Factors Associated With In-Hospital Mortality After Administration of Thrombolysis in Acute Ischemic Stroke Patients
An Analysis of the Nationwide Inpatient Sample 1999 to 2002

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Background and Purpose—The prospective trials evaluating the safety and efficacy of intravenous tissue plasminogen activator have generally been conducted at academic medical centers and community hospitals with an institutional commitment to stroke care. Relatively little is known about the safety of this therapy as it is used in the community. We therefore examined outcomes in acute stroke patients treated with thrombolysis using the largest discharge database available in the United States for the years 1999 to 2002.

Methods—Data were derived from the Nationwide Inpatient Sample for the years 1999 to 2002. Using the appropriate International Classification of Disease—Clinical Modification, 9th revision, codes, patients admitted through the emergency room with a primary diagnosis of acute ischemic stroke were selected for analysis. From these patients, those coded as receiving thrombolysis were identified. Multivariate logistic regression was performed on the thrombolysis and nonthrombolysis cohorts to identify independent predictors of in-hospital mortality from among those clinical elements available in the database.

Results—We identified 2594 patients treated with thrombolysis from a group of 248 964 patients admitted through the emergency room with a primary diagnosis of acute ischemic stroke. The thrombolysis cohort had a higher in-hospital mortality rate compared with the nonthrombolysis patients (11.4% versus 6.8%). The rate of intracerebral hemorrhage was 4.4% for the thrombolysis cohort and 0.4% for nonthrombolysis patients. Multivariate logistic regression showed advanced age, Asian/Pacific Islander race, congestive heart failure, and atrial fibrillation/flutter to be independent predictors of in-hospital mortality after thrombolysis. Thrombolysis volume, overall ischemic stroke volume, and teaching status were not significant predictors of in-hospital mortality after thrombolysis.

Conclusions—Thrombolysis, as it is used in the community, has a safety profile that is similar to that observed in the large, prospective clinical trials. (Stroke. 2006;37:440-446.)

Key Words: stroke, ischemic – thrombolysis

Intravenous treatment with tissue plasminogen activator (tPA) is the only therapy approved in the United States, Canada, and the European Union for acute ischemic stroke. A favorable risk-to-benefit relationship has been established for this treatment in large, prospective clinical trials, and it has been endorsed by prominent stroke associations. Nevertheless, only a minority of patients who present with acute ischemic stroke are treated with tPA. One factor that may contribute to this low rate is clinician concern about the safety of the treatment. Because the prospective trials evaluating this therapy were conducted at academic and community hospitals with institutional commitment to stroke care, relatively little data are available regarding the safety of thrombolysis as it is used in a broad range of hospitals in the community. In an effort to address this question, we examined outcomes in acute ischemic stroke patients treated with thrombolysis using the Nationwide Inpatient Sample (NIS), the largest all-payer discharge database available in the United States.

Methods

Data for the study were derived from the NIS for the years 1999 to 2002. The NIS, which is maintained as part of the Healthcare

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Utilization Project of the Agency for Healthcare Quality and Research, is the largest all-payer inpatient care database in the United States. It represents an ≈20% stratified random sample of all patients admitted at nonfederal hospitals. Nonfederal hospitals represent the majority of hospitals in the United States; they include hospitals run by city and state governments and for-profit and not-for-profit organizations. They encompass academic (teaching) and nonacademic institutions. Federal hospitals in the United States are mainly Veterans Administration hospitals, which treat military veterans exclusively. Five hospital characteristics, geographic region, ownership, location (urban or rural), teaching status, and bed size, are used for stratification in an attempt to create a sample that is maximally representative of hospitalizations in the United States. During the years considered in this study, between 984 and 995 hospitals from between 24 and 35 states contributed 100% of their discharges to the database. The annual number of total discharges reported in the database ranged from 7 198 929 to 7 853 982 during the study period. The database codes discharge level information for each patient admission included admission source, discharge destination, up to 15 diagnoses and procedures, patient demographics, and hospital characteristics. Information on the structure, maintenance, and validity of the data set, as well as a list of publications based on analysis of the data set, can be found on the Healthcare Utilization Project of the Agency for Healthcare Quality and Research website.

Adult patients with acute ischemic stroke were identified by querying the database for all patients ≥18 years old admitted through the emergency room with a primary diagnosis of ischemic stroke. The International Classification of Disease—Clinical Modification, 9th revision, (ICD-9 CM) codes used to identify patients were 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, and 436. Data from Kansas, where admission source was not coded, was excluded from analysis. Data from Illinois, Ohio, Utah, Washington, and West Virginia were also excluded because data from these states do not include the hospital day on which procedures are performed.

From the cohort of acute stroke patients (n=250 005), those receiving thrombolysis on hospital day 0 or 1 were identified using the ICD-9 CM procedure code 99.10. In a survey that included 42 academic medical centers in 1999, Johnston et al found the code 99.10 to have a specificity of 100% for thrombolysis but a sensitivity of only 50%. The thrombolysis group identified using this code included 2600 patients.

Patients’ age, gender, and race were recorded directly from the database. Age was categorized into <55 years, 55 to 64 years, 65 to 74 years, 75 to 84 years, and ≥85 years. Disposition of the patient on discharge was missing for 6 (0.2%) thrombolysis patients and 1035 (0.4%) nonthrombolysis patients. These patients were excluded from further analysis.

Querying all diagnosis fields based on the appropriate ICD-9 CM codes identified comorbid medical conditions. The following comorbidities were identified: history of myocardial infarction, congestive heart failure, atrial fibrillation/atrial flutter, valvular disease, hypertension, peripheral vascular disease, diabetes mellitus, chronic pulmonary disease, renal disease, chronic liver disease/cirrhosis, nonmetastatic solid tumor, and metastatic malignancy. Querying all diagnosis fields with the ICD-9 CM codes for intracerebral hemorrhage (ICH), pneumonia, pulmonary embolism, and blood product transfusion identified serious complications during the hospitalization. No specific data were available for National Institutes of Health Stroke Scale (NIHSS) or measures of functional disability such as the Barthel index, Rankin scale, or the like, nor did the database

Results

Table 1 shows the characteristics of the patients with acute ischemic stroke grouped according to whether the patient was treated with thrombolysis. The majority of patients in both groups were between 65 and 84 years old, although a higher proportion of patients not treated with thrombolysis were ≥75 years of age. Male patients were slightly in excess of female patients in the thrombolysis group, whereas females outnumbered males in the nonthrombolysis group. Whites were the most prevalent race in both groups, with whites being slightly over-represented in the thrombolysis group. Comorbid medical conditions were frequently present in thrombolysis and nonthrombolysis patients. The rates of the various comorbidities were similar in both groups, with the exception of atrial arrhythmia, which was more common in the thrombolysis cohort, and diabetes and malignancy, which were less common in the thrombolysis group. About one third of thrombolysis patients were treated at centers with an annual thrombolysis volume of ≥5, whereas <10% of nonthrombolysis patients were treated at these centers. Approximately 70% of thrombolysis patients were treated at centers with an annual volume of >124 acute stroke patients, whereas slightly less than two thirds of nonthrombolysis patients were treated at these high-volume centers.

Table 2 shows outcomes of acute stroke patients, grouped according to whether they were treated with thrombolysis. The in-hospital mortality rate was 11.4% for thrombolysis patients and 6.8% for nonthrombolysis patients. When patients with ICH are excluded from analysis, the in-hospital mortality rate in the thrombolysis group remained higher than that of the nonthrombolysis group (10.2% versus 6.7%; P<0.001). The in-hospital mortality rate for patients >80 years old was 15.2%. The rate of discharge to home was 37.5% for the thrombolysis cohort and 46.4% for the nonthrombolysis cohort. The rate of ICH was 4.4% for thrombolysis patients and 0.4% for nonthrombolysis patients; the rate of transfusion of blood products was <2% for both groups.

Table 3 examines the effect of various patient and hospital characteristics on the probability of in-hospital death using
Thrombolysis patients, with the oldest patients approximately twice as likely to die as patients in the youngest age group. Female sex slightly decreased the odds of death in both groups, although this variable did not reach significance in the thrombolysis patients. Compared with whites, blacks and Asian/Pacific Islanders had significantly higher odds of in-hospital mortality in the nonthrombolysis cohort, and Asian/Pacific Islanders had significantly higher odds of death in the thrombolysis cohort. Congestive heart failure and atrial fibrillation/flutter similarly increased the odds of in-hospital death in both groups. Patients treated at low-volume centers had higher odds of in-hospital mortality in the nonthrombolysis group, but this effect was not seen in the thrombolysis cohort.

There was not a significant effect of treatment at a high-volume thrombolysis center or at a teaching hospital for thrombolysis patients, whereas treatment in these settings predicted slightly higher odds of mortality in the nonthrombolysis patients. An analysis of the effect of annual hospital ischemic stroke volume and annual thrombolysis volume of >5 cases on the rate of hemorrhagic conversion after thrombolysis was performed (Table 4). There was no significant effect either of these markers of expertise on the hemorrhage rate.

### Discussion

This study examines the short-term outcomes for a cohort of 2594 patients treated with thrombolysis for acute ischemic stroke and compares them with a group of 246 370 acute ischemic stroke patients not treated with thrombolysis. The comparisons in our study are not the result of a randomized clinical trial and are almost certainly subject to bias, given that thrombolysis-eligible patients typically have more severe strokes than the average ischemic stroke patient and that the
database lacks variables that would permit adjustment for presenting stroke severity, such as patient-specific NIHSS or imaging estimates of stroke location or size. Further, it may be that in-hospital mortality is a poor marker for the quality of stroke care or appropriateness of thrombolysis usage. However, the data are drawn from a database that contains the discharge information for 20% of all patients treated at nonfederal hospitals in the United States from 1999 to 2002. The thrombolysis cohort represents the largest series of thrombolysis patients that has been reported and provides insight regarding the application of thrombolytic therapy outside of the structure of clinical trials.

The overall in-hospital mortality rate for thrombolysis patients in our study was 11.4%, whereas for nonthrombolysis patients, the rate was 6.8%. The higher mortality rate in thrombolysis patients contrasts with the findings of the National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group trial, which reported similar short-term (90-day) mortality rates in patients randomized to thrombolysis and to placebo (17% versus 21%), which was a randomized trial. Although not from a randomized trial, the disparity in mortality rate that we observed is consistent with the findings from community-based samples. Katzan et al., in an analysis of the experience of 29 Cleveland-area hospitals with thrombolysis in 1997 to 1998, reported a higher mortality rate in the thrombolysis patients compared with nonthrombolysis patients (15.7% versus 5.1%). Similarly, Reed et al., in an analysis of 137 community hospitals in 1998 to 1999, found a higher in-hospital mortality rate in thrombolysis patients (9.9% versus 6.8%). The higher mortality rates in thrombolysis patients in community samples, but not in randomized trials, almost certainly results from baseline differences in clinical status, which is not reflected in the NIS. It should be noted that even when patients with ICH are excluded from our analysis, the

| TABLE 3. Multivariate Logistic Regression Analysis of Predictors of In-Hospital Mortality |
|---------------------------------|---------------------------------|-----------------|-----------------|-----------------|
|                                 | Patients Treated With Thrombolysis | Patients Not Treated With Thrombolysis |
|                                 | Died | OR (95% CI) | P Value | Died | OR (95% CI) | P Value |
| Age group, y                    |      |             |      |      |             |      |
| <55                             | 31 (7.1) | Ref | 0.39 | 959 (3.6) | Ref | 0.02 |
| 55–64                           | 40 (9.3) | 1.25 (0.76–2.05) | 0.39 | 1360 (4.1) | 1.11 (1.02–1.20) | 0.02 |
| 65–74                           | 85 (10.9) | 1.41 (0.90–2.19) | 0.13 | 3098 (5.4) | 1.36 (1.26–1.46) | <0.01 |
| 75–84                           | 97 (13.8) | 1.64 (1.04–2.59) | 0.03 | 6122 (7.5) | 1.73 (1.61–1.86) | <0.01 |
| ≥85                             | 42 (17.4) | 1.95 (1.14–3.34) | 0.01 | 5201 (11.0) | 2.33 (2.16–2.51) | <0.01 |
| Sex                             |      |             |      |      |             |      |
| Male                            | 152 (10.8) | Ref | 0.95 | 7019 (6.5) | Ref | 0.01 |
| Female                          | 143 (12.0) | 0.99 (0.77–1.28) | 0.95 | 9721 (7.0) | 0.96 (0.93–0.99) | 0.01 |
| Race*                           |      |             |      |      |             |      |
| White                           | 193 (10.8) | Ref | 0.95 | 11 056 (7.1) | Ref | 0.01 |
| Black                           | 29 (13.6) | 1.51 (0.98–2.35) | 0.06 | 1764 (5.6) | 1.06 (1.00–1.12) | 0.04 |
| Hispanic                        | 14 (9.7) | 0.99 (0.55–1.77) | 0.97 | 740 (5.6) | 0.98 (0.91–1.06) | 0.62 |
| Asian/Pacific Islander          | 15 (22.1) | 2.28 (1.24–4.20) | 0.01 | 335 (6.5) | 1.13 (1.01–1.27) | 0.04 |
| Missing                         | 39 (11.9) | 1.15 (0.78–1.68) | 0.48 | 2554 (7.1) | 1.07 (1.02–1.12) | 0.01 |
| Comorbidity                     |      |             |      |      |             |      |
| Congestive heart failure        | 66 (21.7) | 1.93 (1.40–2.68) | <0.01 | 4350 (14.6) | 2.00 (1.92–2.07) | <0.01 |
| Atrial fibrillation and flutter | 121 (18.0) | 1.78 (1.35–2.34) | <0.01 | 6278 (12.9) | 1.92 (1.86–1.99) | <0.01 |
| Hypertension                    | 173 (11.0) | 0.85 (0.66–1.09) | 0.20 | 8036 (5.3) | 0.60 (0.58–0.62) | <0.01 |
| Diabetes mellitus               | 71 (14.1) | 1.31 (0.97–1.76) | 0.08 | 4491 (6.1) | 1.01 (0.97–1.04) | 0.73 |
| Chronic pulmonary disease       | 37 (10.6) | 0.89 (0.61–1.30) | 0.56 | 2920 (8.6) | 1.15 (1.10–1.20) | <0.01 |
| Annual thrombolysis volume >5 cases | 102 (10.9) | 0.88 (0.66–1.16) | 0.35 | 1625 (6.9) | 1.07 (1.01–1.13) | 0.03 |
| Annual hospital ischemic stroke volume |      |             |      |      |             |      |
| >124                            | 209 (11.6) | Ref | 0.95 | 9932 (6.5) | Ref | 0.01 |
| 56–124                          | 65 (10.7) | 0.93 (0.68–1.28) | 0.66 | 4313 (7.0) | 1.10 (1.06–1.15) | <0.01 |
| 20–55                           | Data not shown* | 0.80 (0.45–1.39) | 0.42 | 1945 (7.7) | 1.16 (1.10–1.23) | <0.01 |
| 1–19                            | Data not shown* | 1.40 (0.47–4.23) | 0.55 | 550 (8.4) | 1.24 (1.13–1.36) | <0.01 |
| Teaching status                 |      |             |      |      |             |      |
| Nonteaching                     | 169 (10.7) | Ref | 0.95 | 10 833 (6.8) | Ref | 0.01 |
| Teaching                        | 126 (12.5) | 1.13 (0.87–1.47) | 0.36 | 5899 (6.7) | 1.09 (1.05–1.13) | <0.01 |

*Data not shown as there were not enough patients in individual cells for tabulation in compliance with the requirements of the Agency for Healthcare Research and Quality (AHRQ) to protect individual personal patient information.
in-hospital mortality rate in the thrombolysis group remained higher than that of the nonthrombolysis group (10.2% versus 6.7%; \( P<0.001 \)), further emphasizing that the higher mortality in this group is a function of baseline differences in the patients and is not treatment related. Further, the mortality rate of thrombolysis patients in our study is similar to those of the prospective trials and postapproval large case series (mortality rate 9% to 15.7%).1,5,8,9,12,13,15,16 Assuming that the baseline clinical neurological characteristics of our patients are comparable to patients in these studies, the mortality rate we report suggests that thrombolysis treatment, as it is applied in a broad community sample, has a comparable safety profile to that achieved in clinical trials that established the benefit of treatment.

The overall rate of ICH in our thrombolysis cohort was 4.4%. This is lower than the symptomatic ICH rates reported in the prospective trials (6.4% to 8.8%)1,20,21 but falls within the range of rates reported in the open-label series (2.7% to 15.7%).6,8,10–14,16,22–28 The low hemorrhage rate found in our study, although encouraging, should be interpreted with caution because the accuracy of the discharge coding for ICH has been shown to not be completely reliable18,29,30 and because patients who are transferred to other hospitals after thrombolysis and who subsequently hemorrhage are not detected in our study.

The demographic data available our study identified several patient characteristics that independently predicted in-hospital mortality in thrombolysis patients, including older age, congestive heart failure, and atrial arrhythmia.

Several studies have specifically examined the effect of advanced age on in-hospital mortality rate after thrombolysis,16,25,31 with each of them finding a tendency for high mortality among the very old. Tanne et al, in a retrospective analysis of 189 patients treated with intravenous tPA at 13 hospitals, found that patients \( \geq 80 \) years of age were more likely to die during the initial hospitalization than patients \(< 80 \) years old (OR, 2.8; 95% CI, 0.81 to 9.62).23 Similarly, the German Stroke Registers Study Group, in a prospective, observational study of 1658 patients treated with tPA, found an adverse effect of advanced age on outcome, such that patients \( \geq 75 \) years of age had significantly higher odds of inpatient death than patients \(< 55 \) years of age (OR, 3.2; 95% CI, 1.8 to 5.7).16 The Calgary Stroke Program, in a prospective study of 62 patients \( \geq 80 \) years of age treated with tPA, found a very high mortality rate of 24.2% among these very elderly patients.31 Interestingly, the effect of advanced age on in-hospital mortality rate was smaller in magnitude in our cohort than in these studies. The in-hospital mortality rate for patients \( > 80 \) years of age in our cohort was only 15.2%. Compared with patients \(< 55 \) years of age, the likelihood of death was only modestly increased for patients 75 to 84 years of age (OR, 1.64; 95% CI, 1.04 to 2.59) and patients \( \geq 85 \) years of age (OR, 1.95; 95% CI, 1.14 to 3.34). Further, for our cohort, the effect of advancing age on in-hospital mortality in thrombolysis patients was very similar in magnitude to the effect in nonthrombolysis patients, suggesting that the excess mortality in the elderly is not thrombolysis related but rather merely a function of the increased susceptibility of elderly patients to complications from stroke that result in death.

Congestive heart failure and atrial fibrillation also independently predicted in-hospital mortality in our thrombolysis cohort. Pre-existing congestive heart failure32–34 and atrial arrhythmia32,33,35–37 are well-documented risk factors for mortality after stroke, and our findings suggest a prognostic significance of these conditions in thrombolysis patients. However, in our study, the increased risk of mortality attributable to these conditions is very similar in thrombolysis and nonthrombolysis patients, suggesting that these conditions should probably not be considered contraindications to thrombolysis.

Surprisingly, the Asian/Pacific Islander race predicted higher odds of in-hospital mortality for thrombolysis and nonthrombolysis patients, although the magnitude of the effect was much greater for thrombolysis patients. However, the number of Asian thrombolysis patients in our study is relatively small (\( n = 68 \) for thrombolysis; \( n = 5146 \) for nonthrombolysis patients), and it is entirely possible that there are important baseline differences in prognostic variables between Asians and non-Asians in our study that we are unable to identify. Whether Asian race is a true risk factor for adverse outcome after stroke, and particularly thrombolysis, is something that will need to be determined in future stroke registries that include a greater amount of clinical detail than is available in the NIS.

We did not observe a significant reduction in mortality rate for patients treated at hospitals experienced in administering thrombolysis (defined as an annual thrombolysis volume of \( > 5 \) cases), although the point estimate of the OR showed a reduction in risk of in-hospital mortality associated with treatment at a high-volume center. This contrasts with results from the German Stroke Registers Study Group,13 which found a much higher mortality rate for thrombolysis patients treated at hospitals with \( \leq 5 \) patients receiving tPA per year compared with hospitals with higher volumes (in-hospital mortality rate 24.1% versus 9.4%). It may be that our study is underpowered to show an effect of experience with tPA, or that there are baseline differences in patients that mask better

### TABLE 4. Analysis of Thrombolysis Volume and Annual Ischemic Stroke Volume on the Risk of Hemorrhagic Conversion After Thrombolysis, Adjusting for Patients’ Age, Race, and Sex

<table>
<thead>
<tr>
<th>Age Group</th>
<th>ICH No. (ICH rate, %)</th>
<th>Thrombolysis OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>55 years of age</td>
<td>36 (3.9)</td>
<td>0.86 (0.57–1.30)</td>
<td>0.47</td>
</tr>
<tr>
<td>20–55 Data not shown*</td>
<td>29 (4.8)</td>
<td>1.08 (0.70–1.68)</td>
<td>0.73</td>
</tr>
<tr>
<td>1–19 Data not shown*</td>
<td>5.3 (0.19–1.48)</td>
<td>0.23</td>
<td></td>
</tr>
</tbody>
</table>

*There were not enough patients in individual cells for tabulation in compliance with the requirements of the Agency for Healthcare Research and Quality (AHRQ) to protect individual personal patient information.
outcomes in high-volume centers. Another possible explanation for the failure to see a significant reduction in mortality may be that some experienced centers were misclassified, as the ICD-9 code for thrombolysis, whereas it has a specificity of 100%, it has a sensitivity of only 50%. Misclassification as low experience centers would result in a tendency toward no effect of this variable on mortality. Yet another potential explanation is that there may be emergency department to emergency department transfers (which are not tracked in the NIS database) of patients with particularly devastating strokes to high-volume thrombolysis centers that confounds our analysis. In keeping with this explanation is the fact that for patients not treated with thrombolysis, admission at a high-volume thrombolysis center correlated with higher mortality. It will be important for future prospective studies to carefully evaluate the effect of thrombolysis volume on outcome and to determine thresholds predictive of good outcome as the criteria for qualifying as a “stroke center” are delineated.

Our study found that for thrombolysis patients, neither treatment at a hospital with a high annual ischemic stroke patient volume nor at a teaching hospital predicted lower in-hospital mortality. This is surprising in light of randomized, controlled trials that have shown decreased mortality for patients treated in a setting in which there exists stroke expertise, and our finding that in nonthrombolysis patients, higher stroke volume predicted lower odds of in-hospital mortality. One possible explanation for this discrepancy is that treatment with thrombolysis is a marker for a hospital with a high competence in treating stroke, irrespective of overall volume or teaching status.

In conclusion, the NIS data suggest that thrombolysis, as it is being applied in the community, has a safety profile that is similar to that observed in the large, prospective clinical trials. Further, there do not appear to be patient or hospital characteristics that should be considered unique risk factors for in-hospital mortality after thrombolysis.

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