Organizational models for thrombolysis in acute ischemic stroke
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Proportion of patients treated with thrombolysis in a centralized versus a decentralized acute stroke care setting

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Abstract

Background and Purpose
Nowadays treatment of acute stroke consists of tissue plasminogen activator (tPA), admission to a stroke unit and aspirin. Although tPA treatment is the most effective, there is substantial undertreatment. Centralized care may affect rate, timing, and outcome of thrombolysis compared to decentralized treatment in community hospitals. The present study aimed to assess the impact of organizational models on the proportion of patients undergoing tPA treatment.

Methods
A prospective multicenter observational study among 13 hospitals in the North of the Netherlands was conducted. In the centralized model, tPA treatment for 4 hospitals was administered in one stroke center. The decentralized model comprised 9 community hospitals. Primary outcome was the proportion of patients treated with tPA. Secondary outcome measures were proportion of patients arriving within 4.5 hours, safety, 90 days functional outcome, onset-to-door, door-to-needle and onset-to-needle times. Potential confounders were adjusted using logistic regression analysis.

Results
283 and 801 ischemic stroke patients were enrolled in the centralized and decentralized setting. Numbers of patients treated with tPA were 62 (21.9%) and 113 (14.1%) (OR 1.72, 95% CI 1.22 – 2.43). Adjusting for potential confounders did not alter results (OR 2.03, 95% CI 1.39 – 2.96). In the centralized setting significantly more patients arrived at the hospital within the 4.5 hours time-window (P<0.01), and shorter door-to-needle times were reached (35 vs 47 min.). Other secondary outcome measures did not differ across setting.

Conclusions
In a centralized setting, the results demonstrate a 50% increased likelihood of treatment. Prehospital factors seem to contribute to this result.

Introduction
Treatment with intravenous tissue plasminogen activator (tPA) is the most effective therapy for acute ischemic stroke in the first hours after stroke. Nonetheless, many potentially eligible patients do not receive this treatment. Of all stroke patients, 2-10% globally and 5-7% in the Netherlands are treated with tPA. Notably, a proportion up to 25% may be attained in optimized settings. Unfamiliarity of patients with stroke symptoms and how to act, late hospital arrival, the narrow therapeutic window of opportunity, and variance in the selection of patients for
thrombolysis are among the elements possibly contributing to the under treatment signalled\(^6\). These factors in fact are components of acute stroke care organization. Three dominant models in acute stroke care are encountered. On the one hand there is centralized stroke care, which requires patients eligible for thrombolysis to be transported to a single specialized stroke center, bypassing smaller community hospitals that may be located closer to the patient. On the other hand, a decentralized model assumes patients to be transported to the nearest general hospital offering tPA treatment. As a third model, telemedicine support across multiple community hospitals is available for remote hospitals without on-site stroke expertise.

Centralized care in stroke centers has been associated with rapid referral and early access to tPA treatment, better functional outcome, and high quality of care\(^7-11\). However, reports on a head-to-head comparison between centralized and decentralized care for proportion of patients treated with tPA and outcome are lacking. The aim of this study was to establish a direct comparison of the proportion of patients treated with tPA in a centralized versus decentralized organizational setting of acute stroke care.

**Materials and methods**

**Study design and patients**

This study was a six-month prospective, multicenter, observational, study enrolling all patients admitted with a stroke to hospitals in the three Northern provinces of the Netherlands (Figure 1). The Northern region of the Netherlands is an 8.981 km\(^2\) predominantly urban area with a population of 1.7 million, and a population density of 209 inhabitants/ km\(^2\). Part of the region, covering the catchment area of 4 hospitals, is served according to a centralized model for acute stroke care. The centralized model serves a population of 577 081 inhabitants with a population density of 247 inhabitants/km\(^2\). The function of central stroke center is executed by the Groningen University Medical Center. Within this catchment area, arrangements are made with emergency medical services and general practitioners to transport patients directly to the central stroke center for examination and possible treatment with tPA. The stroke center has 24-hour, 7-day immediate access to neurological consultation and neuroimaging at the emergency department, stroke physicians available for phone consultation for all referring general hospitals and interventional neuroradiology. The remainder of the region is served by 9 general or community hospitals, each attending to acute stroke patients within its catchment area. This region serves a population of 1 137 188 inhabitants with a population density of 181 inhabitants/km\(^2\). At the community hospitals general neurologists and neuroimaging were available 24 hours, 7 days a week. Both regions consist of urbanized areas with short distances to surrounding hospitals, and similar access to healthcare services such as the general practitioners office in- and outside business hours, emergency medical services, and hospital services\(^12\). Emergency Medical Services (EMS) protocols for suspected stroke victims were similar for both regions. High prioritization by
EMS was defined as ambulance arrival within 15 minutes from 911 call until ambulance arrival at the location of the patient.

Figure 1. Organizational models in the 3 Northern provinces of the Netherlands

Patients eligible for treatment were treated within a 4.5 hours time window after onset of stroke symptoms according to the ECASS-3 protocol, with the exception that age above 80 years was allowed, based on our experience in our stroke center and others. Experimental forms of thrombolysis such as local intra-arterial thrombolysis and thrombectomy were not part of the assessment. Data on all patients admitted or referred to hospital and suspected of stroke were collected from February through July 2010. Demographics (age and sex), symptom onset, arrival time at the hospital, diagnosis, onset time, and treatment with tPA inside and outside business hours and in the weekends were recorded. Initial stroke severity was assessed using the short version of the National Institute of health Stroke Scale (sNIHSS).

Outcome measures
The primary outcome measure was the proportion of ischemic stroke patients treated with thrombolysis. Secondary outcome measures were (1) proportions of patients arriving in time for tPA treatment, (2) the proportion of these patients actually treated with tPA, (3) safety,
characterized by the occurrence of symptomatic intracerebral haemorrhage (sICH) (defined according to the SITS-MOST as a 4-point increase on the NIHSS score within 36 hours after stroke onset\textsuperscript{10}), (4) functional outcome at 90 days (favorable defined as modified Rankin Score 0-2), (5) onset-to-door, door-to-needle, onset-to-needle times and (6) proportion treated outside business hours.

**Statistical analysis**
We compared the proportion (inclusive of 95% CIs) of patients treated with tPA in both organizational models. We considered variables with P<0.15 on univariate testing for entry into a multivariate logistic regression model. The regression model was used to adjust for possible differences in baseline characteristics potentially confounding the association between determinants and outcome. Odds ratios and 95% confidence intervals were estimated for determinants of treatment with tPA, functional outcome, and safety. Continuous variables and the different process times were evaluated using ANOVA or the Mann-Whitney U test. A p-value < 0.05 was considered significant in the final model. All statistical analyses were performed using SPSS 18 software (Chicago, IL).

**Informed consent**
Informed consent was obtained from all patients participating in this study.

**Results**

**Patient Characteristics**
A total of 1432 patients were included in the study. Figure 2 shows the distribution of the patients across both settings and the reasons for exclusion from tPA treatment. In the centralized model more patients were excluded, because they had diagnoses other than stroke or because of a transient ischemic attack. In both groups, a comparable proportion of patients were not treated with tPA for various reasons as shown in Figure 2. In Table 1 the baseline characteristics of the overall group of ischemic stroke patients, those arriving at the hospital within 4.5 hours after stroke onset, and finally those treated with tPA are shown. In the overall group, patients in the centralized model were more often male and significantly younger. Stroke severity did not differ across setting. For all patients arriving within 4.5 hours and all patients treated with thrombolysis, there were no differences in patient characteristics between both models.
Figure 2. Flow chart of the study.

Outcome Measures

Primary outcome
In the centralized model, 62/283 patients (21.9%) were treated with thrombolysis compared to 113/801 (14.1%) in the decentralized model (OR, 1.72; 95% CI, 1.22 – 2.43). After adjustment for stroke severity, age and gender, the odds ratio for likelihood of treatment with tPA was 2.03 for centralized versus decentralized care (95% CI, 1.39-2.96).

Secondary outcomes and safety
Table 2 shows the secondary outcome measures. The proportion of patients arriving in time for tPA treatment was significantly higher in the centralized model (124/283 versus 227/801, P<0.01). In both models the proportion of treatment of stroke patients arriving within 4.5 hours after stroke onset was the same (62/124 versus 113/227, P=0.81). In the centralized model 41/62 (66%) of the patients displayed a favorable functional outcome compared to 59/113 (52%) in the decentralized model. This was, however, not statistically significant in univariate (OR, 1.79; 95% CI, 0.94 – 3.40) or multivariate analysis (OR, 1.62; 95% CI, 0.76 – 3.42). sICH occurred in 1/62 patients (1.6%) in the centralized model and 3/113 patients (4.1%) in the decentralized model (OR, 0.60; 95% CI, 0.06 – 5.90). Odds for sICH remained similar after adjustment for
Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Centralized model</th>
<th>Decentralized model</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All ischemic stroke patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>283</td>
<td>801</td>
</tr>
<tr>
<td>Age (y), mean (SD)</td>
<td>70 (14)</td>
<td>73 (13)*</td>
</tr>
<tr>
<td>Male, (%)</td>
<td>158 (56)</td>
<td>391 (49)*</td>
</tr>
<tr>
<td>sNIHSS on arrival (IQR), median</td>
<td>1 (0-3)</td>
<td>1 (0-3)</td>
</tr>
<tr>
<td>Referral GP (%)</td>
<td>135 (48)</td>
<td>456 (57)</td>
</tr>
<tr>
<td>First responder EMS (%)</td>
<td>84 (30)</td>
<td>184 (23)*</td>
</tr>
<tr>
<td>Transported by EMS (%)</td>
<td>213 (75)</td>
<td>460 (57)*</td>
</tr>
<tr>
<td>High prioritization by EMS (%)</td>
<td>170 (80)</td>
<td>311 (68)*</td>
</tr>
<tr>
<td>Median distance to hospital (km)</td>
<td>13.5</td>
<td>8.5**</td>
</tr>
</tbody>
</table>

**Patients arriving within 4.5 hours after stroke onset**

|                                      |                   |                     |
| n (%)                                | 124 (44)          | 227 (28)**          |
| Age (y), mean (SD)                   | 69 (14)           | 71 (13)             |
| Male, (%)                            | 63 (49)           | 124 (54)            |
| sNIHSS on arrival (IQR), median      | 2 (0-4)           | 2 (0-5)             |
| Referral GP (%)                      | 63 (51)           | 108 (48)            |
| First responder EMS (%)              | 53 (43)           | 110 (48)            |
| Transported by EMS (%)               | 115 (93)          | 181 (80)*           |
| High prioritization by EMS (%)       | 109 (95)          | 162 (90)            |
| Median distance to hospital (km)     | 22.1              | 8.3**               |

**Patients treated with tPA**

|                                      |                   |                     |
| n (%)                                | 62 (22)           | 113 (14)            |
| Age (y), mean (SD)                   | 69 (16)           | 70 (14)             |
| Male, (%)                            | 35 (56)           | 60 (53)             |
| sNIHSS on arrival (IQR), median      | 4 (2-7)           | 4 (2-7)             |
| Referral GP (%)                      | 27 (44)           | 35 (31)             |
| First responder EMS (%)              | 31 (50)           | 71 (63)             |
| Transported by EMS (%)               | 59 (95)           | 98 (87)             |
| High prioritization by EMS (%)       | 55 (93)           | 94 (96)             |
| Median distance to hospital (km)     | 23.1              | 8.8**               |

SD indicates standard deviation; NIHSS, National Institutes of Health Stroke Scale; IQR, interquartile range; GP, General Practitioner; EMS, Emergency Medical Services; km, kilometer.

* P<0.05, ** P<0.01
stroke severity, age and gender (OR, 0.82; 95% CI, 0.08 – 8.82). The median onset-to-door time for all patients treated with thrombolysis was 1 hour 24 minutes for the centralized setting, and 1 hour 12 minutes for the decentralized model (P=0.12). The median door-to-needle time was 35 minutes for the centralized model compared to 47 minutes in the decentralized model (P=0.01). The total median onset-to-needle time was 124 minutes for the centralized setting and 120 minutes for the decentralized setting (P=0.75). In both settings, there was no difference in proportion of patients treated inside or outside business hours. In the centralized model 25/62 (40%) patients were treated with tPA outside business hours compared to 54/113 (40%) in the decentralized model.

Discussion

This study demonstrates that the proportion of patients treated with tPA is different for two contrasting organizational models of acute stroke care. The likelihood of treatment was almost twice as high in the centralized setting compared to decentralized setting. Among patients arriving within 4.5 hours at the hospital thrombolysis rates were similar for both models. This suggests that the effect on proportions treated with thrombolysis is mainly caused by prehospital factors. The centralized organizational model yielded a larger proportion of patients arriving within 4.5 hours after stroke onset, and a significantly shorter door-to-needle time. The latter was subsequently offset by a longer onset-to-door time, ultimately leading to a similar overall process time (onset-to-needle time). As far as functional outcome at 90 days was concerned, patients treated with tPA in the centralized model had more favorable outcomes, however the difference was not significantly different from the outcome in the decentralized model in the univariate or multivariate analysis. Safety was similar in both organization models.

The overall results of our study indicate that the organization of acute stroke care across the Northern Netherlands surpassed national averages. The high proportion of patients treated in the centralized model is in line with results published for other stroke centers. Importantly, no interventions were executed to increase thrombolysis rates during the period of data collection, because this was an observational study. Interestingly, any beneficial effect of centralizing stroke care might be further augmented when carried out in regions with lower treatment rates than the ones achieved in the decentralised model in our study.

Stroke patients presenting to the emergency department within 4.5 hours had similar chances of receiving thrombolysis regardless of setting. However, many more patients presented within 4.5 hours in the centralized model. These results suggest that in our region treatment rates may largely depend on prehospital factors. The difference in the proportion of patients arriving within 4.5 hours for both models may have several causes. Firstly, within the centralized model a greater awareness of tPA treatment may exist among caregivers. Within the literature,
the – more experienced – stroke centers report higher treatment percentages and levels of knowledge regarding organizing services for treatment with thrombolysis. Although not directly measured in this study, an increased awareness can be the result of a combination of experience and exposure to tPA, continuing medical education, and new trainees entering the workforce.

Secondly, a referral preference may exist for the centralized model. The better intrahospital logistics, as indicated by shorter door-to-needle time and the trend towards better functional outcome may be among the factors that determine possible preferences. As yet, the extent of and reasons for any such preference are unknown and require further study. Thirdly, within the decentralized model use of EMS and high prioritization were significantly lower. This may have contributed to delayed arrival patterns and subsequent fewer patients arriving within 4.5 hours at the hospital in this group. High prioritization of EMS occurred significantly more frequently in the centralized model, possibly indicating more calls recognized as medical emergency. Patients transported in the decentralized model had significantly shorter median distances to the hospital, explaining the shorter onset-to-door times in this region. Finally, patients were older and more frequently women in the decentralized region possibly reflecting a higher percentage of people living alone, adding to delayed hospital arrival.

Since treatment with thrombolysis remains underused, attempts have been made to improve implementation. Treatment with thrombolysis is a complex multifaceted intervention. It is challenging to identify critical success factors along the entire care pathway, both in the pre- and inhospital phase. Typically, classic experimental study designs are performed. For example, a two-year implementation study for thrombolysis was recently evaluated. This study resulted in a negligible increase of thrombolysis rate from 12% in the control group to 13% in the interventional group. The question arises whether such research methods are an efficient way

Table 2. Secondary outcomes measures in Relation to Organizational Model Acute Stroke care

<table>
<thead>
<tr>
<th></th>
<th>Centralized model n (%)</th>
<th>Decentralized model n (%)</th>
<th>OR (95% CI) unadjusted</th>
<th>OR (95% CI) adjusted for patient characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>283/801 (35%)</td>
<td>3/113 (3)</td>
<td>0.60 (0.06 – 5.90)</td>
<td>0.82 (0.08 – 8.82)</td>
</tr>
<tr>
<td>sICH</td>
<td>1/62 (2)</td>
<td>3/113 (3)</td>
<td>1.79 (0.94 – 3.40)</td>
<td>1.62 (0.76 – 3.42)</td>
</tr>
<tr>
<td>mRS ≤2 at 90 days</td>
<td>41/62 (66%)</td>
<td>59/113 (52%)</td>
<td>1.94 (1.46 – 2.56)</td>
<td>1.99 (1.49 – 2.66)</td>
</tr>
<tr>
<td>Patient arriving in time for treatment with tPA</td>
<td>124/283 (44%)</td>
<td>227/801 (28%)</td>
<td>1.16 (0.76 – 1.77)</td>
<td>1.30 (0.79 – 2.14)</td>
</tr>
<tr>
<td>Patients arriving in time and treated with tPA</td>
<td>62/124 (50%)</td>
<td>113/227 (50%)</td>
<td>1.01 (0.55 – 1.87)</td>
<td>1.02 (0.55 – 1.90)</td>
</tr>
<tr>
<td>Patients treated with tPA outside business hours</td>
<td>25/62 (40%)</td>
<td>45/113 (40%)</td>
<td>1.00 (0.55 – 1.87)</td>
<td>1.02 (0.55 – 1.90)</td>
</tr>
</tbody>
</table>

OR indicates odds ratio; CI, confidence interval; sICH, symptomatic intracerebral hemorrhage; mRS modified Rankin Scale
** P<0.01
forward to study and improve implementation of complex treatment trajectories. Other research methodologies may be required such as discrete event simulation\textsuperscript{28,29}.

There are some limitations to this study. Sociodemographic factors such as living status and recognition of stroke symptoms by bystanders were not collected in this study and could not be corrected for in the multivariate regression analyses. Initial stroke severity upon hospital arrival may have been slightly underestimated in both organizational models because of use of the shortened version of the NIHSS.

In conclusion, this study revealed that the proportion of patients treated with tPA in a centralized setting of acute stroke care surpassed that achieved in a decentralized setting considerably. Prehospital factors seem particularly relevant targets for improvement.

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**Members of the study group**

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**Disclosures**

None.
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