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

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

Author Affiliations: Division of Cardiology (Fonarow), University of California, Los Angeles CA; Department of Clinical Neurosciences, Hotchkiss Brain Institute, (Smith) University of Calgary, Alberta, Canada; Department of Neurology (Saver), University of California, Los Angeles, CA; Department of Epidemiology (Reeves), Michigan State University, East Lansing, MI; Division of Cardiology (Bhatt) VA Boston Healthcare System, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA; Duke Clinical Research Center (Grau-Sepulveda, Olson, Hernandez, Peterson), Durham, NC; Department of Neurology (Schwamm), Massachusetts General Hospital, Boston, MA

Corresponding author: Gregg C. Fonarow, MD, Ahmanson-UCLA Cardiomyopathy Center, Ronald Reagan UCLA Medical Center, 10833 LeConte Avenue, Room 47-123 CHS, Los Angeles, CA 90095-1679. Phone: 310-206-9112; Fax: 310-206-9111; Email: gfonarow@mednet.ucla.edu.

Short Title: Door-to-Needle Times within 60 Minutes

ABSTRACT

Background: The benefits of intravenous tissue plasminogen activator (tPA) in acute ischemic stroke are time dependent and guidelines recommend an arrival to treatment initiation (door-to-needle) time of 60 minutes or less.

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 4/1/2003 to 9/30/2009 were studied to determine frequency, patient and hospital characteristics, and temporal trends in patients treated with door-to-needle times ≤60 minutes. Among 25,504 ischemic stroke patients treated with tPA, door-to-needle time was ≤60 minutes in only 6790 (26.6%). Patient factors most strongly associated with door-to-needle time ≤60 minutes were younger age, male, white race, or no prior stroke. Hospital factors associated with ≤60 minute door-to-needle times included greater annual volumes of tPA treated stroke patients. The proportion of patients with door-to-needle times ≤60 minutes varied widely by hospital (0%-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 0.69-0.90, P<0.0003) and symptomatic intracranial hemorrhage was less frequent (4.7% vs 5.6%, P<0.0017) for patients with door-to-needle times ≤60 minutes compared to patients with door-to-needle times >60 minutes.

Conclusions: Less than one-third of patients treated with intravenous tPA had door-to-needle times ≤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.

Key Words: stroke, thrombolytics, mortality, hospitals, registry

Tissue plasminogen activator (tPA) is a proven intervention for acute ischemic stroke patients.[1,2] 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.[3] The therapeutic benefit of tPA is greatest when given early after ischemic stroke onset and declines over 3 to 4.5 hours.[3-6] 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.[2,7-9]

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 ≤60 minutes have not been well studied in the US or elsewhere. To address this need, the Get With The Guidelines-Stroke national registry 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 ≤60 minutes was achieved, patient and hospital characteristics associated with door-to-needle times ≤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 Get With The Guidelines-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.[10,11] Details of

the design and conduct of the Get With The Guidelines-Stroke program have been previously described.[11] Get With The Guidelines uses a Web-based patient management tool (PMT, Outcome, Cambridge, MA) to collect clinical data on consecutively admitted patients, provide decision support, and enable real-time online reporting features. Following an initial pilot phase, the Get With The Guidelines-Stroke Program was made available in April 2003 to any hospital in the US.[10] Data from hospitals that participated in the program anytime between April 1st 2003 and September 31st 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 Get With The Guidelines. The Duke Clinical Research Institute serves as the data analysis center and has an agreement to analyze the aggregate de-identified data for research purposes.

Trained hospital personnel were instructed to ascertain consecutive patients admitted with the principal clinical diagnosis of acute stroke or transient ischemic attack (TIA) by either prospective clinical identification, retrospective identification using 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* (ICD-9) 433.xx, 434.xx, and

436 for ischemic stroke. The eligibility of all acute stroke admissions was confirmed prior to chart abstraction.[11]

Patient data including demographics, past 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 exam findings would be scored 0, mild examination findings typically not warranting thrombolysis are usually scored 1-5, and very severe deficits from middle cerebral artery or basilar artery occlusion would typically score $\geq$20.[1,2] All patient data were de-identified before submission. Data on hospital-level characteristics (i.e., bed size, academic or non-academic status, annual stroke volume, and geographical region) were obtained from the American Hospital Association.[12] Whether the hospital had been certified by The Joint Commission as a Primary Stroke Center and duration of participation in Get With The Guidelines-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, 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 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[2], 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 ≤60 minutes. Percentages and means ± standard deviations (SDs) were reported for categorical and continuous variables, respectively. Pearson Chi-square test and Wilcoxon rank-sum tests were used to compare the categorical and continuous variables, respectively, between door-to-needle time ≤60 minutes and >60 minutes patients. The relationships between patient and hospital characteristics associated with door-to-needle time ≤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. The adjusted models included the following pre-specified potential confounders: age, race, sex, past medical history (including atrial fibrillation, prosthetic heart valve, previous stroke/TIA, coronary heart disease

or prior myocardial infarction [CAD/prior MI], carotid stenosis, peripheral vascular disease, hypertension, dyslipidemia, and current smoking), stroke severity (NIH Stroke Score), arrival time during regular work hours (7 AM – 5 PM Monday-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 the 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 ≤60 minutes compared to door-to-needle times >60 minutes for other binary clinical outcome measures (i.e., in-hospital mortality, discharge status [home vs other], discharge status [home or acute rehabilitation vs other], ambulatory without assistance, hospital length of stay ≤4 days). The relationship between door-to-needle times ≤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 pre-specified potential confounders in all of these outcomes based models. Missing values were imputed as follows: sex: male; medical history: no; race: white; arrival mode: emergency medical services. Finally, we explored temporal trends in door-to-needle times ≤60 minutes by both calendar time and program time participating in Get With The Guidelines-Stroke. P-values were based on chi-square one degree of freedom rank correlation statistics. GEE logistic regression models were also developed to determine temporal trends in door-to-needle times ≤60 minutes adjusting for patient and hospital characteristics. Statistical significance was defined as $P \leq 0.05$. All statistical analyses were performed using SAS Version 9.1 software (SAS Institute, Cary, NC). The authors had full access to the data and take responsibility for its integrity. 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 Get With The Guidelines-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 ± 28.1 minutes and the median 78 minutes (25^{th}-75^{th} 60-98 minutes). There were 6790 (26.6%) patients with door-to-needle times ≤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 ≤60 minutes compared to those with door-to-needle times >60 minutes. Door-to-needle time ≤60 minute patients were slightly younger and more often male compared to >60 minute patients. Patients in whom door-to-needle times were 60 minutes or less 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 door-to-needle time >60 minutes patients and door-to-needle time ≤60 minutes patients (median NIHSS 12 for both). Notably, patients with door-to-needle time ≤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 time ≤60 minutes and those with door-to-needle time >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 time ≤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 ≤60 minutes varied widely with a median rate of 21.1%, 25^{th}-75^{th} 13.0%-33.3%, and range of 0%-79.2%. Among hospitals with at least 10 patients treated with tPA within 3 hours of symptom onset, the proportion of patients where door-to-needle times ≤ 60 minutes was achieved was 0-<20% at 290 hospitals (45.2%), 21-<40% at 242 (37.8%), 40-<60% at 95 (14.8%), and 60-<80% at 14 (2.2%). There were only 6.7% of hospitals which achieved door-to-needle times ≤60 minutes in 50% or more of patients.

Patient and hospital factors independently associated with door-to-needle time ≤60 minutes are shown in Table 3. The most powerful patient characteristics independently associated with door-to-needle time ≤60 minutes were more severe neurologic 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 ≤60 minutes included older age, female sex, black race, and medical history of atrial fibrillation, diabetes, and prior stroke/TIA. Hospital factors independently associated with increasing odds of door-to-needle time ≤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 of ≤60 minutes increased modestly over time, from 19.5% in 2003 to 29.1% in 2009, with trend line showing an increase of approximately 1.6% per year. There was also an unadjusted relationship of achievement of door-to-needle times ≤60 minutes with the duration of hospital participation in the Get With The Guidelines-Stroke Program. The proportion of patients with door-to-needle time ≤60 minutes increased from 21.1% in 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 ≤60 minutes, adjusted OR 1.09, 95% CI 1.04-1.14, P=0.0004. In contrast, after adjusting for calendar year and other variables each successive Get With The Guidelines-Stroke Program year was not associated with shorter door-to-needle times, adjusted OR 1.01, 95% CI 0.97-1.05, 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 minutes to 75 minutes (P<0.0001), with a trend line showing a decrease of approximately 1.6 minutes per year. In multivariable GEE models, each successive calendar year was associated with 1.7% improvement (95% CI 1.0-2.5%) decrease in door-to-needle times (approximately 1.6 minute decrease per year).

Differences were observed in certain clinical outcomes between patients with door-to-needle time ≤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 time ≤60 minutes compared

to those with door-to-needle time >60 minutes (8.6% vs 10.4%, P<0.0001) (Table 4). Patients with door-to-needle time ≤60 minutes had similar ambulatory status at discharge, but were slightly more often discharged to home or acute rehabilitation (71.7% vs 69.0%, P = 0.0146) (Table 4). Hospital lengths of stay were similar in the two 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 time ≤60 minutes compared with those with door-to-needle time >60 minutes (4.7% vs 5.6%, P=0.002) and overall tPA complications rates were also lower (Table 4). Adjustment for potential confounding variables including stroke severity and accounting for the correlation of data within hospitals demonstrates that patients with door-to-needle time ≤60 minutes had lower odds of in-hospital mortality (adjusted odds ratio 0.78, 95% confidence interval 0.69-0.90, P<0.0003) (Table 5). There were similar results 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% CI 0.92-0.98, P=0.0007). There were no significant differences in the risk adjusted odds for discharge home, ambulatory status, and length of stay ≤4 days. Multivariable GEE analyses revealed an adjusted OR of 0.88 (95% CI 0.75-1.02, P=0.09) for the tPA complication of intracranial hemorrhage for patients with door-to-needle times ≤60 minutes compared with those with door-to-needle times >60 minutes.

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 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.[1-6] 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 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.[3] Odds for improved functional outcomes were 2.8 (95% CI 1.8-4.5) for 0-90 minutes, 1.6 (1.1-2.2) for 91-180 minutes, 1.4 (1.1-1.9) for 181-270 minutes, and 1.2 (0.9-1.5) for 271-360 minutes. This pooled analysis demonstrates that the sooner intravenous tPA is given to stroke patients, the greater the benefit, 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

1-3 hour treatment time period, there was 1 fewer patient having an improved disability outcome.[6]

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.[7] 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.[2,9] The Brain Attack Coalition's target for Primary Stroke Centers is to achieve a door-to-needle time within 60 minutes in 80% or more of patients.[8]

Among hospitals participating in Get With The Guidelines-Stroke, the speed of initiation of tPA treatment after hospital arrival was frequently below the recommended national target of a door-to-needle time ≤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 US found a median door-to-needle time of 96 minutes.[13] In contrast, there have been more rapid reperfusion therapy times reported in other studies. 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.[14] In the two NINDS-tPA trials, the median door-to-needle was 64 minutes despite the need to obtain research informed consent by virtue of trial participation.[1] 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.[15,16] Many of these are dedicated stroke centers that benefit from regionalization of acute stroke care.

In the GWTG-Stroke dataset, the most powerful independent determinants of door-to-needle times ≤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 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 ≤60 minutes in the majority of patients. The number of hospitals with greater experience administering tPA is likely to increase in coming years due to the regionalization of emergency stroke care in the US 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.[17] The finding that the length of time participating in the GWTG-Stroke Program and The Joint Commission Primary Stroke Center Certification were not independently associated with an

increase in the proportion of patients with door-to-needle times ≤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 provide best practice strategies for its achievement.

Successful efforts to accelerate door-to-needle times in acute ischemic stroke have been previously reported.[17-22] These include pre-arrival notification by emergency medical service providers, written protocols for acute triage and patient flow, single call systems to activate all stroke team members, CT or MRI scanner clearance as soon as center is made aware of an incoming patient, locating the CT scanner in the Emergency Department, storage and rapid access to thrombolytic drug 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.[17-22] 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.[9]

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,[17] in this study there was no evidence of worse in-hospital outcomes or increased bleeding complications from tPA for patients with door-to-needle times ≤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 been previously reported with more timely tPA therapy within the first three hours after stroke onset, so this finding should be interpreted cautiously and should be replicated in independent datasets. This finding is, however, consonant with meta-analysis data indicating that late thrombolytic therapy beyond 3 hours after onset increases mortality while earlier thrombolytic therapy within 3 hours does not.[23,24] Importantly, the rate of symptomatic intracerebral hemorrhage in tPA treated patients with door-to-needle time within 60 minutes was 4.7%, lower than the 5.6% rate of reported in patients with door-to-needle above 60 minutes. These rates may also compare favorably to those observed in the NINDS trial (6.4%) and other phase IV studies.[1] 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 upon the hospital to perform rapid diagnostic evaluation/imaging and, in eligible patients without contraindications, promptly initiate intravenous tPA therapy.[5,9] It is important to acknowledge that a door-to-needle time ≤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 there is a critical need for a targeted campaign tailored to increase the portion of patients with door-to-needle times ≤60 minutes such as the recently launched American Stroke Association Target: Stroke initiative.

Limitations

There are a number of potential limitations that should be considered in interpreting the results of this study. Hospitals participating in Get With The Guidelines-Stroke are self-selected and tend to be larger, teaching institutions, and have an interest in stroke quality improvement.[10,11] 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 ≤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 Get With The Guidelines-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.[11] Limited source documentation audits at the individual state and site level have shown high data quality. Participating hospitals are instructed to include all consecutive admissions for ischemic stroke. However, since these processes are not audited, the potential exists for selection bias. While we investigated the influence of multiple patient and hospital level factors upon door-to-needle ≤60 minutes, a number of additional factors that may be important in timely reperfusion were not captured in Get With The Guidelines-Stroke and could not be analyzed. These include pre-hospital notification by EMS, 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 CT or MRI scanners in the Emergency Department, and timely feedback of performance.[17] 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.[2] NIHSS was not documented in 16.6% of

patients, though 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 post discharge stroke-related outcomes are currently collected in the Get With The Guidelines-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 Get With The Guidelines-Stroke, target door-to-needle times ≤60 minutes are achieved in only 26.6% of acute ischemic stroke patients treated within 3 hours of symptom onset. Further, over the past 6.5 years there has been only modest improvement in the proportion of patients where this time-related goal was achieved. A number of patient and hospital characteristics were associated with door-to-needle times ≤60 minutes. While door-to-needle times vary substantially by hospital, there are certain hospitals participating in Get With The Guidelines-Stroke in which door-to-needle times ≤60 minutes are achieved 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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Conflicts of Interest/Disclosures

Dr. Fonarow receives research support from the National Institutes of Health (significant), served as a consultant to Pfizer, Merck, Schering Plough, Bristol Myers Squibb, and Sanofi-Aventis (all modest); received honoraria from Pfizer, Merck, Schering Plough, Bristol Myers Squibb, and Sanofi-Aventis (all significant); and is an employee of the University of California, which holds a patent on retriever devices for stroke (significant).

Dr. Smith serves as a member of the Get With the Guidelines Science Subcommittee and receives research support from the NIH (NINDS R01 NS062028). the Canadian Stroke Network, the Canadian Institutes of Health Research and the Heart and Stroke Foundation of Canada, and has served on an advisory board for Genentech.

Dr. Saver serves as a member of the Get With the Guidelines Science Subcommittee, 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; is an employee of the University of California, which holds a patent on retriever devices for stroke.

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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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References

1. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995;333:1581-1587.
2. Adams HP Jr, del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, Grubb RL, Higashida RT, Jauch EC, Kidwell C, Lyden PD, Morgenstern LB, Qureshi AI, Rosenwasser RH, Scott PA, Wijdicks EF. Guidelines for the early management of adults with ischemic stroke. *Circulation.* 2007;115:e478-534.
3. Hacke W, Donnan G, Fieschi C, Kaste M, von Kummer R, Broderick JP, Brott T, Frankel M, Grotta JC, Haley EC Jr, Kwiatkowski T, Levine SR, Lewandowski C, Lu M, Lyden P, Marler JR, Patel S, Tilley BC, Albers G, Bluhmki E, Wilhelm M, Hamilton S. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet.* 2004;363:768-774.
4. Marler JR, Tilley BC, Lu M, Brott TG, Lyden PC, Grotta JC, Broderick JP, Levine SR, Frankel MP, Horowitz SH, Haley EC Jr, Lewandowski CA, Kwiatkowski TP. Early stroke treatment associated with better outcome: the NINDS rt-PA Stroke Study. *Neurology*. 2000;55:1649-1655.
5. Saver JL. Time is brain--quantified. *Stroke.* 2006;37:263-266.
6. Lansberg MG, Schrooten M, Bluhmki E, Thijs VN, Saver JL. Treatment time-specific number needed to treat estimates for tissue plasminogen activator therapy in acute stroke based on shifts over the entire range of the modified Rankin Scale. *Stroke.* 2009;40:2079-2084.
7. Marler JR, Winters Jones P, Emr M. The National Institute of Neurological Disorders and Stroke: Proceedings of National Symposium on Rapid Identification and Treatment of Acute Stroke. Bethesda, MD: National Institute of Neurological Disorders and Stroke, 1997
8. Alberts M J, Hademenos G, Latchaw RE, Jagoda A, Marler JR, Mayberg MR, Starke RD, Todd HW, Viste KM, Girgus M, Shephard T, Emr M, Shwayder P, Walker MD. Recommendations for the establishment of primary stroke centers. Brain Attack Coalition. *JAMA.* 2000; 283: 3102-9.
9. Summers D, Leonard A, Wentworth D, Saver JL, Simpson J, Spilker JA, Hock N, Miller E, Mitchell PH; on behalf of the American Heart Association Council on Cardiovascular Nursing and the Stroke Council. Comprehensive overview of nursing and interdisciplinary care of the acute ischemic stroke patient: a scientific statement from the American Heart Association. *Stroke.* 2009;40:2911–2944.
10. LaBresh KA, Reeves MJ, Frankel MR, Albright D, Schwamm LH. Hospital treatment of patients with ischemic stroke or transient ischemic attack using the "Get With The Guidelines" program. *Arch Intern Med.* 2008;168:411-417.
11. Schwamm LH, Fonarow GC, Reeves MJ, Pan W, Frankel MR, Smith EE, Ellrodt G, Cannon CP, Liang L, Peterson E, Labresh KA. Get With the Guidelines-Stroke is associated with sustained improvement in care for patients hospitalized with acute stroke or transient ischemic attack. *Circulation.* 2009;119:107-115.
12. American Hospital Association. American Hospital Association Hospital Statistics 2009. Chicago, IL: American Hospital Association, 2009.

13. Albers GW, Bates VE, Clark WM, Bell R, Verro P, Hamilton SA. Intravenous tissue plasminogen activator in the treatment of acute stroke. The standard treatment with alteplase to reverse stroke (STARS) Study. *JAMA.* 2000;283:1145-1150.
14. Wahlgren N, Ahmed N, Davalos A, Ford GA, Grond M, Hacke W, Hennerici MG, Kaste M, Kuelkens S, Larrue V, Lees KR, Roine RO, Soinne L, Toni D, Vanhooren G; SITS-MOST investigators. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. *Lancet.* 2007;369:275-282.
15. Sobesky J, Frackowiak M, Weber OZ, Hahn M, Moller-Hartmann W, Rudolf J, Neveling M, Grond M, Schmulling S, Jacobs A, Heiss W. The Cologne Stroke Experience: Safety and outcome in 450 patients treated with intravenous-thrombolysis. *Cerebrovasc Dis.* 2007;24:56–65.
16. Tveiten A, Mygland A, Ljostad U, Thomassen L. Intravenous thrombolysis for ischaemic stroke: short delays and high community-based treatment rates after organisational changes in a previously inexperienced centre. *Emerg Med J.* 2009;26:324-326.
17. Schwamm LH, Pancioli A, Acker JE, 3rd, Goldstein LB, Zorowitz RD, Shephard TJ, Moyer P, Gorman M, Johnston SC, Duncan PW, Gorelick P, Frank J, Stranne SK, Smith R, Federspiel W, Horton KB, Magnis E, Adams RJ. Recommendations for the establishment of stroke systems of care: recommendations from the American Stroke Association's Task Force on the Development of Stroke Systems. *Stroke.* 2005;36:690-703.
18. Kim SK, Lee SY, Bae HJ, Lee YS, Kim SY, Kang MJ, Cha JK. Pre-hospital notification reduced the door-to-needle time for iv t-PA in acute ischaemic stroke. *Eur J Neurol.* 2009;16:1331-1335.
19. Tveiten A, Mygland A, Ljostad U, Thomassen L. Intravenous thrombolysis for ischaemic stroke: short delays and high community-based treatment rates after organisational changes in a previously inexperienced centre. *Emerg Med J.* 2009;26:324-326.
20. Lindsberg PJ, Happola O, Kallela M, Valanne L, Kuisma M, Kaste M. Door to thrombolysis: ER reorganization andreduced delays to acute stroke treatment. *Neurology.* 2006; 67: 334–6.
21. Mehdiratta M, Woolfenden AR, Chapman KM, Johnston DC, Schulzer M, Beckman J, Teal PA. Reduction in IV t-PA door to needle times using an Acute Stroke Triage Pathway. *Can J Neurol Sci.* 2006; 33: 214–6.
22. The National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study Group. A systems approach to immediate evaluation and management of hyperacute stroke. Experience at eight centers and implications for community practice and patient care. *Stroke.* 1997;28:1530-1540.
23. Wardlaw JM, Murray V, Berge E, del Zoppo GJ. Thrombolysis for acute ischaemic stroke. *Cochrane Database Syst Rev.* 2009;4:CD000213.
24. Lees KR, Bluhmki E, von Kummer R, Brott TG, Toni D, Grotta JC, Albers GW, Kaste M, Marler JR, Hamilton SA, Tilley BC, Davis SM, Donnan GA, Hacke W; ECASS, ATLANTIS, NINDS and EPITHET rt-PA Study Group, Allen K, Mau J, Meier D, del Zoppo G, De Silva DA, Butcher KS, Parsons MW, Barber PA, Levi C, Bladin C, Byrnes G. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet.* 2010;375:1695-1703.

Table 1: Characteristics of Ischemic Stroke Patients with Door-to-Needle Time ≤60 Minutes Compared to those with Door-to-Needle Times >60 Minutes

	Door-to-Needle Times ≤60 Minutes	Door-to-Needle Times >60 Minutes	P value
N	6790	18,714	
Patient Level Characteristics			
Age, Years, Mean, (SD)	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%	
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 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, 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%	
Atrial Fibrillation/Flutter	22.1%	25.0%	<0.0001
Prior Stroke/Transient Ischemic Attack	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, 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

Door-to-Needle Time, Minutes, Mean (SD)	46.0 (12.2)	91.4 (21.7)	<0.0001
Median (25^{th}-75^{th})	49 (40-55)	88 (74-105)	

CT indicates computerized tomography, NIHSS, National Institute of Health Stroke Scale, and SD standard deviation. *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%.

Table 2: Hospital Characteristics of Ischemic Stroke Patients with Door-to-Needle Time ≤60 Minutes Compared to those with Door-to-Needle Time >60 Minutes

	Door-to-Needle Time ≤60 Minutes	Door-to-Needle Time >60 Minutes	P value
N	6790	18,714	
Hospital Level Characteristics			
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
Time in GWTG-Stroke, Months, Median, (25^{th}–75^{th})	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%	

GWTG indicates Get With The Guidelines, TJC The Joint Commission, and tPA tissue plasminogen activator. Bedsize was missing in 4.11% and academic status was missing in 3.20%.

Table 3. Patient and Hospital Level Characteristics Associated with Door-to-Needle Time ≤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
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

Variables	Adjusted Odds Ratio	Lower 95% CI	Upper 95% CI	P-Value
Dyslipidemia	1.01	0.94	1.09	0.7223
Stroke/Transient Ischemic Attack	0.81	0.74	0.88	<.0001
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 Admissions/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

CI indicates confidence interval, NIHSS National Institute of Health Stroke Scale, and tPA tissue plasminogen activator. Table reflects multivariable modeling performed with 20358 patients with full data available, including NIHSS. No major differences (apart from NIHSS) were observed when model was constructed using the more complete cohort of patients (n=24,385) without recorded NIHSS. There were also similar findings 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 Time ≤60 Minutes Compared to Those with Door-to-Needle Time >60 Minutes

	Door-to-Needle Time ≤60 Minutes	Door-to-Needle Time >60 Minutes	P value
N	6790	18,714	
Hospital Events and Discharge Status			
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*			
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, SD standard deviation, and tPA tissue plasminogen activator.
*Excludes transfer out patients
†Excludes transfer in and out patients

Table 5: Unadjusted and Adjusted Odds Ratios for Clinical Outcomes in Patients with Door-to-Needle Time ≤60 Minutes Compared with Those with Door-to-Needle Time >60 Minutes

	Unadjusted			Adjusted *		
Outcome	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 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 and tPA tissue plasminogen activator. *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, 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, PSC, bed size, annual number of strokes, annual number of stroke. 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.