Within-Day and Weekly Variations of Thrombolysis in Acute Ischemic Stroke

Results From Safe Implementation of Treatments in Stroke-International Stroke Thrombolysis Register

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Background and Purpose—Temporal variations of thrombolysis delivery and their influence on outcome have been reported with controversial results. In this large cohort study, we evaluated whether thrombolytic treatment has a within-day and weekly variability corresponding to circadian and weekly patterns of ischemic stroke onset, and whether these have impact on clinical outcome.

Methods—We retrospectively analyzed patients with acute ischemic stroke receiving intravenous alteplase, prospectively included in the Safe Implementation of Treatments in Stroke-International Stroke Thrombolysis Register. Patients were grouped by treatment on day hours (08:00–19:59) or night hours (20:00–07:59) and treatment on weekdays and weekends. For each subgroup, we analyzed frequency of thrombolytic treatments, time intervals, and outcomes (3-month modified Rankin Scale score 0–2 as good functional outcome, mortality, symptomatic intracerebral hemorrhage).

Results—We included 21 513 patients. Considering the mean expected number of patients treated per hour (0.4) and per day of the week (9.8), if no temporal variations were present, patients were significantly treated more during day hours and weekdays (P<0.0001). Median door-to-needle and onset-to-treatment times were longer for patients treated during night hours and on weekends (P<0.01). After adjustment for confounding variables, treatment during day hours was an independent predictor of good functional outcome (odds ratio, 1.12; 95% confidence interval, 1.04–1.21; P=0.004), and patients treated during weekdays were at risk of higher mortality (odds ratio, 1.15; 95% confidence interval, 1.04–1.28; P=0.008).

Conclusions—Frequency of thrombolytic treatment seems to follow the same circadian pattern of stroke incidence, whereas its correspondence to a weekly pattern is less clear. Time of treatment is an independent predictor of outcome. (Stroke. 2014;45:176-184.)

Key Words: circadian rhythm ■ outcome assessment ■ stroke ■ thrombolytic therapy ■ tissue-type plasminogen activator
with thrombolysis with cerebrovascular events occurring during day time and those with stroke onset during night time.\textsuperscript{21}

Despite strong evidence of safety and efficacy of intravenous (IV) alteplase ≤4.5 hours after symptom onset,\textsuperscript{22} thrombolysis is still accessible only for a limited number of patients with ischemic stroke. Hence, it is urgent to understand whether the access to thrombolytic treatment is always guaranteed, and with the same safety and efficacy, irrespective of time and day of treatment. Few recent studies on this issue found controversial results,\textsuperscript{16,23--29} one reporting higher case fatality rates in patients treated during working hours,\textsuperscript{23} whereas another reporting that diurnal IV tissue-type plasminogen activator (t-PA) administration was independently associated with early recanalization and better 90-day functional outcome.\textsuperscript{24} Other studies showed that the majority of patients with stroke received thrombolysis during nonworking hours and that time of hospital admission was not an independent predictor of outcome.\textsuperscript{16,25--29}

In a large cohort of patients treated with IV thrombolysis in several centers from European and non-European countries and entered into the Safe Implementation of Treatments in Stroke-International Stroke Thrombolysis Register (SITS-ISTR), we aimed to evaluate whether thrombolytic treatment for acute ischemic stroke has a within-day variation corresponding to the circadian pattern of stroke onset and a weekly variability, and whether these have an impact on clinical outcome.

Methods

Study Population

We retrospectively analyzed data of patients with acute ischemic stroke receiving IV thrombolysis during a period of 6 years, and prospectively registered in the SITS-ISTR, a prospective, multinational, Internet-based register of IV thrombolysis (www.sitsinternational.org).\textsuperscript{30}

Patients were selected according to criteria reported in the European summary of product characteristics, although the register also includes patients treated without a strict adherence to some contraindications of the treatment protocol. Approval by local ethics committees or patient consent was obtained in countries where required; other countries approved the register as an anonymized audit.

For each patient, demographic and clinical characteristics were collected, including time intervals for treatment (that is, onset-to-door time, door-to-imaging time, door-to-needle time, and onset-to-treatment time), radiological early ischemic signs, and hyperdense middle cerebral artery sign (HMCAS). For the purposes of the present study, time and day of thrombolytic treatment were also considered.

Outcome Measures

We considered the following outcome measures: symptomatic intracerebral hemorrhage (SICH), mortality, and functional independence at 3-month follow-up.

SICH per SITS-MOST protocol\textsuperscript{\textsuperscript{30}} was defined as local or remote parenchymal hemorrhage type 2\textsuperscript{\textsuperscript{3}} on the 22- to 36-hour post-treatment imaging scan combined with a neurological deterioration of ≥4 points on the National Institutes of Health Stroke Scale (NIHSS) from baseline or from the lowest NIHSS value between baseline and 24 hours, or leading to death. SICH per National Institute of Neurological Disorders and Stroke (NINDS)\textsuperscript{\textsuperscript{2}} was intended as any hemorrhage combined with any neurological deterioration (NIHSS score ≥1) or that leads to death within 7 days. Finally, SICH according to the European Cooperative Acute Stroke Study (ECASS) II trial\textsuperscript{\textsuperscript{1}} was any hemorrhage plus a neurological deterioration of ≥4 points on the NIHSS from baseline or from the lowest NIHSS value after baseline to 7 days or leading to death. Hemorrhage rates were calculated from computed tomography or MRI scans done between 22 and 36 hours after therapy and also from any additional post-treatment scan evaluated at the local centers.

For the death end point, survival was assessed ≤3 months from therapy through contact with the patient’s family or caregiver.

Functional independence was defined as a modified Rankin Scale score of 0 to 2 (good functional outcome) at 3 months after stroke onset. Additional outcome measure was no or minimal disability (ie, modified Rankin Scale score of 0–1 at 3 months).

Statistical Analysis

For the purposes of this study, to obviate the wide heterogeneity of work shift organization and definition of working and nonworking hours/days because of the multicenter and multinational nature of the SITS-ISTR, we divided the population into paired subgroups by t-PA treatment time, considering 2 exact 12-hour intervals as day (08:00–19:59) versus night (20:00–07:59) hours, and 2 exact patterns of days of weekdays, from Sunday midnight to Friday midnight, versus weekend days, from Friday midnight to Sunday midnight (although, for example, Saturday, at least in the morning, is usually considered a working day in some countries of Southern Europe and a nonworking day in most countries of Northern Europe). We calculated frequencies of thrombolytic treatments for each subgroup. We also considered distribution of treatments along 6-hour time intervals (00:00–5:59; 06:00–11:59; 12:00–17:59; 18:00–23:59). The paired subgroups were compared with each other to find possible significant differences in the frequencies of thrombolysis.

Assuming that stroke onset was evenly distributed during the hours of the day and the days of the week, biasing toward the null hypothesis of lack of circadian variation, the χ² test for goodness of fit to the null model of equal distribution of thrombolytic treatments was applied to the observed number of thrombolytic treatments compared with the expected number if no temporal variation was present for the day versus night hours and weekdays versus weekends.

Then we performed the same analysis by considering only countries that entered >900 treatments (ie, 150 per year) in the registry during the study period.

Continuous variables were expressed as median (interquartile range) or mean (±SD), categorical variables as counts (percentages), and we calculated percentage proportions by dividing the number of events by the total number of patients, excluding missing or unknown cases. Univariate analysis with Mann–Whitney U test and χ² test was performed to compare demographics, clinical characteristics, and outcome measures of the paired subgroups.

To evaluate whether treatments by hour of the day and day of the week were independently related to outcome measures, 2 different multivariate logistic regression models for each outcome measure were performed, 1 including day/night treatment and another including weekday/weekend treatment, along with variables presenting with univariate associations of P ≤0.25, and those variables potentially influencing outcome such as age, sex, baseline NIHSS, and time intervals to treatment, irrespective of the univariate association. Statistical significance was set at P ≤0.05. All statistical analyses were performed with Statistica version 7.0.

Results

During a period of 6 years, 21,513 patients receiving IV t-PA were included in the SITS-ISTR, of whom 15,462 (71.9%) were treated during day hours (8:00–19:59) and 6051 (28.1%) during night hours (20:00–07:59; Table 1). Considering the 6-hour time frames, 5039 patients (23.4%) were treated from 6:00 to 11:59, 8489 (39.5%) from 12:00 to 17:59, 6124 (28.5%) from 18:00 to 23:59, and 1840 (8.6%) from 00:00 to 5:59.

Overall, 15,953 (74.2%) received IV thrombolysis during weekdays and 5560 (25.8%) on weekends (Table 1). Considering the whole week, 3291 patients (15.3%) were treated on Wednesday, with a progressive decline on the weekend down to 2750 patients (12.8%) on Sunday (ie, the smallest number of thrombolyces per day of the week with a significant difference compared with Wednesday [odds ratio [OR], 1.23;
were observed between day and night hours ($P<0.0001$). When we considered the 6-hour groups (00:00–05:59: 18.8%; 06:00–11:59: 18.7%; 12:00–17:59: 18.9%; 18:00–23:59: 26.6%) and on weekdays (10.2 versus 8.9 on weekends; OR: 1.15; 95% CI: 1.01–1.20; $P<0.0001$).

Assuming that stroke onset was evenly distributed during day hours and weekdays, with a mean expected number of treated patients of 0.4 per hour and 9.8 per weekday if no within-day and weekly variations were present, patients were more frequently treated with thrombolysis during day hours (0.6 versus 0.2 during night hours; OR: 2.56; 95% CI: 2.46–2.66; $P<0.0001$) and on weekdays (10.2 versus 8.9 on weekends; OR: 1.15; 95% CI: 1.01–1.20; $P<0.0001$).

The distribution of modified Rankin Scale in the subgroups paired with the expected numbers ($P<0.0001$; Figure 1B). Multivariate logistic regression analysis confirmed the significant results of the univariate analysis for outcomes (Table 3).

In our study, there were more thrombolyses during weekdays, which the highest numbers of treatments between midnight and 5.59 AM, with a 50% increase during day hours and a 50% decrease during night hours compared with the expected numbers if no within-day variation was present. When we considered the countries that included $>900$ patients in the registry during the study period, in each country, patients were more frequently treated during day hours compared with the expected numbers ($P<0.0001$; Figure 1A), whereas no difference was found between weekdays and weekends, except for United Kingdom, where patients were more frequently treated during weekdays (OR: 1.09; 95% CI: 1.01–1.17; $P=0.004$) and on weekdays (OR: 1.04; 95% CI: 1.01–1.17; $P=0.03$), and of a lower risk of developing SICH/NINDS (OR: 0.84; 95% CI: 0.75–0.95; $P=0.005$), whereas treatment during weekdays was related to a higher mortality rate (OR: 1.15; 95% CI: 1.04–1.28; $P=0.008$).

### Discussion

This study shows that temporal variability of thrombolytic treatment seems to correspond to circadian rhythm of stroke onset, maintaining a similar diurnal pattern. We found the highest proportion of treatments from noon to 17:59, which may be explained by the delay between stroke onset and hospital arrival, and the lower proportion of treatments between midnight and 5:59 AM, with a 50% increase during day hours and a 50% decrease during night hours compared with the expected numbers if no within-day variation was present. When we considered the countries that included $>900$ patients in the registry, no difference was found in treatment frequencies between weekdays and weekends, except for United Kingdom where patients were significantly more frequently treated during weekdays.
confirming the results of a previous study.33 These data would agree with reported weekly variation in stroke onset, the incident of which would peak on Monday or on Wednesday and would be the lowest during the weekend.7,10 In contrary to our observations, in other studies, the majority of patients with stroke received thrombolysis during the weekend,16,20,25–27 particularly in comprehensive or primary stroke centers compared with nonstroke centers.20 Some authors reported stroke onset as being more frequent during the weekend,3,6,8 and hence, it is not clear whether the differences found in our study have to be related to weekly changes of stroke onset or to differences in stroke service organization.

Patients’ characteristics were mostly homogeneous across all the subgroups, particularly, as previously reported,23,28 with regard to the median baseline stroke severity. There is the exception for some, more statistically than clinically, significant differences, probably related to the large sample size that allows the detection of even small imbalances. That could reflect the lack of a substantial influence of time or day of treatment on patient selection for thrombolysis. We did not find statistical differences in the door-to-imaging time between the paired subgroups, suggesting that there were no disparities at least in the availability of diagnostic procedures, similar to what was reported in recent studies.23,28 The longer door-to-needle time and onset-to-treatment time in the range of a few minutes during night hours and on weekends may suggest a tendency to a delay, although little, in certain procedures for the management of patients with stroke during these time periods.

Regardless of the statistical significance, differences in outcome measures between the paired subgroups were relatively small, but treatment during day hours resulted as an independent predictor of good functional outcome and no or minimal disability and of a lower risk of developing SICH/NINDS. The worse outcomes of patients treated during night hours might be related to the longer time intervals from stroke onset to therapy and to the higher proportion of patients with atrial fibrillation, an important cardiological comorbidity that can have an influence on functional recovery.34 Longer time intervals might speculatively point at differences in quality of care provided to patients during night hours, which could potentially make the confirmation of eligibility for thrombolysis more difficult, although we do not have data to support this hypothesis. Besides an off-hour effect, circadian rhythm in the efficacy of thrombolysis might also account for these differences in outcome. In fact, t-PA seems to be more effective particularly during diurnal hours, whereas a higher resistance to
Table 2. Demographic Data and Baseline Clinical and Radiological Characteristics of All Patients and of Patients Treated During Day vs Night Hours and Weekdays vs Weekends

<table>
<thead>
<tr>
<th></th>
<th>All Patients (n=21513)</th>
<th>Day Hours (08:00–19:59; n=15462)</th>
<th>Night Hours (20:00–07:59; n=6051)</th>
<th>P Value</th>
<th>Weekdays (n=15953)</th>
<th>Weekend (n=5560)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, median (IQR)</td>
<td>69 (60–76)</td>
<td>70 (60–77)</td>
<td>68 (58–75)</td>
<td>&lt;0.0001</td>
<td>69 (60–76)</td>
<td>69 (59–76)</td>
<td>0.17</td>
</tr>
<tr>
<td>Sex (% men)</td>
<td>12.8</td>
<td>12 (%)</td>
<td>12 (%)</td>
<td></td>
<td>12 (%)</td>
<td>12 (%)</td>
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<tr>
<td>EDCI</td>
<td>107%</td>
<td>107%</td>
<td>107%</td>
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<td>107%</td>
<td>107%</td>
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<tr>
<td>Hyperlipidemia (%)</td>
<td>65/85/19</td>
<td></td>
<td></td>
<td></td>
<td>65/85/19</td>
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<tr>
<td>Atrial fibrillation</td>
<td>5347/20</td>
<td></td>
<td></td>
<td></td>
<td>5347/20</td>
<td></td>
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<tr>
<td>Congestive heart failure (%)</td>
<td>175/20</td>
<td></td>
<td></td>
<td></td>
<td>175/20</td>
<td></td>
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</tr>
<tr>
<td>Previous stroke (%)</td>
<td>2716/2118 (12.8)</td>
<td>1956/2127 (12.9)</td>
<td>760/5964 (12.7)</td>
<td>0.83</td>
<td>2020/1569 (12.9)</td>
<td>696/5488 (12.7)</td>
<td>0.72</td>
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<tr>
<td>Cigarette smoking (%)</td>
<td>0.00001</td>
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<tr>
<td>SBP, mm Hg, median (IQR)</td>
<td>117 (102–142)</td>
<td>117 (102–142)</td>
<td>117 (103–143)</td>
<td></td>
<td>117 (102–142)</td>
<td>117 (102–142)</td>
<td>0.82</td>
</tr>
<tr>
<td>DBP, mm Hg, median (IQR)</td>
<td>788 (74–90)</td>
<td>81 (74–90)</td>
<td>82 (75–90)</td>
<td>0.026</td>
<td>81 (74–90)</td>
<td>82 (75–90)</td>
<td>0.25</td>
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<td>NIHSS</td>
<td>9.7</td>
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</tr>
<tr>
<td>Mean (±SD)</td>
<td>12.8 (±6.1)</td>
<td>12.8 (±6.2)</td>
<td>12.8 (±5.9)</td>
<td></td>
<td>12.8 (±6.1)</td>
<td>12.8 (±6.1)</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>12 (8–17)</td>
<td>12 (8–18)</td>
<td>12 (8–17)</td>
<td></td>
<td>12 (8–17)</td>
<td>12 (8–17)</td>
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<tr>
<td>Early ischemic signs (%)</td>
<td>0.34</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>0.002</td>
</tr>
<tr>
<td>HMNCAS (%)</td>
<td>8.9</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Cause of stroke (%)</td>
<td>33.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>0.33</td>
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<tr>
<td>Large vessel disease with substantial CAS</td>
<td>2447/20210 (12.1)</td>
<td>1742/14507 (12.0)</td>
<td>705/5703 (12.4)</td>
<td>0.49</td>
<td>1817/14981 (12.0)</td>
<td>630/5229 (12.0)</td>
<td>0.88</td>
</tr>
<tr>
<td>Large vessel disease other than substantial CAS</td>
<td>5051/20210 (25.0)</td>
<td>3694/14507 (25.5)</td>
<td>1357/5703 (23.8)</td>
<td>0.014</td>
<td>3769/14981 (25.2)</td>
<td>1282/5229 (24.5)</td>
<td>0.36</td>
</tr>
<tr>
<td>Cardiac origin</td>
<td>7057/20140 (34.9)</td>
<td>5040/14507 (34.7)</td>
<td>2017/5703 (35.4)</td>
<td>0.40</td>
<td>5268/14981 (35.2)</td>
<td>1789/5229 (34.2)</td>
<td>0.21</td>
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<tr>
<td>Lacunar stroke</td>
<td>1396/20110 (9.6)</td>
<td>1401/14507 (9.7)</td>
<td>535/5703 (9.4)</td>
<td>0.55</td>
<td>1418/14981 (9.5)</td>
<td>518/5229 (9.9)</td>
<td>0.35</td>
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<tr>
<td>Other</td>
<td>892/20140 (4.4)</td>
<td>638/14507 (4.4)</td>
<td>254/5703 (4.4)</td>
<td>0.86</td>
<td>652/14981 (4.3)</td>
<td>240/5229 (4.6)</td>
<td>0.47</td>
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<td>Unknown</td>
<td>2662/20210 (13.2)</td>
<td>1887/14507 (13.0)</td>
<td>775/5703 (13.6)</td>
<td>0.27</td>
<td>1943/14981 (13.0)</td>
<td>719/5229 (13.8)</td>
<td>0.15</td>
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<tr>
<td>Not ischemic stroke</td>
<td>165/20210 (0.8)</td>
<td>105/14507 (0.7)</td>
<td>60/5703 (1.0)</td>
<td>0.020</td>
<td>114/14981 (0.8)</td>
<td>51/5229 (1.0)</td>
<td>0.14</td>
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</tbody>
</table>

CAS indicates carotid artery stenosis; DBP, diastolic blood pressure; DIT, door-to-imaging time; DNT, door-to-needle time; HMNCAS, hyperdense middle cerebral artery sign; IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; ODT, onset-to-door time; OTT, onset-to-treatment time; SBP, systolic blood pressure; and SGL, serum glucose level.
Outcome Measures in All Patients, in Patients Treated During Day Hours vs Night Hours, and in Patients Treated During Weekdays vs Weekends

<table>
<thead>
<tr>
<th></th>
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<th>Weekdays (n=15953)</th>
<th>Weekend (n=5560)</th>
<th>P Value</th>
<th>MV, OR, MV, OR P Value</th>
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</thead>
<tbody>
<tr>
<td><strong>SICH (%; 95% CI)</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>SITS-MOST</td>
<td>358/21033 (1.7; 1.5–1.9)</td>
<td>267/15121 (1.8; 1.6–2.0)</td>
<td>91/5912 (1.5; 1.3–1.9)</td>
<td>273/15601</td>
<td>85/5432</td>
<td>0.25</td>
<td>1.11</td>
</tr>
<tr>
<td>ECASS II</td>
<td>1095/20507 (5.3; 5.0–5.7)</td>
<td>778/14731 (5.3; 4.8–5.7)</td>
<td>317/5778 (5.4; 4.9–6.1)</td>
<td>816/15206</td>
<td>279/5303</td>
<td>0.56</td>
<td>0.94</td>
</tr>
<tr>
<td>NINDS</td>
<td>1599/20545 (7.8; 7.4–8.2)</td>
<td>1107/14762 (7.5; 7.1–7.9)</td>
<td>492/5873 (8.0; 7.5–8.3)</td>
<td>1196/15229</td>
<td>403/5316</td>
<td>0.015</td>
<td>0.84</td>
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<tr>
<td><strong>Good outcome, 3-month mRS 0–2 (%; 95% CI)</strong></td>
<td></td>
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<tr>
<td>SITS-ISTR</td>
<td>9710/18173 (53.4; 52.7–54.2)</td>
<td>7043/1344 (54.0; 53.1–54.9)</td>
<td>2667/5129 (52.0; 50.6–53.4)</td>
<td>7185/13501</td>
<td>2525/4672</td>
<td>0.015</td>
<td>1.12</td>
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<tr>
<td>ECASS</td>
<td>6864/18173 (37.8; 37.1–38.5)</td>
<td>4866/1344 (38.2; 37.4–39.1)</td>
<td>1878/512 (35.6; 35.3–38.0)</td>
<td>5060/13501</td>
<td>1804/4672</td>
<td>0.044</td>
<td>1.09</td>
</tr>
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<td>NINDS</td>
<td>2742/8414 (14.9; 14.4–15.4)</td>
<td>1967/13203 (14.9; 14.3–15.9)</td>
<td>775/521 (14.9; 14.3–15.9)</td>
<td>2089/13679</td>
<td>653/4735</td>
<td>0.015</td>
<td>0.95</td>
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<tr>
<td><strong>No or minimal disability, 3-month mRS 0–1 (%; 95% CI)</strong></td>
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<tr>
<td>SITS-ISTR</td>
<td>8776/18173 (49.0; 48.3–50.0)</td>
<td>5849/1344 (53.1; 52.3–53.8)</td>
<td>2327/5129 (50.0; 48.6–51.4)</td>
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<td>3423/4672</td>
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<td>6466/18173 (36.4; 35.7–37.1)</td>
<td>4486/1344 (35.9; 35.1–36.7)</td>
<td>1728/512 (34.6; 33.9–35.3)</td>
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<td>3286/4672</td>
<td>0.044</td>
<td>0.96</td>
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<td>NINDS</td>
<td>2682/8414 (14.8; 14.3–15.2)</td>
<td>1907/13203 (14.7; 14.2–15.2)</td>
<td>705/521 (14.6; 14.1–15.0)</td>
<td>2682/13679</td>
<td>604/4735</td>
<td>0.015</td>
<td>0.97</td>
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<td><strong>Death (%; 95% CI)</strong></td>
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<tr>
<td>SITS-ISTR</td>
<td>2742/8414 (14.9; 14.4–15.4)</td>
<td>1967/13203 (14.9; 14.3–15.9)</td>
<td>775/521 (14.9; 14.3–15.9)</td>
<td>2089/13679</td>
<td>653/4735</td>
<td>0.015</td>
<td>0.97</td>
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</tbody>
</table>

CI indicates confidence interval; ECASS, European Cooperative Acute Stroke Study; mRS, modified Rankin Scale; MV, Multivariate analysis; NINDS, National Institute of Neurological Disorders and Stroke; OR, odds ratio; SICH, symptomatic intracerebral hemorrhage; and SITS-ISTR, Safe Implementation of Thrombolysis in Stroke - Monitoring Study.

Within-Day and Weekly Variations of Thrombolysis

Thrombolysis in the early morning associated with plasmactivator inhibitor-1 level increase, has been reported.5,12,35–37 This has also been suggested by a significant difference in outcomes between patients treated during the early morning and those treated during later times.18,19,27,28,38 Other potential biological mechanisms could involve platelet activation, such as circadian changes in platelet activity and diurnal variations in thromboxane production.18,19,27,28,38 Other potential biological mechanisms, such as circadian changes in platelet activity and diurnal variations in thromboxane production, might be involved. This hypothesis is further supported by the finding that patients treated during the early morning have a higher mortality rate compared to those treated during later times.18,19,27,28,38 Other potential biological mechanisms could include platelet activation, such as circadian changes in platelet activity and diurnal variations in thromboxane production.18,19,27,28,38 Other potential biological mechanisms, such as circadian changes in platelet activity and diurnal variations in thromboxane production, might be involved.
in the morning and too-late hospital arrival because of lack of witnesses or evidence of symptoms at wake-up in the morning. We do not have detailed information about the structural and personnel stroke care organization of each center, and hence, we cannot exclude that temporal variation in thrombolysis delivery may reveal a lack of homogeneity in acute stroke care services. A survey published in 2007, conducted all over Europe in a large random sample of hospitals, showed that only few centers provide an optimal level of care and meet the criteria listed by the European Stroke Initiative.42 In fact, when we considered the countries that included >900 patients in the registry, the weekend effect on thrombolysis use disappeared. The heterogeneity across the participating centers and countries in the definition of nonworking/working hours and of nonworking/working days, including some local religious or national feasts, might have had an influence on the results, but the wide definitions we adopted may have, at least partially, balanced this limitation.

Another important limitation of this study is that it is a retrospective analysis of data collected prospectively, but because the register is about a specific treatment with a strict protocol on the time window, we hypothesized that there was not bias of reporting stroke onset and treatment time. Moreover, there are no reasons to assume that recording errors on mortality and outcome are significantly different between the paired subgroups.

The major strength of this study is the large sample size, which allowed us to detect small differences and to reach some reasonable results. Moreover, this is a multicenter study, including expert and nonexpert centers, which gives more generalizability and a good external validity to our results.

In conclusion, we found that the number of thrombolytic treatments delivered follows the same diurnal/morning pattern of stroke incidence, but it is difficult to draw definitive conclusions for a weekly temporal pattern. Time of treatment is an independent predictor of outcome in our large multicenter cohort study. Our results indicate that each center needs to carefully review local procedures and can give preliminary information that, if confirmed in future prospective studies, could definitely address whether differences in outcomes and numbers of treated patients are natural variations or consequence of inappropriate resource allocation.

**Acknowledgments**

We thank all the centers and patients for their participation in SITS-ISTR.

**Sources of Funding**

SITS-ISTR is funded by EU FP7, Boehringer-Ingelheim, Ferrer, EU Public Health Executive Authority, Vinnova, Medical Training and Research (ALF) fund from Stockholm County Council and the Karolinska Institute, Fighting Stroke project supported by Swedish Heart-Lung Foundation and Karolinska Institutet, Friends of Karolinska Institutet, United States, and Johanniterorden. Dr Mikulik has received research support from the European Regional Development Fund-Project FNUSA-ICRC (No.CZ 1.05/1.1.00/02.0123). None of the...
funding sources were involved in this study design, patient recruitment, data collection, data analysis, data interpretation, article writing, the decision to submit it for publication, or any aspect pertinent to the study. Authors have not been paid to write this article by a pharmaceutical company or other agency. The corresponding author had full access to all the study data, takes responsibility for the integrity of data and accuracy of data analysis, and had final responsibility for the decision to submit for publication.

Disclosures

Dr Ahmed is an employee of SITS International, which received a grant from Boehringer-Ingelheim and Ferrer for the SITS-MOST/ SITS-ISTR study with alteplase; Dr Tatlisumak has a research contract with Boehringer-Ingelheim, Sanofi-Aventis, and Pfizer Inc. The other authors report no conflicts.

Project FNUSA-ICRC (No.CZ.1.05/1.1.00/02.0123). Dr Wahlgren has received honoraria and travel support for Boehringer-Ingelheim and research support from the European Regional Development Fund Project FNUSA-ICRC (No.CZ.1.05/1.1.00/02.0123). Dr Wahlgren is chairman of SITS International, which received funds from EU FP7, Vinnova, Boehringer-Ingelheim, and Ferrer. Dr Toni serves as a consultant for Boehringer Ingelheim and received speaker honoraria from Boehringer-Ingelheim, Sanofi-Aventis, and Pfizer Inc. The other authors report no conflicts.

References


Within-Day and Weekly Variations of Thrombolysis in Acute Ischemic Stroke: Results From Safe Implementation of Treatments in Stroke-International Stroke Thrombolysis Register

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Stroke. 2014;45:176-184; originally published online November 21, 2013;
doi: 10.1161/STROKEAHA.113.002133

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急性缺血性卒中日间和周间溶栓差异
来自国际卒中溶栓登记治疗安全性结果

Within-Day and Weekly Variations of Thrombolysis in Acute Ischemic Stroke
Results From Safe Implementation of Treatments in Stroke-International Stroke Thrombolysis Register

Svetlana Lorenzano; Niaz Ahmed, et al; for the SITS Investigators

背景与目的：关于溶栓治疗的时间差异及其对溶栓结果影响的研究尚无一致结论。在该大型队列研究中，我们评估了溶栓治疗是否具有与缺血性卒中发病昼夜和周模式相对应的日间及周内差异，以及这种节律变化是否影响临床结局。

方法：本研究回顾性分析了接受静脉阿替普酶治疗并在国际卒中安全溶栓登记处（SITS-ISTR）登记的急性缺血性卒中患者，患者分为日间（08:00-19:59）或夜间（20:00-7:59）接受治疗，以及工作日和周末接受治疗。在每个亚组中，分析了溶栓治疗的频率，时间间隔以及临床结局（3个月良好功能结局 [mRS 评分 0-2]，死亡率，症状性颅内出血）。

结果：研究共纳入 21513 例患者。鉴于每小时（0.4 例）和每个工作日（9.8 例）平均治疗的患者数，如果不存在时间差异，则在日间和日间接受溶栓治疗的患者显著增多（P < 0.0001）。夜间和周末接受溶栓治疗的患者入院至给药（door-to-needle）以及发病至接受治疗（onset-to-treatment）的中位时间更长（P < 0.01）。校正混杂因素后发现，日间治疗为患者良好功能结局的独立预测因子（OR 1.12, 95% CI 1.04-1.21, P=0.004），而工作日接受溶栓治疗的患者死亡风险更高（OR 1.15, 95% CI 1.04-1.28, P=0.008）。

结论：溶栓治疗频率与卒中发病具有相似的昼夜模式，但是否存在与卒中发病相对应的周模式尚不清楚。溶栓治疗时间是临床结局的一个独立预测因素。

关键词：昼夜节律，结局评估，卒中，溶栓治疗，组织型纤溶酶原激活物（tPA）
随访时的功能独立性。

根据 SITS-MOST 标准，SICH 是指治疗后 22-36 小时影像学上出现局部或远隔部位的 2 型脑实质出血并伴神经功能恶化，即 NIHSS 评分较基线或基线与 24 小时后最低 NIHSS 评分值增加≥ 4 分，或死亡。美国国家神经疾病及卒中研究（NINDS）定义的 SICH 是指治疗后 22-36 小时内有影像学证据并伴神经功能恶化，NIHSS 评分较基线或基线至 24 小时最低 NIHSS 评分值增加≥ 4 分，或死亡。

ECASS II 定义的 SICH 是指治疗后 22-36 小时内有影像学证据并伴神经功能恶化（NIHSS 评分较基线或基线至 7 天最低 NIHSS 评分值增加≥ 4 分，或死亡）。

出血率是根据治疗后 22-36 小时头颅 CT 或 MRI 结果，以及治疗后其它任何扫描计算的。

对于死亡终点，是通过联系患者家属或照料者，评估 3 个月内的生存情况。

功能独立性定义为 3 个月时的 mRS 评分 0~2（良好功能结局）。

另一结局评估指标为无或极轻度残疾（即 3 个月 mRS 0-1 分）。

统计分析
为避免 SITS-ISTR 多机构多国家工作组织方式和工作时间定义的差异，我们根据 t-PA 治疗时间将病例分为配对的亚组，2 个精确的 12 小时间隔亚组为日间组（08:00–19:59）与夜间组（20:00–07:59），2 个精确的周亚组为从周日午夜至周五午夜的工作日组与从周五午夜至周日午夜的周末组（例如一些南欧国家周六，尤其是上午，通常属于工作日而大部分北欧国家属于周末）。本研究计算每个亚组溶栓治疗频数，并记录了 6 小时时间间隔（00:00-5:59, 06:00-11:59, 12:00-17:59, 18:00–23:59）溶栓治疗的分布情况，同时对各配对亚组进行比较以观察亚组间溶栓频次是否存在显著差异。

拟合优度卡方分析过程：假设脑卒中发病时间平均分布于一天每小时和一周每日，即脑卒中的发病与时间变量无关。这样我们把每组溶栓频数也平均分布在每小时和每天作为零假设（H0），计算出各组期望溶栓频数，然后和每组实际溶栓频数进行比较，计算出统计量卡方值和概率 p 值，统计推断出溶栓病例数是否与时间变量相关。

然后我们仅对登记病例数大于 900 的国家（比如每年 150 个）进行同样的分析。

连续变量以中位数（±四分位数间距）或平均数（±标准差）描述，分类变量以频数（百分数）描述。剔除丢失和未知病例后，每个组的病例数（即溶栓频数）除以总病例数为百分比率。单因素 Mann-Whitney U 检验和卡方检验用于比较配对亚组间的人口统计学资料、临床资料和结局评估。

为评价一天中不同时间或一周中不同日给药是否为临床结局的一个独立影响因素，用多因素 logistic 回归模型分析每一结局指标，包括日间 / 夜间给药和工作日 / 周末给药，以及单因素分析中有统计学意义的变量（P ≤ 0.25）和年龄、性别、基线期 NIHSS 评分和治疗时间间隔等可能影响结局的变量（不论有无单因素分析时的统计学差异）。P < 0.05 为存在统计学差异。所有的统计分析用 Statistica 7.0 版本完成。

结果
在 SITS-ISTR 研究的 6 年期间共纳入静脉注射 t-PA 患者 21513 例，其中 15462 例（71.9%）治疗时间为日间 8:00-19:59，6051 例（28.1%）治疗时间为夜间 20:00-07:59，见表 1。基于 6 小时时间窗，分别有 5039 (23.4%) 、8489 (39.5%) 、6124 (28.5%) 和 1840 (8.6%) 例患者于 6:00-11:59、12:00-17:59、18:00-23:59 和 00:00-5:59 接受治疗。

总体而言，有 15953 例(74.2%)患者于工作日接受静脉溶栓治疗，5560 例(25.8%)患者于双休日接受治疗（见表 1）。就一周而言，周三有 3291 例(15.3%)患者被治疗，之后这一数量逐渐下降，至周末仅有 2750 例(12.8%)（溶栓患者数量最少的一天与周三相比存在显著差异，OR 1.23, 95% CI 1.17-1.30, P < 0.0001）。我们发现随后周一溶栓数量增加，但与周三相比无显著差异(OR 0.97, 95% CI 0.92-1.02, P = 0.20)。

假设日间每小时和工作日每天卒中的发生是平均分布的，不存在日与日或周与周之间的差异，平均每小时被治疗的患者就有 0.4 例，每个工作日有 9.8 例。结果提示日间接受溶栓治疗的患者显著多于夜间（分别为 0.6 和 0.2, OR 2.56, 95% CI 2.46-2.66, P<0.0001），工作日的显著多于周末（分别为 10.2 和 8.9, OR 1.15, 95% CI 1.01-1.20, P<0.0001）。

就研究期间在登记处纳入患者超过 900 例的国家而言，每个国家日间治疗的患者数量显著超过预计数目(P < 0.0001, 图 1A)，而除英国患者数量在工作日显著高于周末外，其它国家患者数量在工作日和周末间无显著差异(OR 1.77, 95% CI 1.52-2.06, P < 0.0001，图 1B)。

表 2 和 3 显示了所有亚组的人口统计学资料，基线特征和结局评估。患者大部分基线特征一致，尤其是基线卒中严重程度，除外一些明显的例外。日间就诊的患者多为老年 （P < 0.001）、女性患者（P = 0.026），卒中发生前独立性较差(P = 0.001)，多源于不伴明显颈动脉狭窄的大血管病 (P = 0.014)，而非类卒中 (P = 0.020)。夜间就诊的患者往往有房颤 (P = 0.008)，为目前吸烟者 (P < 0.0001)，较日间就
诊者基线血糖水平高 1mg/dl (P = 0.003)、心脏舒张压高 1mmHg (P = 0.026)。日间和夜间就诊患者的 HMCAS 出现率无显著差异，即使我们进一步将其分为 6 小时亚组 (00:00–05:59: 18.8%, 06:00–11:59: 18.7%, 12:00–17:59: 18.9%, 18:00–23:59: 18.2%; P=0.79)，各亚组间 HMCAS 出现率亦无显著差异。影像随访基线存在 HMCAS 的患者，以动脉征逆转作为血管再通的标志，在日间和夜间就诊患者中出现的比例一致 (分别为 53.9% 和 52.1%; P = 0.34)，在 6 小时段各亚组间亦一致 (00:00–5:59: 52.7%, 06:00–11:59: 54.4%, 12:00–17:59: 54.3%, 18:00–23:59: 52.7%; P = 0.59)。尽管工作日治疗的患者有更高比例的充血性心衰 (P=0.014) 和基线影像的早期缺血征 (P=0.002)，但其基线 (P=0.84) 和溶栓后 (P=0.20) 都发现 HMCAS 征的存在比例都类似于周末治疗组的患者。夜间就诊患者发病至到院的平均时间间隔较日间就诊者长 1 分钟 (P = 0.002)，到院至给药及发病至治疗的平均时间间隔在夜间 (分别 P < 0.001 和 P < 0.001) 和周末 (分别为 P=0.001 和 P < 0.001) 的无显著性差异。

图 2 以 mRS 对患者亚组进行结局评估，图 2A 和图 2B 分别表示患者日间时间分布和周内日期分布，数据从 Logistic 回归分析进一步确定与结局有统计学意义的单因素变量（见表 3）。结果发现，白天治疗是功能转归良好、无或极轻度残疾以及出现低风险症状性脑出血的独立预测因子 (分别 OR 1.12, 95% CI 1.04–1.21, P = 0.004; OR 1.09, 95% CI 1.01–1.17, P = 0.03; OR 0.84, 95% CI 0.75–0.95, P = 0.005)，而工作日治疗与高死亡率相关 (OR 1.15, 95% CI 1.04–1.28, P = 0.008)。

讨论

该研究显示溶栓治疗的时间差异似乎与卒中发生的生理节律相关，具有类似的昼夜模式 [1–6]。我们发现溶栓治疗比例最高的时间段为正午至 17:59，这可能与卒中发生至到院间的时间耽搁以及午夜至次日 5:59 治疗比例低相关。假设不存在昼夜差异，与预期值相比，日间患者治疗率增加 50%，而夜间下降 50%。在我们的研究中，溶栓大多发生在工作日，尤其是周三和周一。与预期值相比，工作日的总治疗量上升了 4.1%，而周末下降了 9.2%。而就溶栓登记中纳入超过 900 例溶栓患者的国家而言，除英国工作日治疗比例高于周末外，其它国家在工作日和周末间治疗率无差异，英国的数据与以往的一项研究结果一致 [33]。这些数据符合每周卒中发生的规律，即：周一或周三达到高峰，周末最少 [7, 10]。与我们观察相反的是，一些研究发现大多数患者接受溶栓治疗是在周末 [16, 20, 21–27]，尤其是综合性或初级卒中中心 (与非卒中中心相比较) [29]。一些学者报道卒中更易于周末发生 [3, 6, 8]。因此，目前仍不明确溶栓治疗率与卒中发生的周变化规律还是卒中医疗组织相关。

患者各亚组间临床特征一致，与既往研究相似 [22, 28]，尤其是基
表2. 两组患者与不同治疗时间亚组（白天 vs 夜间；工作日 vs 周末）患者的人口学及基线临床与影像学特征

<table>
<thead>
<tr>
<th></th>
<th>白天</th>
<th>夜间</th>
<th>工作日</th>
<th>周末</th>
</tr>
</thead>
<tbody>
<tr>
<td>病例总数</td>
<td>21513</td>
<td>15462</td>
<td>6051</td>
<td>5560</td>
</tr>
<tr>
<td>年龄，年，中位数 (IQR)</td>
<td>68 (60-76)</td>
<td>70 (60-77)</td>
<td>68 (58-75)</td>
<td>68 (59-76)</td>
</tr>
<tr>
<td>性别（% 男）</td>
<td>0.026</td>
<td>0.014</td>
<td>0.008</td>
<td>0.007</td>
</tr>
<tr>
<td>卒中前独立性（mRS 0-1）（%）</td>
<td>0.17</td>
<td>0.45</td>
<td>0.24</td>
<td>0.96</td>
</tr>
<tr>
<td>卒中前血栓（%）</td>
<td>0.001</td>
<td>0.20</td>
<td>0.08</td>
<td>0.72</td>
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<tr>
<td>患者吸烟（%）</td>
<td>0.00001</td>
<td>0.08</td>
<td>0.038</td>
<td>0.15</td>
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<tr>
<td>高血压（%）</td>
<td>0.20</td>
<td>0.05</td>
<td>0.15</td>
<td>0.43</td>
</tr>
<tr>
<td>高脂血症（%）</td>
<td>0.0007</td>
<td>0.0002</td>
<td>0.0004</td>
<td>0.0007</td>
</tr>
<tr>
<td>高血糖（%）</td>
<td>0.0007</td>
<td>0.0002</td>
<td>0.0004</td>
<td>0.0007</td>
</tr>
<tr>
<td>卒中史（%）</td>
<td>0.0001</td>
<td>0.08</td>
<td>0.038</td>
<td>0.15</td>
</tr>
<tr>
<td>体重，kg，中位数 (IQR)</td>
<td>75 (67-85)</td>
<td>76 (67-85)</td>
<td>75 (67-85)</td>
<td>75 (67-85)</td>
</tr>
<tr>
<td>BMI，m²/㎡，中位数 (IQR)</td>
<td>117 (102-142)</td>
<td>117 (102-142)</td>
<td>117 (103-143)</td>
<td>117 (102-142)</td>
</tr>
<tr>
<td>SBP，mmHg，中位数 (IQR)</td>
<td>150 (137-168)</td>
<td>151 (137-167)</td>
<td>150 (138-158)</td>
<td>151 (138-168)</td>
</tr>
<tr>
<td>DBP，mmHg，中位数 (IQR)</td>
<td>82 (74-90)</td>
<td>82 (74-90)</td>
<td>82 (74-90)</td>
<td>82 (74-90)</td>
</tr>
<tr>
<td>NHSS</td>
<td>0.97</td>
<td>0.92</td>
<td>0.97</td>
<td>0.92</td>
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<tr>
<td>平均分 (± SD)</td>
<td>12.8 ± 6.2</td>
<td>12.8 ± 6.2</td>
<td>12.8 ± 6.1</td>
<td>12.8 ± 6.1</td>
</tr>
<tr>
<td>中位数 (IQR)</td>
<td>12±8-17</td>
<td>12±8-17</td>
<td>12±8-17</td>
<td>12±8-17</td>
</tr>
<tr>
<td>SSS</td>
<td>0.34</td>
<td>0.0001</td>
<td>0.0004</td>
<td>0.0001</td>
</tr>
<tr>
<td>脑梗死的病因（%）</td>
<td>0.34</td>
<td>0.0001</td>
<td>0.0004</td>
<td>0.0001</td>
</tr>
<tr>
<td>临床基线特征（%）</td>
<td>0.34</td>
<td>0.0001</td>
<td>0.0004</td>
<td>0.0001</td>
</tr>
<tr>
<td>进展性CMAH（%）</td>
<td>0.34</td>
<td>0.0001</td>
<td>0.0004</td>
<td>0.0001</td>
</tr>
</tbody>
</table>
线卒中的严重程度。但也有些例外，主要为统计学上的显著差异而非临床上的，可能与样本量低或存在小偏差有关。说明不同时段的治疗对卒中患者溶栓选择缺乏实质性的影响。我们发现亚组间到院-影像学检查时间无统计学差异，提示至少在诊断流程中不存在差异，这与最近的相关报道结果类似[22-23]。夜间和周末的卒中-给药时间及发病-治疗时间更长，一般延长数分钟，提示此时间段中患者管理的某一程序存在一定延迟倾向。

不考虑统计学差异，配对亚组间的结局评估差异较小，但白天溶栓治疗是功能转归良好，无或极轻度残疾以及出现低风险症状性脑出血的一个独立预测因子。夜间溶栓的患者临床结局更差，可能与卒中发生至治疗时间间隔更长及房颤发生率更高相关，而房颤作为重要的心源性疾病可能影响功能恢复[24]。尽管我们无证据，但可推测夜间溶栓时较长的时间间隔与护理质量差异相关，这可能使得判断患者是否适合溶栓更加困难。除了下班效应，溶栓疗效的昼夜节律可能是造成不同结局的原因。事实上，t-PA 似乎日间更有效，而在清晨存在溶栓治疗抵抗，这与人纤维蛋白原酶抑制因子-1水平增加相关[25-27]，这也表明了 t-PA 溶栓治疗 2 小时后的早期再通率在日间和夜间有显著差异[24]。SITS 队列研究无法获得早期再通的数据，但我们的研究发现 HMCAS 高密度逆转征作为血管再通的标志[38]在日间和夜间溶栓后 22-36 小时出现率一致。其它潜在的生理性凝血机制，如血小板活性变化及血栓构成的昼夜区别，可能与溶栓疗效的时间差异有关[39，40]。

工作日溶栓的患者具有更高的死亡风险。与我们研究相似，Bodenant 等[23]发现相比非工作时间，工作日溶栓患者的 7 天和 3 个月死亡率均明显增加，提示工作时间专业人员更多，如非卒中神经科医生，可能导致更多的方案违背，而非卒中神经科医生可能会更严格按照决策的溶栓方案操作，最终导致死亡率轻度增高。可惜我们无法证实这个假设，因为我们无法从卒中中心获得数据。其它因素也会影响我们的结果，比如不愿周末就诊或喜欢周末外出活动，都可能导致治疗中心周末与工作日人数的差异。但它同样不能从 SITS-ISTR 数据库证实，因此，这一结论需进一步前瞻性研究予以评价。

除去溶栓治疗部分，我们的研究结果与卒中患者相关的其它研究结果存在部分矛盾，这些报道称周末以及周一接受溶栓通常疗效不佳，死亡率[7，14-16]。另一些研究指出，综合性卒中治疗中心有 24 小时 /7 天在岗的专业人员及先进的影像设备，它们不存在下班效应[19，20]。一些学者认为，周末效应可能是人为的，因为当我们考虑卒中发生时间，而非到院时间，以消除延迟入院的非致死性患者被潜在排除入组的偏倚之后，周末溶栓的高死亡率就不显著[41]。最后，包括专门针对溶栓患者在内的其它研究没有观察到夜间或周末效应[25-29]。

这些研究都是在单中心或一个国家的少许几个中心开展的，可能存在中心效应的偏差，它们的结论可能不具普遍性。

本研究存在一些局限性。SITS 研究仅登记的 t-PA 治疗的患者，因此很难确定我们在卒中患者中观察到的治疗时间变化规律是否存在于一个相对一致的人群中。由于在不同时间段患病的急性卒中患者缺乏一个共同的标准，因此，夜间或清晨发病，以及清晨服药时缺乏目击者或缺乏发病证据以致到院时间过迟的这部分患者，我们不能确定他们是否被排除在外。我们没有卒中中心结构及人员的详细信息，因此我们不能排除溶栓治疗的时间差异可能源于急性卒中医疗机构的不一致性。2007 年公布的针对整个欧洲医院的大型随机调查显示，只有极少数几家中心提供最佳的医疗管理并达到欧洲卒中联盟的标准[42]。事实上，据记载患者超过 900 例的国家而言，溶栓治疗的周末效应基
图 2. 溶栓治疗 3 个月后 mRS（改良的 Rankin 量表）评分分布图（A：白天 vs 夜间；B：工作日 vs 周末）

本消失，参与研究的国家及卒中中心对工作日与非工作日或工作时间与非工作时间定义（包括地方宗教性节日或国家性节日）的差异可能会对结果产生影响。但我们采用的广义，至少能部分减少本研究的局限性。

本研究另一重要局限在于其为一项对前瞻性研究的回顾性分析，但由于登记的均为严格处于时间窗内的溶栓治疗，我们认为不存在记录卒中发病时间及治疗时间的偏差。且无理由认为各匹配组组间在记录死亡率和结局误差上有显著性差异。

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综上所述，我们发现进行溶栓治疗的患者数与卒中发病具有相同的昼夜模式，但尚不清楚是否存在与卒中发病相对应的周模式。本次大型多中心队列研究发现溶栓治疗时间为临床结局的一个独立预测因素。我们的结果提示卒中中心应认真检查当地的溶栓流程并能提供初步数据，如果在未来前瞻性研究中得到证实，就可明确阐明临床结局与溶栓治疗患者数的差异是自然变化还是由于资源分配不合理。

参考文献