

Original Investigation

Effect of the Use of Ambulance-Based Thrombolysis on Time to Thrombolysis in Acute Ischemic Stroke

A Randomized Clinical Trial

Martin Ebinger, MD; Benjamin Winter, MD; Matthias Wendt, MD; Joachim E. Weber, MD; Carolin Waldschmidt, MD; Michal Rozanski, MD; Alexander Kunz, MD; Peter Koch, MD; Philipp A. Kellner, MD; Daniel Gierhake, MD; Kersten Villringer, MD; Jochen B. Fiebach, MD; Ulrike Grittner, PhD; Andreas Hartmann, MD; Bruno-Marcel Mackert, MD; Matthias Endres, MD; Heinrich J. Audebert, MD; for the STEMO Consortium

IMPORTANCE Time to thrombolysis is crucial for outcome in acute ischemic stroke.

OBJECTIVE To determine if starting thrombolysis in a specialized ambulance reduces delays.

DESIGN, SETTING, AND PARTICIPANTS In the Prehospital Acute Neurological Treatment and Optimization of Medical care in Stroke Study (PHANTOM-S), conducted in Berlin, Germany, we randomly assigned weeks with and without availability of the Stroke Emergency Mobile (STEMO) from May 1, 2011, to January 31, 2013. Berlin has an established stroke care infrastructure with 14 stroke units. We included 6182 adult patients (STEMO weeks: 44.3% male, mean [SD] age, 73.9 [15.0] y; control weeks: 45.2% male, mean [SD] age, 74.3 [14.9] y) for whom a stroke dispatch was activated.

INTERVENTIONS The intervention comprised an ambulance (STEMO) equipped with a CT scanner, point-of-care laboratory, and telemedicine connection; a stroke identification algorithm at dispatcher level; and a prehospital stroke team. Thrombolysis was started before transport to hospital if ischemic stroke was confirmed and contraindications excluded.

MAIN OUTCOMES AND MEASURES Primary outcome was alarm-to-thrombolysis time. Secondary outcomes included thrombolysis rate, secondary intracerebral hemorrhage after thrombolysis, and 7-day mortality.

RESULTS Time reduction was assessed in all patients with a stroke dispatch from the entire catchment area in STEMO weeks (3213 patients) vs control weeks (2969 patients) and in patients in whom STEMO was available and deployed (1804 patients) vs control weeks (2969 patients). Compared with thrombolysis during control weeks, there was a reduction of 15 minutes (95% CI, 11-19) in alarm-to-treatment times in the catchment area during STEMO weeks (76.3 min; 95% CI, 73.2-79.3 vs 61.4 min; 95% CI, 58.7-64.0; $P < .001$). Among patients for whom STEMO was deployed, mean alarm-to-treatment time (51.8 min; 95% CI, 49.0-54.6) was shorter by 25 minutes (95% CI, 20-29; $P < .001$) than during control weeks. Thrombolysis rates in ischemic stroke were 29% (310/1070) during STEMO weeks and 33% (200/614) after STEMO deployment vs 21% (220/1041) during control weeks (differences, 8%; 95% CI, 4%-12%; $P < .001$, and 12%, 95% CI, 7%-16%; $P < .001$, respectively). STEMO deployment incurred no increased risk for intracerebral hemorrhage (STEMO deployment: 7/200; conventional care: 22/323; adjusted odds ratio [OR], 0.42, 95% CI, 0.18-1.03; $P = .06$) or 7-day mortality (9/199 vs 15/323; adjusted OR, 0.76; 95% CI, 0.31-1.82; $P = .53$).

CONCLUSIONS AND RELEVANCE Compared with usual care, the use of ambulance-based thrombolysis resulted in decreased time to treatment without an increase in adverse events. Further studies are needed to assess the effects on clinical outcomes.

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← Editorial page 1615

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Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The STEMO Consortium members are listed at the end of the article.

Corresponding Author: Martin Ebinger, MD, Klinik und Hochschulambulanz für Neurologie, Charité-Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany (martin.ebinger@charite.de).

Stroke is a leading cause of death and disability.¹ In acute ischemic stroke, thrombolysis with intravenous tissue plasminogen activator (tPA) is the treatment of choice after exclusion of intracerebral hemorrhage by brain imaging.² Neurons die rapidly during ischemia, and randomized placebo-controlled trials have shown time-dependent benefits of tPA: early treatment is associated with better outcomes.³⁻⁷ Within 90 minutes of symptom onset, the number needed to treat for 1 excellent outcome is 4.5; the number is 9 between 91 and 180 minutes and 14 between 181 and 270 minutes.⁵ However, only a minority of stroke patients receive tPA,⁸ and in a European stroke registry only 11% of this minority were treated within the first 90 minutes.⁹ Apart from delayed patient response, prehospital and intrahospital management (“onset-to-door” and “door-to-needle”) contribute to delays. Onset-to-door times range from 46 to 150 minutes,¹⁰ and recent data from the United States indicate that less than 30% of patients have a door-to-needle time within the recommended 60 minutes.^{2,8} Recently, one study reported time saving in 12 tPA administrations performed in a special ambulance with integrated computed tomography (CT) scanner and point-of-care laboratory.¹¹ Little is known about the overall effects and risks of specialized ambulances for patients with stroke and also for patients with other diseases. After a 3-month pilot study with the Stroke Emergency Mobile (STEMO),¹² we investigated the effects of its deployment on time to treatment and safety in a larger controlled study.¹³

Methods

The Prehospital Acute Neurological Treatment and Optimization of Medical care in Stroke Study (PHANTOM-S) was conducted in Berlin, Germany. Berlin has an established stroke care infrastructure with 14 stroke units treating approximately 11 000 stroke patients per year (median age, 74 years; 49.6% male; 66.3% arriving at hospitals via ambulances).¹⁴ A quality audit of these stroke units revealed a 13% intravenous thrombolysis rate in 2012.¹⁵ The Berlin Fire Brigade (Berliner Feuerwehr) organizes the Berlin emergency medical system and runs the dispatch center. Standard policy is to transport patients with suspected stroke to hospitals with stroke units. In Berlin, emergency physicians accompany ambulances attending critically ill patients. However, for patients with acute stroke, they are deployed only if patients have reduced consciousness or unstable vital signs.

Study Design

PHANTOM-S is a randomized-week, open-label clinical trial. The study was conducted in accordance with the published protocol and approved by the Charité Ethics Committee.¹³ The STEMO consortium consisted of the Charité-Universitätsmedizin Berlin, Berliner Feuerwehr, MEYTEC (Werneuchen, Germany), and Thermo Scientific BRAHMS (Hennigsdorf, Germany). The intervention included a stroke identification algorithm at dispatcher level,¹⁶ an ambulance (STEMO)

equipped with a CT scanner plus point-of-care laboratory, and a specialized prehospital stroke team.^{12,13} The CT facility (CereTom, NeuroLogica; adaptation and integration by MEYTEC) was approved by the Berlin State Authority for Radiation Protection (LaGeTSt) and the entire ambulance was certified by the German Technical Inspection Association (TÜV). Telemedicine technology (VIMED-STEMO, MEYTEC) assured teleradiology communication between STEMO and a neuroradiologist on call. All equipment on board had CE marking (conformity marking for products sold in Europe). The point-of-care laboratory offered tests for blood count, electrolytes, creatinine, glucose, and international normalized ratio (INR).

Preliminary data on feasibility, technical reliability, and safety were established in a 3-month pilot phase with 23 patients receiving thrombolysis.¹² For the current randomized study, we allocated weeks to either STEMO services (STEMO weeks) or routine care (control weeks). For randomization, we used 2 alternative blocks of 4 weeks, either “STEMO-control-STEMO-control” or “control-STEMO-control-STEMO.”¹³ To evaluate STEMO effects on overall stroke care, we compared the prespecified outcome parameters of all patients included during STEMO weeks with those of control weeks.¹³ However, we expected that STEMO would not be available for a substantial proportion of patients during STEMO weeks. To assess the effects on stroke care in patients for whom STEMO was available and deployed, we compared patients for whom STEMO was deployed with patients of the control week. To avoid a selection bias in favor of STEMO, we also included patients in the STEMO deployment group who had emergency care in STEMO but received tPA after hospital arrival and patients with STEMO cancellation.

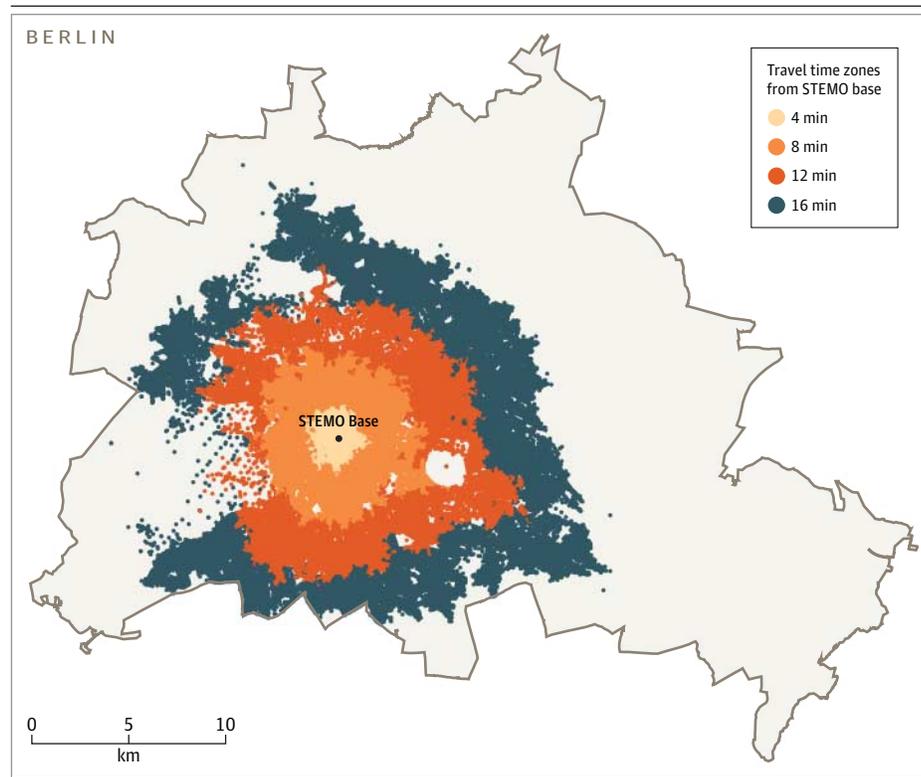
Patients

The study catchment area included about 1.3 million inhabitants and was predefined as being within 16 minutes of travel (75% probability) for emergency vehicles from base (Figure 1). Patients were included if the emergency call dispatcher activated a stroke dispatch, independent of randomized weeks or STEMO availability. Symptom onset had to be either within 4 hours or unknown. The 4-hour cutoff was chosen to allow for travel and diagnostic work-up prior to the end of the 4.5-hour tPA time window. If symptom onset remained unknown during the emergency call, the emergency team tried to establish symptom onset after arrival. Patients younger than 18 years or with known pregnancy were excluded. Only emergency calls between 7:00 AM and 11:00 PM Monday to Sunday were included during STEMO weeks or control weeks. If a stroke dispatch was activated during a control week or during a STEMO week but STEMO was not available (because of simultaneous calls or maintenance), patients received routine care. The dispatcher algorithm was the same during STEMO and control weeks.

Interventions

On board the STEMO were a neurologist, a paramedic, and a radiology technician. The neurologists (involving 7 persons)

Figure 1. Map of Berlin, Germany, With Color-Coded STEMO Catchment Area Around STEMO Base



The Stroke Emergency Mobile (STEMO) catchment area (colored zones) is defined by a 75% probability of reaching the emergency site within 16 minutes from base (Fire Station 3400, Berlin-Wilmersdorf). Courtesy of the Berliner Feuerwehr.

were physicians with at least 4 years of training in clinical neurology and special emergency medical training that included at least 6 months of full-time work experience on an intensive care unit, 80 hours of teaching certified by the medical board, practical training in obstetrics and pediatrics, and supervised emergency treatments in the field. The paramedics of the Berlin fire brigade (comparable with an emergency medical technician or paramedic) had at least 2 years of emergency care training. The radiology technicians, all with a background of 2 years of professional education, received 3 months of additional training in emergency care. During STEMO weeks, both STEMO and a first-response ambulance with a paramedic were dispatched simultaneously. First responders were capable of cancelling STEMO without further explanation based on their assessment. On STEMO arrival, the neurologist assessed the patient and called the neuroradiologist for endorsement of CT indication if suspicion of stroke and time from onset within 4.5 hours were confirmed. At a minimum, INR, complete blood count, and blood glucose were determined with the point-of-care laboratory. After undergoing CT scans and exclusion of contraindications, patients received tPA within 4.5 hours of symptom onset according to European guidelines.¹⁷ The standard treatment criteria used at Charité University hospitals were applied on STEMO. Age older than 80 years, previous stroke in diabetic individuals, and concomitant epileptic seizure were not regarded as absolute contraindications. Patients who were able to communicate were asked for informed consent for STEMO-specific care before tPA was

given. In accordance with ethics approval and standard in-hospital routine, we did not withhold tPA from patients who could not communicate because of coma or severe dysphasia (waived consent).

After tPA administration, patients were transported to the nearest adequately equipped hospital with a stroke unit. Summary reports were printed and CT images were saved on compact disc on board the STEMO for hand over to hospital staff on arrival.

Outcome Measures

The primary outcome of duration from alarm to thrombolytic treatment was defined as the time the dispatcher activated the alarm to tPA bolus administration.¹³ Secondary end points included in-hospital mortality, separately analyzed in patients with stroke and nonstroke diagnoses, and tPA treatment rates. Safety parameters of patients with tPA treatment after STEMO deployment comprised intracerebral hemorrhage (ICH) on imaging after thrombolysis and mortality and were compared with patients receiving conventional care (combining patients during control weeks with patients during STEMO weeks but without STEMO deployment). Symptomatic ICH was reported for patients treated in STEMO and defined as any new hemorrhage on brain imaging in the context of any decline in neurological status.³ For calculation of the thrombolysis rate (tPA frequency in ischemic stroke), we excluded patients with thrombolysis occurring in other parallel stroke studies or based on MRI in patients with unknown time of onset.

Patients who initially presented after complete symptom remission or without disabling symptoms but received thrombolysis after symptom recurrence or progression were not included in calculations of alarm-to-tPA and other process times. For calculations of onset-to-tPA times, time of onset was considered to be the time the patient was last known well prior to start of stroke symptoms.²

Adverse events were registered and adjudicated by the safety board. Three-month survival rates among patients who received tPA in STEMO and provided informed consent were assessed using standard telephone follow-up. Vital status was otherwise collected from community registration offices.

Data Collection

The ethics committee, the Berlin State data protection regulatory office, and the data protection representatives of participating hospitals allowed the collection of (1) personal information for patients after informed consent or (2) deidentified information for patients who could not be approached for informed consent. Informed consent for data use was obtained in STEMO or as soon as possible during in-hospital stay. The dispatch center informed participating hospitals of patients included in the study; the clinical course of their hospital stay and 3-month vital status in patients with tPA treatment were documented in case report forms. An abbreviated version was used for nonstroke patients. The case report forms were sent with alphanumeric codes to the Center for Stroke Research Berlin. Using these codes, data were linked with deidentified data sets of included patients provided by the dispatch center and the Berlin Stroke Registry. Additional information was retrieved from the STEMO documentation system and 3-month telephone follow-up, the latter only among patients with signed informed consent. Data monitoring and audits were performed by an independent quality management team at the Center for Stroke Research Berlin. We restricted our analyses to hospitals with at least 10 admissions of patients.

Statistical Analyses

Details of sample size calculation and statistical analyses have been described previously.¹³ Sample size calculations revealed that 456 patients were required for a power of 90% to detect a 20-minute difference between groups. The study had to be stopped if 8 or more deaths within 7 days among the first 75 patients or 16 or more deaths within 7 days among the first 204 patients occurred after prehospital thrombolysis (including the 23 patients from the pilot study). If a continuous parameter was normally distributed, we applied the *t* test for independent samples. For nonnormally distributed data, we used the Mann-Whitney U test. Pearson χ^2 test or Fisher exact test was used to compare categorical variables. For the safety end points, we additionally calculated univariate and multiple logistic regression models. A 2-sided significance level of $\alpha = .05$ 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 21 (IBM SPSS).

Results

During the 21-month study period from May 1, 2011, to January 31, 2013, a stroke dispatch was activated 7098 times by the dispatch center (Figure 2). We analyzed data for 6182 patients with inpatient information provided by 28 hospitals (3213 patients during STEMO weeks, 2969 during control weeks). STEMO could not be deployed for 1409 patients (44%) during STEMO weeks because STEMO was already in operation (1288 patients, 91%) or undergoing service and maintenance (139 hours; 121 patients, 9%).

Except for slightly lower rates of atrial fibrillation and diabetes mellitus among patients during control weeks, baseline parameters were balanced (Table 1). No significant differences were seen for 7-day in-hospital mortality between treatment groups, both across the entire cohort and in the subgroups of patients with a cerebrovascular diagnosis (2.3% in control weeks, 2.9% in STEMO weeks, and 2.9% after STEMO deployment; $P = .33$ and $P = .41$, respectively) and a noncerebrovascular diagnosis (2.1% in control weeks, 1.6% in STEMO weeks, and 2.0% after STEMO deployment; $P = .33$ and $P = .87$, respectively) (Table 2).

Interventions

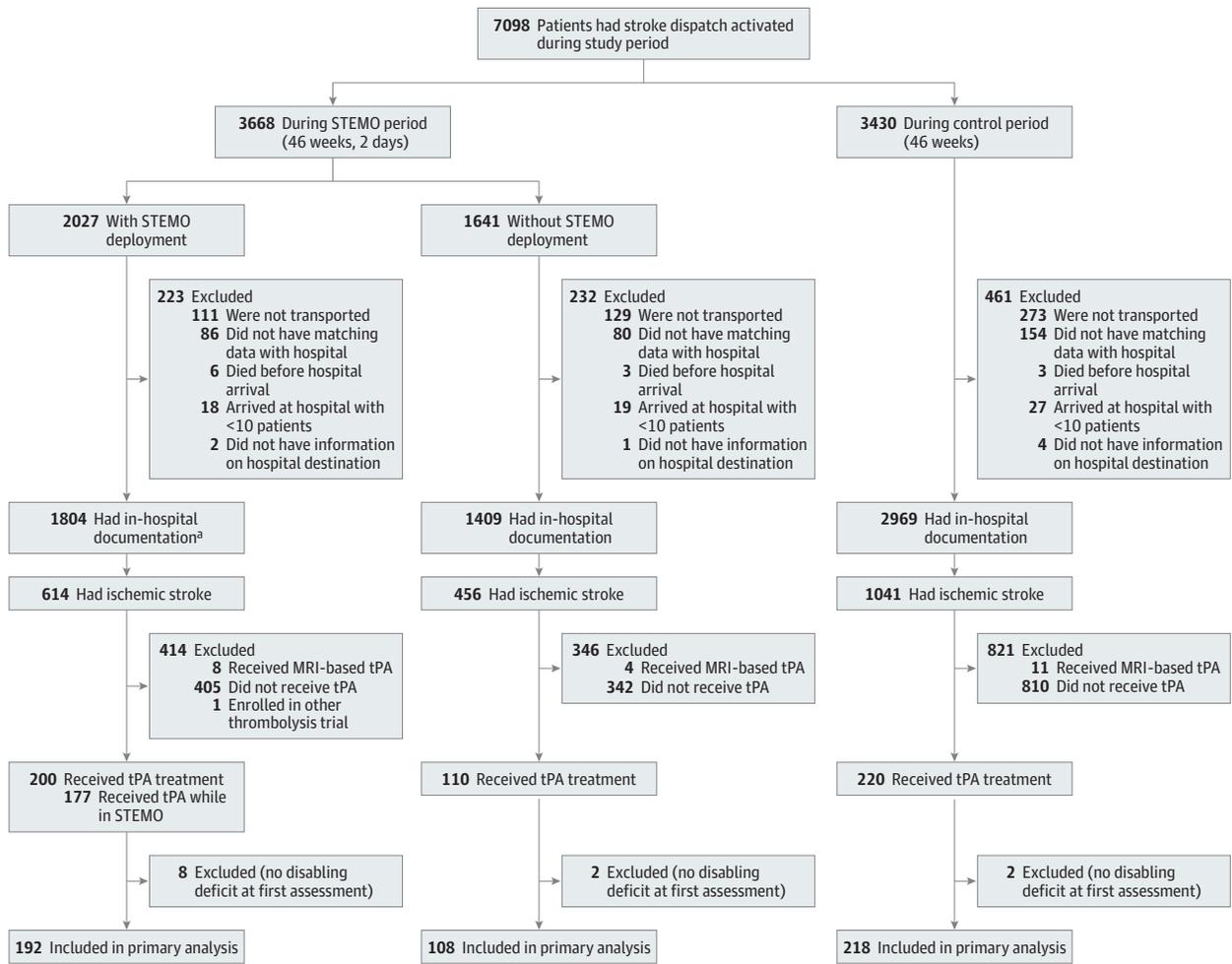
Fewer patients with cerebrovascular disease were transported to hospitals without a stroke unit during STEMO weeks (107 patients, 7.1%) and after STEMO deployment (48 patients, 5.5%) than during control weeks (186 patients, 12.7%; both $P < .001$).

Twenty-three patients with unknown symptom onset received tPA after MRI in hospital, and 1 patient (after STEMO deployment) was enrolled in another placebo-controlled thrombolysis study. These patients (13 in STEMO weeks, 11 in control weeks) were not included in further analyses regarding tPA treatment.

The rate of tPA treatment in ischemic stroke was higher after STEMO deployment (200/614, 32.6%) and during STEMO weeks (310/1070, 29.0%) than during control weeks (220/1041, 21.1%; both $P < .001$). The thrombolysis rate in patients during STEMO weeks without STEMO deployment was 24.1% (110/456). Proportions of patients treated within 90 minutes from onset were 58% after STEMO deployment, 48% during STEMO weeks, and 37% in control weeks ($P < .001$ and $P = .02$, respectively).

Of 1804 STEMO deployments, 349 were cancelled before STEMO arrival (6 of these patients received tPA in hospitals). The remaining 1455 patients received emergency care in STEMO (including 559 patients with acute ischemic stroke). Seventeen patients with ischemic stroke received emergency care in STEMO but were treated with tPA only after hospital arrival. Reasons for this postponed tPA administration were blood pressure above 180/110 mm Hg ($n = 1$), agitation precluding CT imaging ($n = 2$), not judged as eligible for tPA by STEMO physicians (decision overridden by hospital physician, $n = 6$), and symptom progression or early recurrence after hospital arrival ($n = 8$). Among the patients for whom tPA was started in STEMO (177/200 tPA treatments after STEMO de-

Figure 2. Study Flowchart According to STEMO Weeks and Control Weeks



During Stroke Emergency Mobile (STEMO) weeks, there were 2027 patients with STEMO deployment; 1804 of these patients had in-hospital documentation. Patients without disabling neurological deficits at first assessment who received thrombolysis after a secondary worsening or recurrence of symptoms were excluded from primary outcome

analysis. MRI indicates magnetic resonance imaging; tPA, tissue plasminogen activator.

^a Of these deployments, 349 were cancelled before STEMO arrival (6 of these patients received tPA in hospitals).

ployment), mean (SD) alarm-to-tPA time was 47.5 (11) minutes (median, 47 min; IQR, 39-54 min).

Outcomes

Outcomes are shown in Table 2. For primary outcome analyses, we excluded 10 of 310 patients receiving tPA during the STEMO weeks (8 after STEMO deployment) and 2 of 220 during control weeks because these patients had no disabling neurological deficits at first assessment but received tPA after a secondary worsening or recurrence of symptoms. We included 300 of 310 patients from the STEMO weeks with 192 of 200 patients from the STEMO deployment group and 218 of 220 from control weeks in the analysis of the primary outcome. Compared with control weeks, mean alarm-to-treatment time reduction was 15 minutes (95% CI, 11-19) among patients during STEMO weeks (76.3 min; 95% CI, 73.2-79.3 vs 61.4 min; 95% CI, 58.7-64.0; *P* < .001) and 25

minutes (95% CI, 20-29) among patients receiving tPA after STEMO deployment (51.8 min; 95% CI, 49.0-54.6; *P* < .001). The null hypothesis of no difference between alarm-to-treatment times was rejected in all sufficiently powered analyses stratified according to dichotomized age and National Institutes of Health Stroke Scale (NIHSS) (eTable 1 in the Supplement). Times from alarm to imaging, alarm to INR, alarm to blood count, and imaging to treatment were all shorter during STEMO weeks and after STEMO deployment than during control weeks. Proportions of patients who received tPA after knowledge of INR were higher in the STEMO groups (STEMO deployment, 92%; STEMO weeks, 87%) compared with the control weeks (79%).

Analyses of available data on functional outcome after 3 months can be found in eTables 2 through 4 in the Supplement. In a post hoc multiple regression analysis, the odds ratio (OR) for discharge home from acute hospital after STEMO

Table 1. Baseline Characteristics of Patients in STEMO Groups Compared With Control Weeks

	Patients With STEMO Deployment	P Value ^a	Patients During STEMO Weeks	P Value ^a	Patients During Control Weeks
All Patients					
No. of patients	1804		3213		2969
Age, mean (SD), y	73.9 (15.0)	.40	73.9 (15.0)	.34	74.3 (14.9)
Male sex, No. (%)	795 (44.1)	.46	1424 (44.3)	.50	1341 (45.2)
Comorbidities, No. (%)					
Atrial fibrillation	440 (24.4)	.04	756 (23.5)	.10	646 (21.8)
Diabetes mellitus	451 (25.0)	.02	782 (24.3)	.03	652 (22.0)
Discharge diagnoses, No. (%)					
Nonneurological	520 (28.8)		935 (29.1)		795 (26.8)
Neurological, noncerebrovascular	418 (23.2)	.30 ^b	762 (23.7)	.12 ^b	714 (24.0)
Neurological, cerebrovascular	866 (48.0)		1516 (47.2)		1460 (49.2)
Cerebrovascular discharge diagnoses (from CVD), No (%)					
Transient ischemic attack	182 (21.0)		328 (21.6)		315 (21.6)
Ischemic stroke	614 (70.9)		1070 (70.6)		1041 (71.3)
Intracerebral hemorrhage	45 (5.2)	.94 ^c	78 (5.1)	.87 ^c	67 (4.6)
Subarachnoid hemorrhage	3 (0.3)		7 (0.5)		4 (0.3)
Others	22 (2.5)		33 (2.2)		33 (2.3)
Patients With Ischemic Stroke Treated With Thrombolysis					
No. of patients	200		310		200
Age, mean (SD)	76.6 (12.4)	.22	75.9 (12.7)	.34	74.9 (13.1)
Male sex, No. (%)	92 (46.0)	.53	153 (49.4)	.95	108 (49.1)
Comorbidities, No. (%)					
Atrial fibrillation	69 (34.5)	.78	113 (36.5)	.44	73 (33.2)
Diabetes mellitus	50 (25.0)	.91	83 (26.8)	.56	54 (24.5)
Stroke severity, NIHSS scores^d					
At treatment (7 missing), mean	10.5	.04	10.0	.12	9.2
Median (IQR)	8 (5-17)		8 (5-15)		7 (4-13)
Groups according to IST-3^e (7 missing), No. (%)					
0-5	61 (30.5)		101 (32.8)		81 (37.7)
6-10	53 (26.5)		87 (28.2)		59 (27.4)
11-15	30 (15.0)	.19 ^e	45 (14.6)	.64 ^e	33 (15.3)
16-20	32 (16.0)		48 (15.6)		29 (13.5)
≥20	24 (12.0)		27 (8.8)		13 (6.0)

Abbreviations: CVD, cerebrovascular disease; IST-3, third International Stroke Trial; NIHSS, National Institutes of Health Stroke Scale; STEMO, Stroke Emergency Mobile.

^a Tested against control weeks.

^b P value for comparison of discharge diagnoses (nonneurological, neurological but noncerebrovascular, and cerebrovascular) between groups.

^c P value for comparison of different cerebrovascular diseases between groups.

^d NIHSS scores describe stroke-related neurological deficits and range from 0 (no symptoms) to 42; strokes with scores above 20 are considered very severe.

^e P value for comparison of NIHSS groups according to IST-3^e between groups.

deployment was 1.16 (95% CI, 0.77-1.74; P = .48) when adjusting for age, sex, atrial fibrillation, diabetes status, and NIHSS groups.

Safety in Patients With tPA Treatment

Among patients with tPA treatment, there were 5 patients (2.2%) with final nonstroke diagnoses during control weeks, 5 (1.6%) during STEMO weeks, and 4 (2.0%) after STEMO deployment. There were no significant differences in rates of ICH or death between the groups (Table 2).

In multiple regression analyses adjusting for age and NIHSS score, tPA treatment after STEMO deployment was associated with a nonsignificantly lower probability of ICH (7/200 in STEMO deployment group vs 22/323 in conventional care, OR, 0.42; 95% CI, 0.18-1.03; P = .06) (Table 3).

There was no association between treatment after STEMO deployment and deaths.

In patients who received tPA in STEMO, ICH occurred in 7 patients (3.5%) with 4 (2.2%) of them fulfilling National Institute of Neurological Disorders and Stroke symptomatic ICH criteria. Twenty-nine additional serious adverse events were reported for patients treated with tPA in STEMO. None of these events was adjudicated as being clearly related to STEMO-specific interventions by the safety board (1 respiratory and 1 neurological worsening during transportation were judged as possibly related to STEMO intervention).

There were no breakdowns of the CT scanner but 1 breakdown of the compact disc writer and printer (handwritten hand over) as well as 1 malfunction of the blood cell counter (noticed during daily inspection).

Table 2. Outcomes in All Patients and Patients With Ischemic Strokes Receiving Thrombolysis Comparing STEMO Groups With Control Weeks

	Patients With STEMO Deployment	P Value ^a	Patients During STEMO Weeks	P Value ^a	Patients During Control Weeks
All Patients					
No. of patients	1804		3213		2969
Days in hospital (5 missing), mean (95% CI)	6.4 (6.0-6.7)	.92	6.3 (6.0-6.5)	.89	6.2 (6.0-6.5)
Median (IQR)	5 (0-9)		5 (0-9)		5 (1-9)
In-hospital deaths, No. (%) [95% CI]					
Within 7 d	44 (2.4) [1.8-3.3]	.63	72 (2.2) [1.8-2.8]	.96	66 (2.2) [1.8-2.8]
Total (12 missing)	62 (3.4) [2.7-4.4]	.32	116 (3.6) [3.0-4.3]	.41	119 (4.0) [3.4-4.8]
Patients With Ischemic Stroke Treated With Thrombolysis					
No. of patients	200		310		220
Process indicators					
Days in hospital, mean (95% CI)	9.3 (8.3-10.2)	.37	9.0 (8.3-9.7)	.38	8.9 (7.9-10.0)
Median (IQR)	7 (5-12)		7 (5-11)		7 (5-11)
INR known before start of tPA (1 missing), No. (%) [95% CI]	184 (92.0) [87.4-95.0]	<.001	270 (87.1) [82.9-90.4]	.009	172 (78.5) [72.6-83.5]
Patients treated within 90 min of symptom onset, No. (%) [95% CI]	115 (57.5) [50.6-64.1]	<.001	149 (48.1) [42.6-53.6]	.02	82 (37.4) [31.3-44.0]
Onset-to-treatment time (1 missing), mean (95% CI), min	102.7 (93.9-111.5)	<.001	110.1 (103.4-116.8)	.003	118.5 (111.8-125.2)
Median (IQR), min	81 (56-129)		95 (65-142)		105 (81-145)
Clinical outcomes, No. (%) [95% CI]					
Hemorrhagic complications	7 (3.5) [1.7-7.0]	.18	15 (4.8) [3.0-7.8]	.45	14 (6.4) [3.8-10.4]
In-hospital deaths	14 (7.0) [4.2-11.4]	.79	20 (6.5) [4.2-9.8]	.97	14 (6.4) [3.8-10.4]
Primary safety end point					
Deaths within 7 d (1 missing)	9 (4.5) [2.4-8.4]	.99	14 (4.5) [2.7-7.5]	.99	10 (4.5) [2.5-8.2]
Discharge home, post hoc	87 (43.5) [36.8-50.4]	.39	134 (43.2) [37.8-48.8]	.31	105 (47.7) [41.2-54.3]
Death within 90 d (4 missing)	33 (16.7) [12.1-22.5]	.21	48 (15.6) [12.0-20.1]	.30	27 (12.4) [8.7-17.4]
Times in tPA Treatments at First Assessment^b					
No. of patients	192		300		218
Hospital door to needle, mean (95% CI), min					
Median (IQR), min					42.0 (39.1-44.9)
Alarm to hospital arrival, mean (95% CI), min					
Median (IQR), min	84.6 (80.8-88.5)	<.001	66.9 (63.2-70.6)	<.001	34.6 (33.5-35.7)
Alarm to imaging, mean (95% CI), min					
Median (IQR), min	84.5 (72-95)		71 (36-89)		34 (29-40)
Imaging to treatment, mean (95% CI), min					
Median (IQR), min	37.7 (35.6-39.7)	<.001	44.0 (42.0-46.0)	<.001	52.4 (50.3-54.4)
Alarm to INR, mean (95% CI), min					
Median (IQR), min	35 (30-42)		39 (32-52)		50 (43-59)
Alarm to blood cell count, mean (95% CI), min					
Median (IQR), min	14.1 (12.4-15.8)	<.001	17.4 (15.7-19.0)	<.001	23.8 (21.6-26.1)
Primary end point					
Alarm to treatment (1 missing), mean (95% CI), min	30.8 (28.4-33.2)	<.001	40.4 (36.6-44.3)	<.001	74.9 (55.5-94.3)
Median (IQR), min	26 (20-37)		35 (23-50)		48 (39-70)
Alarm to treatment (1 missing), mean (95% CI), min	35.1 (32.1-38.2)	<.001	42.6 (38.7-46.4)	<.001	78.0 (55.4-100.7)
Median (IQR), min	31 (24-41)		37 (27-51)		48 (39-62)
Primary end point					
Alarm to treatment (1 missing), mean (95% CI), min	51.8 (49.0-54.6)	<.001	61.4 (58.7-64.0)	<.001	76.3 (73.2-79.3)
Median (IQR), min	48 (39-56)		55 (44-75)		72 (62-85)

Abbreviations: INR, international normalized ratio; IQR, interquartile range; STEMO, Stroke Emergency Mobile; tPA, tissue plasminogen activator.

^a Tested against control weeks.

^b Patients without disabling neurological deficit at first assessment who received tPA after secondary worsening or recurrence of symptoms were excluded from time analyses.

Discussion

Our study showed that the ambulance-based thrombolysis was safe, reduced alarm-to-treatment time, and increased thrombolysis rates. With a single STEMO prototype and total ser-

vice time of less than 1 year, we were able to treat close to 1500 patients in a catchment area of 1.3 million inhabitants. Time to thrombolysis, one of the most crucial parameters for outcome after acute ischemic stroke,¹⁸ was 25 minutes shorter when tPA was administered after STEMO deployment. This reduction in alarm-to-treatment time is composed of reduced

Table 3. Adjusted Analyses of Safety End Points for Patients With Thrombolysis

	Secondary Intracerebral Hemorrhage (29 Events) (n = 523) ^a				Mortality Within 7 Days (24 Events, 1 Missing) (n = 522) ^a				Mortality Within 90 Days (74 Events, 4 Missing) (n = 519) ^a			
	No. of Events	Total No. of Patients	OR (95% CI)	P Value	No. of Events	Total No. of Patients	OR (95% CI)	P Value	No. of Events	Total No. of Patients	OR (95% CI)	P Value
Age, decades			1.28 (0.91-1.78)	.15			1.55 (1.03-2.32)	.04			2.52 (1.80-3.52)	<.001
Female sex	16	267	1 [Reference]		11	266	1 [Reference]		45	264	1 [Reference]	
Male sex	13	256	NS ^b		13	256	NS ^b		29	255	1.42 (0.77-2.62)	.26
No atrial fibrillation	20	340	1 [Reference]		14	339	1 [Reference]		37	337	1 [Reference]	
Atrial fibrillation	9	183	NS ^b		10	183	NS ^b		37	182	0.95 (0.53-1.70)	.86
No diabetes mellitus	24	389	1 [Reference]		18	388	1 [Reference]		53	385	1 [Reference]	
Diabetes mellitus	5	134	NS ^b		6	134	NS ^b		21	134	NS ^b	
NIHSS score												
At treatment, per point (7 missing) ^c			1.07 (1.01-1.13)	.03			1.12 (1.05-1.19)	<.001				
0-5 (reference) ^c									6	180	1 [Reference]	
6-10 ^c									14	145	2.74 (1.00-7.49)	.05
11-15 ^c									14	78	5.49 (1.96-15.41)	.001
16-20 ^c									21	76	8.68 (3.19-23.65)	<.001
≥20 ^c									19	40	24.48 (8.20-73.08)	<.001
Patients without STEMO deployment	22	323	1 [Reference]		15	323	1 [Reference]		41	321	1 [Reference]	
Patients with STEMO deployment	7	200	0.42 (0.18-1.03)	.06	9	199	0.76 (0.31-1.82)	.53	33	198	1.02 (0.58-1.82)	.94

Abbreviations: NIHSS, National Institutes of Health Stroke Scale; NS, not significant; OR, odds ratio; STEMO, Stroke Emergency Mobile.

^a Sample size of multiple regression.

^b Not significant in univariate logistic regression; therefore, no odds ratio was calculated in adjusted analyses.

^c Event rates for secondary intracerebral hemorrhage and mortality within 7 days did not allow for further adjustment according to NIHSS subgroups, which was used for mortality within 90 days. Scores range from 0 (no symptoms) to 42; strokes with scores above 20 are considered very severe.

alarm-to-imaging time and imaging-to-treatment time. The effects of STEMO cannot be attributed to 1 single factor alone. The time reduction was achieved by starting treatment prior to transportation, with speedy clinical and ancillary examinations preventing double assessments and time-consuming hand overs. The time reduction for the whole catchment area, albeit significant, was diluted by more than 1400 patients (44%) during STEMO weeks for whom STEMO was not available. Simultaneous stroke dispatches occurred 1288 times and additional STEMO vehicles would have offered better coverage. Nevertheless, even the 15-minute time reduction detected in the catchment area has been associated with better outcomes in larger cohorts.⁷

These effects have to be weighed against costs of the STEMO concept. Depending on the configuration of the vehicle, a single STEMO ambulance costs about €1 million (US\$1.4 million). Cost-effectiveness analyses by an independent research group who also takes personnel costs into account are currently under way. With similar numbers of tPA treatments in clinical situations mimicking stroke (such

as paresis after epileptic seizures, migraine aura, conversion disorders), the thrombolysis rate in patients with ischemic stroke was increased by more than 50% compared with regular care and entailed no safety hazards. Several reasons might have contributed to this rise in treatment rates. First, patients otherwise presenting too late for thrombolysis were shifted into the time window of tPA; 10 patients in the STEMO deployment group received tPA 241 to 270 minutes after onset but would have been very unlikely to receive tPA in conventional care. Second, some patients who received tPA in the prehospital setting may have experienced spontaneous recovery if untreated before hospital arrival (transient ischemic attacks). Third, more patients were admitted to hospitals with a stroke unit, increasing the likelihood of tPA treatment there. Fourth, some patients (n = 8) had no disabling deficits during prehospital assessment but received tPA after worsening at arrival in the emergency department. Fifth, the STEMO team had special expertise in assessing patients for thrombolysis, making it less likely suitable patients would be missed.

A limitation in our study was the use of randomized time periods rather than randomization at patient level. This was because informed consent in Germany cannot be given via telephone. With only 1 STEMO prototype vehicle, our single-city study can be interpreted as monocentric, even though treatment occurred at multiple centers after hospital admission. Generalizability may therefore be limited. Furthermore, physicians are regularly engaged in prehospital care in the German health system. In other countries, ambulances are equipped with paramedics only, and there may be a shortage of vascular neurologists. Telemedicine may facilitate implementation and reduce costs,¹⁹ but there is an ongoing debate about the reliability of videoconferencing in emergency vehicles.²⁰

Functional outcome as measured with the modified Rankin Scale at 3 months was a prespecified secondary outcome parameter in the study protocol. However, data on this outcome are incomplete (Supplement). This was due to the German data protection legislation requirement for written informed consent before patients can be approached for follow-up assessment. Such informed consent was available for the majority of patients treated with tPA in STEMO but could not be retrieved from most patients treated in conventional care, particularly among patients who were treated in external hospitals. Even with complete 3-month outcome data, the study would not have been powered to detect differences in functional outcome. However, there is a well-established association between earlier treatment and increased benefit,^{5-7,21} and guidelines emphasize that

tPA should be given as soon as possible (class I, level of evidence A).² The post hoc analysis of discharge status was in line with expected time-dependent treatment effects, albeit not significant.

Strengths of the study include the size of our study sample with 28 documenting hospitals. The control group received high-quality care with a 21% thrombolysis rate and a median door-to-tPA time of 36 minutes, well below the 68 minutes (mean) and 78 minutes (median) reported from international and US thrombolysis registries.^{8,22} Even shorter median door-to-tPA times of less than 30 minutes have been reported.^{23,24} However, prehospital times in these reports were rather long (106 and 73 minutes, respectively). STEMO can shorten the entire rescue chain, shifting treatment start into the ultra-early therapeutic window. This may seem counterintuitive because STEMO places time-consuming diagnostics in the prehospital phase despite a broad agreement that prehospital times should be kept at a minimum. STEMO challenges this dogma and sets an example that with advancing technology, certain time-critical interventions might preferably be performed before hospital arrival.

Conclusions

Compared with usual care, the use of ambulance-based thrombolysis resulted in decreased time to treatment without an increase in adverse events. Further studies are needed to assess the effects on clinical outcomes.

ARTICLE INFORMATION

Author Affiliations: Department of Neurology, Charité-Universitätsmedizin Berlin (Ebinger, Winter, Wendt, Weber, Waldschmidt, Rozanski, Kunz, Koch, Endres, Audebert); Center for Stroke Research Berlin (CSB), Charité-Universitätsmedizin Berlin (Ebinger, Winter, Rozanski, Kunz, Gierhake, Villringer, Fiebach, Grittner, Endres, Audebert); Vivantes-Klinikum im Friedrichshain, Rettungsstelle, Berlin (Kellner); Department for Biostatistics and Clinical Epidemiology, Charité-Universitätsmedizin Berlin (Grittner); Rhön-Klinikum-Klinikum Frankfurt (Oder), Frankfurt (Oder) (Hartmann); Vivantes-Auguste-Viktoria-Klinikum, Berlin (Mackert); ExcellenceCluster NeuroCure, Charité-Universitätsmedizin Berlin (Endres); German Center for Neurodegenerative Diseases (DZNE), Berlin (Endres); German Center for Cardiovascular Research (DZHK), Berlin (Endres).

Author Contributions: Drs Ebinger and Audebert had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Ebinger, Kellner, Endres, Audebert.

Acquisition, analysis, or interpretation of data: Ebinger, Winter, Wendt, Weber, Waldschmidt, Rozanski, Kunz, Koch, Kellner, Gierhake, Villringer, Fiebach, Grittner, Hartmann, Mackert, Endres, Audebert.

Drafting of the manuscript: Ebinger, Audebert.
Critical revision of the manuscript for important intellectual content: Ebinger, Winter, Wendt, Weber,

Waldschmidt, Rozanski, Kunz, Koch, Kellner, Gierhake, Villringer, Fiebach, Grittner, Hartmann, Mackert, Endres, Audebert.
Statistical analysis: Grittner, Audebert.
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Study supervision: Ebinger, Gierhake, Villringer, Fiebach, Endres, Audebert.

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