Role of Preexisting Disability in Patients Treated With Intravenous Thrombolysis for Ischemic Stroke

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Background and Purpose—Little is known about the effect of thrombolysis in patients with preexisting disability. Our aim was to evaluate the impact of different levels of prestroke disability on patients’ profile and outcome after intravenous thrombolysis.

Methods—We analyzed the data of all stroke patients admitted between October 2003 and December 2011 that were contributed to the Safe Implementation of Treatments in Stroke–Eastern Europe (SITS-EAST) registry. Patients with no prestroke disability at all (modified Rankin Scale [mRS] score, 0) were used as a reference in multivariable logistic regression.

Results—Of 7250 patients, 5995 (82%) had prestroke mRS 0, 791 (11%) had prestroke mRS 1, 293 (4%) had prestroke mRS 2, and 171 (2%) had prestroke mRS ≥3. Compared with patients with mRS 0, all other groups were older, had more comorbidities, and more severe neurological deficit on admission. There was no clear association between preexisting disability and the risk of symptomatic intracranial hemorrhage. Prestroke mRS 1, 2, and ≥3 were associated with increased risk of death at 3 months (odds ratio, 1.3, 2.0, and 2.6, respectively) and lower chance of achieving favorable outcome (achieving mRS 0–2 or returning to the prestroke mRS; 0.80, 0.41, 0.59, respectively). Patients with mRS ≥3 and 2 had similar vascular profile and favorable outcome (34% versus 29%), despite higher mortality (48% versus 39%).

Conclusions—Prestroke disability does not seem to independently increase the risk of symptomatic intracranial hemorrhage after thrombolysis. Despite higher mortality, 1 in 3 previously disabled patients may return to his/her prestroke mRS. Therefore, they should not be routinely excluded from thrombolytic therapy. (Stroke. 2014;45:770-775.)

Key Words: comorbidity • stroke • thrombolytic therapy • treatment outcome

T
reatment with recombinant tissue plasminogen activator (rt-PA; alteplase) within the first 4.5 hours from the onset of symptoms has become the standard of stroke care in developed countries.12 The availability of treatment has significantly improved over time,1 and there is a growing body of evidence supporting treatment in patients not eligible for rt-PA according to the original European license.4

The issue of prestroke disability has not been previously addressed in the literature, including guidelines. It was not listed as an exclusion criterion for the National Institute of Neurological Disorders and Stroke (NINDS) trial.3 However, patients with preexisting disabling neurological disease were excluded from the European Cooperative Acute Stroke Study (ECASS),4 and patients dependent in the activities of daily living were excluded from the Third International Stroke Trial (IST-3).7 As a consequence, many physicians tend to refrain from thrombolysis in this particular group of patients.

According to international stroke registries, at least slight preexisting disability is reported in only 10% of treated cases.4,8 The aims of our study were to establish the frequency

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of intravenous rt-PA treatment administered to stroke patients with preexisting disability in routine clinical practice and to investigate patients’ profile and outcome corresponding to the level of preexisting disability. Special emphasis was put on those with at least moderate prestroke disability.

Methods

We analyzed the data of all patients treated with intravenous rt-PA for stroke between October 2003 and December 2011 that were contributed to the Safe Implementation of Treatments in Stroke—Eastern Europe (SITS–EAST) registry by 144 centers from 10 countries (Czech Republic, Poland, Slovakia, Hungary, Estonia, Slovenia, Croatia, Lithuania, Turkey, and Russia).

SITS–EAST is an international study of implementation of evidence-based stroke care using the SITS–International Stroke Thrombolysis Registry (SITS-ISTR) platform for data collection. Its methodology and rationale have been described in detail elsewhere.8,9 Briefly, SITS was designed as a prospective, multinational, academic-driven, monitoring study to confirm the safety and effectiveness of thrombolysis in clinical practice of the European Union member states by 2003.10 This goal was achieved in 2006,8 but the registry has been constantly expanding. Currently, it is the largest database of patients treated with rt-PA for stroke.

Since the beginning of SITS, many stroke units from Central and Eastern Europe have joined the registry and started contributing cases on a voluntary basis.

All patients with reported prestroke modified Rankin Scale (mRS) scores were considered potential candidates for the study. In the course of mRS validity check, we decided to exclude from the final analysis (1) all cases contributed by centers reporting that ≥10% of patients had prestroke mRS score of 4 to 5; (2) cases in which mRS score reported 3 months after thrombolysis was ≥2 points lower than before stroke onset. This procedure aimed to minimize the bias introduced by incorrect understanding of the registry questionnaire (eg, reported prestroke mRS score reflected patient status at admission instead of the actual status before the onset of symptoms) or by temporary prestroke disability (eg, recent injury or exacerbation of chronic conditions). Additionally, we performed a sensitivity analysis with exclusion of patients who scored 1 point less on mRS at 3 months.

According to prestroke disability, patients were stratified into 4 groups: group 0, no disability at all (mRS, 0); group 1, no significant disability (mRS, 1); group 2, slight disability (mRS, 2); group 3, at least moderate disability (mRS, 3–5).

Our major end points were: symptomatic intracranial hemorrhage (sICH), significant neurological improvement at day 7 (defined as improvement of ≥4 points on the National Institutes of Health Stroke Scale [NIHSS] from baseline or achieving an NIHSS score of 0), significant neurological worsening at day 7 (defined as deterioration of ≥4 points on the NIHSS from baseline or death), and favorable outcome 3 months after stroke (defined as achieving mRS 0–2 or returning to the prestroke mRS score). The composite definition of favorable outcome was introduced to allow adequate comparison between long-term outcome of patients with at least moderate prestroke disability and those less disabled. For groups 0, 1, and 2, the composite end point was equivalent to the classical good outcome (mRS, 0–2).

We distinguished between sICH definitions according to SITS (ie, local or remote parenchymatous hemorrhage type 2 combined with NIHSS score ≥4 points or leading to death <22–36 hours),3 ECASS II (ie, any hemorrhage combined with NIHSS score ≥4 points or leading to death ≤7 days),11 and NINDS (ie, any hemorrhage combined with NIHSS score ≥1 point or leading to death ≤7 days). For the purpose of multivariable analysis, we have chosen the ECASS II definition of sICH because it combines high interrater agreement12 with high predictive value for the worst outcome after thrombolysis.13

Statistics

Categorical variables were presented as a number of valid observations with ratio. Proportions were calculated with exclusion of missing values from the denominator. Because of nonnormal distribution, continuous variables were presented as median with interquartile range (IQR). For basic comparisons, χ2 test or Mann–Whitney U test was used. If the expected value in ≥1 cell of a 2×2 contingency table was ≤5, Yates correction was applied. Each disability group was compared with group 0 (patients with no prestroke disability at all) and the group with 1 level lower disability (eg, group 3 was compared with group 0 and group 2). Accounting for the Bonferroni correction, a P value <0.01 was considered statistically significant.

To calculate odds ratios (ORs) with 95% confidence interval (95% CI) for each primary end point, we used multivariable logistic regression adjusted for age, sex, hypertension, atrial fibrillation, congestive heart failure, diabetes mellitus, previous stroke, and baseline NIHSS score. Additionally, 2 separate models were calculated: (1) for patients with disability accompanied by a positive history of previous stroke and (2) for patients whose prestroke disability was not accompanied by a history of previous stroke. All regression models were made using group 0 as a reference, and a P value <0.05 was considered statistically significant. Calculations were performed using STATISTICA 10.0 software package (StatSoft Inc, Tulsa, OK).

Results

In the course of data validation, the original data set of 8156 potentially eligible records (including 285 with prestroke mRS 3, 182 with prestroke mRS 4, and 129 with prestroke mRS 5) was limited to 7244 (88.8%) cases.

Among the analyzed cases (for contribution of particular countries, see Appendix) 5995 (82.4%) patients had preexisting mRS of 0, 791 patients (10.9%) had preexisting mRS of 1, 293 patients (4.0%) had preexisting mRS of 2, 125 patients (1.7%) had preexisting mRS of 3, 42 patients (0.6%) had preexisting mRS of 4, and 4 (0.1%) patients had preexisting mRS of 5.

Patients With No Significant Prestroke Disability (mRS 1)

Patients with no significant prestroke disability (group 1) compared with patients from group 0 were significantly more burdened with all evaluated vascular risk factors (Table 1).

The rates of sICH were significantly higher in group 1 according to SITS (3.1% versus 1.7%), ECASS II (8.5% versus 5.1%), and NINDS (10.5% versus 7.2%) definitions. There were no differences in the proportion of patients experiencing neurological improvement or worsening after 24 hours. However, patients from group 1 had a significantly higher rate of neurological worsening on day 7 and worse 3-month outcome (Figure; Table 2).

Multivariable logistic regression showed that patients with prestroke mRS of 1 had a tendency for increased risk of sICH according to ECASS II definition (OR, 1.36; 95% CI, 0.99–1.86), were more likely to die ≤3 months (OR, 1.30; 95% CI, 1.01–1.66), and less likely to achieve favorable outcome (OR, 0.80; 95% CI, 0.65–1.00; Table 3).

Patients With Slight Prestroke Disability (mRS 2)

The general characteristics of patients with slight prestroke disability (group 2) differed from group 0 in the same features as did the patients from group 1 (Table 1). The rates of sICH according to SITS (3.2%) and NINDS (10.6%) tended to be higher compared with group 0, whereas the overall prognosis was significantly worse (Figure; Table 2).

According to multivariable logistic regression, patients with prestroke mRS of 2 were at increased risk of death in a 3-month follow-up (OR, 1.98; 95% CI, 1.37–2.86) and...
In comparison to group 1, patients from group 2 were significantly older and more frequently burdened with atrial fibrillation and congestive heart failure. There were no significant differences in terms of stroke severity, prethrombolytic management, and sICH rates (Table 1). However, patients from group 2 had worse overall prognosis (Figure; Table 2).

Patients With Moderate or More Severe Disability (mRS 3–5)

The general characteristics of patients with at least moderate prestroke disability (group 3) differed from group 0 in the same features as did groups 1 and 2 (Table 1). The rates of sICH according to ECASS II (11.7%) and NINDS (15.3%) were significantly higher, and overall prognosis was worse (Figure; Table 2).

According to multivariable logistic regression, patients from group 3 were at increased risk of death in a 3-month follow-up (OR, 2.59; 95% CI, 1.53–4.39). They were also less likely to achieve neurological improvement on day 7 (OR, 0.59; 95% CI, 0.38–0.90) and a similar tendency for 3-month favorable outcome (OR, 0.59; 95% CI, 0.34–1.01; Table 3).

In comparison to group 2, group 3 was similar in terms of age, distribution of vascular risk factors, and prestroke medication use. There were also no significant differences in stroke severity, prethrombolytic management, and sICH rates (Table 1). However, patients from group 2 had worse overall prognosis (Figure; Table 2).

Table 1. General Patients Characteristics According to the Prestroke Level of Disability

<table>
<thead>
<tr>
<th>Prestroke mRS, 0</th>
<th>Prestroke mRS, 1</th>
<th>Prestroke mRS, 2</th>
<th>Prestroke mRS, 3–5</th>
</tr>
</thead>
<tbody>
<tr>
<td>N Value</td>
<td>N Value</td>
<td>P Value</td>
<td>N Value</td>
</tr>
<tr>
<td>Age, y, median (IQR)</td>
<td>5990</td>
<td>67 (58–75)</td>
<td>790</td>
</tr>
<tr>
<td>Female sex, no. (%)</td>
<td>5990</td>
<td>2479 (41.4)</td>
<td>790</td>
</tr>
<tr>
<td>Hypertension, no. (%)</td>
<td>5897</td>
<td>4244 (72.0)</td>
<td>782</td>
</tr>
<tr>
<td>Atrial fibrillation, no. (%)</td>
<td>5864</td>
<td>1422 (24.3)</td>
<td>774</td>
</tr>
<tr>
<td>Congestive heart failure, no. (%)</td>
<td>5855</td>
<td>614 (10.5)</td>
<td>763</td>
</tr>
<tr>
<td>Diabetes mellitus, no. (%)</td>
<td>5892</td>
<td>1208 (20.5)</td>
<td>781</td>
</tr>
<tr>
<td>Hyperlipidemia, no. (%)</td>
<td>5194</td>
<td>1719 (33.1)</td>
<td>683</td>
</tr>
<tr>
<td>Previous stroke, no. (%)</td>
<td>5912</td>
<td>509 (8.6)</td>
<td>784</td>
</tr>
</tbody>
</table>

Baseline characteristics

At hospital before thrombolysis

Stroke severity (NIHSS), median (IQR)

Time to treatment, min, median (IQR)

Hyperdense artery sign on CT, no. (%)

SBP, mmHg, median (IQR)

DBP, mmHg, median (IQR)

Blood glucose, mmol/L, median (IQR)

Figure. Distribution of modified Rankin Scale (mRS) scores 3 months after the onset of stroke according to preexisting disability.
prestroke mRS 3 to 5 tended to develop more sICH according to ECASS II definition and to have higher 3-month mortality. However, favorable outcome was achieved by similar proportions of patients from both groups (Figure; Table 2).

Sensitivity Analysis
The results of multivariable analysis after exclusion of patients whose mRS score on follow-up was reported to be lower than before stroke onset were generally in line with the main analysis. However, strong trends for increased risk of sICH in patients with prestroke mRS of 2 were reduced to trends; and (3) the tendency for lower likelihood of favorable outcome in patients with prestroke mRS of 3 to 5 gained statistical significance (Table I in the online-only Data Supplement).

Multivariable analysis in the subgroup with prestroke disability and a positive history of previous stroke showed that prestroke mRS 3 to 5 tended to develop more sICH in comparison to those with prestroke mRS of 0, (1) patients with prestroke mRS of 1 were not at increased risk of death or unfavorable outcome; (2) all significant differences in patients with prestroke mRS of 2 were reduced to trends; and (3) the tendency for lower likelihood of favorable outcome in patients with prestroke mRS of 3 to 5 had a tendency toward increased risk of sICH, but their likelihood of achieving favorable outcome was similar to the control group (Table III in the online-only Data Supplement).

Table 2. Short-Term and Long-Term Outcome According to the Prestroke Level of Disability

<table>
<thead>
<tr>
<th>Prestroke mRS, 0</th>
<th>Prestroke mRS, 1</th>
<th>Prestroke mRS, 2</th>
<th>Prestroke mRS, 3–5</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Value</td>
<td>N</td>
<td>Value</td>
</tr>
<tr>
<td>sICH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>According to SiTS definition, no. (%)</td>
<td>5876</td>
<td>100 (1.7)</td>
<td>775</td>
</tr>
<tr>
<td>According to ECASS II definition, no. (%)</td>
<td>5848</td>
<td>296 (5.1)</td>
<td>769</td>
</tr>
<tr>
<td>According to NINDS definition, no. (%)</td>
<td>5851</td>
<td>422 (7.2)</td>
<td>769</td>
</tr>
</tbody>
</table>

Outcome at 3 mo

| Death, no. (%) | 4532 | 788 (17.4) | 594 | 164 (27.6) | <0.001 | 213 | 82 (38.5) | <0.001 | 0.003 | 126 | 61 (48.4) | <0.001 | 0.074 |
| Good (mRS 0–2), no. (%) | 4427 | 2393 (54.1) | 589 | 249 (42.3) | 0.001 | 209 | 60 (28.7) | <0.001 | 0.001 | 125 | 11 (8.8) | <0.001 | <0.001 |
| Favorable (mRS 0–2 or not worsening), no. (%) | 4427 | 2393 (54.1) | 589 | 249 (42.3) | 0.001 | 209 | 60 (28.7) | <0.001 | 0.001 | 125 | 43 (34.4) | <0.001 | 0.276 |

Favorable outcome at 3 mo is defined as achieving mRS 0–2 or returning to the prestroke mRS score; neurological improvement at d 7 is defined as improvement of ≥4 points on the NIHSS from baseline or achieving an NIHSS score of 0; and neurological worsening at d 7 is defined as deterioration of ≥4 points on the NIHSS from baseline or death. CI indicates confidence interval; ECASS, European Cooperative Acute Stroke Study; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NINDS, National Institute of Neurological Disorders and Stroke; sICH, symptomatic intracranial hemorrhage; and SiTS, Safe Implementation of Thrombolysis for Stroke.

Table 3. ORs for Particular End Points in Comparison to Patients With No Prestroke Disability Adjusted for Age, Sex, Hypertension, Atrial Fibrillation, Congestive Heart Failure, Diabetes Mellitus, Previous Stroke, and Baseline NIHSS Score

<table>
<thead>
<tr>
<th>Prestroke mRS, 1</th>
<th>Prestroke mRS, 2</th>
<th>Prestroke mRS, 3–5</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR (95% CI)</td>
<td>P Value</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Death at 3 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.30 (1.01–1.66)</td>
<td>0.039</td>
<td>1.98 (1.37–2.86)</td>
</tr>
<tr>
<td>sICH according to ECASS II definition</td>
<td>1.36 (0.99–1.86)</td>
<td>0.055</td>
</tr>
<tr>
<td>Neurological improvement at d 7</td>
<td>1.00 (0.85–1.18)</td>
<td>0.986</td>
</tr>
<tr>
<td>Neurological worsening at d 7</td>
<td>1.11 (0.86–1.42)</td>
<td>0.423</td>
</tr>
<tr>
<td>Favorable outcome at 3 mo</td>
<td>0.80 (0.65–1.00)</td>
<td>0.047</td>
</tr>
</tbody>
</table>

Favorable outcome at 3 mo is defined as achieving mRS 0–2 or returning to the prestroke mRS score; neurological improvement at d 7 is defined as improvement of ≥4 points on the NIHSS from baseline or achieving an NIHSS score of 0; neurological worsening at d 7 is defined as deterioration of ≥4 points on the NIHSS from baseline or death. CI indicates confidence interval; ECASS, European Cooperative Acute Stroke Study; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; and sICH, symptomatic intracranial hemorrhage.
Discussion

This is the first study that extensively addresses the issue of preexisting disability in patients with stroke treated with thrombolysis. It is based on a large, prospectively collected data set of patients receiving rt-PA as a standard of care and distinguishes between 4 different levels of disability. The only other similar analysis by Foell et al14 was limited by the small sample size and used simple dichotomous approach toward disability (88 Canadian patients with prestroke mRS of 0–1 and 24 patients with mRS of 2–5).

Our findings show that in routine clinical stroke practice in Central and Eastern Europe, patients with at least slight preexisting disability account for ≈8% of all cases treated with rt-PA. This proportion is similar to the proportions reported in previous analyses of SITS-EAST and SITS-Monitoring Study (SITS-MOST) data sets.4,8 It may mean that the willingness to treat disabled patients has not increased, despite growing experience with alteplase and the tendency for limiting the list of strong contraindications.

According to our data, prestroke disability may be associated with higher burden of vascular risk factors, increasing age, and increasing stroke severity, which were also observed by Foell et al.14 Differences in these features may turn significant between patients with preexisting mRS of 0 and 1. It showed that there was no homogeneity even among patients with no significant prestroke disability. Patients with prestroke mRS of 2 seem even older and more burdened with atrial fibrillation. However, the vascular profile of patients thrombolysed despite preexisting dependency (mRS, 3–5) does not seem to be worse. It does not mean that their general medical condition stops deteriorating with increasing disability. It rather shows that patients who received rt-PA despite preexisting disability were carefully selected, which is in line with lower thrombolysis rates among patients with prestroke dementia.15 Interestingly, the proportion of patients with a history of previous stroke is ≈40% across all groups with preexisting disability, starting from those with mRS of 1.

The occurrence of sICH in patients with prestroke mRS of 1 was significantly higher than in patients with mRS of 0 and remained more or less stable across all disabled groups. Multivariable analysis did not confirm that prestroke disability independently increases the odds for sICH, which concurs with previous studies.16–18 However, the results of sensitivity analysis suggest that patients with disability not related to previous stroke may be slightly more likely to experience sICH.

Prestroke disability seems to affect both short-term and long-term prognosis. We observed less neurological improvement starting from the prestroke mRS of 2, whereas the rate of neurological worsening at day 7 became higher at mRS of 1 and even progressed with the prestroke mRS of 2. It contradicts the observation of Foell et al.,14 who showed that >50% of patients achieved improvement in NIHSS of ≥4 points at 24 hours, irrespective of preexisting disability. Interestingly, in patients with moderate to severe disability, the odds for achieving favorable outcome were significantly decreased only in the subset with a positive history of stroke.

It has been estimated that nonmodifiable risk factors, including age, stroke severity, preexisting disability, and atrial fibrillation, may be responsible for two thirds of early deaths and poor outcome in acute stroke.19,20 Older age, stroke severity, and preadmission dependency additionally increase the risk of stroke-related pneumonia, which also strongly predicts poor outcome.21 According to our data, 3-month mortality is higher with every level of prestroke disability, starting from 28% (preexisting mRS of 1) up to 48% (preexisting mRS of 3–5). Trends for achieving favorable outcome are obviously the opposite. It is generally in line with previous reports.14,16–20 However, our findings show that if the effectiveness of treatment is measured using a composite end point of mRS 0 to 2 or returning to prestroke mRS, the benefit in patients with prestroke mRS of 3 to 5 may match the benefit in patients with prestroke mRS of 2. During 3 months after thrombolysis, ≈1 in 3 patients from both groups returned to his/her previous mRS score. There is no simple way how to select good candidates for rt-PA among already dependent patients. However, we may speculate that in the group of patients with moderate to severe preexisting disability, the benefit may be more pronounced if there is no history of previous stroke, even accounting for potentially higher risk of sICH. The recently validated risk scoring systems may be of some help in bedside decision making.16,22,23

Study Limitations

Our study has a few limitations, which are mostly due to the voluntary character of the registry. As a consequence, it was not possible to determine how many patients, and because of what reasons, have not been reported to the database or why there are missing values in particular variables. The physicians involved in the SITS registry should be experienced in treating stroke. However, it was not possible to determine how proficient they are in applying the stroke scales. We made a conservative attempt to minimize the bias caused by incorrect assessment of prestroke mRS, but it was possible that several such cases remained in the analysis. The fact that 8% to 15% of patients were reported to score 1 point better on mRS at 3 months than before stroke onset may be partially explained by the nature of collecting historic data versus follow-up data. It is likely that mRS in those 2 time points was assessed by different physicians. In some patients, disability could have been caused by conditions that fluctuate or may improve over time. Importantly, the main results were confirmed by sensitivity analysis performed after the exclusion of cases with improved mRS scores. Outcomes may also be biased by nonrandom sampling because patients with prestroke disability were definitely selected for thrombolysis, but there was no uniform selection policy among stroke units. The Bonferroni correction was used to account for multiple comparisons. Despite limitations, the study provides a detailed description of the disability profile of patients. This allows us to draw indirect conclusions about treatment outcome based on everyday practice of an average stroke center in Central and Eastern Europe.

Conclusions

In Central and Eastern Europe, ≈1 in 16 stroke patients treated with intravenous thrombolysis has at least slight preexisting disability, including a marginal proportion of patients already dependent in the activities of daily living. Prestroke disability per se does not seem to independently increase the risk of
sICH, but it may be associated with less neurological improvement and higher mortality. The burden of vascular risk factors in patients receiving rt-PA seems to be increasing with each level of disability until mRS 2. It is more difficult to measure the benefits in previously disabled patients, especially using conventional end points. More than one third of patients with prestroke mRS of 3 to 5 is capable of returning to their pre-stroke functional status, which from the patient’s and carer’s perspective may be as important as achieving good outcome by a patient with prestroke mRS of ≤2. It is possible that the negative history of previous stroke may be in favor of treating patients with moderate to severe disability. However, further analyses and prospective studies are needed to identify the optimal selection criteria for rt-PA treatment in those patients.

Appendix

Countries participating in SITS-EAST with national coordinators and number of cases contributed: Czech Republic (Robert Mikulik; 3319), Poland (Anna Czlonkowska; 1361), Slovakia (Miroslav Brozman; 794), Hungary (Laszlo Csiba; 530), Estonia (Janika Kõrv; 458), Slovenia (Viktor Svigeli; 341), Croatia (Vida Dermarin; 257), Lithuania (Dalius Jatuzis and Aleksandras Vilionskis; 93), Turkey (Yakup Krespi; 69), and Russia (Nikolay Shamalov; 46).

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Disclosures

Dr Karlinski has received conference travel costs from Boehringer Ingelheim. Dr Kobayashi has received lecture fees and conference travel costs from Boehringer Ingelheim. Dr Czlonkowska has received lecture fees and travel costs from Boehringer Ingelheim. Dr Mikulik has received honoraria payments and travel support from Boehringer Ingelheim. Dr Vilionskis has received honoraria and travel support from Boehringer Ingelheim. Dr Jatuzis has received honoraria and travel support from Boehringer Ingelheim. Dr Wahlgren has received honoraria for lectures and for advisory boards from Boehringer Ingelheim, Astra-Zeneca, Bayer, and Thrombogenics. The other authors have no conflicts to report.

References

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SUPPLEMENTAL MATERIAL

**Supplemental table I.** Odds ratios (OR) for particular endpoints in comparison to patients with no pre-stroke disability adjusted for age, sex, hypertension, atrial fibrillation, congestive heart failure, diabetes, previous stroke and baseline NIHSS score after excluding patients whose modified Rankin Scale (mRS) score 3 months after stroke was reported to be lower than before the onset of symptoms.

<table>
<thead>
<tr>
<th></th>
<th>Pre-stroke mRS 1</th>
<th></th>
<th>Pre-stroke mRS 2</th>
<th></th>
<th>Pre-stroke mRS 3-5</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95%CI)</td>
<td>P</td>
<td>OR (95%CI)</td>
<td>P</td>
<td>OR (95%CI)</td>
<td>P</td>
</tr>
<tr>
<td>Death at 3 months</td>
<td>1.42 (1.12-1.79)</td>
<td>0.004</td>
<td>2.21 (1.54-3.17)</td>
<td>&lt;0.001</td>
<td>3.87 (2.40-6.25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>sICH according to ECASS II</td>
<td>1.42 (1.04-1.93)</td>
<td>0.026</td>
<td>1.16 (0.70-1.92)</td>
<td>0.561</td>
<td>1.61 (0.91-2.83)</td>
<td>0.099</td>
</tr>
<tr>
<td>Neurological improvement at day 7</td>
<td>0.97 (0.82-1.15)</td>
<td>0.729</td>
<td>0.63 (0.48-0.83)</td>
<td>0.001</td>
<td>0.58 (0.40-0.84)</td>
<td>0.004</td>
</tr>
<tr>
<td>Neurological worsening at day 7</td>
<td>1.12 (0.88-1.42)</td>
<td>0.366</td>
<td>1.87 (1.35-2.60)</td>
<td>&lt;0.001</td>
<td>1.46 (0.94-2.26)</td>
<td>0.094</td>
</tr>
<tr>
<td>Favorable outcome at 3 months</td>
<td>0.68 (0.55-0.84)</td>
<td>&lt;0.001</td>
<td>0.31 (0.21-0.46)</td>
<td>&lt;0.001</td>
<td>0.40 (0.23-0.68)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

sICH, symptomatic intracranial hemorrhage; NIHSS, National Institutes of Health Stroke Scale.

Favorable outcome at 3 months, defined as achieving mRS 0-2 or returning to the pre-stroke mRS score; neurological improvement at day 7, defined as improvement of at least 4 points on the NIHSS from baseline or achieving an NIHSS score of 0; neurological worsening at day 7, defined as deterioration of at least 4 points on the NIHSS from baseline or death.
Supplemental table II. Odds ratios (OR) for particular endpoints in comparison to patients with no pre-stroke disability adjusted for age, sex, hypertension, atrial fibrillation, congestive heart failure, diabetes, previous stroke and baseline NIHSS score in patients whose pre-stroke disability was accompanied by a positive history of previous stroke.

<table>
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<th>Pre-stroke mRS 1</th>
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<tr>
<td></td>
<td>OR (95%CI)</td>
<td>P</td>
<td>OR (95%CI)</td>
<td>P</td>
<td>OR (95%CI)</td>
<td>P</td>
</tr>
<tr>
<td>Death at 3 months</td>
<td>1.22 (0.85-1.74)</td>
<td>0.280</td>
<td>1.62 (0.95-2.74)</td>
<td>0.075</td>
<td>3.55 (1.87-6.74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>sICH according to ECASS II</td>
<td>1.12 (0.69-1.85)</td>
<td>0.642</td>
<td>0.84 (0.36-1.96)</td>
<td>0.685</td>
<td>0.93 (0.35-2.41)</td>
<td>0.874</td>
</tr>
<tr>
<td>Neurological improvement at day 7</td>
<td>1.13 (0.88-1.44)</td>
<td>0.353</td>
<td>0.74 (0.48-1.13)</td>
<td>0.166</td>
<td>0.36 (0.20-0.65)</td>
<td>0.001</td>
</tr>
<tr>
<td>Neurological worsening at day 7</td>
<td>0.87 (0.59-1.28)</td>
<td>0.474</td>
<td>1.58 (0.95-2.64)</td>
<td>0.080</td>
<td>1.92 (1.06-3.49)</td>
<td>0.032</td>
</tr>
<tr>
<td>Favorable outcome at 3 months</td>
<td>0.89 (0.65-1.21)</td>
<td>0.449</td>
<td>0.61 (0.36-1.03)</td>
<td>0.065</td>
<td>0.49 (0.25-0.99)</td>
<td>0.047</td>
</tr>
</tbody>
</table>

sICH, symptomatic intracranial hemorrhage; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

Favorable outcome at 3 months, defined as achieving mRS 0-2 or returning to the pre-stroke mRS score; neurological improvement at day 7, defined as improvement of at least 4 points on the NIHSS from baseline or achieving an NIHSS score of 0; neurological worsening at day 7, defined as deterioration of at least 4 points on the NIHSS from baseline or death.
**Supplemental table III.** Odds ratios (OR) for particular endpoints in comparison to patients with no pre-stroke disability adjusted for age, sex, hypertension, atrial fibrillation, congestive heart failure, diabetes, previous stroke and baseline NIHSS score in patients whose pre-stroke disability was not accompanied by a history of previous stroke.

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<td>OR (95%CI) P</td>
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<td>OR (95%CI) P</td>
</tr>
<tr>
<td>Death at 3 months</td>
<td>1.40 (1.05-1.87) 0.021</td>
<td>2.28 (1.44-3.62) &lt;0.001</td>
<td>2.20 (1.22-4.00) 0.009</td>
</tr>
<tr>
<td>sICH according to ECASS II</td>
<td>1.52 (1.05-2.20) 0.025</td>
<td>1.28 (0.70-2.35) 0.627</td>
<td>1.90 (0.97-3.72) 0.060</td>
</tr>
<tr>
<td>Neurological improvement at day 7</td>
<td>0.96 (0.79-1.18) 0.733</td>
<td>0.61 (0.43-0.85) 0.004</td>
<td>1.06 (0.69-1.63) 0.798</td>
</tr>
<tr>
<td>Neurological worsening at day 7</td>
<td>1.20 (0.90-1.60) 0.204</td>
<td>1.89 (1.26-2.83) 0.002</td>
<td>0.87 (0.47-1.63) 0.179</td>
</tr>
<tr>
<td>Favorable outcome at 3 months</td>
<td>0.75 (0.58-0.98) 0.032</td>
<td>0.32 (0.20-0.52) &lt;0.001</td>
<td>1.03 (0.55-1.90) 0.928</td>
</tr>
</tbody>
</table>

sICH, symptomatic intracranial hemorrhage; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

Favorable outcome at 3 months, defined as achieving mRS 0-2 or returning to the pre-stroke mRS score; neurological improvement at day 7, defined as improvement of at least 4 points on the NIHSS from baseline or achieving an NIHSS score of 0; neurological worsening at day 7, defined as deterioration of at least 4 points on the NIHSS from baseline or death.