Supplemental Online Content

Hubert GJ, Hubert ND, Maegerlein C, et al. Association Between Use of a Flying Intervention Team vs Patient Interhospital Transfer and Time to Endovascular Thrombectomy Among Patients With Acute Ischemic Stroke in Nonurban Germany. *JAMA.* Published online May 5, 2022. doi:10.1001/jama.2022.5948

Supplement 3**. Trial protocol**

This supplemental material has been provided by the authors to give readers additional information about their work.

Flying Intervention Team: Study description

15.07.2019

Introduction

The "Flying Intervention Team" project was launched on February 1, 2018. Its goal is to provide mechanical thrombectomy for stroke patients in Southeast Bavaria significantly faster than it was provided before.

The treatment success of mechanical thrombectomy is time-dependent: the later the occluded vessel is reopened, the lower the probability of achieving a good outcome (1–5). Since there are only few experts in rural regions available who are able to perform this procedure, the TEMPiS stroke network has initiated the Flying Intervention Team: If, in a TEMPiS cooperating clinic, a patient is telemedically identified as a candidate for thrombectomy, an intervention team consisting of a neuroradiologist and an angiography assistant is immediately flown to the clinic by helicopter to perform the procedure on-site. During the approach of the Flying Intervention Team, the patient is already prepared for the intervention in the angiography suite of the respective clinic. At the end of the thrombectomy, the patient remains at the TEMPiS clinic, while the intervention team is flown back to Munich. Since the start of the project, the new care structure has been available for 26 weeks/year between 8:00 am and 10:00 pm.

The teleconsultation teams of the two TEMPiS centers Regensburg (MedBo/Universitätsklinik) and München Klinik Harlaching along with the neuroradiological teams set the indication for thrombectomy. Five experienced interventional neuroradiologists of Klinikum rechts der Isar and München Klinik Harlaching were recruited for the intervention teams. In addition to their activities in the FIT project, all interventionalists continue to perform thrombectomies in the centers on a regular basis. The selection of the participating TEMPiS clinics is based on pre-defined minimum requirements. Subsequently, treatment standards (SOPs) for thrombectomy on-site as well as for post-procedural care, criteria for the deployment of the FIT team, and the elaboration of individual procedural protocols adapted to local conditions were developed. Intensive training and teaching rounds are used to familiarize all persons involved in the processes.

A registry has been established with the goal of recording process times, treatment and safety parameters as well a short- and long-term patient outcomes. All patients from TEMPiS clinics eligible for thrombectomy are included in the registry. Follow-up is also provided for patients potentially eligible for thrombectomy, who are transferred to a center for performing advanced imaging (CT perfusion) in order to test for a possible thrombectomy indication. Severe complications in the course of treatment are reported separately to the project management to enable timely quality assurance measures, if required. In two major safety meetings, the respective cases are additionally reviewed by external consultants.

The aim of thestudy is to answer two questions:

1. Can thrombectomy be performed faster by the Flying Intervention Team at the regional hospital than after the inter-hospital transfer of patients to a comprehensive stroke center (CSC)?
2. Is thrombectomy performed by the Flying Intervention Team at the regional hospital equivalent to thrombectomy after transfer to a CSC in terms of technical feasibility, safety, and clinical outcome?

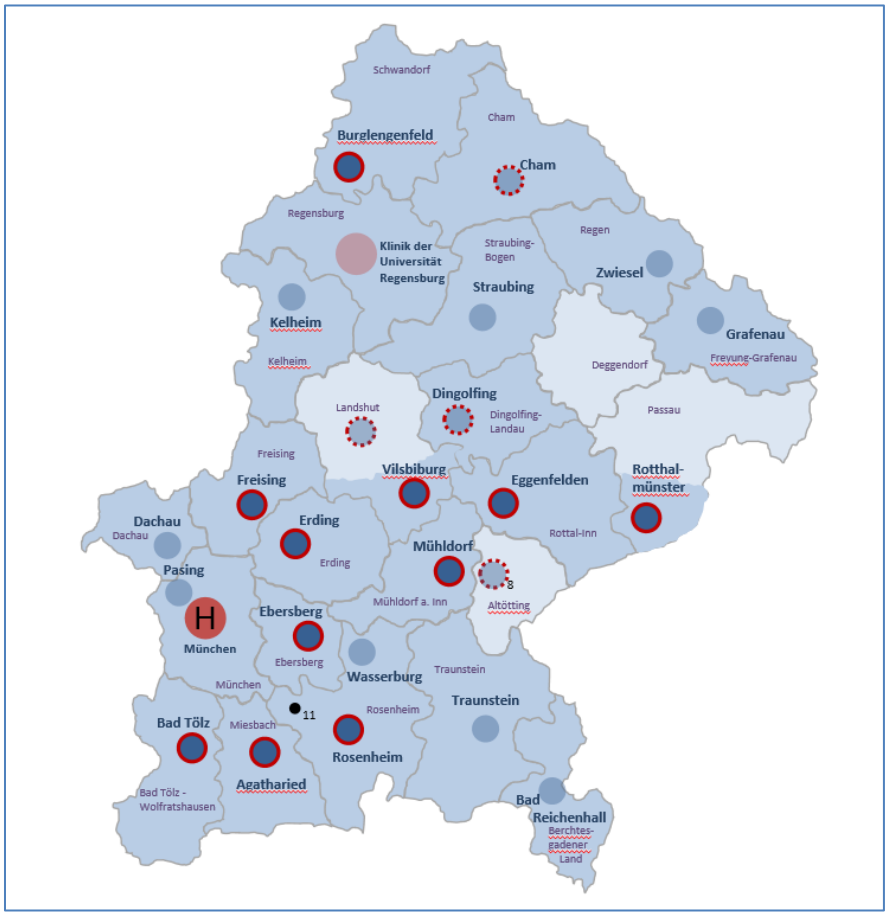

Figure 1: TEMPiS network in southeast Bavaria. Blue dots: TEMPiS cooperating clinics, red outer circle: TEMPiS clinics with existing FIT supply since February 1, 2018, red outer circle (dashed line): clinics with connection to FIT supply in 2019.; H: helicopter site;
TEMPiS clinics with existing FIT supply since February 1, 2018:
Krankenhaus Agatharied - Krankenhaus Agatharied GmbH, Asklepios Stadtklinik Bad Tölz GmbH, Asklepios Klinik Burglengenfeld - Asklepios Südpfalzkliniken GmbH, Kreisklinik Ebersberg gemeinnützige GmbH, Klinikum Landkreis Erding - Kommunalunternehmen des Landkreises Erding, Krankenhaus Eggenfelden - Rottal-Inn Kliniken Kommunalunternehmen, Klinikum Freising GmbH - Gemeinnützige Krankenhausgesellschaft des Landkreises Freising, Klinik Mühldorf a. Inn - Kreiskliniken des Landkreises Mühldorf a. Inn GmbH, RoMed Klinikum Rosenheim - RoMed Kliniken GmbH, Krankenhaus Rotthalmünster - Landkreis Passau Krankenhaus gGmbH, Krankenhaus Vilsbiburg - LAKUMED Kliniken Landshuter Kommunalunternehmen
Transfer centers:
Klinikum Harlaching - Städtisches Klinikum München GmbH, Klinikum rechts der Isar - Technische Universität München, Bezirksklinikum Regensburg - Medizinische Einrichtungen des Bezirks Oberpfalz, Krankenhaus Barmherzige Brüder Regensburg, Klinikum Passau Eigenbetrieb der Stadt Passau und Lehrkrankenhaus der Universität Regensburg.
Telemedical centers: Medizinische Einrichtungen des Bezirk Oberpfalz, Regensburg; München Klinik Harlaching

Methods

Study Design

The Flying Intervention Team is on call from 08:00 am to 10:00 pm in 26 of 52 weeks during the evaluation period. In FIT flight weeks, the Flying Intervention Team approaches patients eligible for

thrombectomy, who meet the indications for on-site intervention at the regional hospital, and thrombectomy is performed in the angiography facility on-site.

During the remaining weeks, patients are transferred to a stroke center for thrombectomy. If patients can not be approached within the FIT flight period, they are also transferred.
The analysis is supported by the Bavarian State Ministry of Health and Care and the Björn Steiger Foundation.

Patients

To compare the two concepts of care, basic requirements must be comparable between the groups; therefore, only patients who meet the following inclusion and exclusion criteria are included in the analysis:
Inclusion criteria:

i) Admission to one of the 11 participating primary stroke centers between February 1, 2018 and January 31, 2019
ii) Aged between 18 and 85 years
iii) Evidence of vessel occlusion of the middle cerebral artery (M1 or proximal M2), intracranial internal carotid artery or basilar artery
iv) Time window from symptom onset to decision for thrombectomy: 0-6h for anterior circulation occlusions, 0-24h for basilar artery occlusions, and 0-24h for anterior circulation occlusions with evidence of appropriate mismatch of on-site perfusion imaging
v) Decision for thrombectomy between 8.00 am and 10.00 pm
vi) Performance of mechanical thrombectomy

Exclusion criteria:

vii) ASPECTS < 6 (Alberta Stroke Program Early CT Score; scale of 0-10: 10 = irreversible damage not visible in any of the ten defined brain areas, 0 = irreversible damage visible in all ten defined brain areas)
viii) Premorbid functional status (need of assistance in everyday life) or more specifically a score > 3 on the modified Rankin Scale (mRS)
ix) Severe pre-existing conditions with significantly increased mortality (acute myocardial infarction < 7 days, severe heart failure, severe tumor disease, etc.)

Allocation of supply structure

The distribution of FIT weeks is freely chosen in the first six months of the study and randomized afterwards. Two 2-week blocks are randomly distributed in each 8-week block. Half of the weeks are allocated to the team of the Klinikum rechts der Isar and half to the team of München Klinik Harlaching. Departure points are the helipads of the two centers.

Data

Data for the comparison are taken from the FIT registry. Survey forms for the entire course of treatment (4 survey forms per patient) are created for the registry. The survey forms are completed by the teleconsultation team, the neurointervention team, the attending physicians of the TEMPiS clinics and the telephone interviewers of the 3-month follow-up. The establishment of the registry was

approved by the ethics committee of the Bavarian State Medical Association and reviewed by the data protection officer.

Data are collected prospectively, transferred to a central database, and double-checked. Individual data points that are not available in the existing survey forms are taken from the discharge letters of the in-patient stay. For FIT patients, the online mapping service Google Maps (Google LLC) is used to calculate the air-line distance between departure center and regional clinic. For transfer patients, the air-line distance between the regional clinic and the comprehensive stroke center is calculated.

Outcomes

The primary outcome is

- Time period from decision to thrombectomy to start of therapy (defined as groin puncture).

The outcomes regarding feasibility, safety and clinical outcome are

- clinical outcome at 3 months, measured by the modified Rankin Scale, which describes the extent of disability after stroke with a score ranging from 0-7 (0 = no deficit, 1 = minor deficit without limitations, 2 = deficit with limitations, 3 = dependence, but independent walking possible, 4 = dependence, independent walking no longer possible, 5 = bedriddenness, 6 = death),
- endovascular recanalization in the final angiogram as measured by the modified Thrombolysis in Cerebral Infarction (mTICI) score (0 = no perfusion; 1 = perfusion past the initial occlusion site with limited filling of peripheral branches and little or slow peripheral perfusion; 2a = perfusion of < 50% of the dependent flow area of the initially occluded vessel; 2b = perfusion of ≥ 50% of the dependent flow area of the initially occluded vessel; 3 = complete perfusion of the dependent flow area incl. all peripheral branches),
- 3-month mortality,
- symptomatic intracranial hemorrhage during in-patient stay,
- further complications during the procedure and during in-patient stay.

Definitions

The term "thrombectomy" is defined as endovascular treatment using at least one thrombectomy device, regardless of whether the thrombus was successfully removed. By definition, the timing of the decision to perform thrombectomy is the same as the timing of the decision to fly or transfer for the purpose of performing thrombectomy. The start of thrombectomy is defined as the time of puncture of the inguinal artery ("groin puncture"). Recanalization is defined as reopening of the occluded vessel with a perfusion of ≥ 50% of the dependent flow area (mTICI ≥ 2b) in the angiogram. The time of recanalization is defined as the time at which this very degree of perfusion is first achieved. In cases where the vessel can not be recanalized, the time of the last intracranial series of digital subtraction angiography (DSA) is used as a surrogate time point to calculate process times. Symptomatic intracranial hemorrhage is defined as any intracranial hemorrhage detected on control imaging during in-patient stay with simultaneous worsening of neurological status on the National Institute of Health Stroke Scale (NIHSS) of ≥ 4 points.

Statistical analysis:

Statistical analysis is performed using the IBM SPSS Statistics program (version 22.0). Baseline characteristics, procedural data, and outcomes are evaluated for both patient groups (on-site thrombectomy performed by the Flying Intervention Team vs. thrombectomy after transfer to a CSC). Continuous variables are presented by median and 1st and 3rd quartile (interquartile range), categorical variables by absolute (n) and relative (%) frequencies. Standard statistical procedures are performed to calculate two-sided p-values. For the continuous variables age, NIHSS, ASPECTS as well as for process times, nonparametric tests are used (Mann-Whitney U). For categorical variables, the chi-square test or, for small sample sizes, Fisher's exact test are performed. Values of $p < 0.05$ are considered significant.

References:

1. Saver JL, Goyal M, van der Lugt A, Menon BK, Majoie CBLM, Dippel DW, u. a. Time to Treatment With Endovascular Thrombectomy and Outcomes From Ischemic Stroke: A Meta-analysis. JAMA. 27. September 2016;316(12):1279–88.

2. Fransen PSS, Berkhemer OA, Lingsma HF, Beumer D, van den Berg LA, Yoo AJ, u. a. Time to Reperfusion and Treatment Effect for Acute Ischemic Stroke: A Randomized Clinical Trial. JAMA Neurol. Februar 2016;73(2):190–6.

3. Goyal M, Jadhav AP, Bonafe A, Diener H, Mendes Pereira V, Levy E, u. a. Analysis of Workflow and Time to Treatment and the Effects on Outcome in Endovascular Treatment of Acute Ischemic Stroke: Results from the SWIFT PRIME Randomized Controlled Trial. Radiology. Juni 2016;279(3):888–97.

4. Ribo M, Molina CA, Cobo E, Cerdà N, Tomasello A, Quesada H, u. a. Association Between Time to Reperfusion and Outcome Is Primarily Driven by the Time From Imaging to Reperfusion. Stroke. April 2016;47(4):999–1004.

5. Menon BK, Sajobi TT, Zhang Y, Rempel JL, Shuaib A, Thornton J, u. a. Analysis of Workflow and Time to Treatment on Thrombectomy Outcome in the Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE) Randomized, Controlled Trial. Circulation. 7. Juni 2016;133(23):2279–86.