Ultra-Early Intravenous Stroke Thrombolysis
Do All Patients Benefit Similarly?

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Background and Purpose—We previously reported increased benefit and reduced mortality after ultra-early stroke thrombolysis in a single center. We now explored in a large multicenter cohort whether extra benefit of treatment within 90 minutes from symptom onset is uniform across predefined stroke severity subgroups, as compared with later thrombolysis.

Methods—Prospectively collected data of consecutive ischemic stroke patients who received IV thrombolysis in 10 European stroke centers were merged. Logistic regression tested association between treatment delays, as well as excellent 3-month outcome (modified Rankin scale, 0–1), and mortality. The association was tested separately in tertiles of baseline National Institutes of Health Stroke Scale.

Results—In the whole cohort (n=6856), shorter onset-to-treatment time as a continuous variable was significantly associated with excellent outcome (P<0.001). Every fifth patient had onset-to-treatment times≤90 minutes, and these patients had lower frequency of intracranial hemorrhage. After adjusting for age, sex, admission glucose level, and year of treatment, onset-to-treatment times≤90 minutes was associated with excellent outcome in patients with National Institutes of Health Stroke Scale 7 to 12 (odds ratio, 1.37; 95% confidence interval, 1.11–1.70; P=0.004), but not in patients with baseline National Institutes of Health Stroke Scale>12 (odds ratio, 1.00; 95% confidence interval, 0.76–1.32; P=0.99) and baseline National Institutes of Health Stroke Scale 0 to 6 (odds ratio, 1.04; 95% confidence interval, 0.78–1.39; P=0.80). In the latter, however, an independent association (odds ratio, 1.51; 95% confidence interval, 1.14–2.01; P<0.01) was found when considering modified Rankin scale 0 as outcome (to overcome the possible ceiling effect from spontaneous better prognosis of patients with mild symptoms). Ultra-early treatment was not associated with mortality.

Conclusions—IV thrombolysis within 90 minutes is, compared with later thrombolysis, strongly and independently associated with excellent outcome in patients with moderate and mild stroke severity. (Stroke. 2013;44:2913-2916.)

Key Words: emergencies ■ ischemic stroke ■ onset to needle time ■ outcome ■ thrombolysis

I
n acute stroke care, time is brain,1 and the earlier thrombolysis is given the better the final functional outcome is.2 Our recently published single-center analysis showed robust benefit of ultra-early compared with later thrombolysis in terms of better outcome and lower mortality,3 outcomes supported by the most recently published pooled analysis.2 In our study,4 we identified 10% of patients with onset-to-treatment time (OTT) within 70 minutes, whereas 29% had OTT within 90 minutes. Patients presenting with National Institutes of Health Stroke Scale (NIHSS) 7 to 12 treated within these OTT intervals had >5-fold and ε2-fold higher likelihood of favorable outcome compared with patients treated later, respectively.

Because not all patients benefit from early IV thrombolysis equally,3 in this study, we aimed to explore, in a large multi-center dataset, whether the extra benefit (of better outcome and lower mortality) is distributed equally among predefined

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2913
stroke severity subgroups of acute ischemic stroke patients. Because only 6% of patients had OTT <70 minutes in this study, we evaluated effect of OTT≤90 minutes. This is a relevant time-point, because the number needed to treat doubles from 4.5 to 9 for patients with OTT 91 to 180, compared with OTT≤90 minutes.²

### Patients and Methods

#### Study Setting

The current observational study is a joint project of 10 European stroke centers. The study was approved by the relevant authorities in each participating center, if required. This study was approved in the coordinating center (Helsinki) as a registry, but did not require ethical board review.

Data from individual consecutive patients were collected as previously described.¹ The merged cohort included 7106 patients treated between 1998 and 2012. OTT or 3-month modified Rankin scale (mRS) values were not available for 250 patients, who were excluded. The final cohort comprised 6856 eligible patients. Excellent outcome was defined as 3-month mRS 0 to 1. None of the patients received additional therapies, such as an endovascular procedure.

#### Statistical Analyses

Because of non-normal distribution of all treatment delays, age, and NIHSS, data are presented as median and interquartile range. Groups were compared with the independent samples Mann–Whitney U or χ² test, as appropriate. First, for the whole population, we constructed a model of logistic regression with excellent outcome (and separately mortality) as dependent variable. This model included age as continuous variable, baseline NIHSS, sex, OTT, glucose level on admission, presence of symptomatic intracranial hemorrhage (sICH) according to European Cooperative Acute Stroke Study-2 (ECASS-2) criteria, and year of admission (to counteract possible effect of overall improvement in stroke care over time). Thereafter, population was divided into 3 subgroups, based on tertiles of baseline NIHSS: 0 to 6 points, 7 to 12 points, and >12 points.¹ Separately for each NIHSS subgroup, similar models of binary logistic regression were constructed, and following parameters were forced into the model: age, sex, OTT≤90 minutes, glucose level on admission, intracranial hemorrhage (ICH), year of admission, and also age*sex interaction to exclude confounding. Statistical significance was set at 0.05 (2-tailed). Analyses were performed on IBM SPSS version 18 (IBM Corp, Armonk, NY).

### Results

Demographics and baseline characteristics are outlined in the Table. Altogether, 19% of patients received thrombolysis within 90 minutes from symptom onset. For the whole cohort, OTT decrease per minute was independently associated with excellent outcome after adjusting for age, sex, baseline NIHSS, admission glucose level, and year of treatment (odds ratio [OR], 0.999; 95% confidence interval [CI], 0.998–0.999; P<0.001).

Focusing on early versus late treatment, OTT≤90 minutes was independently associated with 3-month mRS 0 to 1 in patients with baseline NIHSS 7 to 12 (OR, 1.37; 95% CI, 1.11–1.70; P=0.004), but not in patients with NIHSS>12 (OR, 1.00; 95% CI, 0.76–1.32; P=0.99) nor NIHSS 0 to 6 (OR, 1.04; 95% CI, 0.78–1.39; P=0.80). To overcome the possible ceiling effect from spontaneous better prognosis of patients with mild symptoms (NIHSS, 0–6), in the secondary analysis, we studied association of OTT≤90 minutes with 3-month

### Table. Demographics and Baseline Characteristics of the Merged Cohort

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All Patients, n=6856</th>
<th>NIHSS, 0–6; n=2161</th>
<th>NIHSS, 7–12; n=2164</th>
<th>NIHSS&gt;12; n=2531</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>72 (61–79)</td>
<td>69 (59–77)</td>
<td>72 (61–79)</td>
<td>74 (64–81)</td>
</tr>
<tr>
<td>Women</td>
<td>3133 (45.7%)</td>
<td>41.6%</td>
<td>45.4%</td>
<td>50.7%</td>
</tr>
<tr>
<td>Baseline NIH Stroke Scale</td>
<td>10 (6–16)</td>
<td>4 (3–5)</td>
<td>9 (8–11)</td>
<td>17 (15–20)</td>
</tr>
<tr>
<td>Baseline NIH Stroke Scale, mean (range)</td>
<td>11 (0–41)</td>
<td>4.2 (0–6)</td>
<td>9.3 (7–12)</td>
<td>18 (13–41)</td>
</tr>
<tr>
<td>Onset-to-treatment time, min</td>
<td>135 (101–178)</td>
<td>140 (104–180)</td>
<td>136 (103–177)</td>
<td>133 (100–175)</td>
</tr>
<tr>
<td>Onset-to-treatment time, 3–4.5 h, %</td>
<td>16.0</td>
<td>19.6</td>
<td>16.1</td>
<td>12.6</td>
</tr>
<tr>
<td>Onset-to-door time, min</td>
<td>82 (59–120)</td>
<td>87 (60–127)</td>
<td>85 (60–120)</td>
<td>75 (55–114)</td>
</tr>
<tr>
<td>Door-to-needle time, min</td>
<td>45 (27–67)</td>
<td>43 (26–65)</td>
<td>44 (26–67)</td>
<td>45 (28–69)</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1118 (16.3%)</td>
<td>21.1%</td>
<td>18.2%</td>
<td>20.6%</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>864 (12.6%)</td>
<td>15.3%</td>
<td>16.2%</td>
<td>14.7%</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>1042 (15.2%)</td>
<td>19.1%</td>
<td>18.4%</td>
<td>22.3%</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1680 (24.5%)</td>
<td>22.8%</td>
<td>26.9%</td>
<td>37.9%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3901 (56.9%)</td>
<td>69.5%</td>
<td>68.4%</td>
<td>70.4%</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>2242 (32.7%)</td>
<td>46.2%</td>
<td>39.4%</td>
<td>35.4%</td>
</tr>
<tr>
<td>Pathogenesis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large artery atherosclerosis</td>
<td>1118 (16.3%)</td>
<td>15.7%</td>
<td>16.5%</td>
<td>16.0%</td>
</tr>
<tr>
<td>Cardioembolism, high source</td>
<td>3085 (45.0%)</td>
<td>36.1%</td>
<td>41.4%</td>
<td>53.5%</td>
</tr>
<tr>
<td>Small vessel disease</td>
<td>425 (6.2%)</td>
<td>11.3%</td>
<td>7.2%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Other determined</td>
<td>267 (3.9%)</td>
<td>3.3%</td>
<td>3.8%</td>
<td>4.4%</td>
</tr>
<tr>
<td>Unknown, multiple, not studied</td>
<td>1961 (28.6%)</td>
<td>32.6%</td>
<td>30.2%</td>
<td>24.3%</td>
</tr>
</tbody>
</table>

If not otherwise stated, continuous data are presented as median (IQR). IQR indicates interquartile range; NIH, National Institutes of Health; and NIHSS, National Institutes of Health Stroke Scale.
mRS=0 in this subgroup of patients. An independent association was observed with the corresponding OR of 1.51 (95% CI, 1.14–2.01); P<0.01. There was no interaction between age and sex in any of the models. We did not find any association between ultra-early thrombolysis and 3-month mortality in the whole cohort (P=0.85) or in subgroups of NIHSS (P=0.48/0.89/0.33).

Patients with OTT≤90 minutes had smaller proportion of any ICH (14.8% versus 17.6%; P=0.027) and nonsignificantly smaller proportion of symptomatic ICH (3.7% versus 4.5%; P=0.20). Both any ICH and sICH were independently inversely associated with excellent outcome in a regression model comprising the entire cohort (OR, 0.06; 95% CI, 0.03–0.12 for sICH and OR, 0.30; 95% CI, 0.25–0.36 for any ICH; both P<0.001), and separately per all tertiles of NIHSS score (ORs in tertiles 0.06/0.08/0.04 for sICH and 0.29/0.43/0.40 for any ICH; all P<0.001).

Discussion

We validated our single-center findings on effect of early versus late thrombolysis in a cohort from 10 stroke centers. Almost 20% of all patients were treated within 90-minute OTT. In the primary analysis, thrombolysis within this time period was independently associated with excellent outcome in patients with moderate baseline stroke severity (NIHSS, 7–12), but not in patients with mild or severe symptoms. Possible explanation for this seemingly selective extra benefit may be explained by predictive effect of NIHSS>10 on presence of proximal cerebral artery occlusion, and less likely excellent outcome in such patients. NIHSS>10 is also a common cut-off in patient selection for endovascular approaches. Another possible explanation is higher proportion of cardioembolism and lower proportion of small vessel disease in patients with NIHSS>12. Based on the detailed analysis of relevant parameters studied in patients treated within 90 minutes and >90 minutes (Table I in the online-only Data Supplement), we observed larger percentage of any ICH in patients with NIHSS>12 treated >90 minutes (*P<0.05), but not in case of sICH. Furthermore, there was higher proportion of females in patients with NIHSS 7 to 12 treated >90 minutes, but sex and age*sex interaction was not associated with outcome.

Our finding that patients with mild symptoms (NIHSS<7) seem to benefit less from ultra-early treatment may be explained by a ceiling effect from the spontaneously better prognosis and is supported by recently published International Stroke Trial-3 (IST-3), although a smaller recent study suggested differently. Patients with mild symptoms usually have small infarcted brain volumes because of peripheral vessel occlusions or central occlusions with good collaterals. In both cases, infarct volume reduction because of ultra-early treatment might be very small to be detectable by mRS. Indeed, when excellent 3-month outcome was set to mRS 0, we found an independent association of ultra-early thrombolysis in this subgroup of patient.

As opposed to our previous report, we did not find any association of ultra-early thrombolysis with mortality. This may be because of the limited number of patients treated ultra-early in the current cohort. Most cases of cardioembolism were caused by atrial fibrillation, but we do not have data on more detailed analysis of other high-risk sources of cardioembolism. This higher percentage might have had influenced the effects observed; however, the proportions were very similar in subgroups of patients treated within and >90 minutes, and presence of cardioembolism did not influence the results of the primary analysis.

In conclusion, ultra-early IV thrombolysis increases the likelihood of excellent outcome in patients with moderately severe symptoms, and in secondary analysis also in those with mild symptoms. A portion of benefit might stem from lower frequencies of ICH in these patients. All measures must be taken to reduce OTT as much as possible.

Disclosures

Dr Ringleb has received lecture fees (<10000€) from Boehringer Ingelheim, the manufacture of Alteplase, and is German national coordinator of Safe Implementation of Thrombolysis in Stroke. Dr Michel has received speaker fees from Boehringer Ingelheim; honoraria from scientific advisory boards from Boehringer Ingelheim; and travel support from Boehringer Ingelheim. He uses all this funding and honoraria for stroke research and education. Dr Ollikainen is a member of Speaker’s Bureau from Boehringer Ingelheim. Dr Mattle has received speaker’s and consulting fees and educational and research grants from Boehringer Ingelheim, Genzyme. Dr Egelter has received honoraria for advisory boards or travel grants; modest: Boehringer Ingelheim. Dr Leys has received travel grants from Boehringer Ingelheim and is a member of advisory board at Boehringer Ingelheim. Dr Numminen has received travel grants or lecture fees from Boehringer Ingelheim. Dr Köhrmann is a member of advisory boards for Boehringer Ingelheim and has received speaker’s honoraria from Boehringer Ingelheim. Dr Hacke has received honoraria for advisory boards and steering committee duties from Boehringer Ingelheim. He has also received honoraria for presentations at satellite symposia from Boehringer Ingelheim. He has received an unlimited scientific grant to perform European Cooperative Acute Stroke Study-4 from Boehringer Ingelheim. Dr Tatlisumak has received research grant from Boehringer Ingelheim. He is a member of consultant/advisory board and Speaker’s bureau at Boehringer Ingelheim. The other authors have no conflicts to report.

References


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Ultra-early intravenous stroke thrombolysis: do all patients benefit similarly?

(Brief Report)

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Supplemental Table I. Analysis of selected parameters per NIHSS and OTT category

<table>
<thead>
<tr>
<th>parameter</th>
<th>NIHSS 0-6</th>
<th>NIHSS 7-12</th>
<th>NIHSS&gt;12</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OTT &lt;=90</td>
<td>OTT&gt;90</td>
<td>OTT &lt;=90</td>
</tr>
<tr>
<td>mRS</td>
<td>1 (0-2)</td>
<td>1 (0-2)</td>
<td>1 (1-3)</td>
</tr>
<tr>
<td>age</td>
<td>68 (58-75)</td>
<td>69 (59-77)</td>
<td>70 (60-77)</td>
</tr>
<tr>
<td>females</td>
<td>35.4%</td>
<td>41.5%</td>
<td>40.0%</td>
</tr>
<tr>
<td>NIHSS</td>
<td>5 (4-5)</td>
<td>4 (3-5)</td>
<td>9 (8-11)</td>
</tr>
<tr>
<td>any ICH, %</td>
<td>6.9%</td>
<td>8.9%</td>
<td>14.5%</td>
</tr>
<tr>
<td>sICH, %</td>
<td>1.5%</td>
<td>2.2%</td>
<td>3.4%</td>
</tr>
<tr>
<td>CE, %</td>
<td>33.9%</td>
<td>36.6%</td>
<td>39.5%</td>
</tr>
<tr>
<td>SVD, %</td>
<td>13.8%</td>
<td>10.7%</td>
<td>9.5%</td>
</tr>
</tbody>
</table>

Data are presented as median (interquartile range) or %. *p<0.05

mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; OTT: onset-to-treatment time; ICH: intracerebral hemorrhage; sICH: symptomatic ICH; CE: cardioembolism; SVD: small-vessel disease.