Frequency of Thrombolytic Therapy in Patients With Acute Ischemic Stroke and the Risk of In-Hospital Mortality

The German Stroke Registers Study Group

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Background and Purpose—There is little information about early outcome after intravenous application of tissue-type plasminogen activator (tPA) for stroke patients treated in community-based settings. We investigated the association between tPA therapy and in-hospital mortality in a pooled analysis of German stroke registers.

Methods—Ischemic stroke patients admitted to hospitals cooperating within the German Stroke Registers Study Group (ADSR) between January 1, 2000, and December 31, 2000, were analyzed. The ADSR is a network of regional stroke registers, combining data from 104 academic and community hospitals throughout Germany. Patients treated with tPA were matched to patients not receiving tPA on the basis of propensity scores and were analyzed with conditional logistic regression. Analyses were stratified for hospital experience with the administration of tPA.

Results—A total of 13,440 ischemic stroke patients were included. Of these, 384 patients (3%) were treated with tPA. In-hospital mortality was significantly higher for patients treated with tPA compared with patients not receiving tPA (11.7% versus 4.5%, respectively; \( P \leq 0.0001 \)). After matching for propensity score, overall risk of inpatient death was still increased for patients treated with tPA (odds ratio [OR], 1.7; 95% CI, 1.0 to 2.8). Patients receiving tPA in hospitals that administered \( \leq 5 \) thrombolytic therapies in 2000 had an increased risk of in-hospital mortality (OR, 3.3; 95% CI, 1.1 to 9.9). No significant influence of tPA use for risk of inpatient death was found in hospitals administering >5 thrombolytic treatments per year (OR, 1.3; 95% CI, 0.8 to 2.4).

Conclusions—In-hospital mortality of ischemic stroke patients after tPA use varied between hospitals with different experience in tPA treatment in routine clinical practice. Our study suggested that thrombolytic therapy in hospitals with limited experience in its application increase the risk of in-hospital mortality. (Stroke. 2003;34:1106-1113.)

Key Words: hospital mortality ■ stroke ■ thrombolytic therapy

T
reatment of acute ischemic stroke with intravenous tissue-type plasminogen activator (tPA) has proven efficacy in clinical trials by reducing the proportion of patients who were dependent at follow-up.\(^1\)\(^2\) Most of the information about the outcome of patients treated outside clinical trials is reported from hospitals experienced in the administration of tPA\(^3\)-\(^5\) or from centers integrated in special stroke treatment networks.\(^6\)\(^7\) Only limited information is available about treatment outcomes in unselected community-based settings.\(^8\)\(^9\) Some of these studies replicated the favorable outcomes of tPA use reported from randomized controlled trials.\(^3\)-\(^7\) Other studies however, demonstrated adverse effects of thrombolytic treatment in routine clinical practice, causing an excess of in-hospital mortality for patients receiving tPA.\(^8\)\(^9\) On the basis of these conflicting results, caution was suggested when thrombolytic therapy in acute ischemic stroke was extended for widespread use.\(^10\) Valid information about the safety of thrombolytic treatment in routine clinical practice can best be provided by systematic data collection in community settings assessing a large number of patients and
hospitals with different levels of experience in tPA administration.

In a pooled analysis of 104 hospitals from 4 regional stroke registers in Germany, we evaluated whether tPA treatment in patients with acute ischemic stroke was associated with an increased in-hospital mortality.

**Patients and Methods**

Regional hospital-based stroke registers have been established since 1994 in several German states for continuous monitoring of the quality of stroke care.11,12 This registration is part of a legal act implemented in Germany through which hospitals participate in programs for quality assurance of acute clinical care.13 The implementation of regional stroke registers is based on local agreements between healthcare providers, health insurance companies, and medical authorities, usually a regional board of physicians. Hospitals within defined regions collected data on sociodemographic variables, diagnostic procedures, acute treatment strategies, and comorbidities of their stroke patients. These data were sent anonymously to the coordinating center of the respective regional stroke register for regular external evaluation of the quality of stroke care.

The German Stroke Registers Study Group (Arbeitsgemeinschaft Deutscher Schlaganfall Register, ADSR) is a network of these ongoing stroke registers. The ADSR was founded in 1993 to standardize stroke terminology and data collection; regular combined analyses of the collected data were agreed on.14 In the present analysis, data from the stroke registers in Hamburg,11 Hesse,12 Westphalia, and Bavaria, as well as from the population-based Erlangen Stroke Project,13 were included. In total, 104 hospitals participated in the study, representing >5% of all 2242 acute-care hospitals in Germany.16 The registers combined data from academic and community hospitals and from departments of neurology, internal medicine, and geriatric medicine. All ischemic stroke patients admitted to the participating hospitals between January 1, 2000, and December 31, 2000, were taken into consideration in the analysis.

**Data Collection**

Data were collected prospectively by the treating hospital physician of an individual stroke patient. Information was documented continuously from admission to discharge on a standardized form. After discharge, these forms were sent to the regional stroke register. There, all forms were checked for plausibility and completeness before data entry. In case of implausible or incomplete data, the respective hospitals were contacted, and the data were corrected. Before starting the current analysis, we tested the logistics of data pooling and the feasibility of data analysis.17

Variable definitions and the methods of data collection were standardized among the registers. All registers agreed to a mandatory data set before pooling.14 Standardized questionnaires were used, and each study physician was guided by a manual of operation. Information on the following variables was assessed: thrombolytic treatment (intravenous use of tPA, intra-arterial thrombolysis, none); time from stroke onset to hospitalization (admission within 3 hours of stroke onset); admission after 3 hours of stroke onset, unknown stroke onset); admission from other acute facility; hypertension (reported blood pressure systolic \( \geq 160 \) mm Hg or diastolic \( \geq 95 \) mm Hg, or patient’s self-report of treated hypertension); diabetes mellitus (reported pathological elevated fasting blood glucose level, patient’s self-report of diabetes, or use of antidiabetic drugs); hypercholesterolemia (reported pathological elevated plasma total cholesterol level >240 mg/dL or use of lipid-lowering medication); previous stroke (neurological deficit \( >24 \) hours before the current event); atrial fibrillation (documented by ECG); neurological deficits of current stroke (weakness or paresis, aphasia, dysarthria, and disturbances of consciousness); discharge destination (dead, home, residential/nursing home, rehabilitation unit, other hospital); and pathological subtype of stroke (cerebral infarction, primary intracranial or subarachnoidal hemorrhage, transient ischemic attack, undefined type). Stroke was defined according to the World Health Organization criteria.18 Stroke subtype was diagnosed from the results of the first CT or MRI scan. The experience of an individual hospital in tPA administration was defined by the number of patients treated with tPA per year. This definition is based on the study of Katzan and colleagues.19 In that study, the proportion of patients receiving thrombolytic therapy was substantially increased in hospitals administering tPA to >5 patients per year. Therefore, in our analysis, hospitals administering tPA to \( \leq 5 \) patients in 2000 were classified as centers with limited experience, and hospitals treating >5 patients were classified as experienced centers, regardless of other hospital characteristics.

**Propensity Score Analysis**

Obviously, stroke patients in observational studies are not assigned at random to receive thrombolytic treatment. Therefore, the current data set was analyzed with a propensity score approach. The propensity score defines the probability of each individual patient to be treated based on a given set of covariates.19 The use of propensity score analyses balances the distribution of covariates between treatment and control groups and therefore minimizes the influence of potential biases.20,21 Variables related to the decision to treat patients with tPA were included in a logistic regression model. The resulting propensity score for the treatment of ischemic stroke patients with tPA included the following 14 variables: age (continuous), sex, diabetes mellitus, hypertension, hypercholesterolemia, atrial fibrillation, previous stroke, admission from other acute facility, admission within 3 hours of stroke onset, presence of limb paresis or weakness, presence of aphasia, presence of dysarthria, disturbed level of consciousness, and the treating hospital. Interaction terms between sex, time of hospitalization, neurological deficits, and risk factors were added to the model. Calculation of the propensity score was restricted to centers administering tPA in 2000. The multivariate regression model for the propensity of being treated with tPA had a c statistic of 0.94 (95% CI, 0.93 to 0.95), which represents the area under the receiver-operating characteristic curve and indicates very good discrimination between patients who did and who did not receive thrombolytic therapy.

**Case-Matching Procedures**

Ischemic stroke patients treated with tPA were matched individually to patients not receiving tPA within the same hospital. For constructing the matched sample, the nearest available matching on the estimated propensity score method as described by Rosenbaum and Rubin22 was used. Treated subjects within a hospital were ordered at random; then, the first treated subject was selected and matched with the control subject with the nearest logit of the propensity score within the same hospital. Both cases and controls were then removed, and the next treated subject was chosen. Altogether, the propensity scores of 90% of the matched control subjects were within the defined caliper (one quarter of an SD of the logit of the propensity score of subjects treated with tPA).

**Statistical Analysis**

The t test was used to test differences in continuous variables, and the \( \chi^2 \) test was used for those in proportions. To estimate the odds ratio (OR) and the resulting 95% CI for the matched case-control pairs, conditional logistic regression was performed. The risk of in-hospital mortality was calculated before and after adjustment for the number of patients treated with tPA per hospital. Subgroup analyses were performed by running different regression models for patients admitted within 3 hours and after 3 hours of stroke onset. Eight patients treated with tPA and 745 patients not treated with tPA were excluded from statistical analyses because of missing values. The 77 patients treated with intra-arterial thrombolysis were removed from the study because it was restricted to intravenous application. To estimate potential selection effects in this hospital-based cohort, we compared its age and sex distributions to those of the unselected population-based Erlangen Stroke Project, which includes all hospitalized and all nonhospitalized stroke patients.
within a defined region of 100 330 inhabitants. All tests were 2
tailed, and statistical significance was determined at

Ethics
Patient identity was completely anonymous. Therefore, no specific
informed consent was signed by patients. The investigator who
performed the data pooling was blinded to hospital identities. These
identities were known only to the regional stroke registers.

Results
A total of 13 440 patients with ischemic stroke were admitted
to the 104 hospitals within the ADSR network from January
1, 2000, to December 31, 2000: 3359 patients (25%) were
admitted within 3 hours of stroke onset. Mean age of the total
patient population was 69.8 years (median, 71 years); 53%
were men. Compared with the results of the population-based
Erlangen Stroke Project, the ischemic stroke patients assessed
within the ADSR network were younger (69.8 versus 71.7
years, respectively; \( P < 0.037 \)) and more often male (53%
versus 46%, respectively; \( P < 0.001 \)). The younger age distri-
bution within the ADSR network might be due to the fact
that, unlike the population-based sample, no data on nonhos-
pitalized stroke patients, who were known to be older,15 were
collected. Half of the hospitals administered thrombolytic
treatment. Of these, 54% treated 1 to 5 patients and 46%
treated >5 patients with tPA in 2000. The characteristics of
the hospitals administering tPA compared with hospitals not
administering tPA are shown in Table 1. tPA was adminis-
tered more often in neurological departments (\( P < 0.0001 \)), in

Use of tPA
A total of 384 patients were treated with tPA (range per
hospital, 1 to 32); 351 of them were admitted within 3 hours
of stroke onset (range per hospital, 1 to 27) (Table 1). We
found that 2.9% of all ischemic stroke patients and 10.4% of
patients admitted within 3 hours of stroke onset received
thrombolytic therapy.

Patient Characteristics
The overall cohort had a mean propensity score of 0.04
(median, 0.002; range, 0 to 0.88) for receiving thrombolytic
therapy, indicating a low probability of being treated with
tPA within the ADSR network. For patients treated with tPA,
the mean propensity score was 0.28 (median, 0.24; range,
0.001 to 0.88) compared with 0.03 (median, 0.002; range, 0 to
0.81) for patients not receiving treatment. Patients receiving
tPA were significantly younger, more often male, and more
often admitted within 3 hours of stroke onset (Table 2). Patients
treated with tPA had a significantly lower prevalence of diabetes,
hypertension, and previous stroke and a higher
prevalence of atrial fibrillation. Differences in the presence of
neurological signs were also observed, indicating a higher
stroke severity among patients receiving thrombolytic ther-
apy. After matching for propensity score, no significant
differences in baseline characteristics, comorbidities, and

| TABLE 1. Hospital Characteristics According to Administration of tPA in 2000 |
|---------------------------------|-------------------|---------------|-----------|
| Hospitals Administering tPA (n=52) | Hospitals Not Administering tPA (n=52) | \( P \) |
| Department, n (%) | | | |
| Neurology | 47 (90) | 17 (33) | 0.0001 |
| Internal medicine | 4 (8) | 32 (62) | 0.0001 |
| Geriatric medicine | 1 (2) | 3 (6) | 0.0001 |
| Stroke unit service provided, n (%) | | | |
| <50 | 3 (6) | 32 (62) | 0.0001 |
| 50–99 | 11 (21) | 13 (25) | 0.0001 |
| 100–199 | 17 (33) | 5 (10) | 0.0001 |
| >=200 | 21 (40) | 2 (4) | 0.0001 |
| Median (range) patients per hospital, n | | | 0.0001 |
| Ischemic stroke patients treated with tPA | | | |
| Total treated with tPA, n (%)* | 384 (3.5) | 0.0001 |
| Treated with tPA per hospital (range), %* | 1–32 (0.5–18.2) | 0.0001 |
| Treated with tPA admitted <3 h of onset, n (%)† | 351 (12.5) | 0.0001 |
| Treated with tPA admitted <3 h of onset per hospital (range), %† | 1–27 (2.1–40) | 0.0001 |
| Hospitals administering tPA, n (%) | | | |
| Hospitals treating 1–5 patients with tPA | 28 (54) | 0.0001 |
| Hospitals treating >5 patients with tPA | 24 (46) | 0.0001 |

*Percent from all ischemic stroke patients admitted to hospitals administering tPA.
†Percent from all ischemic stroke patients admitted within 3 h of stroke onset to hospitals administering tPA.
presence of neurological deficits were found between patients treated with tPA and matched control patients not receiving thrombolytic treatment (Table 2).

### In-Hospital Mortality

In-hospital mortality for patients treated with tPA was significantly higher than for matched control subjects (11.7% versus 7.4%, respectively; \( P = 0.047 \)) and for all patients not treated with tPA (4.5%, \( P = 0.0001 \)) (Table 3). Stratification of the patients according to admission within 3 hours of stroke onset yielded a similar but nonsignificant mortality difference between cases and controls in those with early admission (11% versus 7.6%, respectively; \( P = 0.12 \)). This difference increased considerably among those admitted later than 3 hours after stroke onset (18.8% versus 6.3%, respectively; \( P = 0.13 \)). However, because of the small number of cases and controls, this difference was not statistically significant.

Substantial differences in rates of in-hospital death were observed after stratification by hospital experience with tPA use (Table 3). Hospitals that administered tPA to more patients in 2000 had a significantly increased rate of in-hospital death.

### Table 2. Demographic and Clinical Characteristics of Ischemic Stroke Patients Treated and Not Treated With tPA

<table>
<thead>
<tr>
<th></th>
<th>t-PA Patients (n=376)</th>
<th>Matched Patients Not Treated With tPA (n=376)†</th>
<th>( P )‡</th>
<th>All Patients Not Treated With tPA in Hospitals Administering tPA (n=9761)</th>
<th>( P )§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) age, y</td>
<td>64.1 (12)</td>
<td>64.4 (14.1)</td>
<td>0.78</td>
<td>69.3 (12.9)</td>
<td>0.0001</td>
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<tr>
<td>Men, %</td>
<td>55.6</td>
<td>53.2</td>
<td>0.80</td>
<td>52.1</td>
<td>0.045</td>
</tr>
<tr>
<td>Admitted from acute facility, %</td>
<td>10.4</td>
<td>11.2</td>
<td>0.73</td>
<td>10.7</td>
<td>0.82</td>
</tr>
<tr>
<td>Time from stroke onset to hospitalisation, %</td>
<td>0.38</td>
<td></td>
<td></td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>Admitted &lt;3 h</td>
<td>91.5</td>
<td>89.6</td>
<td>23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admitted &gt;3 h</td>
<td>8.5</td>
<td>10.4</td>
<td>64.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown stroke onset</td>
<td>0</td>
<td>0</td>
<td>12.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comorbidities, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>21.8</td>
<td>22.1</td>
<td>0.93</td>
<td>29.0</td>
<td>0.002</td>
</tr>
<tr>
<td>Hypertension</td>
<td>66.2</td>
<td>64.1</td>
<td>0.54</td>
<td>70.8</td>
<td>0.055</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>10.1</td>
<td>10.6</td>
<td>0.81</td>
<td>18.8</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>26.1</td>
<td>23.7</td>
<td>0.45</td>
<td>27.4</td>
<td>0.57</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>29.8</td>
<td>27.4</td>
<td>0.47</td>
<td>21.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>Neurological signs, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weakness/paresis</td>
<td>81.1</td>
<td>81.6</td>
<td>0.85</td>
<td>66.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>Aphasia</td>
<td>45.2</td>
<td>42.8</td>
<td>0.51</td>
<td>23.7</td>
<td>0.0001</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>32.2</td>
<td>34.8</td>
<td>0.44</td>
<td>28.4</td>
<td>0.11</td>
</tr>
<tr>
<td>Disturbed level of consciousness</td>
<td>28.5</td>
<td>26.9</td>
<td>0.63</td>
<td>12.4</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

*Analyses were restricted to patients without missing values.
†Patients were matched on the basis of propensity score using the nearest available matching on the estimated propensity score method.
‡Matched patients not receiving tPA vs tPA patients.
§All patients not receiving tPA vs tPA patients in hospitals administering tPA.

### Table 3. In-Hospital Mortality of Ischemic Stroke Patients Treated and Not Treated With tPA

<table>
<thead>
<tr>
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<th>( P )§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total, n (%)</td>
<td>44 (11.7)</td>
<td>28 (7.4)</td>
<td>0.047</td>
<td>442 (4.5)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Time from stroke onset to hospital admission, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admitted &lt;3 h</td>
<td>38/344 (11.0)</td>
<td>26/344 (7.6)</td>
<td>0.12</td>
<td>136/224 (6.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Admitted &gt;3 h</td>
<td>6/32 (18.8)</td>
<td>2/32 (6.3)</td>
<td>0.13</td>
<td>204/6293 (3.2)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Unknown stroke onset</td>
<td>0</td>
<td>0</td>
<td></td>
<td>102/1220 (8.4)</td>
<td></td>
</tr>
<tr>
<td>Hospital experience with t-PA treatment in 2000, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5 patients receiving tPA</td>
<td>14/58 (24.1)</td>
<td>5/58 (8.6)</td>
<td>0.024</td>
<td>183/3083 (5.9)</td>
<td>0.0001</td>
</tr>
<tr>
<td>&gt;5 patients receiving tPA</td>
<td>30/318 (9.4)</td>
<td>23/318 (7.2)</td>
<td>0.32</td>
<td>259/6678 (3.9)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

*Analyses were restricted to patients without missing values.
†Patients were matched on the basis of propensity score using the nearest available matching on the estimated propensity score method.
‡Matched patients not receiving tPA vs tPA patients.
§All patients not receiving tPA vs tPA patients in hospitals administering tPA.
for patients treated with tPA compared with matched controls not receiving thrombolytic therapy (24% versus 8.6%, respectively; \(P=0.024\)). In contrast, no significant differences in rates of in-hospital death were observed between patients treated in hospitals administering >5 thrombolytic therapies per year and matched controls (9.4% versus 7.2%, respectively; \(P=0.32\)). To investigate a potential bias by differences in time under observation, length of stay was compared between hospitals administering 1 to 5 thrombolytic therapies and hospitals administering tPA to ≥5 patients. No statistically significant difference in mean length of stay for tPA patients and matched controls was found among less experienced and experienced centers (13.3 versus 13.2 days, respectively; \(P=0.91\)).

In multivariate analyses, patients treated with tPA in hospitals with limited experience in tPA application had an increased risk of in-hospital death (OR, 3.3; 95% CI, 1.1 to 9.9) (Table 4). No significant increase in risk of in-hospital mortality was found for patients treated with tPA in experienced hospitals (OR, 1.3; 95% CI, 0.8 to 2.4). Restricting analyses to patients admitted within 3 hours of stroke onset demonstrated similar risks, although the OR of inpatient death in hospitals with limited experience in the use of tPA did not reach statistical significance (OR, 2.8; 95% CI, 0.9 to 8.6).

### Discussion

Our observational study, which reported on a large number of patients treated in 104 hospitals in Germany, provides the first multicenter data on tPA use outside clinical trials for Europe. Our results suggest that, after controlling for differences in demographic variables, risk factor profiles, and neurological deficits, the in-hospital mortality of ischemic stroke patients receiving thrombolytic therapy depends on the number of these treatments administered by the hospital each year. We interpreted this number as the hospital’s experience in thrombolytic therapy and found that patients treated in hospitals with limited experience in tPA use (≤5 thrombolytic treatments per year) were ~3 times more likely to die during the hospital stay compared with patients not treated with tPA. No significant influence of thrombolysis on in-hospital mortality was found in hospitals experienced in thrombolytic therapy (>5 tPA treatments per year).

### Use of tPA

About 3% of all ischemic strokes and 10.4% of patients admitted within 3 hours of stroke onset were treated with tPA within the hospitals of the ADSR network. These proportions were comparable to those in previous multicenter studies reporting on the rates of tPA use outside clinical trials: from 1.6% to 6.3% of all ischemic strokes and 10.4% of patients admitted within 3 hours of stroke onset. The rates of patients with ischemic stroke receiving thrombolysis varied from 0.5% to 18% between hospitals. The highest rate of tPA administration in our study (18%) was similar to that reported from a single-center study in Germany with a special designed referral system for early hospital admission of acute stroke patients. Previous studies on thrombolytic therapy in routine clinical practice found rates from 8% to 13% of patients receiving tPA beyond the 3-hour time window. In our analysis, 8.5% of patients were treated with tPA, although they were admitted to hospital >3 hours after stroke onset. However, the true rate of thrombolytic therapies administered outside the 3-hour time window in our study might be higher because a median time of 55 minutes from admission to hospital to the start of tPA treatment must be added to the admission time.

Half of the hospitals within the ADSR network administered tPA. Thrombolytic therapy was administered more often in neurological departments, in hospitals providing stroke unit services, and in centers treating >100 ischemic stroke patients per year. This variance in administration of tPA might be caused by differences in institutional attitudes, patient characteristics, or individual concerns that treating physicians have about safety and efficacy of thrombolytic therapy. A recently published study by Katz and colleagues reported that only 30% of attending neurologists were very convinced about the efficacy of tPA use, whereas 62% were very concerned about the risk of thrombolysis.

### Use of tPA and In-Hospital Mortality

A meta-analysis of clinical trial data demonstrated no significant excess of early deaths after tPA use. Four previous studies reported on in-hospital mortality after tPA use outside clinical trials in multicenter settings. The proportion of patients who died in hospital varied from 9% to 15.7%. Two studies suggested that administering tPA outside clinical trials did not cause an excess in inpatient death; the other

<table>
<thead>
<tr>
<th>Time from stroke onset to hospital admission</th>
<th>OR†</th>
<th>95% CI</th>
<th>(P)</th>
<th>OR†</th>
<th>95% CI</th>
<th>(P)</th>
<th>OR†</th>
<th>95% CI</th>
<th>(P)</th>
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<tbody>
<tr>
<td>Admitted &lt;3 h</td>
<td>1.5</td>
<td>0.9–2.6</td>
<td>0.12</td>
<td>2.8</td>
<td>0.9–8.6</td>
<td>0.083</td>
<td>1.3</td>
<td>0.7–2.3</td>
<td>0.45</td>
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<tr>
<td>Admitted ≥3 h</td>
<td>5</td>
<td>0.6–42.8</td>
<td>0.14</td>
<td>†</td>
<td>†</td>
<td>†</td>
<td>3</td>
<td>0.3–28.8</td>
<td>0.34</td>
</tr>
</tbody>
</table>

*Analyses were restricted to patients without missing values.
†ORs and 95% CIs were calculated by use of conditional logistic regression; patients were matched on the basis of propensity score using the nearest available matching on the estimated propensity score method.‡
†No deaths were observed among control subjects; thus, no conditional regression model was calculated.
reports showed an increased risk of in-hospital mortality among tPA patients.\textsuperscript{8,9} These divergent results might be caused by differences in the respective control groups chosen for the comparison with the mortality of tPA patients. The studies,\textsuperscript{4} which found tPA use to be safe in routine clinical practice, compared their outcomes with the results of the National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group trial.\textsuperscript{2} The studies, which showed an increased risk of inpatient death after thrombolysis, compared in-hospital mortality after tPA use with patients not receiving tPA recruited from the same study population that gave rise to tPA patients.\textsuperscript{8,9} Characteristics of patients included in randomized controlled trials might not be representative of study populations in routine clinical practice. Therefore, a comparison of outcomes between patients treated with tPA in community settings with control subjects from randomized controlled trials is difficult. A further explanation for the divergent results on outcome after tPA treatment could be the fact that, as in our analysis, rates of in-hospital-death varied with the number of thrombolytic therapies administered by the respective hospital per year. The 2 studies that found tPA use to be safe in clinical routine were performed in 13 hospitals experienced in the administration of tPA\textsuperscript{4} and in 20 hospitals experienced in the use of tPA or integrated in a special stroke treatment network.\textsuperscript{7} The observed in-hospital mortality rate of 9.4\% for tPA patients treated in hospitals with >5 tPA applications per year in our study was comparable to the mortality reported in these 2 studies (9.5\% and 9\%). An increased risk of inpatient death after thrombolysis was found in studies that either included all 29 hospitals within a defined region\textsuperscript{9} or reported on 137 unselected community hospitals that participate in the Healthcare Benchmarking Database.\textsuperscript{8} The multicenter approach suggested that, similar to our analysis, hospitals with different experience levels in tPA use were included in these studies, although this was not explicitly addressed in the study reports. The overall risk of in-hospital mortality for patients treated with tPA compared with patients not receiving tPA was similar in the study of Reed and colleagues\textsuperscript{8} (OR, 1.8; 95\% CI, 1.2 to 2.7) and in our analysis (OR, 1.7; 95\% CI, 1 to 2.8). The higher proportion of in-hospital deaths in the study of Katzan and colleagues compared with our results (15.7\% versus 11.7\%, respectively) might be due to the fact that, in that specific study, a higher proportion of hospitals with limited experience in tPA use (≤5 thrombolytic treatments per year) was found than in our study (75\% versus 54\%, respectively).\textsuperscript{9} It is noteworthy that the rate of in-hospital deaths among matched participants not treated with tPA in the analysis of Katzan and colleagues was similar to our results (7.2\% versus 7.4\%, respectively).\textsuperscript{9} The degree of the individual hospital’s experience in tPA use can be affected by several factors, eg, expertise in CT scan reading, the way classification of stroke severity is done, the identification of exclusion criteria, implementation of training programs to educate physicians, or creation of specific guidelines for tPA use. Previous studies suggest that between 31\%\textsuperscript{2,6} and 50\%\textsuperscript{9} of patients receiving tPA in routine clinical practice were not treated in accordance with national treatment guidelines. Thus, differences in outcome after tPA use between hospitals with limited and high experience in application of tPA might be caused by different rates of violations against existing protocols on thrombolytic treatment. The only available information in this context in our study was the time difference between stroke onset and hospital admission. Therefore, we were unable to further clarify whether protocol violations contributed to the observed differences of in-hospital deaths between hospitals with different levels of experience in tPA treatment. Future studies should aim to carefully assess potential protocol violations, taking into account the sensitivity of the issue, to reveal their potential impact.

Our study has several strengths and limitations. In contrast to randomized controlled trials, which balance all observed and unobserved factors between treatment and control groups, propensity score analyses balance only covariates that were assessed and used to construct the score. However, in several instances, propensity score matching provides better control for matched factors than randomized controlled trials.\textsuperscript{21} We cannot exclude that some unobserved differences in patient characteristics between the cases and control subjects contributed to our results. However, we minimized potential confounding by regional differences in treatment processes or in patient characteristics by recruiting control subjects from the same hospitals as cases. Some of the detected variations in early outcome might be caused by differences in clinical characteristics (eg, different proportions of patients with cerebellar or brain stem infarcts) or stroke severity between patients treated with tPA and untreated patients. However, we controlled the statistical analyses for neurological deficits present on admission, especially for a disturbed level of consciousness, which was identified to be a good predictor of stroke severity.\textsuperscript{27} We were not able to present detailed explanations about the decision to exclude patients admitted within 3 hours of stroke onset from thrombolytic therapy or about reasons to treat patients admitted after 3 hours of stroke onset with tPA. However, our study provides valid and reliable data because data collection within the stroke registries of the ADSR network was standardized, a predefined variable set was used,\textsuperscript{14} and the feasibility of the procedures was tested.\textsuperscript{17} In our study, no information was provided on mortality in the time period after discharge from acute hospital. Therefore, a potential long-term benefit of thrombolysis on mortality could not be evaluated.

Conclusions
In summary, our study identified considerable variance in the impact of tPA use on in-hospital mortality of patients with ischemic stroke in routine clinical practice. Hospitals performing >5 thrombolyses per year had a lower in-hospital mortality compared with hospitals with fewer tPA treatment applications. Our results provide evidence that thrombolytic treatment in patients with ischemic stroke should be administered preferably in hospitals experienced in tPA use.

Acknowledgments
The Erlangen Stroke Project is supported by the German Federal Ministry of Health (BMG) for data collection and registration (317-123002/17 00), the German Federal Ministry of Research (BMBF) for research (NO1 EG 9706/5), and the Bavarian Ministry of Health (3.5/8060/28/01).
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Editorial Comment

tPA in Daily Clinical Practice

In 1995,1 a 2-part randomized trial showed the efficacy of intravenous tissue plasminogen activator (tPA) when given within 3 hours of onset of symptoms of acute ischemic stroke. Postmarketing studies have demonstrated that intravenous recombinant tPA can be administered appropriately in a wide variety of hospitals setting. If treatment guidelines2 are carefully followed, intravenous tPA for acute ischemic stroke is feasible and shows safety and efficacy comparable to the results from the study by the National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group.3–6 However, although the persuasive results of that study have launched some enthusiasm, safety and efficacy concerns about the use of thrombolysis for ischemic stroke prevail among many neurologists because of the risk of hemorrhage and the small proportion of suitable patients. Further concerns are nourished by a report from “the real world” in which the translation of study results into daily clinical practice seemed to be less easy and more harmful than expected.6,7

In European countries, there is little information about early outcomes after intravenous application of tPA for stroke patients treated in community-based settings. In this issue of Stroke, Heuschmann et al report the largest experience from the German Stroke Registers Study Group (Arbeitsgemeinschaft Deutscher Schlaganfall Register [ADSR]). ADSR is a network of regional stroke registers that combines data from 104 academic and community hospitals throughout Germany and represents ~5% of all acute stroke hospitals in Germany. Therefore, the description reflects the special situation of the
German healthcare system. The main result of this study is that the experience level of an individual hospital in tPA treatment influences stroke mortality. The experience of an individual hospital in administration of tPA was based on the study of Katzan and colleagues. Patients receiving tPA in hospitals that administered ≤5 thrombolytic therapies in 2000 had an increased risk of in-hospital mortality (odds ratio, 3.3; 95% confidence interval, 1.1 to 9.9). The next step within the ADSR network should be the audit of causes for early in-hospitals deaths and detailed evaluation of potential protocol violations.

Thrombolytic therapy for acute stroke will not have a major impact on death and dependency unless it is accessible to more patients. Concerns exist regarding the impact of implementing a treatment that only a limited number of stroke patients might be eligible for and that has an associated excess risk of intracerebral hemorrhage. Thrombolysis for acute ischemic stroke, for instance, may have a substantial effect on stroke outcome but has no overall effect in the population than a much less potent treatment such as aspirin unless it can be given safely to more than a small minority of patients. About 3% of all ischemic strokes and 10.4% of patients admitted within 3 hours of stroke onset were treated with tPA in the hospitals of the ADSR network. These proportions were comparable to previous multicenter studies reporting on rates of tPA use outside clinical trials from 1.6% to 6.3%.

Increasing the proportion of patients with acute ischemic stroke who are treated with tPA is an important challenge facing contemporary physicians. In the ADSR network, thrombolytic therapy was administered more often in neurological departments, in hospitals providing stroke unit services, and in centers treating >100 ischemic stroke patients per year. Accordingly, the prehospital and hospital infrastructure needs to be streamlined to handle ischemic stroke with high priority. Further widespread and repetitive public education is needed to increase awareness of warning signs, stroke risk factors, and availability of treatment. The last factor should not be underestimated because stroke has been widely thought to be untreatable.

The generalized efficacy and safety of tPA depend on a network involving an efficient connection between emergency physicians and stroke neurologists. In this setting, tPA can be safely given to acute ischemic stroke patients in rural and community hospitals with or without on-site neurology. In addition, regardless of hospital size, a system for expedited stroke workups can be set up and successfully implemented by a stroke team. In such facilities, it is very likely that these patients will be under the direct care of emergency and/or primary care physicians. To assist physicians in these cases, community hospitals and their physicians must have access to 24-hour neuroscience support. Such neuroscience backup will come only from larger regional medical centers. These regional centers should also assist with or provide community hospitals with physician education and address their concerns regarding tPA therapy. Ultimately, such programs will provide the opportunity for patients to receive stroke therapies that previously were unavailable and may contribute to the decrease in tPA-related morbidity observed in hospitals less trained in acute stroke management.

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Frequency of Thrombolytic Therapy in Patients With Acute Ischemic Stroke and the Risk of In-Hospital Mortality: The German Stroke Registers Study Group

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Stroke. 2003;34:1106-1112; originally published online March 27, 2003;
doi: 10.1161/01.STR.0000065198.80347.C5

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/34/5/1106

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