Hospital Variation in Thrombolysis Times Among Patients With Acute Ischemic Stroke
The Contributions of Door-to-Imaging Time and Imaging-to-Needle Time

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IMPORTANCE Given the limited time window available for treatment with tissue plasminogen activator (tPA) in patients with acute ischemic stroke, guidelines recommend door-to-imaging time (DIT) within 25 minutes of hospital arrival and door-to-needle (DTN) time within 60 minutes for patients with acute ischemic stroke. Despite improvements in DITs, DTN times for tPA treatment in patients with acute ischemic stroke remain suboptimal.

OBJECTIVES To examine the contributions of DIT and imaging-to-needle (ITN) time to delays in timely delivery of tPA to patients with acute ischemic stroke and to assess between-hospital variation in DTN times.


MAIN OUTCOMES AND MEASURES The primary outcome was a continuous measure of DTN time, in minutes, from emergency department arrival to thrombolytic delivery.

RESULTS The mean age was 68.1 years, the median National Institutes of Health Stroke Scale score was 11.0 (interquartile range, 6-17), 51.4% were female, and 37.5% were of nonwhite race/ethnicity. The mean (SD) DTN time was 82.9 (35.4) minutes, the mean (SD) DIT was 22.8 (15.9) minutes, and the mean (SD) ITN time was 60.1 (32.3) minutes. Most patients (68.4%) had DIT within 25 minutes, while 28.7% had DTN time within 60 minutes. Hospital variation accounted for 12.7% of variability in DTN times. Neither annual stroke volume nor primary stroke center designation was a significant predictor of shorter DTN time. Patient factors (age, sex, race/ethnicity, arrival mode, onset-to-arrival time, and stroke severity) explained 15.4% of the between-hospital variation in DTN times. After adjustment for patient-level factors, DIT explained 10.8% of the variation in hospital risk-adjusted DTN times, while ITN time explained 64.6%.

CONCLUSIONS AND RELEVANCE Compared with DIT, ITN time is a much greater source of variability in hospital DTN times and is a more common contributor to delays in timely tPA therapy for acute ischemic stroke. More attention is needed to determine systems changes that can decrease ITN time for patients with acute ischemic stroke.

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Stroke is a leading cause of severe disability. Currently, medical treatments for completed ischemic strokes have little to no effect on neurologic recovery, but timely intravenous administration of tissue plasminogen activator (tPA) within the first hours of onset can substantially reduce disability. Even modest reductions in the time from emergency department arrival to tPA treatment (door-to-needle [DTN] time) significantly increase the likelihood of favorable clinical outcomes. Yet, despite practice guidelines recommending DTN time within 60 minutes and prominent quality improvement efforts to reduce DTN time, the times until tPA treatment in patients with acute ischemic stroke remain suboptimal.

To exclude the possibility of hemorrhagic stroke, brain imaging is a necessary first step in the process of tPA delivery. The time from hospital arrival to brain imaging (door-to-imaging time [DIT]) is generally thought to be the main driver of DTN time. Guidelines recommend DIT within 25 minutes, and the Centers for Medicare and Medicaid Services require hospitals to report the time to imaging interpretation. Quality improvement efforts have included DIT as an important target, and recent studies show that DIT has improved during the past decade. Yet, in a large national sample of patients in the Get With the Guidelines–Stroke registry, more than 70% of ideal tPA candidates with DIT of 25 minutes or less still had DTN times exceeding 60 minutes. This suggests that substantial opportunities remain to reduce DTN times even among patients with optimal brain imaging times. Therefore, imaging-to-needle (ITN) time may be an important focus. To date, we are not aware of any studies that have examined the importance of ITN time, including how much variation in DTN times is explained by ITN time.

In this analysis, our first objective was to examine the contributions of DIT and ITN time to delays in DTN times among tPA-treated patients with acute ischemic stroke in a statewide stroke registry. Our second objective was to assess the amount of hospital-level variation in DTN times that is attributable to DIT or ITN time.

Methods

Data Source

Human participant approval was obtained from each hospital’s institutional review board. Registry protocol does not include informed consent because the registry consists of de-identified data. The Michigan Stroke Registry collects information on the quality of acute stroke care as part of the Centers for Disease Control and Prevention Paul Coverdell National Acute Stroke Registry. A representative sample of 39 statewide hospitals was selected through a stratified complex sampling scheme (based on geography, urban or rural location, and minority population). This analysis uses data between January 2009 and December 2012.

All registry hospitals entered data into the Get With the Guidelines–Stroke Patient Management Tool, which collects patient demographics, history, and hospital course. Data were entered by staff directly involved in patient care or by hospital abstractors, all of whom were trained on the registry and the

Outcome Measure

The primary outcome variable was DTN time, defined as the time in minutes from hospital arrival to tPA delivery. The primary independent variables were DIT, defined as the time from hospital arrival to the time the first brain imaging was obtained, and ITN time, defined as the time between the first brain imaging and tPA delivery (Figure 1).

Statistical Analysis

Patient and hospital characteristics were summarized as percentages, means (SDs), or medians (interquartile ranges) as appropriate. Patient-level relationships among DIT, ITN time, and DTN time for all patients were assessed using scatterplots. Linear correlations between the variables were assessed using Pearson correlation coefficients. Because guidelines recommend DTN time within 60 minutes, we repeated these analyses after stratifying patients by DTN times (≤60 vs >60 minutes) to see if the relationships among DIT, ITN time, and DTN time varied by whether patients had delayed DTN times.

Study Population

Of 39 registry hospitals, we excluded 9 because they had no tPA-treated patients and 5 because they treated fewer than 5 patients with intravenous tPA during the study period, leaving a final sample of 25 hospitals. The final patient population for this analysis was restricted to patients receiving intravenous tPA within 4½ hours of arrival. After excluding patients with in-hospital stroke and transferred patients, a total of 1265 acute ischemic stroke cases were treated with intravenous tPA in the 25 hospitals. We excluded 72 patients with missing or implausible DIT or ITN time, leaving 1193 in the final sample for analysis (Figure 1).
We used a series of multilevel, multivariable linear regression models to examine the associations between the patient-level outcome of DTN time (continuous) and either DIT or ITN time as the primary predictor variable, adjusting for patient and hospital characteristics. All models included hospital-specific random intercepts to account for patient clustering within each hospital. Model 1 contained only these hospital-specific random intercepts and no covariates. This model was used to estimate the intraclass correlation coefficient. Model 2 added patient-level covariates to model 1; patient covariates were selected based on prior relevant literature and included age, sex, race/ethnicity, NIHSS score, OTA time, arrival mode, admission day, and year. Age, sex, and race/ethnicity were retained regardless of statistical significance; other variables that did not reach statistical significance (defined as \( P < .10 \)) were dropped from the final model. Model 2 quantified between-hospital variation in DTN times after controlling for significant patient-level predictors of DTN time. Model 3 added hospital-level covariates to model 2; hospital covariates included primary stroke center status, urban or rural location, teaching hospital status, the presence of a neurology residency program, and hospital annual stroke volume. Again, nonsignificant variables were dropped from the model. Therefore, the final risk-adjusted model included hospital-specific random intercepts and patient age, sex, and race/ethnicity, as well as any other patient-level and hospital-level factors statistically significantly associated with DTN time.

We next added DIT (continuous) as a predictor to the final risk-adjusted model to determine the amount of variation in hospital mean DTN times that was explained by DIT. Next, we added ITN time (continuous) as a predictor to the final risk-adjusted model to determine the amount of explainable variation in hospital mean DTN times that was attributable to ITN time. The variables DIT and ITN time were not included together in the same model because together they would completely explain DTN time (Figure 2). Attributable variation in DTN times was calculated as the proportional change in residual variation from the final risk-adjusted model to the models that included DIT and ITN time individually. All analyses were conducted using PROC MIXED (SAS, version 9.2; SAS Institute Inc.).

We examined whether NIHSS score or OTA time modified the association between DIT and DTN time by testing the statistical significance of 2 interaction terms, DIT × NIHSS score and DIT × OTA time, on the outcome of DTN time. To verify that the final model was appropriate, we examined the distribution of residuals to confirm that they were approximately normally distributed. To explore the effect of hospitals with few cases, we conducted a sensitivity analysis by dropping hospitals with fewer than 10 tPA-treated cases (n = 9) and repeating the final model.

Results

In total, 1193 tPA-treated patients with acute ischemic stroke between 2009 and 2012 were studied. Table 1 summarizes the baseline characteristics. The mean age was 68.1 years (age range, 18-102 years), and the median NIHSS score was 11.0 (interquartile range, 6-17). Half of the patients (51.4%) were female, and 37.5% were of nonwhite race/ethnicity. Most arrived by ambulance (80.7%). The median OTA time was 59.0 minutes (interquartile range, 39.0-93.5 minutes). Of 25 hospitals, 20 were teaching hospitals, and 16 were primary stroke centers. Four were rural hospitals. All hospitals had a protocol for intravenous tPA administration.

The overall patient-level mean (SD) DIT was 22.8 (15.9) minutes. Most patients (68.4%) received brain imaging within the guideline-recommended 25-minute window. However, the overall patient-level mean (SD) ITN time was 60.1 (32.3) minutes. The patient-level mean (SD) DTN time was 82.9 (35.4) minutes, and only 28.7% of patients received tPA within 60 minutes. Figure 3 shows changes in DITs, ITN times, and DTN times during the study period.

Patient-Level Correlations Among DITs, ITN Times, and DTN Times

Among 1193 tPA-treated patients with acute ischemic stroke, DIT was only modestly correlated with DTN time (Pearson correlation coefficient, 0.41; \( P < .001 \)) (Figure 4A). Conversely, ITN time was strongly correlated with DTN time (Pearson correlation coefficient, 0.90; \( P < .001 \)) (Figure 4B). No significant relationship was found between DIT and ITN time (Pearson cor-
In this study of tPA-treated patients with acute ischemic stroke, we found that ITN time had a much larger contribution than DIT to systematic variation in hospital DTN times. Although timely brain imaging is clearly important for optimal tPA delivery and further improvement in DIT is desirable, we found that prolonged ITN time is a much greater problem. To our knowledge, this is the first analysis to examine the separate roles of DIT and ITN time on DIT time for tPA-treated patients with acute ischemic stroke. Although 68.4% of patients with acute ischemic stroke in our study had ITN within 25 minutes, only 28.7% had DTN time within 60 minutes as recommended by guidelines. These results show the critical importance of ITN time to the achievement of optimal DTN time and demonstrate that delays in ITN time are largely responsible for hospital mean DTN times that was not explained by these patient factors.

Table 2 summarizes the final risk-adjusted model, which included patient age, sex, and race/ethnicity and the other patient factors that reached statistical significance (NIHSS score, OTA time, arrival mode, and year). None of the hospital-level factors were significantly associated with DTN time, so they were dropped from the model.

Inclusion of patient-level factors reduced the variation in hospital-level DTN times by 15.4%. However the random effect for hospital remained significant \( (P = .003) \); therefore, considerable unexplained variability in hospital DTN times remained after accounting for patient factors. Arrival by ambulance and OTA time were significantly associated with DTN time. The mean DTN time was 8.12 minutes faster for patients arriving by ambulance (vs private), and the mean DTN time was 0.14 minutes faster for every additional minute delay in OTA time (Table 2). The NIHSS score was only marginally correlated with DTN time (0.25 minutes faster for every NIHSS score point, \( P = .08 \)).

When DIT was added to the final risk-adjusted model, it explained 10.8% of the variation in hospital-level DTN times. For every additional minute of DIT, DTN time increased by 0.81 minutes \( (P < .001) \). When ITN time replaced DIT in the final risk-adjusted model, ITN time explained 64.6% of the variation in hospital-level DTN times. For every additional minute of ITN time, DTN time increased by 0.93 minutes \( (P < .001) \). Even after accounting for patient-level variables and ITN time, the random effect for hospital remained significant \( (P = .01) \), indicating that significant variation remained in hospital mean DTN times that was not explained by these patient factors.

**Discussion**

In this study of tPA-treated patients with acute ischemic stroke, we found that ITN time had a much larger contribution than DIT to systematic variation in hospital DTN times. Although timely brain imaging is clearly important for optimal tPA delivery and further improvement in DIT is desirable, we found that prolonged ITN time is a much greater problem. To our knowledge, this is the first analysis to examine the separate roles of DIT and ITN time on DTN time for tPA-treated patients with acute ischemic stroke. Although 68.4% of patients with acute ischemic stroke in our study had ITN within 25 minutes, only 28.7% had DTN time within 60 minutes as recommended by guidelines. These results show the critical importance of ITN time to the achievement of optimal DTN time and demonstrate that delays in ITN time are largely responsible for hospitals' inability to achieve DTN time within 60 minutes.

The percentage of patients with stroke achieving DTN time of 60 minutes was similar to that in earlier studies.\(^5,21,23\) Consistent with previous work, we found that faster DTN time was associated with arrival by ambulance and with longer OTA time.\(^5,13,21,28\) Previous studies have shown that stroke severity is associated with DTN time; however, our study did not. Our study had a smaller sample size \((n = 1193)\) than the others \((n = 5563\) in the study by Mikulík et al\(^5\) and \(n = 25\) 504 in the
Figure 3. Changes in Door-to-Imaging Time (DIT), Imaging-to-Needle (ITN) Time, and Door-to-Needle (DTN) Time During the 2009 to 2012 Study Period

Among 1193 observations, the median DIT changed from 21 to 18 minutes between 2009 and 2012, the median ITN time changed from 55 to 51 minutes, and the median DTN time changed from 77 to 72 minutes. Trends are shown by the lines connecting the squares (which give the median value for each time period, in minutes); the vertical solid lines between triangles show the interquartile ranges (quartile 3 [Q3] minus Q1).

Figure 4. Associations Between Door-to-Imaging Time (DIT), Imaging-to-Needle (ITN) Time, and Door-to-Needle (DTN) Time

A, Among 1193 observations, the Pearson correlation coefficient is 0.41 (P < .001). B, Among 1192 observations, the Pearson correlation coefficient is 0.90 (P < .001).
Table 2. Final Multilevel, Multivariable Linear Model Results for Predictors of DTN Time

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Change in DTN Time, min</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, per year</td>
<td>0.009</td>
<td>.89</td>
</tr>
<tr>
<td>Nonwhite race/ethnicity</td>
<td>4.47</td>
<td>.06</td>
</tr>
<tr>
<td>Female sex</td>
<td>2.48</td>
<td>.20</td>
</tr>
<tr>
<td>Arrival by ambulance</td>
<td>-8.12</td>
<td>.002</td>
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<tr>
<td>OTA time, per min</td>
<td>-0.14</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>NIHSS score</td>
<td>-0.25</td>
<td>.08</td>
</tr>
<tr>
<td>Year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>2.94</td>
<td>.30</td>
</tr>
<tr>
<td>2010</td>
<td>5.26</td>
<td>.046</td>
</tr>
<tr>
<td>2011</td>
<td>-0.46</td>
<td>.86</td>
</tr>
<tr>
<td>2012</td>
<td>1 [Reference]</td>
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</tr>
</tbody>
</table>

Abbreviations: DTN, door-to-needle; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; OTA, onset-to-arrival.

Because DTN time is simply the sum of DIT and ITN time, substantial improvements in DIT will, by definition, leave a greater proportion of the variation in DTN times explained by ITN time. As processes designed to reduce DIT become more streamlined, delays in DTN times that are due to physician or patient decision making related to tPA treatment may have been shifted into the ITN time. While it is thought that improvements in DITs translate directly into improvements in DTN times, this has not been definitively proven. In fact, previous work in acute stroke has demonstrated that decisions will tend to take more time when physicians have more time, a phenomenon called Parkinson law,26 which is well described in the relationship between faster OTA time and slower DTN time for tPA delivery.13,21,22,26-28 Our results suggest that improvements in the percentage of patients with DITs within 25 minutes did not translate into commensurate increases in the percentage of patients with DTN times within 60 minutes.

Finally, DIT and ITN time are distinct processes that may depend on different personnel, separate departments, and various resources within a hospital. It is possible that DIT is more amenable to systems and process improvements than ITN time, but our findings may, at least in part, be due to inadequate attention to ITN time improvements. The ITN times remain too long despite programmatic efforts to highlight the various points that may contribute to delays in the ITN times, including notifying the stroke team, determining tPA eligibility, medical decision making, dosing, and preparing tPA.11 The period between brain imaging and tPA delivery involves communication among emergency physicians, radiologists, neurologists, nursing, pharmacy, and the patient and family. We need to better understand the critical components of ITN time, including laboratory testing, imaging interpretation, care coordination between physicians, ordering and preparing tPA, and medical decision making involving the physician, patient, and family. In addition, guideline developers may consider greater emphasis on the important role of ITN time.

Our findings must be considered within the context of the study’s limitations. This analysis is based on registry data from a single state and may reflect regional variations. However, the hospitals included in the Michigan registry were selected to be representative of various capacities, sizes, and settings (teaching or nonteaching and rural or urban); therefore, our findings should be broadly generalizable. Also, generalizability is suggested by the fact that these results are concordant with larger reports of Get With the Guidelines-Stroke data.21 We were also unable to verify the accuracy of the imaging time data; however, the other time-related variables, including OTA time, had high interobserver agreement. In addition, we may have failed to capture other unmeasured confounders or other explanatory factors such as differences in the physical location of CT imaging systems, emergency medical services prenotification protocols, or availability of neurology specialists. Future studies may focus on collecting these details and understanding other organizational, structural, and cultural factors that may contribute to treatment delays. Finally, we do not know how many patients with acute ischemic stroke seen at these hospitals were not treated with tPA because of delays in care related to prolonged DIT or ITN time.
Conclusions

We found that DIT and ITN time have important roles in DTN time, but we observed that ITN time contributes to greater variability in DTN times and is a much more common cause of delays in tPA treatment for acute ischemic stroke. Therefore, improving ITN time may be a critical target for improving DTN time to thrombolysis in patients with acute ischemic stroke.

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Study concept and design: All authors.
Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: All authors.

Administrative, technical, or material support: Reeves.
Study supervision: Reeves.

Conflict of Interest Disclosures: Dr Nickles reported being the epidemiologist for the Michigan Stroke Registry at the Michigan Department of Community Health, and Dr Reeves reported serving as a consultant to the registry. No other disclosures were reported.

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REFERENCES