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Senatsverwaltung für Inneres und Sport
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An den

Vorsitzenden des Hauptausschusses

über

den Präsidenten des Abgeordnetenhauses von Berlin

über

Senatskanzlei – G Sen –

Analyse der gesundheitsökonomischen Aspekte des STEMO und der Konsequenzen für das Land Berlin

rote Nummer: 1468,1468 A, 1468 B, 1468 C, 1468 D, 1468 F,1468 G, 1468 H, 1468 I, 1468 J

Vorgang: 79. Sitzung des Hauptausschusses vom 10. Juni 2015
80. Sitzung des Hauptausschusses vom 24. Juni 2015
91. Sitzung des Hauptausschusses vom 11. November 2015
107. Sitzung des Hauptausschusses vom 11. Mai 2016

Ansätze: entfällt

Gesamtausgaben: entfällt

Der Hauptausschuss hat in seiner 91. Sitzung Folgendes beschlossen:

„SenInnSport wird gebeten, dem Hauptausschuss zum Mai 2016 einen Folgebericht zur weiteren Entwicklung aufzuliefern."

Der Hauptausschuss hat in seiner 107. Sitzung am 11.05.2016 einer Fristverlängerung bis zum 22.06. 2016 zugestimmt.

Beschlussvorschlag:

Der Hauptausschuss nimmt den Bericht zur Kenntnis.

Hierzu wird berichtet:

1. Durch den Einsatz des STEMO bei der Schlaganfallversorgung wird die Zeit bis zur Initiierung der Lysebehandlung um durchschnittlich 25 Minuten verkürzt. Ziel des STEMO-Konzeptes ist es, die akute Schlaganfallbehandlung im prähospitalen Rettungsdienst zu be-

schleunigen und damit die Behandlungsprognose der Patientinnen und Patienten zu verbessern. Das STEMO hatte im Jahr 2015 insgesamt 629 (tatsächliche) Einsätze, wobei zu berücksichtigen ist, dass das Fahrzeug wegen eines Verkehrsunfalls zwei Monate außer Betrieb war. In den ersten vier Monaten des Jahres 2016 hatte das STEMO bereits 259 Einsätze. Inwieweit die betroffenen Patientinnen und Patienten durch den Einsatz des STEMO eine nachhaltig verbesserte Prognose haben, ist nur durch eine kontrollierte Studie mit Langzeit-Behandlungsergebnissen zu klären. Ein aktueller Registervergleich der Lysepatienten im STEMO und an der Charité zeigt eine Prognoseverbesserung in Bezug auf spätere Behinderungen, Pflegebedürftigkeit oder den Eintritt des Todes. Die kürzlich abgeschlossene Arbeit wurde beim Fachjournal Lancet Neurology eingereicht und angenommen (Anlage). Für einen endgültigen Nachweis der Prognoseverbesserungen durch den Einsatz von STEMO ist eine ausreichend kontrollierte Studie mit Langzeit- Behandlungsergebnissen erforderlich. Die finanziellen Mittel für eine Evaluationsstudie sind bis Mai 2018 durch die Charité sichergestellt.

2. Das über den Bezirk Marzahn - Hellersdorf beschaffte Fahrzeug befindet sich derzeit im Bau und wird voraussichtlich Ende 2016 in den Dienst der Berliner Feuerwehr genommen werden. Der Bau des Fahrzeuges wird von der Berliner Feuerwehr begleitet. Die Senatsverwaltung für Inneres und Sport als Fachaufsichtsbehörde für die Berliner Feuerwehr hat bereits die Übernahme und Nutzung des STEMO durch die Berliner Feuerwehr nach Erwerb durch das Bezirksamt erklärt. Für die Übernahme in den Regelbetrieb der Berliner Feuerwehr wird eine Nutzungsvereinbarung mit dem Unfallkrankenhaus Berlin (UKB) geschlossen werden.

   In dem Doppelhaushalt 2016 / 2017 sind Mittel für die Beschaffung von drei weiteren Stroke – Einsatzfahrzeugen eingestellt worden (1 Fahrzeug zum Austausch des aktuellen STEMO, ein weiteres Fahrzeug und 1 Reservefahrzeug). Die Planungsunterlage in Höhe von insgesamt 3,42 Mio € für die drei im Haushalt der Feuerwehr veranschlagten STEMO liegt vor. Die Ausschreibung der im Jahr 2016 zu beschaffenden Fahrzeuggestelle wurde begonnen. Die Fertigstellung durch entsprechende Aufbauten erfolgt im Jahr 2017.

3. Das bereits vorgestellte Konzept für eine Nutzung der STEMO – Fahrzeuge (Stand 30.10.2015) besteht unverändert. Danach wird das vom Bezirk Marzahn- Hellersdorf beschaffte Fahrzeug an der Feuerwache Marzahn stationiert werden. Der Standort des zurzeit betriebenen STEMO auf der Feuerwache Wilmersdorf hat sich bewährt und wird beibehalten werden. Der Standort gewährleistet auch in der am weitesten entfernten Einsatzzone noch einen zwanzigminütigen Zeitvorteil.
   Für das zu beschaffende dritte Fahrzeug ist die Stationierung an der Feuerwache Pankow vorgesehen.

Anlage
Artikel über den abgeschlossenen Registervergleich

In Vertretung

Bernd Krömer
Senatsverwaltung für Inneres und Sport

Functional outcomes of pre-hospital stroke thrombolysis compared to treatment in conventional care. A registry based comparison. The Stroke Emergency Mobile (STEMO) project

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Abstract:

Background: Specialized CT-equipped stroke ambulances shorten time to intravenous thrombolysis (IVT) in acute ischaemic stroke by pre-hospital start of treatment. Although IVT is known to be time-sensitive, direct effects of pre-hospital thrombolysis on clinical outcomes have not yet been shown.

Methods: We compared outcomes of consecutive ischemic stroke patients who received IVT either within the Stroke Emergency Mobile (STEMO) concept or within conventional care (normal ambulances and in-hospital care at the Charité Campus Benjamin Franklin Berlin) during STEMO operation times between February 5, 2011 and March 5, 2015. The STEMO operation area coveres approximately 1·3 million inhabitants of Berlin including almost the complete catchment area of the Campus Benjamin Franklin. Treatment and outcomes were documented in prospective STEMO-based or hospital-based registries. Primary outcome was three-month modified Rankin Scale (mRS) ≤1 in patients who had lived at home without assistance before stroke. Secondary outcomes were three-month mRS 0-3 and mortality. Outcomes were adjusted by multivariable logistic regression for demographics, co-morbidities and stroke severity. The trial is registered with ClinicalTrials.gov, number NCT02358772

Findings: Among 431 patients treated on STEMO and 509 in conventional care, 306 and 355 had lived at home without assistance pre-stroke, respectively. Median onset-to-treatment time was 72 (IQR: 53-120) minutes in STEMO compared to 112 (IQR: 85-175, p<0.01) minutes in conventional care. The primary outcome of mRS≤1 was observed in 161 (53%) and 167 (47%) patients, respectively (p=0·15); 254 (83%) vs 261 (74%), had mRS≤3 (p<0·01) and 17 (6%) vs 37 (10%), had died (p=0·02). In patients with complete documentation of co-variables (N=651), adjusted odds ratios were favourable for STEMO care: OR 1·40 (95%-CI: 1·00-1·96; p=0·052) for mRS≤1, OR 1·91 (95%-CI: 1·24-2·96; p<0.01) for mRS≤3 and OR 0·51 (95%-CI: 0·26-1·00; p=0·046) for death.

Interpretation: This study suggests that pre-hospital start of IVT may lead to improved outcome.

Funding: This study was funded by the Zukunftsfonds Berlin, the Technology Foundation Berlin with EU co-financing by the European Regional Development Fund (ERDF) via Investitionsbank Berlin (Grant No. 10142853) and the German Federal Ministry for Education and Research via the Center for Stroke Research Berlin grant.

Trials and meta-analyses have shown that effects of intravenous tissue plasminogen activator (tPA) in acute ischaemic stroke strongly depend on time from onset to start of tPA-infusion.[1|6] Large thrombolysis registries across health systems indicate that the majority of patients is treated relatively late.[7,8] The median onset-to-treatment times (OTT) of 144 min in the US 'Get-with-the-Guidelines Registry'[9] and of 140 min in the mainly European SITS-MOST registry[7] are clearly beyond the time window of highest effectiveness. Numbers needed to treat (NNT) were four to five in patients treated within 90 min, nine when treated 91-180 min and 14 when treated 181-270 min from onset.[4] Median OTT remained above 100min even in best practice models like those reported from Helsinki with centralized stroke care reporting reductions in door-to-needle time down to 20min.[10,11]

Two controlled studies in Germany have shown that acute stroke work-up and treatment on specialized stroke ambulances with integrated computed tomography (CT) scanners reduced OTT compared to conventional emergency medical services (EMS).[12,13] Both studies reported that the majority of patients treated before hospital arrival received tPA within 90min. Approximately one third of the patients treated on the Stroke Emergency Mobile (STEMO) during the Prehospital Acute Neurological Treatment and Optimization of Medical care in Stroke (PHANTOM-S) study received tPA within 60min.[14] The PHANTOM-S study raised no safety concerns regarding secondary haemorrhage or death within seven days. However, data protection restrictions did not allow three-month assessment of disability in patients who had not given written informed consent for follow-up. This applied to most patients who were cared by conventional EMS.[15] Hence, effects of pre-hospital thrombolysis on functional outcome could not be analysed.

Based on prospective registry data, we aimed to compare 3-month functional outcomes between patients who received IVT within the STEMO concept and patients who were given IVT in the conventional hospital-based system.

Methods:

This study compares three-month functional outcomes after IVT in consecutive acute ischaemic stroke patients entered in two separate pre-hospital and in-hospital thrombolysis registries (ClinicalTrials.gov Identifier: NCT02358772).

Study design and patients

Inclusion and exclusion criteria:

All patients with acute ischaemic stroke who received IVT during the study period from starting the STEMO service on February 5, 2011 until reaching the calculated case number, were included in the two registries (N=467 with STEMO care and N=751 with conventional care, see flow-chart in Figure 1). In the STEMO arm, this included patients treated during the pilot phase (Feb 5, 2011 – April 30, 2011), during the controlled trial phase (May 1, 2011 – Jan 31, 2013) and afterwards until the calculated case number was reached (Feb 1, 2013 – March 5, 2015).

In order to avoid bias between the two cohorts, we restricted our analysis to patients who were admitted to hospital either by primary EMS or by STEMO, i.e., not including patients with private transport or in-hospital stroke. For the same reason, we excluded patients with stroke onset between 10:31pm and 3:59am because these patients were unlikely to be cared for by STEMO (with operation times between 7:00 am and 11:00 pm for most of the evaluation period). We further excluded patients with unknown time of symptom onset (if last seen well not within 4·5 hours) who received IVT within the diffusion-FLAIR mismatch MRI concept,[22] patients with non-stroke discharge diagnosis and missing three-month follow-up.

Patients who were primarily cared for by STEMO but received IVT in hospital were analysed within the STEMO cohort based on an intention-to-treat approach. One patient who was cared by STEMO but received thrombolysis in-hospital despite a clear contraindication (ischaemic stroke ten days before) was neither included in the STEMO nor in the conventional care cohort.

The primary study population was restricted to patients who had lived at home without (private or professional) assistance before the event because only these patients had a realistic chance to survive without disability (mRS≤1) and to reach the primary endpoint. Information regarding pre-stroke living situation was obtained from standardized thrombolysis protocols.

Derivation of the methodological approach and Ethics

German data protection regulations require written informed consent for study-related assessment of disability. The majority of patients cared by conventional EMS during PHANTOM-S were neither seen by the STEMO team nor by the Charité University stroke trial team and were not accessible for written informed consent procedures, therefore.[15] Thus, functional outcome was not sufficiently available in the PHANTOM-S control group.

However, written informed consent was collected in almost all patient of the STEMO group and 3-month outcome was available, therefore. As 3-month outcome is regularly assessed in a prospective in-hospital stroke thrombolysis registry run as an ongoing quality assessment tool at the Campus Benjamin Franklin of the Charité [16,17] we compared patients who received IVT in both pre- and in-hospital models.

The ethics committee/institutional review board of the Charité – University Medicine (registration number: EA4/061/14) approved the study. The Charité hospital-based thrombolysis registry had previously been approved by the institutional data protection officer as a quality management tool that includes a routine telephone outcome assessment. Telephone follow-up in STEMO patients was initially performed only after written informed consent within the PHANTOM-S study. After transition of the STEMO concept into an ongoing emergency service, routine telephone follow-up was also allowed in this group for quality assessment purposes and retrospective 3-month follow up was collected from 11 patients who could not provide written informed consent during their acute treatment.

Procedures

Pre-hospital thrombolysis was performed using a STEMO vehicle operated by the Berliner Feuerwehr (Berlin Fire Brigade). STEMO is a specialized ambulance equipped with a CT-scanner and point-of-care laboratory and staffed with a paramedic, a radiology technician and a physician who is specialized in Neurology and Emergency Medicine.[15] Physicians working on STEMO have at least four years of clinical experience in Neurology and are employed at the Department of Neurology of the Charité University hospital. These physicians are involved in stroke care at the Charité when they are not on STEMO shift. Details of acute stroke care in STEMO have previously been described in detail.[13,18] Briefly, STEMO is alarmed by the dispatch centre of the Berlin Fire Brigade when an acute stroke is suspected during emergency calls.[19] In case of acute functionally disabling stroke symptoms and clinical eligibility for thrombolysis, head CT scan and blood analyses are performed at scene. Qualified CT interpretation is enabled by teleradiology. After exclusion of contraindications according to the standardized operating procedures (SOP) of the Charité University hospital, tPA treatment is initiated immediately on STEMO. Subsequently, patients are transferred to the nearest Stroke Unit for further in-hospital treatment. STEMO is operated within a radius of a 16-minutes travel for emergency vehicles from the base fire station (Figure 1).[15] This approach results in a catchment area of approximately 1·3 million inhabitants (roughly one third of Berlin's population). During the pilot phase[20] (February 5 to April 30, 2011), STEMO was operated from 7:00am to 7:00pm. During the controlled PHANTOM-S study[15] (May 1, 2011 to May 31, 2013), STEMO was operated as a two-shift service from 7:00am to 11:00pm. Afterwards, operation times had to be reduced again to a one-shift service from 7:00am to 7:00pm due to limited funding. During the pilot phase and after completion of the PHANTOM-S study, the STEMO service was repeatedly interrupted for technical releases, service and maintenance as well as staffing limitations resulting in 385 days of 16-hour service and 589 days of 12-hour service.

All acute stroke patients who receive IVT at the Charité University hospital, Campus Benjamin Franklin are entered in the ongoing in-hospital stroke thrombolysis registry.[16,17] The Campus Benjamin Franklin is located within the STEMO catchment area and in relatively short distance (nine minutes EMS transportation time) to the STEMO base station. There is a wide overlap of its own catchment area and the STEMO operation area (Figure 1).

Emergency stroke work-up includes clinical evaluation, emergency blood analysis and brain imaging, either by a dedicated stroke (research) MRI or by head CT (beyond MRI service times and if MRI is not feasible).[15] Eligibility for IVT is assessed according to the same SOPs as on STEMO. Over the last years, several measurements have been applied in order to shorten door-to-needle times including implementation of a stroke alarm and revisions of SOPs.[21]

Data acquisition and outcome definitions:

The two registries are prospectively run by separate research groups focusing on quality of care in pre-hospital[15] and in-hospital[17] stroke thrombolysis services. According to the pre-specified study protocol, the following information was collected in both registries: Demographics, co-morbidities, non-invasively measured blood pressure, blood glucose, time of onset if known/witnessed, time 'last seen well' if not known/witnessed, time of hospital arrival (in-hospital registry) or time of arrival at scene (pre-hospital registry), time of treatment start, co-treatment with intra-arterial therapy (e.g. mechanical thrombectomy or intra-arterial thrombolysis), NIHSS before thrombolysis, premorbid status of need of assistance, secondary intracerebral haemorrhage mentioned as symptomatic in the discharge letter, and death within seven days. As part of continuous quality assessment, functional outcome was evaluated in a standardized telephone interview as degree of disability according to the mRS [23,24] at three months after stroke. All raters were certified in performing mRS rating.

The primary outcome was living without disability as defined by mRS of 0-1 in patients who had lived without assistance at home. Secondary outcomes were living without severe disability (or being able

to ambulate without assistance) as defined by mRS of 0-3 and mortality at three month as well as ordinal analysis across the entire mRS.

Power Calculation and statistical analysis

After completion of the PHANTOM-S evaluation, a first comparison of consecutive patients treated on STEMO between February 5, 2011 and July 16, 2013 revealed a non-significant trend towards better outcomes in stroke patients treated on STEMO compared to patients who had received thrombolysis at Campus Benjamin Franklin. Therefore, we based our sample size calculation on results of the above-mentioned preliminary analysis (NCT02358772). In order to show a significantly higher probability for independent outcome (mRS≤1) on STEMO with an estimated odds ratio of 1·44 (95%CI: 1·09-1·91), 900 patients without pre-stroke need of assistance (with at least 33% STEMO patients) had to be included, resulting in a minimum of 297 STEMO patients. The adjusted proportion of patients with independent outcome was expected to be 49% (295 out of 603 patients) in the conventional care and 58% (N=172 out of 297 patients) in the STEMO group (two-sided test with significance level alpha of 0·05, test power: 70%).

We performed statistical tests according to the pre-specified analysis plan. We used the Mann-Whitney U test for comparison of continuous parameters. Pearson $\chi 2$ test was used to compare categorical variables. For the pre-defined primary and secondary outcomes, we additionally calculated multiple logistic regression models. We used NIHSS categories in accordance to the IST-3 trial[6] for adjustment of disability outcomes. Continuous NIHSS was used for adjustment of mortality as a consequence of the lower event number with limited number of co-variables. The pre-specified analysis plan did not include adjustment for two variables that showed differences between the two groups. Blood glucose before thrombolysis had a significant temporal relationship with OTT and was regarded as a time-dependent acute phase parameter. Mean arterial pressure (MAD = diastolic blood pressure + 1/3 (systolic – diastolic blood pressure) was higher in the STEMO care group, possibly related to increased stress during pre-hospital measurements. As these two observations may

therefore bias the results for the different times of measurement in the two groups, they were not entered in the primary logistic regression models. In a sensitivity analysis, we calculated adjusted odds ratios for mRS≤1 and mRS≤3 including glucose and MAD. Pre-specified sensitivity analyses were also conducted in the entire study cohort including patients with pre-stroke need of assistance or institutional care and the entire study cohort excluding patients with intra-arterial co-treatment. In addition to the above-mentioned co-variables, outcomes were adjusted for premorbid assistance status in these sensitivity analyses.

A two-sided significance level of $\alpha=0{\cdot}05$ was used. No correction for multiple testing was applied for secondary outcome analyses. Standardized plausibility checks were carried out under statistical supervision. For statistical analyses of the data, we used IBM SPSS Statistics version 22.

Role of the funding source:

None of the funding sources had a role in study design, in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Results

From February 5, 2011 to March 5, 2015, 940 patients with acute ischaemic stroke and IVT were enrolled in the two registries with 431 patients in the STEMO and 509 patients in the conventional care cohort. Of these patients, 306 (71%) and 355 (70%) patients had lived at home without assistance prior to the qualifying event, respectively. Patient selection is shown in Figure 2.

Except for more females and higher blood pressure values before tPA administration in the STEMO cohort, baseline parameter were balanced (Table 1).

Nineteen patients who initially received STEMO care without IVT but received IV-tPA later in hospital were analysed within the STEMO cohort. Reasons for withholding IVT in STEMO were therapy-resistant high blood pressure (n=1), inability to perform pre-hospital head-CT scan due to technical malfunction (n=3) or agitation (n=1), suspicion of subacute infarct demarcation in CT images (treatment only after MRI, n=2), symptom presentation suggestive for aortic dissection (n=1), unclear time of symptom onset at time of first assessment (n=2) or absence of disabling neurologic deficits (n=7) during first presentation, and decision against thrombolysis due to severe pre-stroke disability (n=2).

Baseline parameters are shown in Table 1. Mean OTT was 33 minutes shorter in STEMO patients (96±60min) compared to conventional care patients (129±55min, p<0·01). Significantly more patients in the STEMO cohort (n=188, 63% versus n=123, 35%, p<0·01) received tPA within 90min of onset.

In unadjusted analysis, the difference in primary outcome (mRS 0-1) was not significant (52·6 vs. 47·0%; p=0·15). While STEMO patients had a non-significant trend towards better outcomes over the entire mRS range (p for trend: 0·097), both dichotomized secondary outcomes (mRS 0-3 and mortality) were more favourable for STEMO patients. There were no significant differences in symptomatic haemorrhage rate or seven-day mortality (Table 2). Similar results were seen in the entire study cohort including patients with pre-stroke need of assistance, with a significantly lower symptomatic haemorrhage rate in the STEMO group (eTable 1).

In the primary study population, 303 patients in the STEMO and 348 patients in the conventional care cohort had complete data and were entered in the multivariable logistic regression analysis. After adjusting for co-variables, STEMO care had a higher probability of survival without disability (mRS 0-1: OR 1·40, 95%-CI: 1·00-1·96; p=0·052) but this difference did not reach the pre-specified level of statistical significance. All secondary outcomes remained favourable for the STEMO cohort (Table 3 and eTable 2).

Fewer patients of the primary study population received endovascular treatment in the STEMO cohort (10·2 vs. 14·6%, p=0.08). Within this subgroup, patients with STEMO care did not have better outcome in univariate analysis (mRS 0-1: 25·8 vs. 34·6%, p=0.40) or after adjustment for age and NIHSS (OR: 0.55, 95%-CI: 0.19-1.55).

Sensitivity analyses

In sensitivity analysis including mean arterial pressure and glucose as co-variables in logistic regression, odds ratios for mRS≤1 (OR 1·45, 95%-CI: 1·01-2·08; p=0·047) and mRS≤3 (OR 2·03, 95%-CI: 1·27-3·25; p<0·01) were both favourable for STEMO care.

In order to examine whether the study outcomes were influenced by hospital care at our institution, we entered hospital allocation (Campus Benjamin Franklin versus others) into the multiple regression analyses. Effects of STEMO care remained favourable (OR 1·58, 95%-CI: 1·16-3·32 for mRS≤1, OR 2·14, 95%-CI: 1·09-4·22 for mRS≤3 and OR 0·47, 95%-CI: 0·17-1·28 for mortality).

Sensitivity analyses of the entire study cohort with 423 patients in the STEMO cohort and 497 patients in the conventional care cohort yielded similar results after multiple logistic regression (eTable 3). After exclusion of patients with intra-arterial treatment, STEMO care remained beneficial (mRS≤1: OR 1·43, 95%-CI: 1·02-2·00; p=0·039, mRS≤3: OR 2·37, 95%-CI: 1·60-3·52; p<0·01, death: OR 0·48, 95%-CI: 0·30-0·78; p<0·01).

Discussion

Patients who were cared for within the STEMO concept received IVT approximately half an hour earlier compared to patients with conventional pre-hospital care and in-hospital thrombolysis. Our study suggests that these time-savings translate to better functional outcome at three months. Although the higher probability of survival without disability did not reach statistical significance, secondary outcomes were consistently more favourable in the STEMO cohort. Better outcomes for survival and survival without severe disability in the entire study cohort including patients with pre-stroke need of assistance strengthen these results.

This is the first study comparing functional three-month outcome in patients who received IVT in a specialized ambulance or in-hospital.

The findings of our study are in line with the results from large thrombolysis trials and registries indicating that earlier treatment translates into better functional outcome and lower mortality.[1,4,9] In a post-hoc analysis of the PHANTOM-S trial, patients who received IVT within the first 60 minutes from onset were more likely of being discharged home from acute hospital.[14] The fact that median OTT (112min; IQR: 85-175min) of the in-hospital thrombolysis cohort was much shorter than those reported in large registries (140min in SITS-MOST[7] and 144 in 'Get-With-The-Guidelines[9]) as well as the relatively short median door-to-needle time of 38min underline that STEMO effects were evaluated in a well-established stroke system of care. A quality improvement initiative in a wide variety of US hospitals including community hospitals could reduce median door-to-needle times from 77 to 67min[25]. However, it seems unlikely that optimization of in-hospital processes alone can achieve median onset-to-needle times like in the pre-hospital group between 72 (patients without dependency) and 80 min (all patients).

In addition to shorter time to treatment, the thrombolysis rate in STEMO was 50% higher compared to conventional care in the PHANTOMS-S trial (33% vs. 21%).[15] The present analysis – only analysing those patients who received IVT - might therefore not reflect the full potential of the STEMO approach.

In the subgroup of patients with intra-arterial co-treatment, STEMO care was not associated with improved outcome. Apart from the small case number, it should be considered that many of the interventions were performed before the new era of stent retrievers and the lower number of patients in the STEMO group may reflect a bias through early recanalisation after pre-hospital thrombolysis.

Several potential limitations should be considered in interpreting our results: First, this study compares patients who received pre-hospital care by one specialized ambulance and treated later in multiple hospitals with patients who had pre-hospital care by multiple normal ambulances and inpatient treatment in a single hospital. It appears unlikely that stroke treatment at the Campus Benjamin Franklin is associated with worse prognosis *per se*. Statistical characteristics of its catchment area indicate the South-West district (Steglitz-Zehlendorf) has the highest average inhabitant's socioeconomic status within Berlin[26] and entering hospital allocation (Campus Benjamin Franklin versus else) in the multiple regression analyses did not indicate that treatment at the Campus Benjamin Franklin was associated with less favourable outcome. Second, although data in both registries were collected prospectively with standardized mRS assessment by certified raters, data acquisition in both arms was performed by separate groups. Outcome assessment was therefore not blinded and we cannot rule out an information bias, particularly as interviewers of the STEMO arm were sometimes directly involved in patient care. However, those outcomes that are not or less prone to bias (mortality and being able to ambulate without assistance [mRS 0-3]) were clearly in favour of the STEMO cohort. Third, stroke severity was on average earlier assessed in STEMO than in conventional care. Given the natural course of stroke related deficits, stroke symptoms in STEMO patients may have improved or worsened until in-hospital assessment and treatment decision. With the very early start of treatment in a relevant proportion of STEMO patients, some of these patients may have had symptom remission until in-hospital evaluation and adjustment for stroke severity carries the inherent problem of such registry-based analyses.[9,27] Fourth, data of pre-hospital care were not documented in the hospital-based registry. Therefore, we cannot rule out that distances from next ambulance station to scene and from scene to admitting hospital were longer in the conventional care cohort. Because of that, time

savings in OTT by STEMO care could be overestimated. Fifth, 3-month functional outcome data of the pre-hospital IVT concept are currently only available from our Berlin project group. Generalisability of our results need to be confirmed in other settings. Finally, the nature of this registry-based comparison also includes the limitation that not all baseline parameters were balanced, some non-observed or non-documented confounders could not be included in adjusted analyses and (the rather low) lost-to-follow-up rate may introduce an additional bias. Conversely, this pragmatic approach helps to evaluate patient groups that are usually not included in randomized controlled trials. In our study, this applies to patients with pre-stroke need of assistance.

The results of this study suggest that time-saving by pre-hospital start of IVT in acute ischaemic stroke translates into improved functional outcome and survival. The results are in line with existing evidence of better clinical results with earlier start of treatment and can be interpreted in the way that very early treatment contributes considerably to the 'time is brain' relationship of acute reperfusion therapies. Given the limitations of this registry-based study, further large-scale prospective controlled trials are required and are currently in preparation to substantiate the accumulating evidence of outcome improvement within the stroke ambulance concept.

Declaration of interests:

Heinrich J. Audebert received speaker honoraria from Boehringer Ingelheim (BI, manufacturer of alteplase; not involved in any form in the trial) and speaker honoraria as well as honoraria for consultancy from Lundbeck Pharma (sponsor of trials with desmoteplase in stroke). Matthias Endres received honoraria for participation in advisory board meetings and symposia from Boehringer Ingelheim. Christian Nolte received speaker honoraria from BI. All other authors do not report any conflicts of interest.

Authors Contribution:

Alexander Kunz, MD: acquisition and interpretation of data; drafting and critical revision of the manuscript; final approval of the version to be published.

Martin Ebinger, MD: substantial contributions to the conception and design of the study, acquisition and interpretation of data; critical revision of the manuscript; final approval of the version to be published.

Frederik Geisler, MD: acquisition of data; critical revision of the manuscript; final approval of the version to be published.

Michal Rozanski, MD: acquisition of data; critical revision of the manuscript; final approval of the version to be published.

Carolin Waldschmidt, MD: acquisition of data; critical revision of the manuscript; final approval of the version to be published.

Joachim E Weber, MD: acquisition of data; critical revision of the manuscript; final approval of the version to be published.

Matthias Wendt, MD: acquisition of data; critical revision of the manuscript; final approval of the version to be published.

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Figure 1: Map of Berlin, Germany, with conventional EMS catchment areas and times of travel of STEMO vehicle (4, 8, 12, and 16minutes) from base fire station (large white dot) coded in different grey shades. Black dots indicate locations of Stroke Units in Berlin, Germany; large black dot indicates location of the Stroke Unit at Charité University Hospital, Campus Benjamin Franklin.


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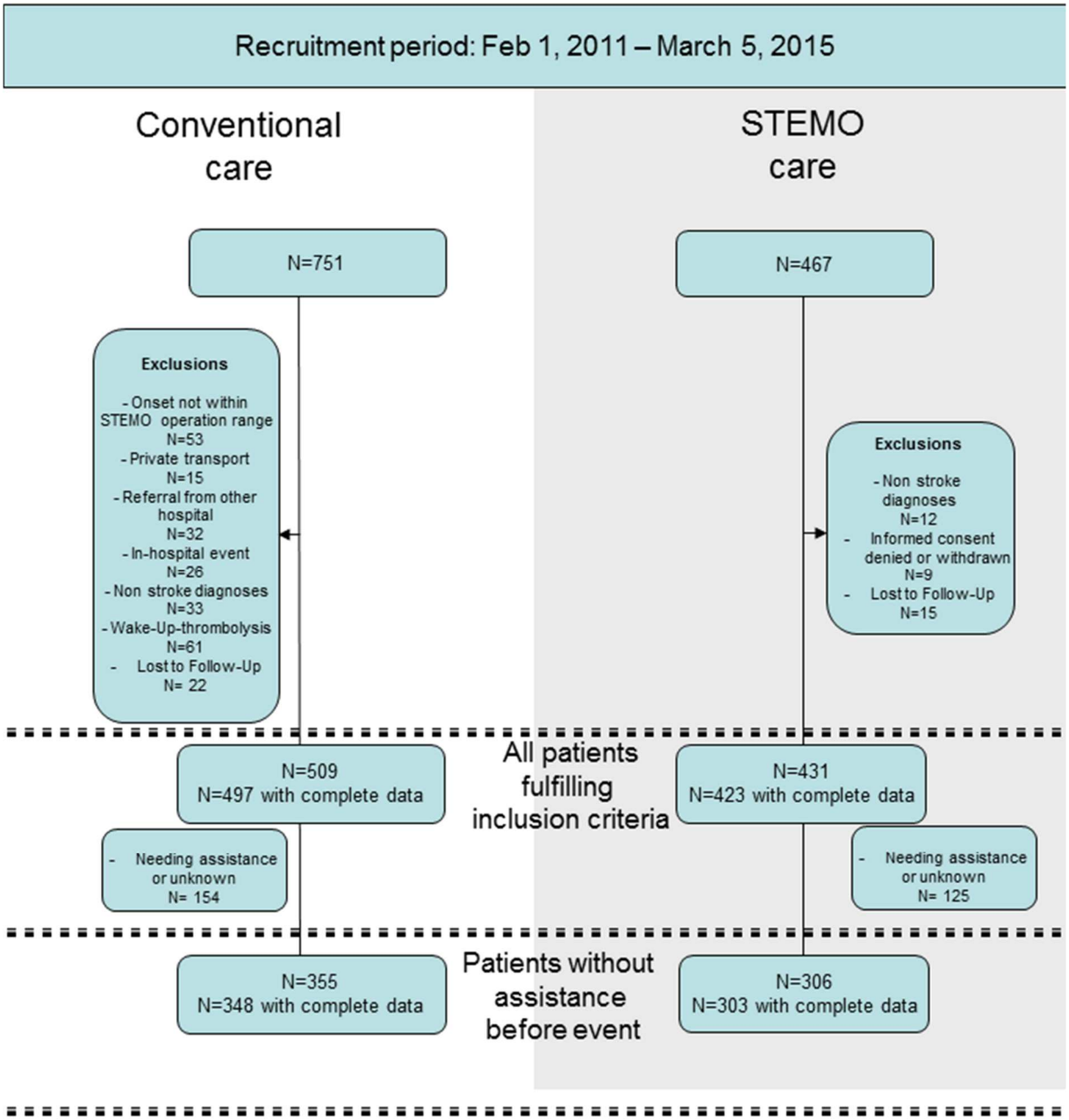
Figure 2: Patient selection in both registries



eFigure 1: Unadjusted outcome at 3 months according to modified Rankin Scale (mRS) by treatment group (in patients living at home without assistance before stroke)

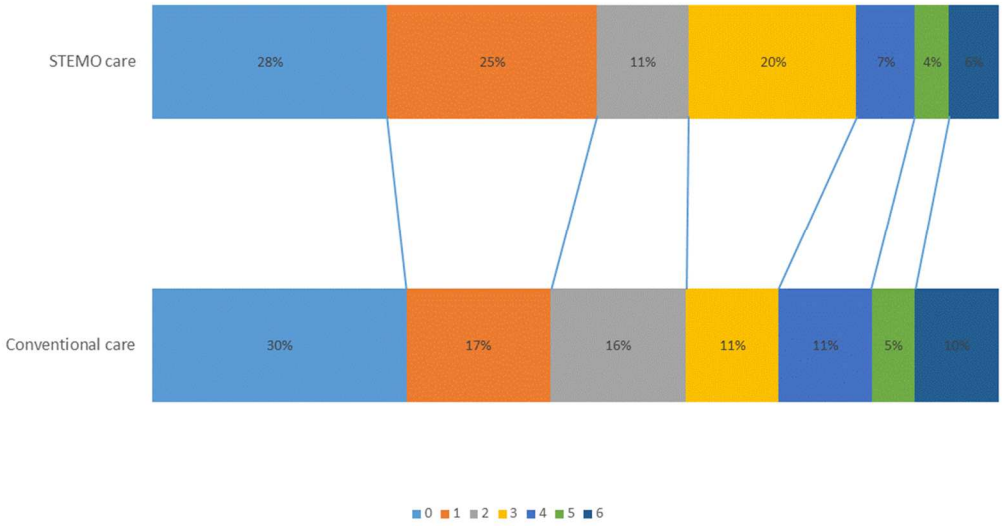


Table 1: Baseline parameters in patients living at home without assistance before stroke

	Conventional care (n=355)	***STEMO Care (n=306)***	***p-value***
Age in years, mean (median, IQR)	70·3 (72, 64-79)	70·7 (72, 63-79)	0·98
Female (%)	130 (36·6)	146 (47·7)	<0·01
Diabetes (%), 9 missing	78 (22·3)	64 (21·1)	0·71
Atrial fibrillation (%), 7 missing	106 (30·4)	101 (33·1)	0·45
Blood pressure before thrombolysis, mean (median, IQR) (mmHg)			
Systolic blood pressure, 16 missing	156·0 (135, 140-172)	163·1 (160, 140-180)	<0·01
Diastolic blood pressure, 18 missing	83·8 (82, 74-90)	93·3 (90, 80-100)	<0·01
Blood glucose before thrombolysis, mean (median, IQR) (mg/dl), 22 missing	135·6 (126, 110-151)	129·8 (119, 107-143)	0·066
NIH Stroke Scale at inclusion, mean (median, IQR)	8·9 (7, 4-13)	8·9 (7, 4-13)	0·53
Intra-arterial co-treatment (%)	52 (14·6)	31 (10·2)	0·081
Time from onset to deployment (dispatch), mean (median, IQR) (min), 95 missing	47 (28, 9-71)	49 (22, 8-64)	0.73
Time from alarm to thrombolysis, mean (median, IQR) (min), 73 missing	82 (76, 64-93)	48 (46 39-54)	<0.01
Time from admission to thrombolysis, mean (median, IQR) (min)	43·1 (38, 29-51)		
Time from onset to thrombolysis (min), 4 missing			
Mean (SD)	129·2 (55.4)	96·2 (60·3)	
Median, IQR	112 (85-175)	72 (53-120)	<0·01
Time from onset to thrombolysis ≤90min (%)	123 (34·6)	188 (62·5)	<0·01
Time from onset to thrombolysis ≤60min (%)	14 (3·9)	111 (36·9)	<0·01

Table 2: Outcomes in patients living at home without assistance before stroke

	Conventional care (n=355)	***STEMO Care (n=306)***	***p-value***
Symptomatic haemorrhages (%), 15 missing	17 (4·8)	9 (3·1)	0·28
7-day mortality (%), 4 missing	14 (4·0)	7 (2·3)	0·23
3 month outcome modified Rankin Scale (mRS)			
0 (%)	106 (29·9)	85 (27·8)	
1 (%)	61 (17·2)	76 (24·8)	
2 (%)	55 (15·5)	33 (10·8)	0·097*
3 (%)	39 (11·0)	60 (19·6)	(linear trend test)
4 (%)	38 (10·7)	22 (7·2)	
5 (%)	19 (5·4)	13 (4·2)	
6 (%)	37 (10·4)	17 (5·6)	
mRS ≤1 (%)	167 (47·0)	161 (52·6)	0·15
mRS ≤3 (%)	261 (73·5)	254 (83·0)	<0·01
3 months mortality (%)	37 (10·4)	17 (5·6)	0·023

Table 3: Adjusted odds ratios of outcomes. Patients living at home without help (multivariable logistic regression)

	Modified Rankin Scale ≤1 N=651 OR (95%CI)	**p-value**	**Modified Rankin Scale ≤3 N=651 OR (95%CI)**	**p-value**	**Mortality within 3 months N=651 OR (95%CI)**	**p-value**
Age (in years)	0·98 (0·97-1·00)	0·018	0·95 (0·93-0·97)	<0·01	1·05 (1·02-1·08)	<0·01
Female	0·69 (0·49-0·97)	0·033	1·09 (0·71-1·68)	0·70	0·83 (0·43-1·60)	0·58
Atrial Fibrillation	0·75 (0·51-1·09)	0·13	0·93 (0·60-1·46)	0·77	0·71 (0·36-1·40)	0·33
Diabetes mellitus	0·59 (0·39-0·89)	0·011	0·84 (0·51-1·39)	0·51	1·39 (0·66-2·94)	0·39
NIHSS as continuous variable					1·20 (1·14-1·26)	<0·01
NIHSS [a] 0-5 (reference)	1·0 (reference)		1·0 (reference)			
NIHSS [a] 6-10	0·51 (0·33-0·76)	<0·01	0·40 (0·22-0·74)	<0·01		
NIHSS [a] 11-15	0·27 (0·16-0·45)	<0·01	0·19 (0·10-0·36)	<0·01		
NIHSS [a] 16-20	0·19 (0·10-0·36)	<0·01	0·16 (0·08-0·32)	<0·01		
NIHSS [a] ≥ 20	0·11 (0·05-0·25)	<0·01	0·08 (0·04-0·16)	<0·01		
Intra-arterial co-treatment	0·88 (0·49-1·59)	0·67	0·49 (0·27-0·90)	0·021	1·75 (0·82 – 3·74)	0·015
Prehospital care by STEMO	1·40 (1·00-1·96)	0·052	1·91 (1·24-2·96)	<0·01	0·51 (0·26-1·00)	0·046

eTable 1: Baseline parameters and outcomes: All patients

	Conventional care (n=509)	***STEMO Care (n=431)***	***p-value***
Age in years, mean (median, IQR)	74·5 (75, 68-85)	74·6 (76, 67-84)	0·84
Female (%)	243 (47·7)	220 (51·0)	0·31
Diabetes (%), 17 missing	125 (25·0)	105 (24·8)	0·95
Atrial fibrillation (%) 12 missing	195 (39·0)	161 (37·6)	0·67
Blood pressure before thrombolysis, mean (median, IQR) (mmHg)			
Systolic blood pressure, 27 missing	155·0 (153, 138-170)	159·3 (160, 140-180)	0·03
Diastolic blood pressure, 29 missing	83·4 (81, 73-91)	90·6 (90, 80-100)	<0·01
Blood glucose before TPA, mean (median, IQR) (mg/dl), 29 missing	136·7 (126, 110-154)	134·2 (122, 108-149)	0·094
Pre-stroke assistance status, 11 missing			
Living at home without help (%)	355 (69·7)	306 (71·0)	<0·01
Living at home with private help (%)	21 (4·1)	48 (11·1)	
Living at home with nursing care (%)	22 (4·3)	20 (4·6)	
Living in institution (%)	100 (19·6)	57 (13·2)	
NIH Stroke Scale at inclusion, mean (median, IQR), 4 missing	9·8 (8, 4-15)	9·9 (8, 5-15)	0·57
Intra-arterial co-treatment (%)	57 (11·2)	34 (7·9)	0·09
Time from onset to deployment (dispatch), mean (median, IQR) (min), 113 missing	49 (28, 10-76)	54 (26, 10-79)	0.72
Time from admission to thrombolysis, mean (median, IQR) (min)	43·6 (38, 30-52)		
Time from alarm to thrombolysis, mean (median, IQR) (min), 3 missing	84 (79, 66-96)	50 (48, 40-56)	
Time from onset to thrombolysis (min), 8 missing			
Mean (SD)	133·7 (56.2)	102·6 (61.2)	<0·01
Median (IQR)	120 (86-177)	80 (57-129)	
Time to thrombolysis ≤60min (%)	17 (3·4)	127 (29·9)	<0·01
Time to thrombolysis ≤90min (%), 6 missing	155 (30·6)	241 (56·7)	<0·01
Symptomatic haemorrhage (%), 21 missing	30 (5·9)	15 (3·6)	0·11
7-day mortality (%), 11 missing	38 (7·5)	17 (4·0)	0·025
3 month outcome modified Rankin Scale (mRS)			

0 (%)	110 (21·6)	89 (20·6)	
1 (%)	70 (13·8)	79 (18·3)	
2 (%)	64 (12·6)	39 (9·0)	
3 (%)	57 (11·2)	96 (22·3)	0·042
4 (%)	67 (13·2)	42 (9·7)	(linear
5 (%)	43 (8·4)	31 (7·2)	trend test)
6 (%)	98 (19·3)	55 (12·8)	
mRS ≤1 (%)	180 (35·4)	168 (39·0)	0·25
mRS ≤3 (%)	301 (59·1)	303 (70·3)	<0·01
3 months mortality (%)	98 (19·3)	55 (12·8)	<0·01

eTable 2: Ordinal regression for mRS at 3 months

	Patients living at home without help[a] n=638, pseudo r^2=0·11 p=0·01 for STEMO care	All patients[b] n=908, pseudo r^2=0·16 p=0·003 for STEMO care
mRS:1-6 (ref: mRS: 0)	1·09 (0·76-1·56)	1·07 (0·75-1·51)
mRS: 2-6 (ref: mRS: 0-1)	0·79 (0·57-1·10)	0·85 (0·62-1·15)
mRS: 3-6 (ref: mRS: 0-2)	0·91 (0·64-1·29)	0·91 (0·67-1·24)
mRS: 4-6 (ref: mRS: 0-3)	0·50 (0·33-0·76)	0·50 (0·36-0·71)
mRS: 5-6 (ref: mRS: 0-4)	0·56 (0·33-0·94)	0·59 (0·41-0·85)
mRS: 6 (ref: mRS: 0-5)	0·54 (0·29-1·03)	0·56 (0·37-0·86)

[a] adjusted for age, gender, NIHSS (log-transformed) , intra-arterial co-treatment, glucose (log-transformed),

[b] adjusted for age, gender, NIHSS (log-transformed), intra-arterial co-treatment, glucose (log-transformed), pre-stroke assistance status

Adjusted odds ratios and 95%CI for STEMO care (ref: conventional care without STEMO), partial proportional odds model package gogolit 2 Stata.

eTable 3: Adjusted analyses of endpoints for patients; all patients (multivariable logistic regression)

	Modified Rankin Scale ≤1 **N=920** **OR (95%CI)**	**p-value**	**Modified Rankin Scale ≤3** **N=920** **OR (95%CI)**	**p-value**	**Mortality within 3 months** **N=920** **OR (95%CI)**	**p-value**
Age (in years)	0·98 (0·97-1·00)	0·019	0·95 (0·93-0·96)	<0·01	1·05 (1·02-1·07)	<0·01
Female	0·78 (0·56-1·07)	0·13	1·28 (0·89-1·85)	0·19	0·60 (0·38-0·97)	0·036
Atrial Fibrillation	0·77 (0·54-1·09)	0·14	0·98 (0·68-1·41)	0·90	0·89 (0·57-1·39)	0·61
Diabetes mellitus	0·58 (0·40-0·85)	<0·01	0·88 (0·59-1·31)	0·54	1·27 (0·79-2·03)	0·33
Living at home without help	1·0 (reference)		1·0 (reference)		1·0 (reference)	
Living at home with private help	0·18 (0.08-0.40)	<0·01	0·47 (0·26-0·87)	0·017	2·50 (1·18-5·31)	0·017
Living at home with nursing care	0·05 (0·01-0·35)	<0·01	0·28 (0·13-0·60)	<0·01	4·04 (1·75-9·34)	<0·01
Living in institution	0·14 (0·07-0·29)	<0·01	0·14 (0·08-0·24)	<0·01	4·82 (2·66-8·74)	<0·01
NIHSS [a] 0-5 (reference)	1·0 (reference)		1·0 (reference)		1·0 (reference)	
NIHSS [a] 6-10	0·57 (0·39-0·83)	<0·01	0·58 (0·36-0·96)	0·032	1·41 (0·67-2·94)	0·37
NIHSS [a] 11-15	0·27 (0·17-0·43)	<0·01	0·23 (0·14-0·39)	<0·01	3·03 (1·47-6·26)	<0·01
NIHSS [a] 16-20	0·17 (0·09-0·31)	<0·01	0·13 (0·07-0·23)	<0·01	7·04 (3·41-14·50)	<0·01
NIHSS [a] ≥ 20	0·10 (0·05-0·23)	<0·01	0·07 (0·04-0·14)	<0·01	14·08 (6·47-30·64)	<0·01
Intra-arterial co-treatment	0·95 (0·53-1·70)	0·85	0·53 (0·30-0·94)	0·029	2·04 (1·05-3·94)	0·035
Prehospital care by STEMO	1·31 (0·95-1·80)	0·10	1·97 (1·38-2·82)	<0·01	0·53 (0·34-0·82)	<0·01

[a] NIHSS = National Institutes of Health Stroke Scale

“Post-hoc analysis of the dichotomized outcome mRS≤2 after 3 months:

Adjusted analysis mRS≤2 after 3 months in the entire study cohort did not result in a significant benefit of STEMO care (OR: 1.02, 95%-CI: 0.74-1.42; p=0.90).”