Effects of Golden Hour Thrombolysis
A Prehospital Acute Neurological Treatment and Optimization of Medical Care in Stroke (PHANTOM-S) Substudy

Martin Ebinger, MD; Alexander Kunz, MD; Matthias Wendt, MD; Michal Rozanski, MD; Benjamin Winter, MD; Carolin Waldschmidt, MD; Joachim Weber, MD; Kersten Villringer, MD; Jochen B. Fiebach, MD; Heinrich J. Audebert, MD

IMPORTANCE The effectiveness of intravenous thrombolysis in acute ischemic stroke is time dependent. The effects are likely to be highest if the time from symptom onset to treatment is within 60 minutes, termed the golden hour.

OBJECTIVE To determine the achievable rate of golden hour thrombolysis in prehospital care and its effect on outcome.

DESIGN, SETTING, AND PARTICIPANTS The prospective controlled Prehospital Acute Neurological Treatment and Optimization of Medical Care in Stroke study was conducted in Berlin, Germany, within an established infrastructure for stroke care. Weeks were randomized according to the availability of a specialized ambulance (stroke emergency mobile unit [STEMO]) from May 1, 2011, through January 31, 2013. We included 6182 consecutive adult patients for whom a stroke dispatch (44.1% male; mean [SD] age, 73.9 [15.0] years) or regular care (45.0% male; mean [SD] age, 74.2 [14.9] years) were included.

INTERVENTIONS The STEM0 was deployed when the dispatchers suspected an acute stroke during emergency calls. If STEM0 was not available (during control weeks, when the unit was already in operation, or during maintenance), patients received conventional care. The STEM0 is equipped with a computed tomographic scanner plus a point-of-care laboratory and telemedicine connection. The unit is staffed with a neurologist trained in emergency medicine, a paramedic, and a technician. Thrombolysis was started in STEM0 if a stroke was confirmed and no contraindication was found.

MAIN OUTCOMES AND MEASURES Rates of golden hour thrombolysis, 7- and 90-day mortality, secondary intracerebral hemorrhage, and discharge home.

RESULTS Thrombolysis rates in ischemic stroke were 200 of 614 patients (32.6%) when STEM0 was deployed and 330 of 1497 patients (22.0%) when conventional care was administered (P < .001). Among all patients who received thrombolysis, the proportion of golden hour thrombolysis was 6-fold higher after STEM0 deployment (62 of 200 patients [31.0%] vs 16 of 330 [4.9%]; P < .01). Compared with patients with a longer time from symptom onset to treatment, patients who received golden hour thrombolysis had no higher risks for 7- or 90-day mortality (adjusted odds ratios, 0.38 [95% CI, 0.09-1.70]; P = .21 and 0.69 [95% CI, 0.32-1.53]; P = .36) and were more likely to be discharged home (adjusted odds ratio, 1.93 [95% CI, 1.09-3.41]; P = .02).

CONCLUSIONS AND RELEVANCE The use of STEM0 increases the percentage of patients receiving thrombolysis within the golden hour. Golden hour thrombolysis entails no risk to the patients’ safety and is associated with better short-term outcomes.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT01382862

Published online November 17, 2014.
Time to treatment with tissue plasminogen activator (tPA) is crucial to outcomes among patients with acute ischemic stroke.\textsuperscript{1,2} Numerous attempts have been made to reduce the time from symptom onset to treatment (OTT).\textsuperscript{3,4} However, many centers struggle to keep the time from arrival at the hospital to initiation of tPA (door-to-needle time) shorter than 60 minutes.\textsuperscript{5,6} When prehospital times are added to in-hospital delays, an OTT within the first 60 minutes of symptom onset, termed the golden hour, seems out of reach for most patients. In fact, most patients undergoing routine care for stroke receive treatment rather late. In the Safe Implementation of Thrombolysis–Stroke Monitoring Study (SITS–MOST) registry,\textsuperscript{7} 10.6% of 6483 patients were treated within 90 minutes and only 1.4% within 60 minutes. The median OTT in the SITS–International Stroke Thrombolyis Register\textsuperscript{8} was 145 (interquartile range [IQR], 115-170) minutes. Structured approaches have been successful in increasing thrombolysis rates and shortening door-to-needle times.\textsuperscript{9-11} Centers with greater numbers of tPA treatments per year tend to have shorter door-to-needle times compared with smaller centers.\textsuperscript{5} However, some of the centers with shortened door-to-needle times still have long prehospital times.\textsuperscript{3,12}

A forceful approach to shorten the OTT is prehospital thrombolysis in emergency vehicles equipped with a computed tomographic scanner and a point-of-care laboratory.\textsuperscript{13,15} A reduced time from the emergency call to treatment after deployment of such an ambulance compared with regular care was observed in the Prehospital Acute Neurological Treatment and Optimization of Medical Care in Stroke (PHANTOM-S) study.\textsuperscript{15} We used data from the PHANTOM-S study to evaluate the rate and effectiveness of golden hour thrombolysis.

Methods

The study was approved by the Charité Ethics Committee and conducted in accordance with published protocol. Written informed consent was obtained from patients able to communicate and waive for those unable to provide consent, as described in detail previously.\textsuperscript{15}

Methodologic details of the PHANTOM-S study have been described previously.\textsuperscript{16-17} In brief, an ambulance, the stroke emergency mobile unit (STEMO), was equipped with a computed tomographic scanner and point-of-care laboratory. The unit was staffed with a neurologist trained in emergency medicine (including M.E., A.K., M.W., M.R., B.W., C.W., and J.W.), a paramedic, and a radiology technician. A neuroradiologist was on call to evaluate images acquired on board the SITEMO via a teleradiology connection. We evaluated the effects of the SITEMO implementation prospectively by comparing weeks with and without SITEMO availability. The SITEMO was deployed when the dispatchers suspected an acute stroke during emergency calls. If SITEMO was not available (during control weeks, while the unit was in operation, or during maintenance), patients received conventional care.

For this post hoc analysis based on data from the PHANTOM-S study, we used the same consecutive patients and baseline variables as in the original study.\textsuperscript{15} Stroke severity at baseline was assessed according to the National Institutes of Health Stroke Scale (NIHSS).\textsuperscript{16} In addition, we calculated the proportion of patients treated in 1-hour intervals. The OTT intervals were dichotomized as 60 minutes or less (the golden hour) or longer than 60 minutes. Only 1 SITEMO was available within a catchment area of more than 1 million inhabitants. Therefore, the SITEMO could not be deployed for all suspected strokes during SITEMO weeks when the SITEMO was occupied with another emergency. In contrast to the original study,\textsuperscript{15} we did not compare SITEMO weeks with control weeks in the data presented here. Instead we compared tPA treatments occurring after SITEMO deployment with tPA treatments during conventional care. Conventional care included tPA treatments during control weeks and tPA treatments during SITEMO weeks without SITEMO deployment (Figure 1). In a second step, we compared stroke patients who received golden hour thrombolysis with stroke patients who received tPA more than 60 minutes after symptom onset, independent of SITEMO deployment or conventional care. Patients with stroke mimics who received tPA were not included in this evaluation of treatment effects.

We calculated unadjusted outcomes for 7- and 90-day mortality, secondary intracerebral hemorrhage, and discharge home among patients with an OTT within 60 minutes compared with those with an OTT longer than 60 minutes. We then performed analyses to achieve the adjusted probability of each outcome.

With relatively few patients who experienced a secondary hemorrhage (n = 29) or died within 7 days (n = 24), we had to restrict the adjustment to 2 variables and adjusted for age (in decades) and stroke severity (NIHSS score per point). For the outcomes of death within 90 days (n = 75) and discharge home (n = 239), we adjusted for age (in decades), sex, atrial fibrillation, and NIHSS score categories according to the Third International Stroke Trial (NIHSS scores, 0-5, 6-10, 11-15, 16-20, and ≥21).\textsuperscript{19} We considered P < .05 to be a statistically significant difference.

Results

STEMO Deployment vs Conventional Care

All data of this post hoc analysis presented herein were recalculated on the basis of the PHANTOM-S data set. During the 21 months from May 1, 2011, through January 31, 2013, there were 3213 emergency calls for suspected stroke during SITEMO weeks and 2969 during control weeks (Figure 1). Of the 1804 patients with SITEMO deployment (44.1% male; mean [SD] age, 73.9 [15.0] years), 200 received tPA treatment. Of those, tPA infusion was started in 17 patients after hospital arrival.\textsuperscript{13} Of 4378 patients in conventional care (45.0% male; mean [SD] age, 74.2 [14.9] years), 330 were treated with tPA (110 of those in SITEMO weeks and 220 in control weeks). Overall, 200 of 614 patients with ischemic stroke (32.6%) received thrombolysis when the SITEMO was deployed and 330 of 1497 (22.0%) received thrombolysis in conventional care (P < .001). The mean NIHSS score was higher among patients with SITEMO deployment com-
pared with patients receiving conventional care (10.5 vs 9.1 [P = .02]). Median OTT was 24.5 minutes shorter after STEMO deployment compared with conventional care (80.5 [IQR, 54-126] vs 105.0 [IQR, 82-146] minutes; P < .01). In all ischemic strokes, the rate of golden hour thrombolysis increased from 16 of 1497 patients (1.1%) during conventional care to 62 of 614 (10.1%) after STEMO deployment (Figure 2). Among all patients who received thrombolysis, the proportion of golden hour thrombolysis was 6-fold higher after STEMO deployment (62 patients [31.0%] vs 16 [4.9%]; P < .01). Of all patients who received golden hour thrombolysis, 66 (84.6%) received tPA during a STEMO week and 12 (15.4%) during a control week.

Golden Hour Thrombolysis vs Later Thrombolysis
Median OTT was 50.0 (IQR, 43-55) minutes in golden hour thrombolysis vs 105.0 (IQR, 85-155) minutes in all other thrombolysis (P < .001). In patients who received golden hour thrombolysis, median NIHSS score was higher than that in patients who received tPA more than 60 minutes after symptom onset (12 [IQR, 5-18] vs 7 [IQR, 4-13]; P = .006) (additional baseline characteristics are given in Table 1). In unadjusted univariate analysis of the outcomes mortality within 7 and 90 days, discharge home, and hemorrhagic complications, we detected no significant differences between golden hour thrombolysis and later thrombolysis (Table 2). In adjusted analysis, patients with golden hour thrombolysis had no higher risks for 7- or 90-day mortality (adjusted odds ratios, 0.38 [95% CI, 0.09-1.70]; P = .21 and 0.69 [95% CI, 0.32-1.53]; P = .36) compared with patients with longer OTT and were more likely to be discharged home (adjusted odds ratio, 1.93 [95% CI, 1.09-3.41]; P = .02) (Table 3).

Discussion
Prehospital stroke treatment within the STEMO concept increased the number of tPA treatments within the golden hour almost 10-fold. Golden hour thrombolysis was associated with improved patient outcomes regarding the discharge destination from acute in-hospital care. We observed no increased risk...
for hemorrhagic complications or mortality in patients undergoing golden hour thrombolysis. Deployment of STEMO led to a significant proportion of patients with extremely early treatment, even in a setting with already short door-to-needle times and OTT in the control group (36.0 [IQR, 28-51] and 105.0 [IQR, 81-145] minutes, respectively). Our results regarding safety and discharge status after golden hour thrombolysis are in line with previous analyses of the association of improved outcomes with shorter OTT.1,2,20

### Table 1. Baseline Characteristics of Patients Who Received Golden Hour Thrombolysis Compared With Later Thrombolysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients With Thrombolysis</th>
<th>P Value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>OTT &gt;60 min (n = 451)</td>
<td>OTT ≤60 min (n = 78)</td>
</tr>
<tr>
<td>Male sex, No. (%)</td>
<td>75.5 (13.0)</td>
<td>75.5 (11.9)</td>
</tr>
<tr>
<td>Comorbidities, No. (%)</td>
<td>226 (50.1)</td>
<td>34 (43.6)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>151 (33.5)</td>
<td>35 (44.9)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>119 (26.4)</td>
<td>18 (23.1)</td>
</tr>
<tr>
<td>Stroke severity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS score at treatment&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Mean</td>
<td>9.3</td>
</tr>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>7 (4-13)</td>
</tr>
<tr>
<td>NIHSS score according to IST-3,19 No. (%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-5</td>
<td>160 (36.0)</td>
<td>21 (26.9)</td>
</tr>
<tr>
<td>6-10</td>
<td>133 (30.0)</td>
<td>13 (16.7)</td>
</tr>
<tr>
<td>11-15</td>
<td>62 (14.0)</td>
<td>16 (20.5)</td>
</tr>
<tr>
<td>16-20</td>
<td>59 (13.3)</td>
<td>18 (23.1)</td>
</tr>
<tr>
<td>≥21</td>
<td>30 (6.8)</td>
<td>10 (12.8)</td>
</tr>
<tr>
<td>Process indicators</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of stay, d</td>
<td>Mean</td>
<td>9.0</td>
</tr>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>7 (5-11)</td>
</tr>
<tr>
<td>OTT, min&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Mean</td>
<td>123.8</td>
</tr>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>105.0 (85-155)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Categorial variables were compared with the χ<sup>2</sup> test and continuous variables with the Mann-Whitney test.

<sup>b</sup> Seven patients were missing from the analysis.

<sup>c</sup> Calculated using the linear trend test.

<sup>d</sup> One patient was missing from the analysis.

### Table 2. Unadjusted Clinical Outcomes After Thrombolysis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Patients With Thrombolysis, No. (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhagic complications</td>
<td>OTT &gt;60 min (n = 451)</td>
<td>OTT ≤60 min (n = 78)</td>
</tr>
<tr>
<td>Discharge</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home</td>
<td>23 (5.1)</td>
<td>6 (7.7)</td>
</tr>
<tr>
<td>Nursing home</td>
<td>200 (44.3)</td>
<td>39 (50.0)</td>
</tr>
<tr>
<td>Referral to other department/hospital/rehabilitation institution</td>
<td>24 (5.3)</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td></td>
<td>198 (43.9)</td>
<td>32 (41.0)</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-hospital</td>
<td>29 (6.4)</td>
<td>5 (6.4)</td>
</tr>
<tr>
<td>Within 7 d&lt;sup&gt;e&lt;/sup&gt;</td>
<td>22 (4.9)</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td>Within 90 d&lt;sup&gt;f&lt;/sup&gt;</td>
<td>64 (14.3)</td>
<td>11 (14.3)</td>
</tr>
</tbody>
</table>

<sup>e</sup> One patient was missing from the analysis.

<sup>f</sup> Four patients were missing from the analysis.

### Table 2. Unadjusted Clinical Outcomes After Thrombolysis

Abbreviations: IQR, interquartile range; IST-3, Third International Stroke Trial; NIHSS, National Institutes of Health Stroke Scale; OTT, time from symptom onset to treatment.

Abbreviation: OTT, time from symptom onset to treatment.

Golden Hour Thrombolysis

28 JAMA Neurology January 2015 Volume 72, Number 1 jamaneurology.com

Copyright 2014 American Medical Association. All rights reserved.
The question of generalizability of the prehospital thrombolysis concept warrants further studies. Not all countries are accustomed to emergency physicians in the field, which may be required for adaptation of the STEMO concept. The OTT found in our study after STEMO deployment (median OTT, 80.5 minutes) and during conventional care (median OTT, 105.0 minutes) were much shorter than in published stroke thrombolysis registries (median OTTs, 144 minutes in Saver et al2 and 140 minutes in Wahlgren et al3) or even in best-practice hospital systems (median OTT, 119 minutes for Meretoja et al5). Apart from a selection bias by restriction to patients with ambulance care, this difference may be explained at least in part by a well-established metropolitan stroke care system with trained dispatchers and paramedics, short distances to stroke units, and rather optimized in-hospital procedures. During the study period, the dispatchers identified patients with typical stroke symptoms during the emergency call and notified the emergency medical services, which may have raised awareness of the entire rescue chain.

Conclusions
The concept of prehospital thrombolysis is still relatively new, and experience is limited to few groups. Further improvements in time reduction may be expected with growing routine.

After analyzing data from the Get With the Guidelines Stroke Program, Saver and colleagues2 concluded that every effort should be made to accelerate thrombolytic treatment in patients with stroke. Our post hoc analysis supports this time-is-brain concept. Golden hour thrombolysis was associated with better short-term outcomes.


