Time to Admission in Acute Ischemic Stroke and Transient Ischemic Attack

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Background and Purpose—The effect of thrombolysis depends on the time from stroke onset to treatment and therefore also on the time when patients come to the hospital. This study was designed to analyze the variables that influence the time from symptom onset to admission (TTA) to the stroke unit.

Methods—We evaluated the medical records of 615 consecutive stroke or transient ischemic attack (TIA) patients admitted to our neurological department within 48 hours after symptom onset.

Results—The median TTA was 180 minutes. Referral by emergency medical services (EMS; $P<0.001$), high National Institutes of Health Stroke Scale (NIHSS) scores ($P<0.001$), strokes in the carotid territory ($P<0.001$), and strokes not attributable to small vessel disease ($P<0.001$) were associated with shorter prehospital delays. The TTA was adjusted for travel times (adjTTA), and all these variables remained significantly associated with time to admission. In addition, patients with previous experience with stroke or TIA had longer adjTTA ($P=0.028$). Regression analysis confirmed the independent association between referral by EMS ($P=0.010$), high NIHSS scores ($P<0.001$), carotid territory stroke ($P<0.001$), and first-ever cerebrovascular event ($P=0.022$) with shorter adjTTA.

Conclusions—Factors such as NIHSS scores and stroke location influence the time to admission but, unlike referral pathways, cannot be modified. Educational programs and stroke campaigns should therefore not only teach typical and less common stroke symptoms and signs but also that EMS provides the fastest means of transportation to a stroke unit and the best chances to get treatment early. (Stroke. 2006;37:963-966.)

Key Words: angiography ■ stroke, acute ■ stroke management ■ thrombolysis

Stroke is one of the leading causes of death, dementia, and disability in industrialized nations. Since the positive findings of the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study, intravenous recombinant tissue plasminogen activator (rt-PA) has become standard treatment of acute stroke for selected patients in many countries. Analysis of the NINDS data and a pooled analysis of the main rt-PA trials have shown that the sooner the treatment is started, the greater the benefit.1,2 Intra-arterial thrombolysis has been proved to be efficacious as well, mainly for patients with M1 or M2 segment occlusion of the middle cerebral artery or with basilar artery occlusion.3,4

In a previous study, we analyzed the prehospital and in-hospital delays from stroke onset to intra-arterial thrombolysis.3 In the corresponding study period, $\approx21\%$ of all stroke victims admitted to our stroke unit received thrombolysis. The main reason for not giving them was late presentation. Because this is potentially remediable, provided that the reasons are known, we extended the present analysis to all the stroke victims who had been admitted. The goal was to determine the variables that influence the time from symptom onset to admission (TTA).

Subjects and Methods

Stroke Center

The Inselspital is a tertiary care center and the main teaching hospital of the University of Bern, Switzerland. Most stroke victims come from the city of Bern and the neighboring communities, although some patients are referred from farther away. Patients admitted from distant locations are mostly young and severely afflicted and are coming from a catchment area up to 1 500,000 inhabitants. Road distances from referring hospitals to the Inselspital varied in this study from 1 to 534 km, and travel times ranged from a few minutes to $>5$ hours. Patients were usually transferred by ambulance or from community hospitals sometimes by helicopter.

Our stroke unit is organized as a combination of a mobile stroke team and a stationary stroke unit. Typically, stroke victims enter the hospital at the emergency department (ED) and are evaluated and treated by stroke neurologists in collaboration with neuroradiologists and other specialists as needed. Patients who undergo intravenous or intra-arterial thrombolysis are brought to intensive care afterward, from there typically to intermediate care, and 2 or 3 days later, to the neurology ward. Treatment responsibilities are always with a neurologist during the whole stay of a stroke victim at our hospital.

In Switzerland, there are 2 complementary emergency systems. On one hand, there are practicing physicians who take regular terms in an emergency service outside the hospital (emergency doctors),
and on the other hand, there is emergency medical services (EMS), a paramedic service that can be called by the emergency phone number 144 (corresponding to 911 in the United States).

Data Collection
Data of 648 consecutive patients with a final diagnosis of acute ischemic stroke or transient ischemic attack (TIA) confirmed by computed tomography (CT), MRI, or both were analyzed. They all entered the ED of the Inselspital from January 1, 2000, to December 31, 2003, within 48 hours after symptom onset and were admitted to the stroke unit. Patients who arrived later than 48 hours after stroke onset were not considered for this study. The data were collected by study physicians prospectively, entered in our computer-based Bernese Stroke Registry, and analyzed in retrospect. The arrival time at the ED was noted in the hospital administration system. Patients with in-hospital strokes (n=22; ie, cerebrovascular events that occurred during the hospital stay) were not included in this study.

Demographic variables, time of symptom onset, mode of referral, history of previous cerebrovascular events (stroke or TIA), National Institutes of Health Stroke Scale (NIHSS) score at admission, and time of arrival were recorded. The time of symptom onset was considered the moment when symptoms started to evolve. When stroke occurred during sleep time, awakening was considered as the time of awareness of symptom and therefore from the patients' point of view the time of stroke onset. When patients were found unconscious or aphasic, the time when they were found was considered as the start of TTA.

The main variable of interest, the interval from TTA, was defined as the time from the onset of new neurological symptoms to the time of hospital arrival. The vessel territory involved by the stroke was determined according to clinical and neuroimaging findings. Etiology was classified using the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) categories. In addition, comorbid conditions were recorded with the Charlson index.

All travel times and distances were calculated based on the World Wide Web route planner map24.com. All analyses were performed with the effectively measured TTA and the TTA adjusted for travel times (adjTTA). adjTTA was defined as TTA minus the travel time calculated by the route planner map24.com.

Statistical Analysis
The Mann–Whitney or Kruskal–Wallis tests were used for univariate testing (Table 3). Direct admission by air rescue services was excluded from univariate testing because of low case numbers. After adjTTA, the associations remained significant, and, in addition, patients with recurrent strokes had longer adjTTA (Table 3). Other variables such as age, sex, day of the week, and on the other hand, there is emergency medical services (EMS), a paramedic service that can be called by the emergency phone number 144 (corresponding to 911 in the United States).

Results
Demographics and Baseline Characteristics
Thirty-three of the 648 patients were excluded from this study: 22 because of in-hospital cerebrovascular events during their hospital stay for another reason and 11 because of incomplete data. Therefore, 615 patients with TIA (n=79) or acute ischemic stroke (n=536) and arrival at ED within 48 hours remained in the analysis: 380 men (61.8%) and 235 (38.2%) women with a mean age of 62±13 years (range 17 to 93 years). Median NIHSS score at admission was 6 (range 0 to 24), and median Charlson index was 1 (range 0 to 12). A total of 290 patients had no comorbidity. Thrombolysis was performed in 167 (27.2%) patients. A total of 429 patients (69.8%) had a cerebrovascular event in the carotid territory:

### TABLE 1. Time From Stroke Onset to Admission and Etiology According to the TOAST Classification

<table>
<thead>
<tr>
<th>Etiology</th>
<th>n (%)</th>
<th>Mean (min)</th>
<th>Median (min)</th>
<th>adjTTA (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Others</td>
<td>56 (9)</td>
<td>352±493</td>
<td>203</td>
<td>286±485</td>
</tr>
<tr>
<td>Large artery</td>
<td>106 (17)</td>
<td>415±596</td>
<td>174</td>
<td>374±592</td>
</tr>
<tr>
<td>Small artery</td>
<td>74 (12)</td>
<td>539±541</td>
<td>337</td>
<td>512±541</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>199 (33)</td>
<td>315±460</td>
<td>159</td>
<td>283±461</td>
</tr>
<tr>
<td>Unclear, complete</td>
<td>69 (11)</td>
<td>371±513</td>
<td>172</td>
<td>337±512</td>
</tr>
<tr>
<td>Unclear, incomplete</td>
<td>111 (18)</td>
<td>367±502</td>
<td>185</td>
<td>326±505</td>
</tr>
</tbody>
</table>

223 patients in the left, 202 in the right, and 4 in both hemispheres. The vertebrobasilar territory was involved in 174 (28.3%) and both the carotid and vertebrobasilar systems in 12 patients (1.9%). The etiologies are given in Table 1.

### TTA and Referral Pathways
Mean TTA was 378±517 minutes (median 180 minutes; range 20 minutes to 47 hours 25 minutes). A total of 314 (51.1%) patients arrived within 3 hours and 150 (24.4%) within 3 to 6 hours. A total of 231 (37.6%) patients were admitted directly to our stroke unit. Of these, 169 (27.5%) were referred by their family physician, 101 (16.4%) by the EMS using an ambulance, 64 (10.4%) by an emergency physician, 4 (0.7%) by air rescue services using a helicopter, and 46 (7.5%) patients arrived directly to the ED using their own means of transportation. TTA of the different referral pathways are given in Table 2. Admission by EMS was fastest, and patients who had contacted their family physicians arrived last (P<0.001).

### Predictors for Time to Admission
High NIHSS scores, carotid territory strokes or TIs, and admission by EMS were associated with shorter and small vessel disease with longer TTA according to univariate testing (Table 3). Direct admission by air rescue services was excluded from univariate testing because of low case numbers. After adjTTA, the associations remained significant, and, in addition, patients with recurrent strokes had longer adjTTA (Table 3).

### TABLE 2. Time Intervals and Referral Pattern

<table>
<thead>
<tr>
<th>Admission</th>
<th>n (%)</th>
<th>Mean (min)</th>
<th>Median (min)</th>
<th>adjTTA (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital</td>
<td>231 (38)</td>
<td>370±514</td>
<td>195</td>
<td>314±512</td>
</tr>
<tr>
<td>EMS</td>
<td>101 (16)</td>
<td>208±351</td>
<td>80</td>
<td>189±351</td>
</tr>
<tr>
<td>Family physician</td>
<td>169 (28)</td>
<td>526±619</td>
<td>224</td>
<td>497±620</td>
</tr>
<tr>
<td>Emergency doctor</td>
<td>64 (10)</td>
<td>335±401</td>
<td>175</td>
<td>304±403</td>
</tr>
<tr>
<td>Self-admission</td>
<td>46 (7)</td>
<td>337±429</td>
<td>174</td>
<td>311±428</td>
</tr>
<tr>
<td>Helicopter</td>
<td>4 (1)</td>
<td>85±32</td>
<td>93</td>
<td>41±26</td>
</tr>
</tbody>
</table>

Emergency doctor is a practicing physician who takes regular terms in an emergency service outside the hospital.
TABLE 3. Factors Associated With Time to Admission (univariate analysis)

<table>
<thead>
<tr>
<th>Factor</th>
<th>TTA P Values</th>
<th>adjTTA P Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.351</td>
<td>0.915</td>
</tr>
<tr>
<td>Sex</td>
<td>0.967</td>
<td>0.817</td>
</tr>
<tr>
<td>Weekday-weekend</td>
<td>0.831</td>
<td>0.297</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>0.655</td>
<td>0.618</td>
</tr>
<tr>
<td>Hemisphere</td>
<td>0.756</td>
<td>0.948</td>
</tr>
<tr>
<td>Previous event (stroke, TIA)</td>
<td>0.414</td>
<td>0.516</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>0.694</td>
<td>0.466</td>
</tr>
<tr>
<td>Referral pattern</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High NIHSS</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke territory</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>First-ever stroke</td>
<td>0.075</td>
<td>0.028</td>
</tr>
<tr>
<td>Small artery (TOAST)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

TABLE 4. Factors Associated With Time to Admission (regression analysis)

<table>
<thead>
<tr>
<th>Factor</th>
<th>TTA P Values</th>
<th>adjTTA P Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referral pattern</td>
<td>&lt;0.001</td>
<td>0.010</td>
</tr>
<tr>
<td>NIHSS</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke territory</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>First-ever stroke</td>
<td>0.035</td>
<td>0.022</td>
</tr>
<tr>
<td>Small artery (TOAST)</td>
<td>0.005</td>
<td>0.053*</td>
</tr>
</tbody>
</table>

*Non-significant variables.

Discussion

This study analyzed factors that influence the interval from stroke onset to hospital admission. A total of 50% of our patients arrived within 3 hours and an additional 25% within 3 to 6 hours, similar to arrival times in other studies.10–14

Patients are admitted to our hospital by family physicians, emergency doctors of the community, paramedics of the EMS, from other hospitals, or they admit themselves. Direct admission by EMS was associated with earlier arrival at the stroke unit compared with other ways and in agreement to findings of other studies.10,12–15 Some authors found that the EMS not only shortens the time to arrival but also decreases the time to CT scanning after admission.13,15 Other referral pathways need more time and decrease the number of patients who receive thrombolysis.16–19 Public information campaigns and continuous medical education for health care professionals should provide this message to increase the number of stroke victims who will benefit from effective stroke treatment.20,21

Patients with severe neurologic deficits expressed as high NIHSS scores tended to arrive early and patients with mild deficits late. This has been observed in other studies as well.10,14,15,22,23 Obviously, more severe symptoms in acute stroke are perceived more often as health or life threatening and prompt patients to seek immediate help.

Patients with carotid territory strokes, whether of the right or left hemisphere, arrived earlier than patients with vertebrobasilar ischemia. A potential explanation is that carotid territory stroke signs are more obvious and more likely recognized as stroke both by laypersons as well as by doctors. Handschu et al found that motor deficits and speech problems were the most dramatic symptoms that led to activation of the EMS.24 However, specific signs of left hemispheric strokes or right hemispheric strokes did not influence arrival times, although one could have expected that specific left or right hemispheric symptoms such as aphasia or neglect could have accelerated or delayed hospital admission. Alternatively, the later arrival of vertebrobasilar stroke victims could be explained by a referral bias. Traditionally, we teach that some patients with basilar artery thrombosis can be treated, unlike carotid territory strokes, even after 6 hours, and this could encourage late referrals.

Stroke patients with small vessel disease were referred later than stroke patients with other etiologies. The median NIHSS of our patients with small vessel disease was 3 only. At first glance, one is inclined to explain late arrival of patients with small vessel disease with a mild neurologic deficit. However, logistic regression showed that this effect was independent of stroke severity (or mildness). Potential explanations might be vascular cognitive impairment or slow evolution of symptoms, which are frequent in small vessel disease.25,26 However, this still remains to be proved. And after correction for travel distance (adjTTA) there was no significant association between stroke etiology and admission time in the regression analysis.

Patients with recurrent cerebrovascular event were not referred earlier; on the contrary, they tended to have longer adjTTA than patients with a first-ever event. These results are in concordance with the study of Derex et al, which demonstrated that experience or knowledge of stroke was not associated with a change in time to ED arrival.10 Possible explanations for these results might be cognitive impairment or insufficient information and education after the first cerebrovascular event in our patients. Other studies have shown that stroke education shortens prehospital delays, and that there is a sustained benefit lasting for ≥6 months from an educational program.27

Conclusion

To summarize, referral by EMS, high NIHSS scores, and strokes in the carotid territory are independently associated with shorter prehospital delays from stroke onset to admission. Of these variables, all are nonmodifiable except the referral pathway. Educational programs and stroke campaigns should therefore not only teach typical and less common stroke symptoms and signs but also that EMS provides the
fastest means of transportation to the stroke unit and the best chances to get treatment early.

Acknowledgments
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References
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