Impact of Hospital Admission During Nonworking Hours on Patient Outcomes After Thrombolysis for Stroke

Karl Georg Haeusler, MD; Lea M. Gerischer; Bijan Vatankhah, MD; Heinrich J. Audebert, MD; Christian H. Nolte, MD

Background and Purpose—Whether the time of hospital admission is relevant for short-term outcome after stroke is under debate and may depend on care facilities.

Methods—We retrospectively analyzed medical records from patients who received thrombolytic therapy within 4.5 hours of stroke onset in a stroke unit of the Charité–University Hospital Berlin (Charité; n=291) or within the stroke telemedicine (TEMPiS) network, comprising 12 community hospitals with telestroke units in Bavaria (n=616).

Results—Thrombolytic therapy was administered during nonworking hours in 59.5% (Charité) and 55.0% (TEMPiS) of patients. A trend toward a lower rate of symptomatic intracranial hemorrhage (3.4% versus 9.2%; P=0.053), clinical worsening (11.9% versus 19.7%; P=0.079), and 7-day mortality (3.4% versus 8.7%; P=0.073) after admission during working hours was seen at Charité. However, multivariable analysis did not show a significant impact of the time of admission on clinical worsening, symptomatic intracranial hemorrhage, or 7-day mortality in both cohorts. Thrombolysis based on brain computed tomography instead of magnetic resonance imaging (odds ratio=4.98, 95% CI, 1.09 to 22.7) and more severe National Institutes of Health Stroke Scale score on admission (odds ratio=1.15 per point; 95% CI, 1.07 to 1.24) were associated with 7-day mortality at Charité. National Institutes of Health Stroke Scale score on admission (odds ratio=1.13 per point; 95% CI, 1.06 to 1.19) and older age (odds ratio=1.05 per year; 95% CI, 1.004 to 1.09) were correlated with 7-day mortality in TEMPiS. National Institutes of Health Stroke Scale on admission was the only independent predictor of symptomatic intracranial hemorrhage or clinical worsening in both cohorts.

Conclusions—The majority of stroke patients received thrombolysis during nonworking hours. The time of hospital admission did not significantly influence the short-term outcome after thrombolysis. (Stroke. 2011;42:2521-2525.)

Key Words: thrombolysis ■ ischemic stroke ■ working hours ■ nonworking hours ■ 7-day mortality ■ clinical worsening ■ level of medical care

The use of alteplase for thrombolysis within the first 4.5 hours after stroke onset is the only approved pharmaceutical treatment for acute ischemic stroke, significantly improving clinical outcomes. Owing to the risk of life-threatening complications, the initiation of thrombolysis is restricted to experienced stroke physicians. Controversial results have been reported in previous studies as to whether the time of hospital admission, with different access to stroke expertise, influences the short-term outcome of stroke. A number of studies have shown increased mortality in patients admitted during weekends, as similarly described for various diseases, including myocardial infarction or pulmonary embolism. This observation remained significant when death rate was adjusted for age, sex and stroke severity, as well as hospital facilities or the involvement of stroke specialists. Other studies did not show an independent correlation of weekend admission with in-hospital mortality after stroke in the total stroke population or in those stroke patients treated with thrombolysis. These incongruent results may be explained at least in part by the different settings of stroke care, for example, hospitals with attendance of stroke specialists only during working hours or stroke units with 24/7 provision of stroke expertise. With the assumption of a lower level of stroke care during nonworking hours, a comparison between working and nonworking hours might be more suitable than between weekends and working days. With this approach, increased mortality in stroke patients admitted during nonworking hours was shown in a hospital-based stroke registry in the United States but not in Germany. Times with limited access to stroke expertise may be particularly hazardous for patients treated with intravenous thrombolysis, but only 1 article has recently addressed this issue. Surprisingly, the data from a French university hospital stroke unit discovered increased 7-day mortality (odds ratio [OR]=3.6; 95% CI, 1.2 to 10.4) in patients receiving thrombolysis during working hours, without providing a sufficient explanation.
To assess the impact of thrombolysis during working versus nonworking hours on 7-day mortality, the occurrence of symptomatic intracranial bleeding (sICH), and clinical worsening, we used data from stroke patients treated either at the University Hospital Charité Berlin (Charité) or within a German telestroke project, the Telemedical Project of Integrated Stroke Care (TEMPiS).

Methods

Study Design and Study Population
The Charité cohort consisted of patients treated in the neurology stroke unit at the Campus Benjamin Franklin, Charité–University Medicine Berlin. The data were retrieved from a prospectively operating stroke register that was approved by the local ethics committee (EA4/019/08). Between January 2008 and June 2010, 313 patients received intravenous thrombolysis according to National Institute of Neurological Disorders and Stroke or ECASS III criteria (48 [16.5%] of all patients received thrombolysis after 3 but within 4.5 hours after stroke onset). Ten registered patients had to be excluded because of incomplete data. The information assessed from medical records is depicted in Tables 1 and 2.

<p>| Table 1. Characteristics of Stroke Patients Receiving Thrombolysis at the Charité |</p>
<table>
<thead>
<tr>
<th>期间</th>
<th>基本特征和过去的医疗历史</th>
<th>期间</th>
<th>基本特征和过去的医疗历史</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>性别，n (%)</td>
<td>62 (52.5)</td>
<td>87 (50.3)</td>
<td>0.71</td>
<td></td>
</tr>
<tr>
<td>年龄，均数（SD）[范围]，y</td>
<td>73.5 (12.0) [36–98]</td>
<td>73.9 (13.5) [32–103]</td>
<td>0.38</td>
<td></td>
</tr>
<tr>
<td>年龄 ≥80 y，n (%)</td>
<td>39 (33.1)</td>
<td>62 (35.8)</td>
<td>0.62</td>
<td></td>
</tr>
<tr>
<td>高血压，n (%)</td>
<td>100 (84.7)</td>
<td>147 (85.0)</td>
<td>0.96</td>
<td></td>
</tr>
<tr>
<td>糖尿病，n (%)</td>
<td>27 (22.9)</td>
<td>40 (23.1)</td>
<td>0.96</td>
<td></td>
</tr>
<tr>
<td>高胆固醇，n (%)</td>
<td>49 (41.5)</td>
<td>70 (40.5)</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>房颤，n (%)</td>
<td>43 (36.4)</td>
<td>73 (42.2)</td>
<td>0.31</td>
<td></td>
</tr>
<tr>
<td>冠心病，n (%)</td>
<td>14 (11.9)</td>
<td>38 (22.0)</td>
<td>0.027</td>
<td></td>
</tr>
<tr>
<td>可逆性/非TNIA，n (%)</td>
<td>33 (28.0)</td>
<td>50 (28.9)</td>
<td>0.86</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>特征</th>
<th>期间</th>
<th>基本特征和过去的医疗历史</th>
<th>期间</th>
<th>基本特征和过去的医疗历史</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIHSS评分，均数（SD）[范围]</td>
<td>10.6 (6.1) [1–25]</td>
<td>12.0 (7.4) [2–36]</td>
<td>0.24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS在入院时，均数（SD）</td>
<td>3.8 (1.2)</td>
<td>3.9 (1.2)</td>
<td>0.32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>血糖，均数（SD），mg/dL</td>
<td>130 (37)</td>
<td>135 (52)</td>
<td>0.59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP, 均数（SD），mg/dL</td>
<td>1.0 (2.3)</td>
<td>1.2 (2.9)</td>
<td>0.65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>起病-穿刺时间，均数（SD），min</td>
<td>135 (46)</td>
<td>138 (50)</td>
<td>0.71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI-基线的溶栓，n (%)</td>
<td>94 (79.7)</td>
<td>31 (17.9)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>结果</th>
<th>期间</th>
<th>基本特征和过去的医疗历史</th>
<th>期间</th>
<th>基本特征和过去的医疗历史</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>sICH，n (%)</td>
<td>4 (3.4)</td>
<td>16 (9.2)</td>
<td>0.053</td>
<td></td>
<td></td>
</tr>
<tr>
<td>临床恶化，n (%)</td>
<td>14 (11.9)</td>
<td>34 (19.7)</td>
<td>0.079</td>
<td></td>
<td></td>
</tr>
<tr>
<td>死亡，在7 d，n (%)</td>
<td>4 (3.4)</td>
<td>15 (8.7)</td>
<td>0.073</td>
<td></td>
<td></td>
</tr>
<tr>
<td>医院停留，均数（SD），d</td>
<td>8.3 (4.4)</td>
<td>7.9 (4.1)</td>
<td>0.70</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TIA indicates transient ischemic attack; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale score; CRP, C-reactive protein; MRI, magnetic resonance imaging; sICH, symptomatic intracranial hemorrhage; SD, standard deviation.

To assess the impact of thrombolysis during working versus nonworking hours on 7-day mortality, the occurrence of symptomatic intracranial bleeding (sICH), and clinical worsening, we used data from stroke patients treated either at the University Hospital Charité Berlin (Charité) or within a German telestroke project, the Telemedical Project of Integrated Stroke Care (TEMPiS).

Methods

Study Design and Study Population
The Charité cohort consisted of patients treated in the neurology stroke unit at the Campus Benjamin Franklin, Charité–University Medicine Berlin. The data were retrieved from a prospectively operating stroke register that was approved by the local ethics committee (EA4/019/08). Between January 2008 and June 2010, 313 patients received intravenous thrombolysis according to National Institute of Neurological Disorders and Stroke or ECASS III criteria (48 [16.5%] of all patients received thrombolysis after 3 but within 4.5 hours after stroke onset). Ten registered patients had to be excluded because of incomplete data. The information assessed from medical records is depicted in Tables 1 and 2.

Outcomes
Death during the hospital stay or within 7 days after admission was chosen as the outcome parameter because the length of hospital stay varied between both cohorts to a certain extend. According National Institute of Neurological Disorders and Stroke criteria, clinical worsening was defined as any neurologic deterioration after thrombolysis. Moreover, any intracranial hemorrhage was regarded as symptomatic if there was clinical worsening before detection of the hemorrhage.

Statistical Analysis
In both cohorts, “working hour” presentation was defined as presentation to the Emergency Department on a regular weekday, and duration from admission to alteplase initiation mainly affected the
Disparities During Working and Nonworking Hours

During patient enrolment at Charité, 15.4% of all stroke patients admitted during working hours and 14.4% of all stroke patients admitted during nonworking hours received thrombolysis (\(P=0.443\)). Of all stroke patients considered eligible for thrombolysis (debilitating neurologic deficit and a limited prehospital delay), 69.4% received thrombolysis during working-hours and 68.6%, during nonworking hours (\(P=0.839\)).

The majority of patients reported on herein (Charité 59.5%, TEMPiS 55.0%) received thrombolysis during nonworking hours. With the exception of coronary artery disease (within the Charité cohort), the distribution of age, sex, and cardiovascular risk factors did not differ with regard to admission during working or nonworking hours for both cohorts (Tables 1 and 2). The majority (79.7%) of decisions for thrombolysis during working hours at Charité was based on magnetic resonance imaging (MRI) findings, whereas thrombolysis within TEMPiS was based almost exclusively on CT. However, the delay from stroke onset to hospital admission, the delay from stroke onset to start of thrombolysis, and blood glucose levels were similar during working and nonworking hours within both cohorts and between the 2 cohorts (Tables 1 and 2). The mean age of TEMPiS patients was significantly lower compared with Charité patients (70.1 ± 11.9 versus 73.8 ± 12.9 years; \(P<0.001\)). Moreover, TEMPiS patients were more often female (51.4% versus 42.5%; \(P=0.013\)).

Seven-Day Mortality and Predictors of Death

Within 7 days after thrombolysis, 19 (6.5%) Charité patients and 39 (6.3%) TEMPiS patients had died. Univariate analysis indicated an insignificant trend (\(P=0.073\)) toward lower 7-day mortality at Charité during working hours (Table 1) but not within TEMPiS (Table 2). Multivariable analysis identified CT- versus MRI-based thrombolysis (OR=4.98; 95% CI, 1.09 to 22.7) and more severe NIHSS score on admission (OR=1.15 per point; 95% CI, 1.07 to 1.24) as significantly associated with 7-day mortality, whereas time of hospital admission (OR=0.89; 95% CI, 0.22 to 3.53 for working versus nonworking hours) was not (Table 3). Moreover, multivariable analysis of the TEMPiS data revealed no significant impact of admission time (OR=1.60; 95% CI, 0.73 to 3.47 for working versus nonworking hours) on 7-day mortality, whereas NIHSS score on admission (OR=1.13 per point; 95% CI, 1.06 to 1.19) as well as older age (OR=1.05 per year; 95% CI, 1.004 to 1.09) predicted 7-day mortality. Coronary artery disease had no effect on 7-day mortality. In
addition, sICH predicted 7-day mortality with highest significance in both cohorts. When forced into the model, there was an OR of 56.4 (95% CI, 14.1 to 224) within the Charité cohort and an OR of 39.4 (95% CI, 15.2 to 103) within TEMPiS.

**sICH or Clinical Worsening After Thrombolysis**  
Clinical worsening after thrombolysis was detected in 48 (16.5%) Charité patients and 92 (14.9%) TEMPiS patients. In multivariable analysis, higher NIHSS score on admission was the only independent factor for clinical worsening and sICH for both cohorts, whereas admission during working hours, age, sex, coronary artery disease, or MRI-based thrombolysis was not (Table 3).

**Discussion**  
Analyzing patient records from stroke patients receiving thrombolysis mainly during nonworking hours at the University Hospital Charité or within the TEMPiS project, we observed sICH rates within the range of the Safe Implementation of Thrombolysis in Stroke-Monitoring STudy registry. In accordance with previous findings, our multivariable analyses indicated that stroke severity on admission independently influenced 7-day mortality, sICH, and clinical worsening after thrombolysis within the Charité as well as the TEMPiS cohort (Table 3). Older age was independently associated with higher 7-day mortality within TEMPiS only, which was probably due to the significant difference in age distribution compared with the Charité cohort.

However, time of hospital admission for thrombolysis was not an independent predictor of sICH, clinical worsening, or 7-day mortality in both cohorts analyzed. Thrombolysis in the TEMPiS cohort was based on CT imaging, resulting in similar rates of sICH, clinical worsening, or 7-day mortality after thrombolysis during working hours and nonworking hours (Table 2). The significantly higher rate of MRI-based thrombolysis during working hours at Charité might have caused a more appropriate patient selection, resulting in lower 7-day mortality (Table 3). A recent MRI study further indicated that the use of MRI-based thrombolysis may be safer compared with CT-based thrombolysis, but further studies are needed to support these results.

So far, only Bodenant et al focused on stroke patients receiving thrombolysis during working or nonworking hours like we did. Compared with the Charité cohort, the cohort reported by Bodenant et al received thrombolysis almost exclusively according to CT data, as done similarly within the TEMPiS project. Nevertheless, even within the TEMPiS cohort, we did not observe a significant impact of hospital admission time (Table 3), as described by Bodenant et al in a smaller cohort. As demonstrated for the Charité data, there was no selection bias due to admission time, as the proportions of patients receiving thrombolysis did not differ between working and nonworking hours.

One strength of our study is the appropriate differentiation of working and nonworking hours. Moreover, the comparable delays from stroke onset to the start of thrombolysis within working and nonworking hours on the one hand and within both cohorts of patients on the other hand strengthen our results. However, there are some limitations of our study, mitigating the validity of the results. First, stroke patients treated at Charité were significantly older and more often female compared with TEMPiS patients. Second, according to the study design, we cannot rule out the possibility that in-hospital deaths were independent of thrombolysis. Third, we were unable to clarify the impact of chronobiologic factors on mortality after stroke, as reported for patients after myocardial infarction. Fourth, because the level of medical care available may be relevant for outcome after thrombolysis, these results can only be applied to patients treated in stroke units. Fifth, the number of stroke patients with sICH was rather low. Therefore, we cannot exclude the possibility that the study was underpowered to detect modest effects on sICH, thus limiting the significance of the results. Sixth, 22 (7.6%) Charité patients receiving thrombolysis were excluded from this analysis because of incomplete data. However, a sensitivity analysis including the Charité patients indicated the validity of our results. Seventh, we do not exactly know the thrombolysis rates during working or nonworking hours in hospitals within the TEMPiS network. Therefore, we were unable to exclude a selection bias regarding the proportion of patients receiving thrombolysis during working or nonworking hours in this part of our data.

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**Table 3. Multivariable Analysis for 7-Day Mortality, Symptomatic Intracranial Hemorrhage (sICH), or Any Clinical Worsening After Thrombolysis for Charité (n=291) and TEMPiS (n=616) Patients**

<table>
<thead>
<tr>
<th></th>
<th>Charité</th>
<th>TEMPIS</th>
<th>Charité</th>
<th>TEMPIS</th>
<th>Charité</th>
<th>TEMPIS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7 Days, OR (95% CI)</td>
<td></td>
<td>sICH, OR (95% CI)</td>
<td></td>
<td>Any Clinical Worsening, OR (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>0.62 (0.22–1.72)</td>
<td>1.16 (0.53–2.56)</td>
<td>0.55 (0.21–1.43)</td>
<td>0.86 (0.41–1.82)</td>
<td>1.31 (0.65–2.65)</td>
<td>0.83 (0.52–1.32)</td>
</tr>
<tr>
<td>Age, per y</td>
<td>1.01 (0.97–1.06)</td>
<td>1.05 (1.004–1.09)</td>
<td>1.00 (0.96–1.04)</td>
<td>1.02 (0.99–1.06)</td>
<td>1.01 (0.98–1.04)</td>
<td>1.02 (0.99–1.04)</td>
</tr>
<tr>
<td>NIHSS score, per point</td>
<td>1.15 (1.07–1.12)</td>
<td>1.13 (1.06–1.19)</td>
<td>1.07 (1.01–1.14)</td>
<td>1.07 (1.01–1.13)</td>
<td>1.10 (1.05–1.14)</td>
<td>1.05 (1.02–1.09)</td>
</tr>
<tr>
<td>Admission during working h</td>
<td>0.89 (0.22–3.53)</td>
<td>1.60 (0.73–3.47)</td>
<td>0.39 (0.12–1.12)</td>
<td>1.01 (0.48–2.08)</td>
<td>0.63 (0.31–1.25)</td>
<td>1.02 (0.65–1.60)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1.32 (0.37–4.76)</td>
<td>*</td>
<td>0.38 (0.08–1.74)</td>
<td>*</td>
<td>0.76 (0.31–1.84)</td>
<td>*</td>
</tr>
<tr>
<td>MRI-based thrombolysis</td>
<td>0.20 (0.04–0.92)</td>
<td>*</td>
<td>0.82 (0.22–2.98)</td>
<td>*</td>
<td>0.95 (0.40–2.22)</td>
<td>*</td>
</tr>
</tbody>
</table>

OR indicates odds ratio; NIHSS, National Institutes of Health Stroke Scale; MRI, magnetic resonance imaging; CI, confidence interval; sICH, symptomatic intracranial hemorrhage.  
*Not available.
Our data suggest that adequate care (for example, qualified staff and appropriate logistics) for stroke patients receiving thrombolysis can be supplied independently from the time of hospital admission. Prospective multicenter studies are needed to identify relevant factors of inappropriate 24/7 stroke care.

Conclusions
Hospital admission during working or nonworking hours had no impact on short-term mortality, sICH, or clinical worsening after thrombolysis. However, nonmodifiable factors such as age and stroke severity predict short-term mortality after thrombolysis.

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References
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