborative national quality improvement initiative comprises a multidisciplinary group of clinicians and a broad alliance of participating hospitals.[13-15] The primary goal of the initiative was for participating hospitals to administer tPA to at least 50% of their patients with acute ischemic stroke within 60 minutes of hospital arrival. An expert working group performed a systematic review of the published data on improving door-to-needle times for tPA administration in patients with acute ischemic stroke and identified 10 key evidence-based strategies associated with timely stroke reperfusion that could be most rapidly, feasibly, and cost-effectively adopted by participating hospitals.[13] These strategies include promoting prenotification of hospitals by emergency medical services personnel, activating the entire stroke team with a single call or page, rapid acquisition and interpretation of brain imaging, use of specific protocols and tools, premixing tPA for high-likelihood candidates, a stroke team-based approach, and rapid feedback to the stroke team on performance (eTable 1 in Supplement).[13]

All Get With The Guidelines (GWTG)—Stroke hospitals were encouraged to participate and each hospital received a detailed tool kit, including the 10 key strategies, protocols, stroke screening tools, order sets, algorithms, time trackers, patient education materials, and other tools.[13] The tools are available on the Target: Stroke website (http://www.targetstroke.org). An implementation manual with a step-by-step guide to executing the program was developed and widely disseminated to all GWTG-Stroke hospitals. A multidimensional education program was created to support the initiative, which included digital materials, source documentation, comprehensive slide sets, webinars, interactive videos by experts, and successful approaches by participating hospitals. An annual honor roll recognition program for hospitals achieving the door-to-needle goal for tPA administration of 60 minutes or less in at least 50% of patients was also integrated. Input, collaboration, and feedback from GWTG-Stroke participating hospital teams was sought and considered essential to the success of the initiative.

Additional best practices, clinical decision support tools, and advice were also sought from clinicians from select GWTG-Stroke hospitals demonstrated to have achieved exceptionally good door-to-needle times for tPA administration. Hospitals were strongly encouraged to organize a multidisciplinary door-to-needle time improvement team and to implement each of the key best practice strategies to improve their times. The AHA/ASA GWTG quality improvement field staff also provided expert assistance to hospitals in their efforts to make improvements in door-to-needle times. A network of stroke champions in every state was used to motivate and facilitate changes at the hospital and clinician level.

Data Source and Study Population

The population consisted of patients receiving intravenous tPA at GWTG-Stroke participating hospitals during the study period. The analysis was confined to those hospitals participating in GWTG-Stroke both during the preintervention and postintervention periods. A national registry, GWTG-Stroke was launched by the AHA/ASA to support continuous quality improvement in hospital systems of care for patients with stroke and transient ischemic attack as previously described.[7,8,16] The registry uses a web-based patient management tool (Real-World & Late Phase Research, Quintiles Inc) to collect clinical data on consecutively admitted patients, to provide decision support, and to enable real-time online reporting features.[16] Data from patients treated with intravenous tPA between April 1, 2003, and September 30, 2013, were included in this analysis; the primary analysis was confined to patients with a class 1, level of evidence A, guideline recommendation for tPA (onset-to-treatment time ≤3 hours); and the sensitivity analyses included patients in the expanded tPA treatment window (onset-to-treatment time ≤4.5 hours).[1]

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.[16] Quintiles 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 agree-

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ment to analyze the aggregate deidentified data for research purposes. The institutional review board of Duke University approved the study.

Patient data, including demographics, medical history, stroke onset time (defined as last known well time), arrival time, in-hospital diagnostic studies, tPA treatment initiation time, tPA complications, in-hospital mortality, ambulatory status at discharge, and discharge destination were abstracted by trained hospital personnel. Stroke severity was measured by the National Institutes of Health Stroke Scale (NIHSS; a 15-item validated neurological examination scale with scores ranging from 0 to 42, with higher scores indicating more severe stroke). Admission staff, medical staff, or both, recorded the patient's self-reported race/ethnicity, usually during registration. Prior studies have suggested differences in outcomes from acute ischemic stroke related to race/ethnicity. Data on hospital-level characteristics (ie, bed size, academic or nonacademic status, and geographic region) were obtained from the American Hospital Association database.

Statistical Analysis

Patient demographic and clinical variables, hospital-level characteristics, door-to-needle times for tPA administration, proportion of patients with times of 60 minutes or less, and clinical outcomes were compared among patients treated during the preintervention period (April 1, 2003, to December 31, 2009) and the postintervention period (January 1, 2010, to September 30, 2013). Standardized differences (calculated as the difference in means or proportions divided by a pooled estimate of the standard deviation) were used to compare categorical and continuous patient and hospital characteristic variables between patients during the preintervention and postintervention periods. The median door-to-needle times and the proportion of patients with door-to-needle times of 60 minutes or less were compared between the preintervention and postintervention periods, as well as by each calendar quarter during the 2003-2013 study period.

The clinical outcomes measured included (1) in-hospital all-cause mortality, (2) discharge status (home vs acute rehabilitation, skilled nursing facility, hospice, or death), (3) ambulatory status at discharge (ambulatory without another's assistance vs ambulatory only with assistance or nonambulatory), (4) tPA complication of symptomatic intracranial hemorrhage within 36 hours of tPA administration, and (5) tPA complications within 36 hours of tPA administration, including symptomatic intracranial, life-threatening, or serious systemic hemorrhage. Symptomatic intracranial hemorrhage was defined in GWTG-Stroke as neurological worsening within 36 hours of tPA administration that is attributed to intracranial hemorrhage by physician documentation and verified by brain imaging.[7]

The relationships between median door-to-needle times for tPA administration, the proportion of patients with times of 60 minutes or less, and clinical outcomes during the preintervention and postintervention periods were further examined with multivariable logistic regression models. To account for within-hospital clustering, generalized estimating equations were used to generate both unadjusted and adjusted models. To compare the temporal change in rates of door-to-needle times within 60 minutes between the preintervention and postintervention periods, piecewise (segmented) logistic regression analyses were performed.

The variables used in the risk models were patient-level and hospital-level risk adjustors that were previously shown to be predictive of outcome and used in prior GWTG-Stroke analyses.[7,8] Patient-level factors included age, race/ethnicity, sex, medical history (including atrial fibrillation, prosthetic heart valve, previous stroke or transient ischemic attack, coronary artery disease or prior myocardial infarction, carotid stenosis, peripheral vascular disease, hypertension, dyslipidemia, and current smoking), stroke severity (NIHSS score), and arrival time during regular work hours (7 AM to 6 PM Monday through Friday), arrival mode (emergency medical services transport, private vehicle). Hospital-level factors included hospital size, region, teaching status, certified primary stroke center status, average number of patients treated with intravenous tPA annually, and average number of annual stroke discharges. All variables were included in the models without use of a stepwise or other formal variable selection process.

To assess whether the intervention may have had any unintended consequences on the use of tPA in patients with acute ischemic stroke, we compared tPA use quality metrics[16] and overall tPA treatment rates before and after the intervention. We also performed comparative analyses evaluating potential changes for in-hospital all-cause mortality among (1) patients with acute ischemic stroke not treated with tPA and (2) patients with hemorrhagic stroke at the 1030 GWTG-Stroke hospitals before and after the quality improvement intervention, using similar modeling methods.

All *P* values were 2-sided and statistical significance was defined as a *P* value of less than .05. All statistical analyses were performed with SAS version 9.1 software (SAS Institute Inc).

Results

We analyzed 71 169 patients treated with tPA from 1030 hospitals (52.8% of the 1952 GWTG-Stroke hospitals with a least 1 patient with acute ischemic stroke entered since 2003 and 64.1% of the 1607 GWTG-Stroke hospitals with at least 1 patient treated with tPA). Details of the study inclusion and exclusion criteria appear in **Figure 1**. In sensitivity analyses, we included those patients treated with tPA and with onset-to-treatment times of 4.5 hours or less (n = 83 220). The patient-level and hospital-level characteristics of hospitals included and excluded from the study appear in eTable 2 in Supplement. Excluded hospitals were smaller, had lower volumes of patients with stroke, and were less likely to be primary stroke centers.

The demographics and clinical characteristics of the patient population overall and for the preintervention and postintervention study periods appear in **Table 1**. The median age of the patient population was 72 years and 50.1% were women. The median onset to arrival time was 51 minutes and the median NIHSS score at time of presentation was 11. Most patient

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characteristics between the preintervention and postintervention periods were similar (standardized differences <10; Table 1). Hospital characteristics also are shown in Table 1. The median intravenous tPA treatment volume per hospital was 19.5 per year. The hospital characteristics during the preintervention and postintervention periods were similar, including the proportion of hospitals that were certified as primary stroke centers.

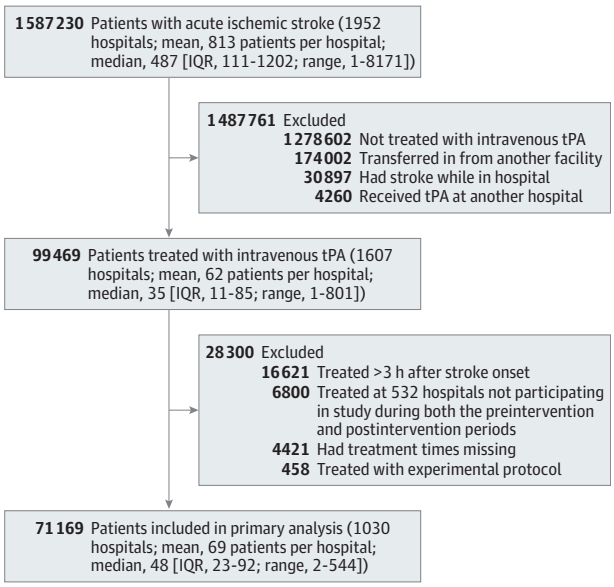
Door-to-Needle Times

The median door-to-needle time for tPA administration for the entire preintervention period was 77 minutes (interquartile range [IQR], 60-98 minutes) and decreased to 67 minutes (IQR, 51-87 minutes) for the entire postintervention period ($P < .001$). Door-to-needle times for tPA administration of 60 minutes or less increased from 26.5% (95% CI, 26.0%-27.1%) of patients during the preintervention period to 41.3% (95% CI, 40.8%-41.7%) during the postintervention period ($P < .001$). The median door-to-needle time was 74 minutes (IQR, 58-95 minutes) during the fourth quarter of 2009 immediately prior to initiation of the quality improvement intervention. The median door-to-needle time declined to 59 minutes (IQR, 46-78 minutes) by the third quarter of 2013 (absolute difference, 15 minutes; $P < .001$).

The temporal trends in the percentage of patients with door-to-needle times of 60 minutes or less are shown in **Figure 2**. The percentage of patients with door-to-needle times of 60 minutes or less increased from 29.6% (95% CI, 27.8%-31.5%) immediately prior to the start of the quality improvement implementation during the fourth quarter of 2009) to 53.3% (95% CI, 51.5%-55.2%) during the third quarter of 2013 ($P < .001$). The median onset-to-treatment time during the entire preintervention period was 137 minutes (IQR, 113-160 minutes) and decreased to 128 minutes (IQR, 103-154 minutes) during the postintervention period ($P < .001$). The median onset-to-treatment time was 135 minutes (IQR, 110-160 minutes) during the fourth quarter of 2009 and declined to 121 minutes (IQR, 97-149 minutes) by the third quarter of 2013.

The annual rate of increase in the proportion of patients with door-to-needle times for tPA administration of 60 minutes or less was 1.36% per 4 quarters (95% CI, 1.04%-1.67%) during the preintervention period. After implementation of the intervention, there was a notable change in slope with the annual rate of increase in patients with door-to-needle times of 60 minutes or less increasing to 6.20% per 4 quarters (95% CI, 5.58%-6.78%; $P < .001$). Piecewise multivariable generalized estimating equation analysis confirmed accelerated improvement during the postintervention period, independent of patient and hospital characteristics ($P < .001$; **Table 2**). The improvement in guideline-recommended door-to-needle times postintervention were observed among clinically relevant subgroups of patients, including men and women; patients older and younger than the median age of 72 years; white, black, and Hispanic patients; and patients with greater and lesser stroke severity (NIHSS score above and below the median of 11). Similar findings were obtained in sensitivity analyses including all patients treated with intravenous tPA with onset-to-treatment times within 4.5 hours (eFigure in Supplement).

Figure 1. Selection of the Study Population



IQR indicates interquartile range; tPA, tissue plasminogen activator.

There was no evidence to suggest that the intervention was associated with a decline in tPA use. A significantly greater proportion of patients with acute ischemic stroke were treated with tPA during the postintervention period (85.2%) compared with the preintervention period (64.7%) among those eligible patients arriving to the hospital within 2 hours of stroke onset and treated with tPA within 3 hours of stroke onset ($P < .001$). Use of tPA in eligible patients arriving to the hospital within 3.5 hours of stroke onset and treated with tPA within 4.5 hours of stroke onset was also higher during the postintervention period (63.9%) compared with the preintervention period (22.5%) ($P < .001$). The use of tPA among all patients with acute ischemic stroke was also higher during the postintervention period (8.1%) compared with the preintervention period (5.7%) ($P < .001$).

Clinical Outcomes

Overall, there were 6054 (8.9%) in-hospital deaths, 3514 (5.1%) symptomatic intracranial hemorrhages within 36 hours, 22 787 (44.1%) patients achieved independent ambulation at hospital discharge, and 26 376 (40.8%) patients were discharged to home. **Table 3** provides the rates along with unadjusted and adjusted odds ratios (ORs) for the clinical outcomes before and after the intervention. The postintervention period was associated with reduced in-hospital mortality, fewer symptomatic intracranial hemorrhages, fewer overall tPA complications, more frequent independent ambulation at discharge, and more frequent discharge to home. For patients treated during the postintervention period compared with the preintervention period, and after adjustment for patient and hospital characteristics, in-hospital mortality was less likely to occur (adjusted OR, 0.89 [95% CI, 0.83-0.94], $P < .001$), symptomatic intracranial hemorrhage was less likely to occur (adjusted OR,

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Table 1. Demographics and Clinical Characteristics of the Overall Patient Population and Hospital Characteristics

	Patients With Acute Ischemic Stroke, %[a]			Standardized Difference, %[b]
	Total (n = 71 169)	Preintervention (n = 27 319)	Postintervention (n = 43 850)	
Patient demographics				
Age, median (25th-75th), y	72 (60-82)	72 (60-82)	72 (60-83)	3.70
Female sex	50.1	49.4	50.5	2.25
Race/ethnicity				
White	72.8	75.1	71.4	8.43
Black	13.8	12.6	14.5	5.80
Hispanic	6.6	5.7	7.3	6.51
Patient arrival and admission				
Via emergency medical services	80.4	84.6	77.7	17.8
On hours[c]	47.4	47.4	47.4	0.10
Onset-to-arrival time, median (25th-75th), min	51 (36-72)	50 (35-70)	52 (36-73)	4.74
Patient medical history				
Atrial fibrillation or flutter	22.8	22.6	22.9	0.69
Prosthetic heart valve	1.2	1.3	1.1	1.17
Previous stroke or TIA	23.7	22.5	24.5	4.79
Coronary artery disease or prior MI	25.7	26.9	24.9	4.48
Carotid stenosis	2.8	3.1	2.7	2.32
Diabetes mellitus	24.6	22.9	25.6	6.28
Peripheral vascular disease	3.5	3.4	3.5	0.87
Hypertension	72.4	71.2	73.1	4.24
Smoking	17.8	18.7	17.3	3.71
Dyslipidemia	39.6	36.5	41.5	10.4
Heart failure	7.8	4.9	9.6	18.2
Patient evaluation				
NIH Stroke Scale score[d]				
Median (25th-75th)	11 (6-18)	12 (7-18)	11 (6-18)	12.9
Documented	90.3	84.0	94.2	32.8
Length of stay, median (25th-75th), d	5 (3-8)	5 (3-8)	5 (3-7)	11.2
Hospital characteristics, median (25th-75th)				
Ischemic stroke admissions/y	233 (163-339)	240 (165-347)	230 (161-337)	2.50
Intravenous tPA administration/y	19.5 (11.6-29.6)	19.2 (11.6-29.3)	19.7 (11.7-29.6)	1.15
No. of beds	403 (283-595)	404 (283-601)	401 (280-588)	2.51
Location of hospital by region				
West	21.5	21.2	21.7	1.23
South	33.9	32.3	34.8	5.27
Midwest	17.3	17.3	17.3	0.17
Northeast	27.3	29.2	26.2	6.83
Teaching hospital	65.2	65.5	65.0	0.94
Hospital in rural location	2.2	2.2	2.2	0.15
Certified primary stroke center	57.3	58.3	56.7	3.12

Abbreviations: MI, myocardial infarction; NIH, National Institutes of Health; TIA, transient ischemic attack; tPA, tissue plasminogen activator.

[a] Values expressed as percentages unless otherwise indicated.

[b] Calculated as the difference in means or proportions divided by a pooled estimate of the standard deviation. A standardized difference greater than 10 is typically considered meaningful.[17,18]

[c] Refers to regular work hours (7 AM to 6 PM Monday through Friday).

[d] Score range from 0 to 42 on this 15-item neurological examination, with higher scores indicating more severe stroke.

0.83 [95% CI, 0.76-0.91], $P < .001$), and discharge to home was more likely to occur (adjusted OR, 1.14 [95% CI, 1.09-1.19], $P < .001$). Improved outcomes were also observed in the sensitivity analyses including all patients treated with intravenous tPA with onset-to-treatment times within 4.5 hours (eTable 3 in Supplement).

In comparative analyses, 1 242 365 patients with acute ischemic stroke were not treated with tPA during the study period, of whom 569 773 were hospitalized during the preintervention period and 672 592 during the postintervention period. The in-hospital all-cause mortality rate for these patients with acute ischemic stroke not treated with tPA was 5.28% during the preintervention period and 4.63% during the postintervention period ($P < .001$). After adjustment for patient and hospital characteristics, in-hospital mortality during the postintervention period vs preintervention was slightly lower (adjusted OR, 0.96; 95% CI, 0.94-0.98). There were 314 061 patients hospitalized with hemorrhagic stroke during the study

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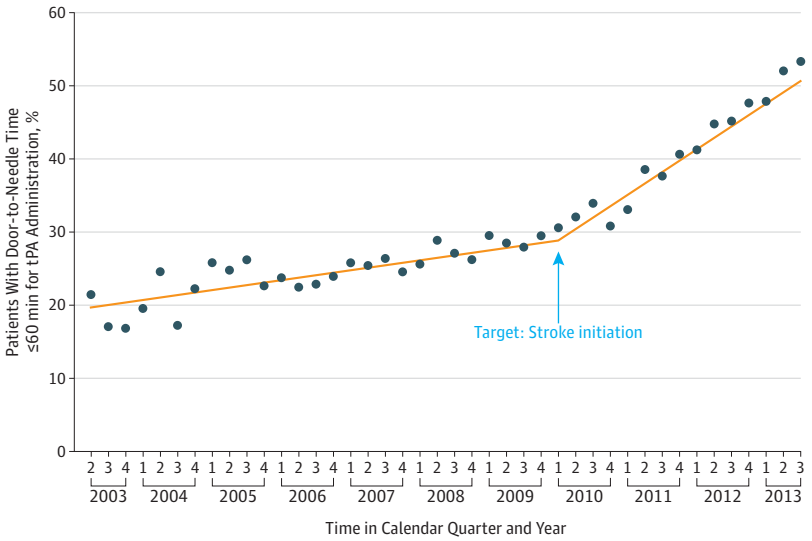
Figure 2. Time Trend in the Proportion of Patients with Door-to-Needle Times for Tissue Plasminogen Activator (tPA) of 60 Minutes or Less During the Preintervention and Postintervention Periods of Target: Stroke



The total number of patients included was 71 169 (per-quarter mean of 1695 patients; median, 1705; interquartile range, 583-2703; and range, 65-3450). The slopes and intercepts of the regression lines were obtained from the unadjusted segmented regression model for trend rate on door-to-needle time of 60 minutes of less. The rate of increase in patients with door-to-needle times of 60 minutes or less was 6.20% (95% CI, 5.58%-6.78%) per each 4 quarters postintervention for Target: Stroke vs 1.36% (95% CI, 1.04%-1.67%) per each 4 quarters preintervention for Target: Stroke ($P < .001$ for comparison of the 2 slopes).

Table 2. Unadjusted and Adjusted Piecewise Generalized Estimating Equation Analyses

	Unadjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)[a]	*P* Value
Door-to-needle time ≤60 min				
Preintervention period (per 4 quarters of calendar time)	1.08 (1.05-1.12)	<.001	1.09 (1.06-1.13)	<.001
Postintervention period (per 4 quarters of calendar time)	1.32 (1.28-1.35)	<.001	1.35 (1.31-1.38)	<.001
Difference between preintervention vs postintervention				
Per 4 quarters of calendar time	1.22 (1.16-1.28)	<.001	1.23 (1.17-1.29)	<.001
Cumulative difference during entire period	1.98 (1.84-2.12)	<.001	2.09 (1.95-2.25)	<.001

Abbreviation: OR, odds ratio.

[a] Adjusted for patient characteristics including age, sex, race, medical history of atrial fibrillation, prosthetic heart valve, previous stroke or transient ischemic attack, coronary artery disease or prior myocardial infarction, carotid stenosis, peripheral vascular disease, hypertension, dyslipidemia, current smoking, stroke severity (National Institutes of Health Stroke Scale score), arrival time during regular work hours, arrival mode, and onset-to-arrival time; and adjusted for the hospital characteristics of size, region, teaching status, certified primary stroke center, annual volume of tissue plasminogen activator, and annual stroke discharge.

Table 3. Clinical Outcomes During the Preintervention and Postintervention Periods

	Patients With Acute Ischemic Stroke, %						
Outcome	Preintervention (n = 27 319)	Postintervention (n = 43 850)	*P* Value	Unadjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)[a]	*P* Value
In-hospital all-cause mortality	9.93	8.25	<.001	0.81 (0.77-0.86)	<.001	0.89 (0.83-0.94)	<.001
Discharged to home	37.6	42.7	<.001	1.23 (1.18-1.27)	<.001	1.14 (1.09-1.19)	<.001
Ambulatory status of independent	42.2	45.4	<.001	1.14 (1.09-1.20)	<.001	1.03 (0.97-1.10)	.31
Symptomatic ICH ≤36 h	5.68	4.68	<.001	0.81 (0.75-0.88)	<.001	0.83 (0.76-0.91)	<.001
tPA Complications	6.68	5.50	<.001	0.80 (0.75-0.87)	<.001	0.83 (0.77-0.90)	<.001

Abbreviations: ICH, symptomatic intracranial hemorrhage; OR, odds ratios; tPA, tissue plasminogen activator.

[a] Adjusted for patient characteristics including age, sex, race, medical history of atrial fibrillation, prosthetic heart valve, previous stroke/transient ischemic attack, coronary artery disease or prior myocardial infarction, carotid stenosis, peripheral vascular disease, hypertension, dyslipidemia, current smoking, stroke severity (National Institutes of Health Stroke Scale score), arrival time during regular work hours, arrival mode, and onset-to-arrival time; and adjusted for the hospital characteristics of size, region, teaching status, certified primary stroke center, annual volume of tPA, and annual stroke discharge.

period, of whom 146 755 were hospitalized during the preintervention period and 167 306 were hospitalized during the postintervention period. The in-hospital all-cause mortality rate for these patients with hemorrhagic stroke was 25.0% during the preintervention period and 23.8% during the postintervention period ($P < .001$). After adjustment for patient and hospital characteristics, in-hospital mortality for hemorrhagic stroke postintervention vs preintervention was also slightly

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lower (adjusted OR, 0.96; 95% CI, 0.93-0.98). The magnitude of benefit associated with the postintervention period for patients treated with tPA (adjusted OR, 0.89; 95% CI, 0.83-0.94) was greater than that found for patients with acute ischemic stroke not treated with tPA (P = .03 for interaction) and that found for patients with hemorrhagic stroke (P < .001 for interaction).

Discussion

Even though historically fewer than 30% of patients treated with intravenous tPA received this therapy within 60 minutes of hospital arrival,[8,13] the initiation of the Target: Stroke quality improvement initiative was associated with a substantial improvement in the timeliness of tPA administration with the proportion of patients with door-to-needle times of 60 minutes or less increasing from 29.6% to 53.3%. There was also a more than 4-fold increase in the annual rate of improvement in the proportion of patients with door-to-needle times of 60 minutes or less after initiation of the intervention. Importantly, the improvement in timeliness in tPA administration following the start of the program was associated with improved clinical outcomes including lower in-hospital mortality, more frequent discharge to a more independently functioning environment, and lower rates of tPA complications, including symptomatic intracranial hemorrhage. These findings further reinforce the importance and clinical benefits of more rapid administration of intravenous tPA.[5-8]

Results from clinical trials and other studies have encouraged multiple organizations to set targets for timely initiation of thrombolytic therapy after hospital arrival. A National Institute of Neurological Disorders and Stroke national symposium on the rapid identification and treatment of acute stroke that recommended a door-to-needle target time for tPA administration of 60 minutes was published in 1997.[9] The national AHA/ASA guidelines[1,11] recommend treatment start with tPA within 60 minutes of the patient's arrival in the emergency department. The Brain Attack Coalition's target for primary stroke centers since 2000 has been to achieve a door-to-needle time within 60 minutes in 80% or more of patients.[11] However, despite the evidence, national guideline recommendations, and prior quality improvement efforts, hospitals initiation of tPA treatment was frequently beyond the recommended national target of a door-to-needle time of 60 minutes or less. In a prior analysis of GWTG-Stroke, only one-quarter of patients with acute ischemic stroke treated with intravenous tPA within 3 hours of symptom onset had door-to-needle times within 60 minutes and little improvement was observed over a 7-year period.[8] Other studies have also shown relatively prolonged door-to-needle times in patients treated with tPA for acute ischemic stroke.[12,19] 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.[12]

Successful efforts to improve door-to-needle times for tPA administration in patients with acute ischemic stroke have been previously reported,[20-23] but have usually involved single hospitals or a small number of centers and a limited period of baseline assessment. To the best of our knowledge, no completed initiative for improving door-to-needle times in patients with acute ischemic stroke has had the size, scope, and depth of that reported with Target: Stroke, though additional efforts launched after this initiative have been announced and certain individual centers have achieved very short door-to-needle times.[24,25] There was a prompt improvement in the percentage of patients meeting guideline-recommended door-to-needle times once this quality improvement initiative was implemented, with times of 60 minutes or less in at least 50% of patients achieved in less than 4 years rather than the expected 15 or more years if the preintervention and intervention slope for the increase in the proportion of patients with door-to-needle times of 60 minutes or less had persisted. These findings suggest that the 10 best practice strategies used with this initiative may have contributed to the benefits observed.[13] Prior experiences of hospitals successful in improving the quality of cardiovascular care suggests that improvement is most effective when integrated into an environment that includes explicit goals; collaborative, interdisciplinary teams; a patient-focused organizational culture; engaged clinical leaders and senior management; and detailed data feedback.[26,27] These organization change elements were integrated into Target: Stroke.[13]

Time to treatment (onset-to-treatment time) with intravenous tPA has been demonstrated to be an important determinant of in-hospital clinical outcomes as well as 90-day and 1-year functional outcomes in patients with acute ischemic stroke.[4-7] There are also data demonstrating that shorter door-to-needle times for tPA administration are associated with improved outcomes in patients with acute ischemic stroke. A cross-sectional analysis of 25 504 patients with ischemic stroke treated with tPA found lower in-hospital mortality (OR, 0.78; 95% CI, 0.69-0.90) and less frequent symptomatic intracranial hemorrhage for patients with door-to-needle times of 60 minutes or less compared with patients with times of more than 60 minutes.[8] Our new findings suggest that the significant decline in door-to-needle times along with acceleration in the percentage of patients meeting the guideline-recommended times within 60 minutes during the postintervention period were associated with substantial improvement in short-term clinical outcomes.

The in-hospital mortality benefit associated with the postintervention vs preintervention periods for patients with acute ischemic stroke treated with tPA was of greater magnitude than the improvement observed for those not treated with tPA and for patients with hemorrhagic stroke cared for during the same time frame in these hospitals, suggesting this finding was the result of more than just general improvements in stroke care and outcomes. These patient groups may not be entirely independent comparators because it is also possible that patients with acute ischemic stroke not treated with tPA and those with hemorrhagic stroke may have also directly benefited from the quality improvement intervention with more rapid evaluation, more rapid brain imaging, and more timely initiation of other acute stroke therapies.[1]

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Even though the clinical outcome improvements observed in this study and their magnitude, including for in-hospital all-cause mortality, are consistent with those expected with more timely tPA treatment based prior studies in acute ischemic stroke,[7,8] these findings stand in contradistinction to a recent analysis conducted in an overlapping 5-year time frame involving 515 hospitals and 96 738 admissions in which reductions in door-to-balloon times in ST-segment elevation myocardial infarction were not accompanied by any changes in short-term mortality rates.[28] This difference potentially reflects greater sensitivity of the brain vs the heart to functionally relevant ischemia progression over time spans of several minutes.[6] Although there have been concerns that attempting to achieve shorter door-to-needle times may lead to rushed assessments, inappropriate patient selection, dosing errors, and greater likelihood of complications, our findings suggest that more rapid reperfusion therapy in acute ischemic stroke is feasible and, importantly, can be achieved not only without increasing rates of symptomatic intracranial hemorrhage, but with actual reductions in complications.

Limitations

There were some limitations to this study. First, participation in GWTG-Stroke and Target: Stroke was voluntary and these hospitals likely have greater interest in stroke quality improvement than nonparticipating hospitals.[16] Second, the quality improvement initiative did not have a concurrent control group of hospitals and it is possible that the improvements in door-to-needle times for tPA administration may have been influenced by other factors. However, efforts in place during the 2003-2009 time frame were observed to have little influence on door-to-needle times,[8,13] and no other national initiatives focused on door-to-needle times were launched during the 2010-2013 period, making it less likely that the observed improvements were due to external factors. Third, it is possible that there were residual measured and unmeasured confounders related to the improvements in door-to-needle times and clinical outcomes. It is also possible that clinical outcomes improved due to other factors, including general improvements in stroke care. Fourth, to increase the precision of the estimate of the preintervention period slope, we used all available data and, as a result, the time span of the preintervention period was nearly twice as long as the postintervention period. Fifth, we did not have access to data on cause of death. Sixth, data collected as part of GWTG-Stroke, including door-to-needle times, are dependent on the accuracy and completeness of abstraction from the medical record.[16] To optimize data quality, the GWTG-Stroke program includes detailed training of site chart abstractors, standardized case definitions and coding instructions, predefined logic and range checks on data fields at data entry, audit trails, and regular data quality reports for all sites.[16] Source documentation audits at the individual state and national level have shown high data quality.[29]

Conclusions

Hospital participation in a multidimensional quality initiative was associated with improvement in the timeliness of tPA administration. This improvement was associated with lower in-hospital mortality, symptomatic intracranial hemorrhage, and overall tPA complications with an increase in the percentage of patients able to be discharged to home.

ARTICLE INFORMATION

Author Contributions: 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.
Study concept and design: Fonarow, Smith, Saver, Bhatt, Xian, Hernandez, Peterson, Schwamm.
Acquisition, analysis, or interpretation of data: Fonarow, Zhao, Smith, Saver, Reeves, Bhatt, Xian, Hernandez, Peterson.
Drafting of the manuscript: Fonarow.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Fonarow, Zhao, Xian, Peterson.
Obtained funding: Fonarow, Hernandez.
Administrative, technical, or material support: Fonarow, Smith, Saver, Xian, Hernandez, Peterson.
Study supervision: Fonarow, Schwamm.

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Fonarow reported serving as a member of the Get With The Guidelines (GWTG) steering committee; receiving significant research support from the National Institutes of Health; and being an employee of the University of California, which holds a patent on retriever devices for stroke. Dr Smith reported serving as a member of the GWTG steering subcommittee. Dr Saver reported serving as a member of the GWTG science subcommittee; the University of California, his employer, receives funding in exchange for his services as a scientific consultant for CoAxia, Grifols, Brainsgate, Lundbeck, Ev3, and Stryker regarding trial design and conduct; and the University of California holds a patent on retriever devices for stroke. Dr Reeves reported receiving salary support from the Michigan Stroke Registry and serving as a member of several American Heart Association (AHA) GWTG subcommittees. Dr Bhatt reported serving on advisory boards for Elsevier Practice Update Cardiology, Medscape Cardiology, and Regado Biosciences; serving on the board of directors for Boston VA Research Institute and the Society of Cardiovascular Patient Care; serving as chair of the AHA GWTG steering committee; being a member of data and safety monitoring committees for Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, and the Population Health Research Institute; receiving honoraria from the American College of Cardiology (editor, *Clinical Trials, Cardiosource*), Belvoir Publications (editor in chief, *Harvard Heart Letter*), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (editor in chief, *Journal of Invasive Cardiology*), Population Health Research Institute (clinical trial steering committee), Slack Publications (chief medical editor, *Cardiology Today's Intervention*), WebMD (continuing medical education steering committees); serving as associate editor for Clinical Cardiology, section editor (pharmacology) for the *Journal of the American College of Cardiology*; receiving research grants from Amarin, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Medtronic, Roche, sanofi-aventis, The Medicines Company; and performing unfunded research for FlowCo, PLx Pharma, Takeda. Dr Hernandez reported receiving AHA pharmaceutical roundtable grant 0675060N and a research grant from Johnson & Johnson; and receiving honoraria from AstraZeneca and Amgen. Dr Peterson reported receiving research grants from Lilly, Johnson & Johnson, Bristol-Myers Squibb, sanofi-aventis, and Merck-Schering Plough partnership; and serving as principal investigator of the data analytic center for the AHA/American Stroke Association's (ASA) GWTG. Dr Schwamm reported being the principal investigator of an investigator-initiated study of extended-window intravenous thrombolysis funded by the National Institute of Neurological Disorders and Stroke (clinicaltrials.gov/show/NCT01282242) for which Genentech provides alteplase free of charge to Massachusetts General Hospital as well as supplemental per-patient payments to participating sites; serving as chair of the AHA/ASA GWTG stroke clinical work group; serving as a stroke systems consultant to the Massachusetts Department of Public Health; and serving as a scientific consultant regarding trial design and conduct to Lundbeck (international

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steering committee, DIAS3, 4 trial) and Penumbra (data and safety monitoring committee, Separator 3D trial). Mr Zhao and Dr Xian reported not having any disclosures.

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