Stroke Thrombolysis in a Centralized and a Decentralized System (Helsinki and Telemedical Project for Integrative Stroke Care Network)

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Background and Purpose—Intravenous thrombolysis with tissue-type plasminogen activator (tPA) for acute ischemic stroke is more effective when delivered early. Timely delivery is challenging particularly in rural areas with long distances. We compared delays and treatment rates of a large, decentralized telemedicine-based system and a well-organized, large, centralized single-hospital system.

Methods—We analyzed the centralized system of the Helsinki University Central Hospital (Helsinki and Province of Uusimaa, Finland, 1.56 million inhabitants, 9096 km²) and the decentralized TeleStroke Unit network in a predominantly rural area (Telemedical Project for Integrative Stroke Care [TEMPiS], South-East Bavaria, Germany, 1.94 million inhabitants, 14992 km²). All consecutive tPA treatments were prospectively registered. We compared tPA rates per total ischemic stroke admissions in the Helsinki and TEMPiS catchment areas. For delay comparisons, we excluded patients with basilar artery occlusions, in-hospital strokes, and those being treated after 270 minutes.

Results—From January 1, 2011, to December 31, 2013, 912 patients received tPA in Helsinki University Central Hospital and 1779 in TEMPiS hospitals. Area-based tPA rates were equal (13.0% of 7017 ischemic strokes in the Helsinki University Central Hospital area versus 13.3% of 14637 ischemic strokes in the TEMPiS area; P=0.078). Median prehospital delays were longer (88; interquartile range, 60–135 versus 65; 48–101 minutes; P<0.001) but in-hospital delays were shorter (18; interquartile range, 13–30 versus 39; 26–56 minutes; P<0.001) in Helsinki University Central Hospital compared with TEMPiS with no difference in overall delays (117; interquartile range, 81–168 versus 115; 87–155 minutes; P=0.45).

Conclusions—A decentralized telestroke thrombolysis service can achieve similar treatment rates and time delays for a rural population as a centralized system can achieve for an urban population. (Stroke. 2016;47:2999-3004. DOI: 10.1161/STROKEAHA.116.014258.)

Key Words: delivery of health care ■ stroke ■ telemedicine ■ telestroke ■ thrombolysis ■ time delays

The earlier thrombolysis is given in stroke patients the better their outcome.1–3 Overall delay can be divided into prehospital delay, commonly referred to as onset-to-door time and in-hospital delay, commonly referred to as door-to-needle time. The sum of the 2 is what is most important for the patient: the onset-to-treatment time. Many efforts have been undertaken to reduce prehospital and in-hospital delays of tissue-type plasminogen activator (tPA) administration.4–9 Although the shortest overall delays can be achieved with a computed tomography (CT)–equipped ambulance,5 the fastest hospital-based delays have been reported from the Helsinki University Central Hospital (HUCH), which covers the city of Helsinki and the surrounding province of Uusimaa in Finland.5 In rural, sparsely inhabited regions, the coverage of tPA service is difficult and achievement of short time delays is more challenging, mainly because of long prehospital distances and reduced experience in tPA delivery in local hospitals compared with stroke centers. The Telemedical Project for Integrative Stroke Care (TEMPiS) attempted to address this challenge by setting up a decentralized system of telemedicine-linked stroke facilities (TeleStroke Units) in rural South-East Bavaria, Germany.10,11 In such decentralized systems, the specialized stroke care facility will be closer to patients’ home, thus reducing prehospital delays, but the volume of

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patients treated per hospital is usually smaller. Door-to-needle
times seem to have an inverse relationship to the annual num-
ber of patients with stroke per hospital, suggesting experience
of the team as a crucial factor for achieving short in-hospital
delays. Thus, a decentralized system may lead to longer
in-hospital time delays.

The aim of this study was to determine whether a decen-
tralized model of stroke care (TEMPiS) can achieve similar
thrombolysis rates and overall treatment delays in a predomi-
nantly rural population compared with the centralized system
in Helsinki and the province of Uusimaa.

Methods

We performed an observational retrospective cohort study with pro-
spectively collected data and a prespecified analysis plan.

Helsinki University Central Hospital Setup

The Health District of Helsinki and Uusimaa covers public special-
ist care in the province of Uusimaa (Figure). In 2011 to 2013, the
province had a mean population of 1.56 million and a surface area of
9096 km². The whole area is defined as urban by the NUTS3 defini-
tion of the European Union (Nomenclature of Units for Territorial
Statistics–level 3, for small regions), because of the therein embedded
metropolitan region of Helsinki.15

The Helsinki thrombolysis service has been described previously.5
Briefly, HUCH is the only hospital in the province providing throm-
bolysis for stroke. All potentially eligible patients with stroke are
brought to this 1 large hospital 24 hours/d, 7 days/wk. Although the
driving distance can be up to 90 minutes, most of the population lives
in the metropolitan area, typically within a 30-minute driving distance
of HUCH. The province-wide ambulance service contacts the HUCH
stroke consultant directly over mobile phone for any patient with a
possible stroke to discuss patient details, medical history, and tPA eli-
gibility during transport. Before the patient’s arrival, the stroke con-
sultant accesses previous medical records, imaging, and laboratory
test results available in electronic format in a province-wide patient
record; preregisters the patient into the hospital, requests blood tests
and imaging, and assembles the team to wait for the patient. Because
of concentrated resources of a centralized system, there is a neurology
resident and a specialist neurologist in the hospital 24/7. The Helsinki
model has been developed over many years and includes constant
collaboration and training of the emergency medical services, con-
tinuous quality improvement utilizing the prospective thrombolysis
registry, and a systematic training program within the stroke team.

The history of the quality improvement program has been described
in detail previously.5

Telestroke Network TEMPiS Setup

The TEMPIS network covers stroke specialist care in 14 districts in
South-East Bavaria (Figure). In 2011 to 2013, the districts had a mean
population of 1.94 million and a surface area of 14992 km².16 Nine of
the districts are defined as rural and 5 as intermediate by the NUTS3
definition of the European Union.15 The network has been described
previously.10,17 Briefly, it consists of 2 hub centers (Munich/Klinikum
Harlaching and Regensburg/University Hospital) and 14 (in 2011) or
15 (in 2012 and 2013) cooperating TEMPIS spoke hospitals, each
covering their administrative district in South-East Bavaria, Germany
(Figure). The network was set up with the aim that patients do not
have a driving distance of >30 minutes to a (Tele-) Stroke Unit. As part
of the TEMPIS concept, regular training sessions for the multidisci-
plinary teams, internal registries, and standard operating procedures
were established. The 24/7 teleconsultation service includes real-
time bidirectional videoconference and imaging transfer. Continuous
stroke-specific program performed by hub centers for spoke hospital
staff includes semiannual stroke updates, semiannual full-day stroke
beginners courses, and annual full-day conference days for nurses
and therapists. Stroke awareness campaigns and stroke-specific

Figure. Geographical catchment area, degree of urbanization, and location of stroke units in the Uusimaa province, Finland, and the Tele-
medical Project for Integrative Stroke Care (TEMPiS) network, Germany. Adapted and modified from EuroStat maps.14 Including Open-
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training of emergency medical services are performed annually by each TEMPiS hospital for their own district. Process improvement programs performed by hub centers include regular analyses of collected data sets for each hospital, annual comprehensive feedback documents including improvement plans and semiannual audits in each spoke hospital. Ambulances are usually staffed with 2 paramedics. Emergency physician maybe deployed in critically ill patients. Patients with suspicion of stroke are to be brought to closest hospital with Stroke Unit. Paramedics are trained in stroke recognition during professional training and in the above-mentioned training.

Four of the TEMPiS hospitals have a Neurology service 24/7, and telemedicine is used in these hospitals mainly for the second opinion and organization of emergency transports. Three hospitals use a full-time neurologist during working hours. Neurological expertise is provided by part-time neurologists during working hours in all other hospitals. Among other indications, video presentation of patients with acute stroke potentially eligible for thrombolysis is mandatory if no neurologist is available at the bedside. If a neurologist is available onsite, thrombolysis may be delivered without telemedicine assistance. This was the case in about one third of the patients. Brief medical history, noncontrast CT scan, blood pressure measuring, and blood sampling are performed before the start of videoconference. If tPA is recommended, administration commences directly after videoconference. Within the districts covered by TEMPiS, 2 other hospitals (not part of the network) offer Stroke Unit service (Wasserburg and Bad Aibling) including tPA treatment.

### Data Collection

All data used in this article were prospectively collected from patients who received intravenous tPA between January 1, 2011, and December 31, 2013, in HUCH and in the TEMPiS spoke hospitals. The Helsinki Stroke Thrombolysis Registry has recorded all intravenous tPA deliveries at HUCH since 1995. The total number of ischemic stroke admissions was taken from the Finnish national stroke registry PERFECT (Performance, Effectiveness, and Cost of Treatment Episodes in Stroke), which uses administrative data linkage to identify in addition to admissions to the major hospital also cases managed at health centers and in the private sector.

The TEMPiS Thrombolysis Registry includes all patients with acute ischemic stroke treated with intravenous thrombolysis in any of the TEMPiS hospitals. Neither data of the 2 hub centers and their catchment areas nor data of adjacent non-network districts were included in the current analysis. One spoke TEMPiS hospital (Pasing) is located in the city of Munich with overlapping catchment areas of the hub center and other non-network Stroke Units and was therefore excluded from this analysis. One spoke TEMPIS hospital (Bad Reichenhall) joined the network end of 2011, and data were therefore only included for the years 2012 and 2013. Two other hospitals joined the network end of 2013 and were therefore not included in this analysis. Hence, data for 13 (for 2011) and 14 (for 2012–2013) TEMPIS hospitals were included. Tests for plausibility and comparisons to other TEMPIS registries are regularly performed.

To calculate area-based thrombolysis rate, the 2 non-network Stroke Units within the districts covered by TEMPIS provided numbers of tPA administrations in their hospitals. Numbers of ischemic stroke admissions in the whole area (including non-network hospitals, but excluding the catchment areas of the hubs and the spoke hospital and was therefore excluded from this analysis). One spoke TEMPIS hospital (Bad Reichenhall) joined the network end of 2011, and data were therefore only included for the years 2012 and 2013. Two other hospitals joined the network end of 2013 and were therefore not included in this analysis. Hence, data for 13 (for 2011) and 14 (for 2012–2013) TEMPIS hospitals were included. Tests for plausibility and comparisons to other TEMPIS registries are regularly performed.

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### Table 1. Regional Characteristics, Number of Acute Ischemic Stroke Admissions and Number of tPA Treatments for 2011 to 2013

<table>
<thead>
<tr>
<th>Regional characteristics</th>
<th>Helsinki</th>
<th>TEMPIS</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhabitants living in the area</td>
<td>1 558 261</td>
<td>1 939 176</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Surface area, km²</td>
<td>9096</td>
<td>14 992</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Population density, population/km²</td>
<td>171</td>
<td>129</td>
<td>&lt;0.001</td>
</tr>
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</table>

### Table 2. Exclusion Profile for Time Delay Analysis

<table>
<thead>
<tr>
<th>Helsinki</th>
<th>TEMPIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number</td>
<td>912</td>
</tr>
<tr>
<td>In-hospital strokes, n (%)</td>
<td>4 (0.4)</td>
</tr>
<tr>
<td>Basilar artery occlusions, n (%)</td>
<td>57 (6.3)</td>
</tr>
<tr>
<td>Onset-to-treatment time &gt;270 min, n (%)</td>
<td>24 (2.6)</td>
</tr>
<tr>
<td>Missing data, n (%)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Included in time delay analyses, n (%)</td>
<td>826 (90.6)</td>
</tr>
</tbody>
</table>

Overlapping exclusion criteria in some patients were only counted once. Exclusions were performed following the criteria top to bottom. TEMPIS indicates the Telemedical Project for Integrative Stroke Care.
patients with acute ischemic stroke admitted to this hospital (denominator). Area-based tPA rate was defined as all patients with acute ischemic stroke treated with tPA in the given hospital (nominator) of all patients with acute ischemic stroke admitted to any hospital within the catchment area of this hospital (denominator).

Data sets from patients with in-hospital stroke or basilar artery occlusion and from patients treated after 270 minutes from onset or with incomplete information on time points were not included in time delay analyses. A sensitivity analysis was performed, in which patients with basilar artery occlusion and in-hospital stroke were included.

Both registries were approved as observational quality registries, patient consent was not required for registration, and all consecutive cases were included.

Statistical Analysis
Because of non-normal distribution of treatment delays, data are presented as median and interquartile range. The data of the 2 registries were compared using Mann–Whitney U test for continuous and Pearson χ² test for dichotomous data. Statistical significance was set at 0.05 (2 tailed). No adjustment for multiple testing was done.

IBM SPSS Statistics 23 (IBM Corp, Armonk, NY) was used for all analyses.

Results
Geographical and patients' characteristics, as well as thrombolysis rates, are shown in Table 1. During the study period, 912 and 1779 patients with stroke were treated with tPA in HUCH and TEMPiS, respectively. Hospital-based annual tPA rates ranged between 7.5% and 20% in the TEMPS hospitals. Hospital-based tPA rate in HUCH was higher than overall tPA rate in TEMPS hospitals (26.9% versus 15.4%; P<0.001). However, there was no statistically significant difference in area-based tPA rates between the areas covered by HUCH and TEMPiS stroke hospitals (13.0% versus 13.3%; P=0.078). Exclusions for the time delay analysis are shown in Table 2 and time delays in Table 3. Onset-to-door time was significantly longer (88 [60–135] versus 65 [48–101] minutes; P<0.001) and door-to-needle time significantly shorter (18 [13–30] versus 39 [26–56] minutes; P<0.001) in HUCH versus TEMPiS. Overall onset-to-treatment time was equal (117 [81–168] versus 115 [87–155] minutes; P=0.452). These results remained similar when patients with basilar artery occlusions and in-hospital strokes were included in the analysis (Table 4).

<table>
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<tr>
<th>Table 3. Time Delays (in Minutes)</th>
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<tr>
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<tr>
<td>Onset-to-door time, median (IQR); mean±SD</td>
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<tr>
<td>Door-to-needle time, median (IQR); mean±SD</td>
</tr>
<tr>
<td>Onset-to-treatment time, median (IQR); mean±SD</td>
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</tbody>
</table>

IQR indicates interquartile range; and TEMPiS, the Telemedical Project for Integrative Stroke Care; and tPA, tissue-type plasminogen activator.

Discussion
Our comparison of 2 systems of stroke care shows that a decentralized telemedicine-supported infrastructure can achieve similar thrombolysis rates and overall time delays in a rural population as a centralized system can achieve in an urban population.

The different catchment areas (urban versus rural) may explain the age difference of the 2 patient groups. The difference in mean NIHSS (National Institute of Health Stroke Scale) is unclear, as in neither system very low or high NIHSS is considered a clear contraindication.

Although hospital-based tPA rate was much higher in HUCH than in TEMPS, area-based tPA rate was similar in both systems. This difference is explained by the prehospital selection of patients with stroke in Helsinki/Uusimaa. Patients eligible for thrombolysis are transferred to HUCH, whereas others may also be treated in a local hospital without a Stroke Unit. This is also reflected by the lower rate of dedicated Stroke Unit treatments in Helsinki/Uusimaa (48%; Table 1). Most of the patients treated outside of HUCH are treated under neurology with typically half of the beds used for patients with stroke but not within a dedicated Stroke Monitoring Unit. In the TEMPiS system, prehospital selection is less frequent, as network hospitals are the local hospitals, close to patients' homes. Only few patients are admitted to other hospitals. As a result, 88% of patients with stroke are treated in hospitals with a (Tele-)Stroke Unit.

The only previous comparison of centralized and decentralized tPA systems of care found a higher hospital-based tPA rate in the centralized system (n=175), but a selection bias cannot be excluded because fewer patients with stroke were admitted to the stroke center of the centralized system (49 compared with 70 per 100 000 inhabitants), and these patients

<table>
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<th>Table 4. Sensitivity Analysis for Time Delays (in Minutes) With All Patients, Except With Missing Data and Treated &gt;270 Minutes After Onset</th>
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<tr>
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<tr>
<td>Onset-to-treatment time, median (IQR); mean±SD</td>
</tr>
</tbody>
</table>

IQR indicates interquartile range; and TEMPiS, the Telemedical Project for Integrative Stroke Care.
*Excluded: n=50 with onset-to-treatment time >270 minutes, n=1 missing dates per time.
†Excluded n=27 with onset-to-treatment time >270 minutes, n=19 missing dates/time.
were younger and more often men. The approach of area-based tPA rates provides better comparability as hospital-based tPA rates are often severely biased by prehospital selection, especially in centralized systems of care.

About time delays, the main advantage of the decentralized system was the short onset-to-door time, which was only 65 minutes in TEMPiS compared with 88 minutes in HUCH. Where driving distances are usually shorter than 30 minutes in the TEMPiS region, distances in the Uusimaa area can be up to 90 minutes. Door-to-needle time was significantly longer in TEMPiS than in HUCH. In the current workflow of telethrombolysis, patients with acute stroke symptoms receive imaging before they are examined via videoconference. In contrast to HUCH, where tPA bolus is given while patient is still on CT table, additional delays are caused in the telestroke setting by transfer from CT table to the telemedicine room and subsequent video examination. Also, the lower number of tPA administrations per hospital is probably associated with less routine and less optimized procedures. tPA administrations in each TEMPiS hospital ranged between 15 and 91 per year. In Helsinki, stroke neurologist is contacted before patient arrival in hospital, which further reduces in-hospital delay, a measure that is also intended in TEMPiS, but because of large number of emergency medical services teams and hospitals, does not seem to be achieved as well. Overall delays from onset to treatment were similar in both systems. The shorter prehospital delays counterbalance the longer in-hospital delays in the decentralized model.

Rates and delays of both systems have been published before In both systems, improvement for further reduction is lower than in previous years, postulating a beginning ceiling effect. Onset-to-door time though seems stable throughout the past 10 years. Possibly, structural changes (such as implementation of new Stroke Units) would have more effect on this latter delay, than educational programs. Hospital-based tPA rates increased in both systems with no ceiling effect to date.

There are several limitations when comparing different systems of care in different countries. First, we were not able to collect detailed information on patients eligible for thrombolysis who finally did not receive tPA. Therefore, we do not know how often delays were responsible for not treating patients. Previous population-based analyses have suggested an extra 30-minute delay would drop thrombolysis rates from 6.3% to 6.0%. As 97.6% of TEMPiS patients and 93% of HUCH patients received tPA within 4 hours of onset, the number of patients excluded because of just missing the 4½-hour time window is likely to be very small. Second, clinical outcomes are not available for the given time period for TEMPiS patients. Therefore, we cannot prove that the TeleStroke thrombolysis protocol was safe and the short delay actually improved patients’ outcome. Previous TEMPiS analyses, and those of other groups, however, have ruled out major differences in outcomes of patients with telethrombolysis compared with patients who received tPA in stroke centers. In addition, data from the Bavarian Stroke Registry indicate that overall in-hospital thrombolysis mortality in TEMPiS hospitals was 8.6%. This is almost identical to the overall Bavarian thrombolysis mortality rate (8.4%) and similar to the national registry in the United States (8.8%). Third, the emergency medical service may be organized differently in each system, influencing prehospital delay and prehospital selection. Fourth, alarm (or emergency call) time was not recorded in either of the 2 registries. Prealarm delay may be different in the 2 countries because of distinct stroke awareness, affecting overall delays beyond long distances to hospitals, thus limiting interpretation of prehospital delay. This should be studied in further prospective analyses. Fifth, as we have only included 1 system for each comparison, external validity is limited, as there are features that may be very network dependent. Also, some of the specific features of our 2 models of care may not be implementable in other settings because of different population densities, catchment areas, healthcare systems, and regional infrastructures. Comparison of 2 different systems of care is always challenging and bares many unknown and uncontrollable confounders. To increase validity, further multicenter comparison is warranted.

Conclusions

The results of our study indicate that a decentralized stroke system of care assisted by telemedicine can achieve equal thrombolysis treatment rates and onset-to-treatment delays in a predominantly rural, sparsely populated region as they are achieved in a mainly urban population with a centralized system.

Acknowledgments

We thank all staff members of Helsinki University Central Hospital and the participating hospitals in Telemedical Project for Integrative Stroke Care (TEMPiS) network that were involved in the care of our patients with stroke and all teleconsultants for their exceptional support. To increase validity, further multicenter comparison is warranted.

Disclosures

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References

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