Predictors of In-Hospital Mortality in Patients With Acute Ischemic Stroke Treated With Thrombolytic Therapy

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INTRAVENOUS TREATMENT WITH TISSUE plasminogen activator (tPA) is currently the only approved treatment for patients with acute ischemic stroke and is recommended in the guidelines of several national and international stroke associations. However, in multicenter studies, only 1.6% to 2.7% of patients with ischemic stroke treated in community hospitals and 4.1% to 6.3% treated in academic hospitals or specialized stroke centers received this treatment. One major cause for the low treatment rates is that a large proportion of patients are admitted more than 3 hours after symptom onset, the time window for which application of tPA treatment is currently approved. But even among patients admitted within 3 hours after stroke onset, treatment rates are only moderately, ranging from 10.4% to 18.8%. In addition to a number of contraindications clearly listed in the drug

Context  Data are limited regarding the risks and benefits of thrombolytic therapy for acute ischemic stroke outside of clinical trials.

Objective  To investigate predictors of in-hospital mortality in patients with ischemic stroke treated with intravenous tissue plasminogen activator (tPA) within a pooled analysis of large German stroke registers.

Design and Setting  Prospective, observational cohort study conducted at 225 community and academic hospitals throughout Germany cooperating within the German Stroke Registers Study Group.

Patients  A total of 1658 patients with acute ischemic stroke who were admitted to study hospitals between 2000 and 2002 and were treated with tPA.

Main Outcome Measure  In-hospital mortality.

Results  One hundred sixty-six patients (10%) who received tPA died during hospitalization, with 67.5% of these deaths occurring within 7 days. Factors predicting in-hospital death after tPA use were older age (for each 10-year increment in age, adjusted odds ratio [OR], 1.6; 95% confidence interval [CI], 1.3-1.9) and altered level of consciousness (adjusted OR, 3.4; 95% CI, 2.4-4.7). The overall rate of symptomatic intracranial hemorrhage was 7.1% and increased with age. One or more serious complications was observed in 27.2% of all patients and in 83.9% of patients who died after tPA treatment. An inverse relation between the number of patients treated with tPA in the respective hospital and the risk of in-hospital death was observed (adjusted OR, 0.97; 95% CI, 0.96-0.99 for each additional patient treated with tPA per year).

Conclusion  In patients with ischemic stroke who are treated with tPA, disturbances of consciousness and increasing age are associated with increased in-hospital mortality.

JAMA. 2004;292:1831-1838

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(Reprinted) JAMA, October 20, 2004—Vol 292, No. 15 1831

For editorial comment see p 1883.
approval, uncertainties about selection criteria for patients who will not benefit from thrombolysis might contribute to the low rates of stroke patients treated with tPA in routine care.\(^8\) Clarification of clinical factors associated with early death in patients treated with tPA can help identify subgroups of patients with increased risks and thereby allow clinicians to give special attention to patients who are at high risk of death after tPA treatment.

The aim of our study was to identify predictors of in-hospital mortality in patients with ischemic stroke treated with tPA outside of clinical trials.

**METHODS**

Data were assessed within the German Stroke Registers Study Group (Arbeitsgemeinschaft Deutscher Schlaganfall Register [ADSR]). The ADSR is a network of regional hospital-based stroke registers that monitors quality of stroke care in Germany.\(^9\) The registers include academic and community hospitals as well as departments of neurology, internal medicine, and geriatric medicine. In the present analyses, data from the stroke registers in Bavaria, Hamburg,\(^10\) Hesse,\(^11\) Rhineland-Palatinate, and Westphalia\(^12\) were included. In total, 225 hospitals participated between 2000 and 2002 in the ADSR network, representing about 10% of all 2240 German acute care hospitals.\(^13\)

All registers applied a common set of variables for all stroke patients.\(^9\) Information gathered for each patient included sociodemographic characteristics, comorbidities, neurological deficits, complications, diagnostic procedures, admission procedures, and treatment strategies during the in-hospital period. Data collection in the treating hospitals was standardized and each hospital sent the documented forms to the coordinating center of the ADSR at the University of Muenster. Ischemic stroke patients admitted to any of the hospitals cooperating within the ADSR network between January 1, 2000, and December 31, 2002, were included.

The following definitions were used:

- **Age:** Age was categorized into younger than 55 years, 55 to 64 years, 65 to 74 years, and 75 years or older; no further age categorization was done because the number of patients aged 85 years or older treated with tPA was too small.
- **Diabetes mellitus:** Diabetic patients were defined as elevated fasting blood glucose level, patient self-report of diabetes, or use of antidiabetic drugs. Hypertension was defined as systolic blood pressure of 160 mm Hg or higher, diastolic blood pressure of 95 mm Hg or higher, or patient self-report of treated hypertension. Previous stroke was a neurological deficit more than 24 hours prior to current event. Atrial fibrillation was documented by electrocardiogram. Neurological deficits of stroke included motor deficits (weakness or paresis), speech disturbances (aphasia, dysarthria), and disturbances of level of consciousness (severely, eg, not fully rousable; comatose, eg, either response to pain only or no response at all).

- **Symptomatic intracranial hemorrhage (ICH):** Defined as clinically relevant bleeding (eg, deterioration of symptoms) and verification of ICH by computed tomography (CT) or magnetic resonance imaging (MRI) scan. Increased intracranial pressure was defined by evidence of symptomatic increased intracranial pressure; eg, by edema, mass effect, or brain shift syndrome in CT or MRI scan, with clinical findings. Recurrent stroke was a new neurological deficit more than 24 hours after the current event. Pulmonary embolism was defined by clinical and/or diagnostic findings. Epileptic seizure was a clinical diagnosis of focal seizure, general seizure, or both in non-epileptic patients. Pneumonia was defined by clinical and/or diagnostic findings.

Stroke was defined according to World Health Organization criteria.\(^14\) The diagnosis of ischemic stroke was confirmed by CT or MRI scan. The experience of the individual hospital in tPA use was defined as number of patients treated with tPA per hospital.\(^7\) Given the fact that not all hospitals participated during the entire 3-year study period, the mean number of patients treated with tPA per hospital per year was defined as the total number of patients receiving tPA divided by number of calendar years under observation for which the respective hospital provided data and administered tPA.

The effect of the number of thrombolytic therapies per hospital per year on early outcome was assessed as a continuous and as a discrete variable. As a discrete variable, the mean number of tPA administrations per hospital per year was classified into categories of 5 per year, up to more than 20. The lower cutoff of 5 or fewer tPA administrations per hospital per year was used in previous studies to classify hospital experience in tPA use.\(^7,15\) No major changes were observed between 6 to 10 and 11 to 15 tPA administrations and between 16 to 20 and more than 20 tPA administrations. Thus, mean number of patients receiving thrombolytic therapy per hospital was categorized into 1 to 5, 6 to 15, and more than 15 thrombolytic therapies per hospital per year.

**Statistical Analyses**

The \(t\) test was used to test differences in continuous variables and the \(\chi^2\) test was used for differences in proportions. Logistic regression analysis was performed to calculate odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for the probability of death during hospitalization in patients receiving thrombolytic therapy. In multivariate analyses, the influence of age, sex, comorbidities, and neurological deficits on risk of early death was investigated. Possible interactions between age, sex, comorbidities, and neurological deficits were controlled by adding terms of interaction to the regression model. Statistical significance of the resulting coefficients was tested using the likelihood ratio test. Significant terms of...
interaction were revealed between disturbances of consciousness and age groups ($\chi^2 = 7.869; P = .048$). Therefore, the effect of age on in-hospital mortality after thrombolytic therapy was also reported separately for disturbances of consciousness. Variables in multivariate analyses were eliminated using backward-elimination procedure. Because we recently demonstrated that risk of in-hospital death after thrombolytic therapy is increased in hospitals with limited experience in its application,7 statistical analyses also controlled for the individual hospitals’ experience in tPA administration. For assessing the fit of the logistic regression model, the Hosmer-Lemeshow goodness-of-fit statistic and $c$ statistic were used. The Hosmer-Lemeshow goodness-of-fit $\chi^2$ value was statistically not significant, indicating that the model seems to fit well. The $c$ statistic of the model was 0.72, which represents the area under the receiver operating characteristic curve and indicates an acceptable discrimination of the model. All tests were 2-tailed, and statistical significance was determined at an $\alpha$ level of .05. Statistical analyses were performed with SAS software, version 8.2 (SAS Institute Inc, Cary, NC).

**Ethics**

The design of the study was approved by the ethics committee of the Westphalian Board of Physicians and the University of Muenster. Identity of individual patients was completely anonymous; thus, no specific informed consent was obtained from patients. The investigators who performed the data analyses were blinded to hospital identities. These identities were known only by the coordinating center of the respective regional stroke register.

**RESULTS**

A total of 56,998 patients with ischemic stroke were registered within the ADSR collaboration between January 1, 2000, and December 31, 2002. Mean age of patients was 70.2 years; 50.5% were men. Two hundred twenty-five hospitals participated in the ADSR network. Forty-four percent of these hospitals were departments of neurology, 51% of internal medicine, and 4% of geriatric medicine. Thirty-two percent of the participating hospitals provided stroke unit services; 37% of the hospitals participated for 3 years, 34% for 2 years, and 29% for 1 year. In 48% of the hospitals, ischemic stroke patients were treated with tPA. Thrombolysis was administered more often in departments of neurology ($P < .001$), in hospitals providing stroke unit services ($P < .001$), and in facilities treating a high number of ischemic stroke patients per year ($P < .001$). Sixty-seven percent of the hospitals offering tPA therapy treated between 1 and 5 patients with thrombolysis per year, 33% of the hospitals treated 6 to 15 patients, and 10% treated more than 15 patients per year.

During the study period, 1796 patients were treated with tPA for acute ischemic stroke (range per hospital, 1–110). A total of 3.2% of all patients and 11.6% of patients admitted within 3 hours of stroke onset were treated with tPA. The median number of patients receiving thrombolysis per hospital per year was 4 (range per hospital per year, 1–48). One hundred thirty-eight patients were excluded from further analysis because of missing values. Because not all registers provided comparable data on symptomatic ICH for the entire study period, 409 additional patients were excluded from the assessment of the impact of complications on risk of in-hospital death. The mean age of patients treated with tPA was 64.9 years (SD, 12.2 years). Demographic and clinical characteristics of patients who received thrombolytic therapy are shown in Table 1.

Overall, 10.0% of patients treated with tPA died during hospitalization. A total of 42.2% of in-hospital deaths occurred within the first 3 days and 67.5% within the first 7 days in the hospital. Percentages of patients treated with tPA who did and did not die in the hospital are shown in Table 2 according to sociodemographic and clinical factors. In univariate analyses, age, diabetes mellitus, disturbances of consciousness, and hospital expertise in tPA treatment significantly influenced proportion of in-hospital death (Table 2). After adjustment for potential confounders, patients with a disturbed level of consciousness and those in higher age groups were at increased risk of death during hospitalization (Table 2). The influence of age on risk of early death was similar if age was investigated as a continuous variable (adjusted OR, 1.6; 95% CI, 1.3–1.9 for each 10-year increment in age).

Hospital expertise with use of tPA also was independently associated with probability of early death after tPA treatment. The risk of in-hospital death decreased by 3% for each additional patient treated with tPA per year (Table 2). In-hospital mortality was 13.4% in hospitals that treated fewer than 6 patients, 11.5% in hospitals treating 6 to 15 patients, and 7.1% in hospitals treating more than 15 patients with tPA per year. Risk of in-hospital mortality was lower in hospitals administering tPA 6
to 15 times and more than 15 times per year (adjusted OR, 0.8; 95% CI, 0.5-1.2 and adjusted OR, 0.5; 95% CI, 0.3-0.8, respectively; test for trend, \( P = .004 \)) compared with those treating 1 to 5 patients.

Because of the differential impact of age on in-hospital mortality after tPA treatment in patients with and without disturbances of consciousness, multivariate analyses were stratified for this condition (Table 3). Risk of death during hospitalization increased with older age in both of these groups. The highest absolute risk of death was observed among patients aged 75 years or older with a disturbance of consciousness. However, relative probability of

<table>
<thead>
<tr>
<th>Table 2. Predictors of In-Hospital Mortality After tPA Treatment: Univariate and Multivariate Analyses*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In-Hospital Mortality Among Patients Treated With tPA, No. (%)</strong></td>
</tr>
<tr>
<td><strong>Survived</strong></td>
</tr>
<tr>
<td>Age group, y</td>
</tr>
<tr>
<td>&lt;55</td>
</tr>
<tr>
<td>55-64</td>
</tr>
<tr>
<td>65-74</td>
</tr>
<tr>
<td>≥75</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Time from stroke onset to hospital admission, h &lt;3</td>
</tr>
<tr>
<td>≥3</td>
</tr>
<tr>
<td>Comorbidities‡</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Previous stroke</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Neurological signs‡</td>
</tr>
<tr>
<td>Weakness/paresis</td>
</tr>
<tr>
<td>Aphasia</td>
</tr>
<tr>
<td>Dysarthria</td>
</tr>
<tr>
<td>Disturbed level of consciousness</td>
</tr>
<tr>
<td>Hospital experience with tPA use, per each additional patient treated with tPA per year§</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio; tPA, tissue plasminogen activator.
*Analyses were restricted to patients without missing values.
†Nonsignificant variables were removed using a backward-elimination procedure; ORs, 95% CIs, and \( P \) values were determined just before removal.
‡Reference categories for respective variables were patients without the respective comorbidities or neurological signs.
§Mean number of patients treated with tPA per hospital per year.

<table>
<thead>
<tr>
<th>Table 3. Relationship of Age and In-Hospital Mortality After tPA Treatment, Stratified by Level of Consciousness</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In-Hospital Mortality, No. (%)</strong></td>
</tr>
<tr>
<td><strong>Survived</strong></td>
</tr>
<tr>
<td>Age group, y &lt;55</td>
</tr>
<tr>
<td>55-64</td>
</tr>
<tr>
<td>65-74</td>
</tr>
<tr>
<td>≥75</td>
</tr>
<tr>
<td>Per 10-y age increment§</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio; tPA, tissue plasminogen activator.
*Disturbed level of consciousness included semiconscious and comatose patients.
†Test for trend among categories.
‡Based on test for trend among categories.
§From younger than 55 years to 75 years or older.
in-hospital death in the oldest compared with the youngest age group was particularly increased in patients without disturbances of consciousness compared with patients with this condition (Table 3).

The frequency of serious complications after tPA use and their association with risk of in-hospital death is shown in Table 4. All assessed complications except seizures were associated with increased risk of early mortality. Symptomatic ICH and increased intracranial pressure were the strongest independent predictors of in-hospital death (Table 4). The rate of ICH after tPA use increased with age, from 4.9% in patients younger than 55 years (n = 11) to 10.3% in patients aged 75 years or older (n = 31) (test for trend, \( P = .02 \)) (data not shown).

**COMMENT**

We identified predictors of early mortality in 1658 ischemic stroke patients treated with tPA in German hospitals. Patient and hospital characteristics influenced risk of in-hospital death. The patient characteristics older age and disturbed level of consciousness were independent predictors of early mortality. Relative probability of in-hospital death was particularly increased in older patients without disturbances of consciousness. Among hospitals, the number of tPA administrations per year was independently associated with early mortality. Risk of in-hospital death after thrombolysis decreased with increasing experience of the treating hospital in tPA administration, indicating an inverse relation.

Few studies have reported outcomes after thrombolytic therapy in old and very old patients. In the National Institute of Neurological Disorders and Stroke (NINDS) trial, only 42 patients older than 80 years were included; in the other clinical trials on tPA, this age group was excluded. In a retrospective survey of 189 patients treated with tPA outside of clinical trials, the 30 patients older than 80 years tended to be at higher risk of death during hospitalization compared with younger patients. This tendency was similar in magnitude to the impact of higher age among patients without disturbances of consciousness. Among hospitals, the number of tPA administrations per year was independently associated with early mortality. Risk of in-hospital death after thrombolysis decreased with increasing experience of the treating hospital in tPA administration, indicating an inverse relation.

Table 4. Frequency of Serious Complications After tPA Use During Acute Care Hospital Stays and Impact on Risk of In-Hospital Death*

<table>
<thead>
<tr>
<th>Specific complications</th>
<th>Survived (n = 1119)</th>
<th>Died (n = 130)</th>
<th>OR (95% CI)†</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial hemorrhage</td>
<td>51 (4.6)</td>
<td>38 (29.2)</td>
<td>8.3 (5.0-13.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Increased intracranial pressure</td>
<td>64 (5.7)</td>
<td>62 (47.7)</td>
<td>13.3 (8.4-21.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Recurrent stroke</td>
<td>35 (3.1)</td>
<td>9 (6.9)</td>
<td>2.5 (1.1-5.5)</td>
<td>.03</td>
</tr>
<tr>
<td>Epileptic seizure</td>
<td>21 (1.9)</td>
<td>4 (3.1)</td>
<td>1.6 (0.5-4.8)</td>
<td>.43</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>7 (0.6)</td>
<td>5 (3.9)</td>
<td>6.6 (1.9-22.8)</td>
<td>.001</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>121 (10.8)</td>
<td>38 (29.2)</td>
<td>2.6 (1.6-4.0)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

†The OR for death in an acute care hospital for each specific complication, adjusted for age, sex, disturbances of consciousness, and hospital expertise in tPA use (mean number of tPA administrations per year, continuously).

The highest absolute proportion of in-hospital deaths was found among patients older than 75 years with disturbances of consciousness. However, a significant interaction between older age and level of consciousness was observed. Relative probability of inhospital death increased to a larger extent with age among patients without a disturbed level of consciousness compared with patients with this condition. An increased risk of death in older patients might be caused by accumu-
label studies on tPA use was slightly lower (5.2%; 95% CI, 4.3-6.0) compared with our findings. This difference in rates of ICH might be caused by different definitions between the studies, especially with an ICH classification of “symptomatic.” In addition, the rate of ICH in our study increased constantly with older age. This finding is in accordance with a pooled analysis of data on 1205 patients collected from centers experienced in tPA use that revealed advancing age among other causes as a factor that independently predicted the rate of symptomatic ICH.

Our study has several strengths and limitations. Information in our study was collected in a uniform, prospective way in 225 community hospitals across Germany. Observing risks of thrombolytic therapy in community settings may provide more realistic information about the effectiveness of this procedure in real clinical practice compared with clinical trials. Because of the large number of patients, subgroup analyses among patients treated with tPA could be performed with sufficient power. We were unable to assess potential violations of existing thrombolysis protocols since time interval from stroke onset to hospitalization was the only available protocol information, and other important data such as tPA dosage, time to tPA administration, and the National Institutes of Health Stroke Scale on admission were not documented. In addition, no information was available about long-term outcome of patients after discharge from the hospital since we investigated predictors for early mortality during hospitalization. Predictors for long-term mortality after tPA use in stroke patients might differ from factors influencing risk of in-hospital death. Furthermore, our observational study did not aim to show a benefit of tPA treatment vs nontreatment, which can only be done within the settings of randomized controlled trials. We used the number of tPA applications per year as an indicator for the expertise of an individual hospital in tPA use. However, we cannot exclude that the inverse association between number of tPA administrations and risk of in-hospital death might be caused by other factors within the hospitals that improve outcome; eg, experience of treating physician or number of physicians per hospital. Our definition of ICH was based on clinical findings and verification of ICH on brain imaging. Thus, we might have missed ICH if no brain imaging was performed after clinical deterioration in a patient.

CONCLUSIONS

In this study, 10% of patients who received tPA for acute ischemic stroke died during hospitalization, and the risk of death increased with age and with disturbances of consciousness and was inversely associated with increasing experience of the treating hospital in tPA administration. Thus, clinicians should give special attention to patients with disturbances of consciousness and older age for reducing rates of in-hospital mortality after tPA treatment.

Author Contributions: Dr Heuschmann had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Heuschmann, Kolominsky-Rabas, Lowitzsch, Leffmann, Sitzer, Berger. Acquisition of data: Roether, Misselwitz, Hermanek, Leffmann, Sitzer, Biegler, Buecker-Nott, Berger. Analysis and interpretation of data: Heuschmann, Leffmann, Hermanek, Sitzer, Berger. Drafting of the manuscript: Heuschmann. Critical revision of the manuscript for important intellectual content: Kolominsky-Rabas, Roether, Misselwitz, Lowitzsch, Heidrich, Hermanek, Leffmann, Sitzer, Biegler, Buecker-Nott, Berger. Statistical analysis: Heuschmann, Berger. Obtained funding: Heuschmann, Kolominsky-Rabas, Leffmann. Administrative, technical, or material support: Kolominsky-Rabas, Roether, Heidrich, Hermanek, Leffmann, Biegler, Buecker-Nott, Berger. Study supervision: Heuschmann, Misselwitz, Lowitzsch, Hermanek, Sitzer, Buecker-Nott.

German Stroke Registers Study Group (Arbeitsgemeinschaft Deutscher Schlaganfall Register [ADSR]): Stroke Register Bavaria: Amberg; Neurologische Abteilung des Klinikums St Marien; Aschaffenburg: Neurologische Klinik des Klinikums; Ausburg: Neurologische Klinik des Klinikums; Bad Aibling: Neurologische Klinik Bad Aibling GmbH; Bad kissingen: Medizinische Klinik des St Elisabeth-Krankenhaus; Bad Neustadt: Neurologische Klinik GmbH; Bad Toelz: Abteilung für Innere Medizin der Asklepios Stadtklinik; Bad Reichenhall: Innere Abteilung des Stadtrischen Krankenhaus; Bad Windsheim: Abteilung für Innere Medizin der Klinik Bad Windsheim; Bayreuth: Neurologische Klinik des Krankenhauses Hohe Warte; Burghausen: Abteilung für Innere Medizin des Kreiskrankenhauses; Cham: Abteilung für Innere Medizin des Kreiskrankenhauses; Dachau: Abteilung für...

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Funding/Support: The data analyses and the data pooling of the German Stroke Registers Study Group are funded by the German Federal Ministry of Research (BMBF) within the Competence Net Stroke.

Role of the Sponsor: The BMBF had no role in the design or conduct of the study; in the collection, analysis, or interpretation or preparation of the data; or in the preparation, review, or approval of the manuscript.