Original Contribution

Bigger, Faster?
Associations Between Hospital Thrombolysis Volume and Speed of Thrombolysis Administration in Acute Ischemic Stroke

Benjamin D. Bray, MRCP; James Campbell, LLB; Cloud C. Geoffrey, FRCP; Alex Hoffman, MSc; Pippa J. Tyrrell, FRCP; Charles D.A. Wolfe, FFPHM; Anthony G. Rudd, FRCP; on behalf of the Intercollegiate Stroke Working Party Group

Background and Purpose—There is evidence that high-volume hospitals may produce better patient outcomes. We aimed to identify whether there were any associations between hospital thrombolysis volume and speed of thrombolysis (tissue-type plasminogen activator [tPA]) administration in patients with ischemic stroke.

Methods—Data were drawn from 2 national clinical audits in England: the Stroke Improvement National Audit Program and the 2012 Sentinel Stroke Audit. Hospitals were categorized into 3 groups based on the annualized volume of thrombolysis: 0 to 24, 25 to 49, and ≥50 cases per annum. Arrival-brain scan, onset-tPA, and arrival-tPA times were compared across groups and stratified by onset-arrival time. Multilevel logistic models were used to estimate the odds of receiving tPA within 60 minutes of arrival.

Results—Of the 42,024 patients with acute ischemic stroke admitted to 80 hospitals, 4,347 received tPA (10.3%). Patients admitted to hospitals with an annual thrombolysis volume of ≥50 cases per annum had median arrival-tPA times that were 28 and 22 minutes shorter than patients admitted to hospitals with volumes of 0 to 24 and 25 to 49, respectively. Onset-tPA times were shorter by 24 to 32 minutes across strata of onset-arrival times. In multivariable analysis, patients admitted to hospitals with a volume of ≥50 cases per annum had 4.33 (2.21–8.50; P < 0.0001) the odds of receiving tPA within 60 minutes of arrival. No differences in safety outcomes were observed, with similar 30-day mortality and complication rates across the groups.

Conclusions—Hospitals with higher volumes of thrombolysis activity achieve statistically and clinically significant shorter delays in administering tPA to patients after arrival in hospital. (Stroke. 2013;44:00-00.)

Key Words: hospitals, high-volume, stroke, thrombolytic therapy

Thrombolysis with tissue-type plasminogen activator (tPA) has been demonstrated in randomized controlled trials (RCTs) to improve functional outcomes after acute ischemic stroke. Evidence from individual RCTs and systematic review showed that tPA is most effective when administered soon after the onset of stroke symptoms, with minimal benefit seen 4.5 hours after stroke onset. Improving the rapidity of tPA administration has, therefore, been an important goal for stroke quality improvement strategies in many countries.

In addition to prehospital delays, the rapidity of tPA treatment is also determined by the speed with which the admitting hospital identifies, investigates, and initiates treatment in patients with suspected stroke. The hospital characteristics that determine this response have not been well studied, although this is an important question for the configuration and certification of stroke services. In particular, there have been few studies describing the association between the volume of thrombolysis performed by a hospital and the rapidity of tPA administration. Studies in some settings, such as subarachnoid hemorrhage and acute myocardial infarction, have found that high-volume hospitals achieve better outcomes, although in other settings there seems to be no relationship between volume and outcomes. We, therefore, set out to identify whether there was an association between the volume of thrombolysis performed by hospitals and the time between stroke onset, arrival at hospital, brain scanning, and tPA administration for patients with acute ischemic stroke.

Methods

Data were collected through the Stroke Improvement National Audit Program (SINAP), which is a prospective national audit of the first 72 hours of stroke care after admission in England. Participation in the
audit is voluntary, and hospitals are not reimbursed for participation. Currently, 106 (66%) hospitals in England admitting patients with acute stroke submit data to SINAP. Data of consecutive patients admitted to participating hospitals were abstracted from local care records and prospectively submitted for the audit via a secure web-based tool. The web tool includes real-time data validation checks, and records of individual episodes of care cannot be submitted for the audit until all data fields are filled. Data were linked at the patient level using a unique patient National Health Service (NHS) number to Hospital Episode Statistics (the national administrative data set of admission diagnoses and hospital activity) and the national register of death notifications. Data linkage was performed by a secure third party (the NHS Information Center for Health and Social Care), and no patient-identifiable information was made available to the investigators.

Adult (≥18 years of age) patients admitted with acute ischemic stroke to an SINAP participating hospital in England between January 1, 2011, and August 31, 2012, were included. Patients who were diagnosed with a stroke while already a hospital inpatient for another condition were excluded. To ensure that an unbiased estimate of thrombolysis volume was obtained, only patients admitted to a hospital with ≥40 records included in SINAP and >80% case ascertainment compared with Hospital Episode Statistics were included (case ascertainment is likely to be higher in Hospital Episode Statistics because the data are submitted by hospitals for the purposes of financial reimbursement). Nine hospitals were excluded on the basis of total stroke admissions of <40, and 17 hospitals were excluded on the basis of <80% estimated ascertainment. The hospital thrombolysis volume per annum was categorized into 3 groups: 0 to 24 (low), 25 to 49 (medium), and ≥50 (high) units (on the basis of <80% estimated ascertainment). The characteristics (stroke unit size and type of thrombolysis provision, etc.) of each hospital were included in the analysis as covariates so as to try to achieve a balance between the numbers of patients and hospitals included in each group. A further subanalysis was performed in hospitals with high volume, defined as a volume of ≥100 per annum. Because of potential confounding between symptom onset-arrival time and arrival-tPA time, analyses were stratified by onset-arrival time into the following categories: <60 minutes, 60 to 119 minutes, 120 to 179 minutes, and ≥180 minutes.

Stroke subtype was classified according to the Oxford Community Stroke Project classification. Post-thrombolysis complications were defined pragmatically; symptomatic intracerebral hemorrhage was defined as evidence of intracerebral hemorrhage on brain imaging in association with a clinically significant decline in neurological function. The duration of each of the stages of the thrombolysis pathway was calculated for each patient receiving tPA: time between onset of stroke symptoms and arrival at hospital (onset-arrival), time between arrival and computed tomography or MRI brain imaging (arrival-scan), and time between arrival and receipt of tPA (arrival-tPA). Prehospital travel distances were estimated using patient and hospital postcodes. For reasons of patient confidentiality, the data set only included the district segments of the patient postcode. Distances were, therefore, estimated from the center of each district. Postcode district latitude and longitude data were sourced from the Ordnance Survey. Great circle distances (the distance between 2 points on a globe) between patient’s postcode district and the admitting hospital were calculated using the GEODIST add-on for Stata.

The characteristics (stroke unit size and type of thrombolysis provision) of the admitting hospital were obtained from the Sentinel Stroke Audit 2012. This is a 2-year cross-sectional survey of stroke service provision and characteristics completed by all hospitals admitting patients with acute stroke in England. The data used in this analysis are those obtained in June 2012 and represent a snapshot of stroke service organization at that time.

Analysis

The distribution of arrival-scan and arrival-tPA times across hospitals was illustrated by plotting scatter plots of median times. The distributions of times between groups were compared with violin plots using the kernel density estimator to represent the distribution of times in each group. Thrombolysis rate (as a percentage of all patients admitted with ischemic stroke) and median arrival-tPA times were plotted against onset-arrival time, grouped by 15-minute intervals. Onset-arrival, arrival-scan, and arrival-tPA times were compared across groups using Kruskal–Wallis tests. Categorical variables were compared using the Pearson χ² test. Adjusted odds ratios of patients having an arrival-tPA time of ≤60 minutes were estimated by fitting multilevel multivariable logistic regression models. Random intercepts for each hospital were included to account for clustering of patients at this level. The other covariates included in the model were age (as a continuous variable), sex, OCSP type, and out-of-hours admission. Out-of-hours admission was defined as admission on a weekday between 6 PM and 8 AM or any time on weekends or public holidays. Models were also fitted with onset-arrival time, prehospital distance, and total annual stroke admissions per hospital. To reduce possible bias from errors in recording times, patients were dropped from the analysis if the arrival-tPA time was ≤50 minutes or >1440 minutes (n=12 patients). A complete case sensitivity analysis was performed using data from all hospitals in SINAP, irrespective of the ascertainment rate estimated from administrative data. Hypothesis tests were 2-tailed, α=0.01. All analyses were performed using Stata MP 12.

Results

Of the 42024 patients admitted with acute ischemic stroke to 80 hospitals, 4347 (10.3%) received tPA. Using the total number of patients with ischemic stroke as the denominator, the thrombolysis rate was highest for hospitals with volume ≥50 per annum (15.3% versus 9.1% and 4.7% for medium and low volumes, respectively). There were significant differences in patient characteristics between the groups of hospitals: patients admitted to hospitals with a volume of ≥50 per annum were older (P=0.004), had longer onset-arrival times (P=0.0001), shorter prehospital travel distances (P=0.0001), and were more likely to have been admitted out of regular hours (P=0.0001; Table 1). There were also differences in stroke type, with a higher proportion of patients with posterior circulation syndromes receiving tPA at the high-volume hospitals (P=0.0001). High-volume hospitals administered tPA to a greater proportion of patients presenting at all thrombolyis-eligible time periods after the onset of stroke symptoms (Figure 1), including patients arriving at hospital ≥3 hours after the onset of symptoms.

Hospital-level characteristics are summarized in Table 1. Hospitals with a volume of ≥50 per annum were larger (absolute difference, 10 beds), admitted a greater number of patients overall, and had on-site 24/7 thrombolysis provision. Thrombolysis volume and total admission volume were strongly positively correlated (Pearson R, 0.81). Hospitals with medium and low volumes had a mixture of thrombolysis provision, although even in the lowest-volume category, 87% offered 24/7 thrombolysis provision either on-site or with local arrangements with other hospitals.

High-volume hospitals (volume ≥50 per annum) achieved the quickest median arrival-scan and arrival-tPA times, with the fastest times achieved by hospitals with a volume ≥100 per annum (Figures 2 and 3). Median arrival-tPA times were 28 and 22 minutes shorter in high-volume hospitals compared with low- and medium-volume hospitals, respectively (P<0.0001; Table 2). Onset-tPA times were 20 to 30 minutes shorter for patients with onset-arrival times ≤180 minutes (Table 2). The fastest times were observed for the 8 hospitals with volumes ≥100 per year, which had a median arrival-tPA time of 41 minutes (interquartile range, 30–60 minutes). More than double
the proportion (63% versus 30%) of patients received tPA within 1 hour of arrival in high-versus low-volume hospitals. In both univariate analysis (odds ratio, 3.75; 95% confidence interval, 1.92–7.27) and multivariate analyses adjusted for case mix (adjusted odds ratio, 4.33; 95% confidence interval, 2.21–8.50), patients admitted to high-volume hospitals were significantly more likely to receive tPA within 1 hour of arrival (Table 3). Similar results were observed after adjusting for onset-arrival time and prehospital distance, but thrombolysis volume was not independently associated with arrival-tPA time when adjusting for total number of admissions. No significant differences were observed between medium- and low-volume hospitals in the odds of receiving tPA within 1 hour of hospital admission. There were no observed differences in any of the specified post-thrombolysis outcomes, with similar rates of 7- and 30-day mortality, symptomatic intracranial hemorrhage, and any tPA complications between the hospital groups (Table 2). Arrival-scan, arrival-tPA times, mortality, and complication rates were not materially different in the complete case sensitivity analysis (results not shown).

**Conclusions**

This analysis demonstrates that hospitals with high volumes of thrombolysis activity achieve clinically and significantly faster arrival-tPA and onset-tPA administration times for patients admitted with acute ischemic stroke. No differences in arrival-tPA times were observed between low- and medium-volume hospitals, suggesting that there may be a threshold effect for thrombolysis volume. The most rapid treatment times were achieved by the highest-volume hospitals, with thrombolysis volumes of ≥100 per annum. There was no evidence that faster times were achieved at the expense of patient safety, with similar mortality and complication rates across all groups. Given the importance of timely treatment with tPA in improving outcomes after stroke, these findings may have implications for the configuration, regionalization, and certification of stroke services.

Evidence from RCTs is consistent in showing that the earlier the tPA is administered after the onset of stroke, the better the outcomes. In 1 pooled analysis of 3 landmark RCTs, the odds ratio for a favorable outcome was 2.8 for tPA administration in 0 to 90 minutes and 1.4 if tPA was administered after 180 to 270 minutes had elapsed after stroke onset.14 In this context, the differences in arrival-tPA times seen in our study are likely to be clinically significant. Arrival-tPA times were 28 and 22 minutes faster in the high-volume versus low- and medium-volume groups, respectively (relative reductions of 36% and 31%). Onset-tPA times were 23 to 32 minutes shorter for patients...
admitted ≤3 hours from onset. These differences would be expected to lead to improved functional outcomes for patients, although these were not directly measured in this study. Overall arrival-tPA times are consistent with those reported in the large international Safe Implementation of Treatments in Stroke (SITS) register, and the times achieved by the high-volume centers are equivalent to those reported from some single centers. At least 1 reason for the faster arrival-tPA times in high-volume hospitals was fewer delays between arrival and brain scanning. More detailed information about the thrombolysis pathway was not available in the data set, and so it is not possible to characterize how the high-volume hospitals achieved faster times. Other studies have reported several methods for reducing thrombolysis times, such as prehospital notification and stroke pathway redesign, and further studies to identify the means by which the high-volume hospitals achieved lower in-hospital delays would be useful.

This study identified significant differences in the patient population being treated with tPA between the volume groups, with high-volume hospitals administering tPA to a greater proportion of patients presenting out of regular hours, with posterior circulation syndromes and longer onset-arrival times. These differences seem to be because of the high-volume hospitals achieving their high volumes not just by having a greater total number of stroke admissions but also by administering tPA to a greater proportion of the potentially eligible stroke population. It is possible that this relates to greater experience or confidence in administering tPA in high-risk or more marginal patients or that the high-volume hospitals have better processes in place for the investigation and decision making required for tPA administration. Studies from other countries have demonstrated that high-volume hospitals achieve higher thrombolysis rates, and although this may be, to some extent, tautological, these data suggest that high volumes are not just the result of high numbers of

Figure 1. Thrombolysis rate (A) and median arrival-tissue-type plasminogen activator (tPA) time (B) by onset-arrival time for each of the 3 groups of thrombolysis volume.

Figure 2. Median arrival-scan (A) and arrival-tissue-type plasminogen activator times (B) by hospital annual thrombolysis volume.

Figure 3. Violin plot of arrival-tissue-type plasminogen activator (tPA) times by thrombolysis volume. The black bars are the inter-quartile range, the white marks the median, the whiskers delineate the upper and lower adjacent values, and the shaded area is the kernel density.
overall stroke admissions but also of greater propensity to administer tPA.

Although there have been studies in many healthcare settings of the relationship between hospital volume and patient outcomes, there have been few that have specifically addressed stroke thrombolysis. Data from the Get with The Guidelines-Stroke Program in the United States identified a similar relationship between hospital volume and the probability of arrival-tPA times of \( \leq 60 \) minutes. However, the volumes reported were much lower than those in our study (the highest-volume category in the cohort was 20+ per annum and so would have categorized hospitals as high volume that would have been classified as low volume in our study), and overall thrombolysis rates were significantly lower in the US cohort (4.3% versus 10.3% of patients with acute ischemic stroke). In contrast, data from the SITS East register

### Table 2. Thrombolysis Times and Outcomes by Hospital Thrombolysis Volume

<table>
<thead>
<tr>
<th>Thrombolysis Volume per Annum</th>
<th>0–24</th>
<th>25–49</th>
<th>( \geq 50 )</th>
<th>( P ) Value</th>
</tr>
</thead>
</table>
| All patients
| Median onset-arrival time, min | 497 (111–1078) | 447 (101–1007) | 505 (110–1150) | <0.0001 |
| tPA recipients
| Median arrival-scan time, min | 30 (18–49) | 27 (16–45) | 20 (13–31) | <0.0001 |
| Median arrival-tPA time, min
| All | 78 (57–105) | 72 (50–101) | 50 (33–75) | <0.0001 |
| Onset-arrival time <60 min | 84 (58–106) | 80 (57–106) | 54 (35–80) | <0.0001 |
| Onset-arrival time 60–119 min | 80 (58–107) | 68 (48–99) | 49 (33–74) | <0.0001 |
| Onset-arrival time 120–179 min | 72 (58–102) | 64 (50–91) | 44 (31–66) | <0.0001 |
| Onset-arrival time \( \geq 180 \) min | 65 (50–76) | 74 (51–122) | 51 (32–74) | <0.0001 |
| Median onset-tPA time, min
| All | 158 (125–195) | 150 (120–195) | 142 (109–194) | <0.0001 |
| Onset-arrival time <60 min | 123 (100–150) | 120 (100–150) | 99 (81–125) | <0.0001 |
| Onset-arrival time 60–119 min | 165 (135–190) | 153 (130–180) | 135 (110–160) | <0.0001 |
| Onset-arrival time 120–179 min | 225 (194–244) | 206 (185–230) | 193 (173–215) | <0.0001 |
| Onset-arrival time \( \geq 180 \) min | 290 (260–270) | 442 (259–945) | 292 (250–720) | 0.10 |
| Arrival to tPA within 1 h, % | 30.4 | 38.4 | 63.3 | <0.0001 |
| 7-day mortality, % | 6.8 | 6.6 | 5.2 | 0.13 |
| 30-day mortality, % | 10.0 | 10.6 | 10.1 | 0.88 |
| sICH rate, % | 5.5 | 4.2 | 4.3 | 0.46 |
| Any tPA complications, % | 11.3 | 10.3 | 9.7 | 0.50 |

Times (in min) are shown as medians and interquartile ranges. sICH indicates symptomatic intracranial hemorrhage; and tPA, tissue-type plasminogen activator.

### Table 3. Odds Ratios of Arrival to tPA Time of \( \leq 60 \) min Using an Annual Volume of <25 as the Reference Category

<table>
<thead>
<tr>
<th>ORs of Arrival-tPA Time ( \leq 60 ) min</th>
<th>Volume</th>
<th>OR</th>
<th>95% CI</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariable</td>
<td>25–49</td>
<td>1.57</td>
<td>0.97–2.84</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td>( \geq 50 )</td>
<td>3.75</td>
<td>1.92–7.27</td>
<td>0.0001</td>
</tr>
<tr>
<td>Multivariable—patient variables*</td>
<td>25–49</td>
<td>1.73</td>
<td>0.95–3.15</td>
<td>0.075</td>
</tr>
<tr>
<td></td>
<td>( \geq 50 )</td>
<td>4.33</td>
<td>2.21–8.50</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Multivariable—patient variables* and onset-arrival time</td>
<td>25–49</td>
<td>1.73</td>
<td>0.94–3.15</td>
<td>0.075</td>
</tr>
<tr>
<td></td>
<td>( \geq 50 )</td>
<td>4.33</td>
<td>2.21–8.49</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Multivariable—patient variables,* onset-arrival time, and prehospital distance</td>
<td>25–49</td>
<td>1.64</td>
<td>0.89–3.01</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>( \geq 50 )</td>
<td>4.14</td>
<td>2.10–8.17</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Multivariable—patient variables* and total annual admissions</td>
<td>25–49</td>
<td>1.32</td>
<td>0.71–2.46</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td>( \geq 50 )</td>
<td>1.99</td>
<td>0.79–5.02</td>
<td>0.14</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; OR, odds ratio; and tPA, tissue-type plasminogen activator.

*All multivariable models include patient-level variables: age, sex, OCSP type, and out-of-hours admission.
of 9 central and Eastern European countries found no relationship between hospital volume and arrival-tPA times of ≤60 minutes. Although there are also methodological differences in these studies (such as registry inclusion criteria), the lack of consistency in the findings suggests that volume effects may be specific to particular health systems.

These findings have important implications for the configuration and certification of stroke services. In particular, they suggest that concentrating stroke thrombolysis services into a smaller number of high-volume centers, where geography and demographics permit, may lead to improved thrombolysis rates and treatment times. However, it is important to note that there was considerable variation in arrival-tPA times, with some low-volume hospitals achieving median arrival-tPA times of ≤60 minutes. In addition, all the high-volume centers were in urban areas, and low volumes of thrombolysis will be partly the result of low population density in the hospital catchment area, geography, and the quality of local transport infrastructure. Service reconfigurations also need to consider the risk of increasing prehospital times, and there was some evidence that high-volume hospitals have longer prehospital times, although the difference between high- and low-volume hospitals was small (8 minutes) and may be confounded by differences in the denominator populations. Some areas of England (such as Greater London) have already gone through planned reorganizations to concentrate stroke services into high-volume centers, and these are likely to have influenced the results of this study.

Strengths and Limitations

This study includes data from a large national cohort of stroke patients and describes the real-world outcomes of contemporary stroke care. We also used clinical data to adjust for potential confounders and statistical techniques to allow for clustering of patients at the hospital level, noting criticisms of previous studies over these issues.

One of the main critiques of previous studies of hospital volume has been the potential for selection bias. This is likely to be less of a concern for an emergency condition such as stroke compared with elective procedures and surgical conditions and for process measures such as treatment times rather than outcome measures such as mortality. However, although we excluded hospitals with low estimated case ascertainment, we cannot rule out variation in stroke ascertainment and reporting rates between hospitals. It is also important to note that these data are observational in nature, and although the analysis controlled for several patient-level confounders, the results may be attributable to unmeasured hospital characteristics. Finally, the outcome measured in this study was treatment time and not a direct measure of patient outcome such as disability, although RCTs of tPA suggest that reduced treatment times are associated with better outcomes.

Summary

Data from a large national cohort suggest that there is a volume effect for stroke thrombolysis in England, with a volume threshold for hospitals achieving clinically and statistically significant quicker thrombolysis for patients with acute ischemic stroke. This is despite high-volume hospitals performing thrombolysis administration to a wider, and more diverse, population of patients. These findings suggest that concentrating thrombolysis services into high-volume sites may reduce thrombolysis delays but also show that volumes could be increased if low-volume centers administered tPA to a greater proportion of stroke admissions.

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Disclosures

A.G. Rudd is National Clinical Director of Stroke, NHS England. The other authors report no conflicts.

References

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Correction

The version of the article “Bigger, Faster? Associations Between Hospital Thrombolysis Volume and Speed of Thrombolysis Administration in Acute Ischemic Stroke” by Bray et al that published ahead-of-print on September 19, 2013 contained an error in the author byline. Dr Geoffrey C. Cloud, FRCP appeared as Cloud C. Geoffrey, FRCP. This will be corrected in the online and print versions as Geoffrey C. Cloud, FRCP.