One-Year Follow-Up in Acute Stroke Patients Treated With rtPA in Clinical Routine

Susanne Schmülling, MD; Martin Grond, MD; Jobst Rudolf, MD; Wolf-Dieter Heiss, MD

Background and Purpose—A recent placebo-controlled study provided evidence of a sustained benefit at 1 year from systemic thrombolysis in patients with acute ischemic stroke. The scope of the present study is to determine whether comparable results may be attained in everyday practice if current management guidelines are closely met.

Methods—Between March 1996 and July 1998, 150 consecutive patients with acute ischemic stroke were treated with systemic thrombolysis using alteplase, strictly in accordance with American Heart Association (AHA) guidelines. The patients were followed up for 12 months after treatment.

Results—Baseline characteristics and complication rates were comparable to those of the National Institute of Neurological Disorders and Stroke (NINDS) study, except for a somewhat younger age (mean 63 years) and lower National Institutes of Health Stroke Scale score (median 11). At 1 year, 41% of our patients showed minimal or no disability (Rankin scale score of 0 or 1), comparable to 41% in the NINDS rtPA group. The overall rate of recurrent stroke was 6.6% and the transient ischemic attack rate 3.3% at 1 year. Six patients (4%) died after the first 3 months, none of them due to recurrent stroke, and 5 had already been severely disabled at 3 months.

Conclusions—These observations further encourage the routine use of rtPA for the treatment of acute ischemic stroke in strict accordance with the AHA guidelines. (Stroke. 2000;31:1552-1554.)

Key Words: outcome ■ stroke, acute ■ thrombolytic therapy ■ tissue plasminogen activator

In a previous study,1 we reported short-term outcome and complication rates comparable to those of the NINDS rt-PA Stroke Study trial2 after intravenous thrombolysis with rtPA in routine management of acute stroke patients. Recently, long-term follow-up of the NINDS rtPA patients3 provided evidence of a sustained benefit at 1 year from systemic thrombolysis in patients with acute ischemic stroke. Compared with the placebo group, patients treated with rtPA within 3 hours after the onset of symptoms were at least 32% more likely to have only minimal or no disability at 1-year follow-up. We also followed up our first 150 patients for 12 months after treatment to determine whether our long-term results are comparable to the NINDS results. In addition, we report early complication rates and early outcome of patients treated under routine conditions in comparison with the rtPA 3-hour intention-to-treat cohorts of the controlled trials.

Subjects and Methods
One hundred fifty consecutive patients with acute ischemic stroke were treated with intravenous rtPA between March 1996 and July 1998, following a protocol1 comparable to the American Heart Association (AHA) guidelines.4 One hundred thirty-two patients suffered from supratentorial and 18 from infratentorial stroke. The presence of cerebral hemorrhage was assessed on CT after 36 hours and classified using the National Institute of Neurological Disorders and Stroke (NINDS) criteria.5 The follow-up of our patients covered a period of 12 months after thrombolytic treatment. At 3 months, clinical outcome was assessed by physical examination with the National Institutes of Health Stroke Scale (NIHSS),6 Rankin Scale,7 and Barthel Index,8 and at 1 year by structured telephone interviews of the patients and/or their caregivers with the Rankin Scale and Barthel Index. Both scales are validated for telephone assessment of stroke outcome.9–11 No patient was missed for follow-up.

Results
Mean age in our patients was 63 years, with a male-to-female ratio of 3:2. Median baseline NIHSS score was 11, with a mean baseline NIHSS of 12. The baseline data in comparison with the NINDS rt-PA Stroke Trial and the ECASS I and ECASS II 3-hour intention-to-treat rtPA cohorts2,12,13 are given in Table 1.

In 2 of the 150 patients treated with rtPA, the protocol was violated, because they were treated even though (contradicting the information available on admission) severe symptoms had been present on their awakening from sleep, so that symptom onset could not clearly be defined and probably was >3 hours previous. They both died from transtentorial herniation due to severe space-occupying edema within the first week after treatment.

Altogether, 16 patients died during the first 3 months of the observation period. In 2 of these patients, the cause of death was considered to be treatment related (hemorrhagic compli-
cations); in 8 other patients it was related to the primary stroke (eg, space-occupying brain edema) and in 6 to concomitant disease (eg, cardiac failure). Asymptomatic parenchymal hemorrhage within the first 3 months occurred in 6 patients (4%) and symptomatic parenchymal hemorrhage in another 6 patients (4%), 2 of whom died.

At 1 year, 41% of our patients showed minimal or no disability (Rankin 0 or 1; Figure 1, Table 2), 24% were moderately disabled (Rankin 2–3), and 20% were severely disabled (Rankin 4–5; Figure 1). Avoidance of death or dependency, defined as Rankin 0–2 at the 12-month follow-up examination, was found in 52% of our patients. Correspondingly, 51% of our patients were functionally independent (with a Barthel Index of 95–100), 21% were moderately disabled (Barthel 55–90), and 13% severely disabled (Barthel 0–50; Figure 2).

The overall rate of recurrent stroke at 1 year was 6.6% and that of transient ischemic attacks 3.3%. Overall death rate at 1 year was 15% (n = 22), because additional 6 patients (4%) died after the first 3 months, none due to recurrent stroke. However, 5 of them had already been severely disabled at 3 months.

Discussion

Even though rtPA treatment is approved in the United States for acute stroke treatment, there still is substantial reluctance to use it in clinical routine.14 The concern is that under routine conditions, complication rates may be higher and effectiveness lower than under ideal study conditions, as has been shown for the Cleveland area.15 We have substantial experience, with >250 patients treated in our stroke unit within 3 hours of symptom onset in a monocenter, community-based approach.1 We present here data of the long-term follow-up of our first 150 patients. Because in routine drug application there naturally is no control group, our data must be evaluated in light of the results of the controlled studies of intravenous thrombolysis within 3 hours after stroke onset.2,12,13

Baseline characteristics and complication rates of our patients were comparable to those of both treatment subgroups of the NINDS study,2 except for a somewhat younger age (mean 63 years versus 67/69 years in NINDS) and a less-severe deficit (median NIHSS 11 versus 14 in NINDS; see Table 1). Baseline stroke severity in our patients was slightly lower than in the ECASS I cohort (median NIHSS 13) but identical with that reported from the ECASS II cohort (median NIHSS 11). Furthermore, the mean age in our patients (63 years) was close to that of the patients in the ECASS II cohort (Table 1). This has to be taken into account when evaluating outcome and safety in our study. Short-term outcome in our patients was nearly identical to that in the ECASS II cohort and better than that in the ECASS I and the NINDS cohorts (Figure 3). Differences may best be explained by differences in the baseline characteristics. These differences must also be taken into account when evaluating the safety of the procedure. Our rate of 4% symptomatic parenchymal hemorrhages and an overall rate of 8% parenchymal hemorrhages within 36 hours is identical to that of the ECASS II cohort, slightly lower than that of the NINDS cohort (6.4 and 10.9, respectively) and distinctly lower than that of the ECASS I cohort (overall rate of 24%). Besides the differences in baseline characteristics, the reliable exclusion of patients with major early infarct signs on their initial CT might explain the low incidence of hemorrhages in our study.1

One-year follow-up data are available from the NINDS rtPA cohort only.3 There, the rate of symptomatic recurrent stroke was 5.4%. In our patients, the rate of recurrent stroke was 6.6% and the transient ischemic attack rate 3.3%. Both our data and those from Kwiatkowski and coworkers3 are concordant with the rates of stroke recurrence in population-based studies.16,17 Thrombolytic therapy does not seem to influence the risk of spontaneous stroke recurrence, which may mainly be influenced by strategies of secondary prevention.

### Table 1. Baseline Characteristics of the Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NINDS rtPA</th>
<th>ECASS I rtPA</th>
<th>ECASS II rtPA</th>
<th>Cologne</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean), y</td>
<td>67–69</td>
<td>68–64.8</td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td>NIHSS score (median)</td>
<td>14–14</td>
<td>13–11</td>
<td>11</td>
<td>11</td>
</tr>
</tbody>
</table>

Note: ITT indicates intention-to-treat.

### Table 2. Association of Baseline NIHSS Score With Outcome at 12 Months

<table>
<thead>
<tr>
<th>NIHSS Score</th>
<th>No. of Patients</th>
<th>Favorable Barthel Index (95–100), %</th>
<th>Favorable Modified Rankin Scale (0–1), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤9</td>
<td>65</td>
<td>71</td>
<td>60</td>
</tr>
<tr>
<td>10–14</td>
<td>37</td>
<td>43</td>
<td>30</td>
</tr>
<tr>
<td>15–20</td>
<td>32</td>
<td>31</td>
<td>28</td>
</tr>
<tr>
<td>&gt;20</td>
<td>16</td>
<td>25</td>
<td>13</td>
</tr>
</tbody>
</table>

Note: Percentages given are percentages of patients.
The overall rate for death or dependency (Rankin 3–6) after 1 year was 48%; thus, 52% of our patients were still independent after 1 year (Rankin 0–2). Favorable outcome with only minimal or no disability, defined as Rankin scores of 0–1, was achieved in 41% of our patients at 12 months (Figure 1, Table 2), a result identical with 41% in the NINDS cohort. Favorable outcome with regard to the activities of daily living (Barthel 95–100) was found in 51%, a finding also comparable to that in the NINDS cohort (50%).

The death rate of 15% at 1 year in our study was lower than in the NINDS cohort (24%). Here again, the population differences (age, NIHSS) may be responsible, because survival at 12 months has been shown to be associated with initial NIHSS score, age, diabetes, and the interaction of diabetes and age.

**Conclusion**

The sustained benefit at 1 year from systemic thrombolysis within 3 hours after symptom onset in acute stroke patients may also be attained in clinical practice. The risk of rtPA treatment under routine conditions is not higher than under the optimal conditions of controlled studies. These observations further encourage the routine use of rtPA for the treatment of acute ischemic stroke, if current guidelines for treatment and management are closely met.

**Acknowledgment**

The authors wish to express their gratitude to all members of the Cologne Stroke Cooperative for the effective patient referral.

**Figure 2.** Barthel Index, stratified according to good (95–100), moderate (55–90), and poor (0–50) functional outcome and death assessed at the 12-month follow-up examination of the patients reported from the NINDS rt-PA Stroke Trial placebo and treatment groups (adapted from Kwiatkowski et al.3), with corresponding rates from the Cologne Study.

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