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Pre-hospital thrombolysis - a manual from Berlin

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Abstract:	In acute ischemic stroke, time from symptom onset to intervention is a decisive prognostic factor. In order to reduce this time pre-hospital thrombolysis at the emergency site would be preferable. However, apart from neurological expertise and laboratory investigations a computed tomography (CT) scan is necessary to exclude hemorrhagic stroke prior to thrombolysis. Therefore, a specialized ambulance equipped with a CT scanner and point-of-care laboratory was designed and constructed. Further, a new stroke identifying interview algorithm was developed and implemented in the Berlin emergency medical services. Since February 2011 the

	identification of suspected stroke in the dispatch center of the Berlin Fire Brigade prompts the deployment of this ambulance, a stroke emergency mobile (STEMO). On arrival, a neurologist, experienced in stroke care and with additional training in emergency medicine, takes a neurological examination. If stroke is suspected a CT scan excludes intracranial haemorrhage. The CT-scans are telemetrically transmitted to the neuroradiologist on-call. If coagulation status of the patient is normal and patient's medical history reveals no contraindication, pre-hospital thrombolysis is applied according to current guidelines (intravenous recombinant tissue plasminogen activator, iv rtPA, alteplase, Actilyse®). Thereafter patients are transported to the nearest hospital with a certified stroke unit for further treatment and assessment of stroke aetiology. After a pilot-phase, weeks were randomized into blocks either with or without STEMO care. Primary end-point of this study is time from alarm to the initiation of thrombolysis. We hypothesized that alarm-to-treatment time can be reduced by at least 20 minutes compared to regular care.
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*Cover Letter

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Berlin, den 15. November 2012

Submission of our manuscript
„Pre-hospital thrombolysis – a manual from Berlin“

Dear Ms. Sheeley,

Hereby, we are submitting our manuscript for publication in JoVE. The article is original and has not been previously published or is currently being considered for publication elsewhere.

Please contact me if you have any questions.

Yours faithfully,

Sascha Lindenlaub
On behalf of Dr. Ebinger

Pre-hospital thrombolysis - a manual from Berlin

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Keywords
stroke, thrombolysis, pre-hospital, emergency medical services, ambulance

Short abstract
Identification of suspected stroke in the dispatch center of the Berlin Fire Brigade prompts the deployment of a CT-equipped ambulance. If ischemic stroke is confirmed and contraindications are excluded pre-hospital thrombolysis is applied.

Long abstract
In acute ischemic stroke, time from symptom onset to intervention is a decisive prognostic factor. In order to reduce this time, pre-hospital thrombolysis at the emergency site would be preferable. However, apart from neurological expertise and laboratory investigations a computed tomography (CT) scan is necessary to exclude hemorrhagic stroke prior to thrombolysis. Therefore, a specialized ambulance equipped with a CT scanner and point-of-care laboratory was designed and constructed. Further, a new stroke identifying interview algorithm was developed and implemented in the Berlin emergency medical services. Since February 2011 the identification of suspected stroke in the dispatch center of the Berlin Fire Brigade prompts the deployment of this ambulance, a stroke emergency mobile (STEMO). On arrival, a neurologist, experienced in stroke care and with additional training in emergency medicine, takes a neurological examination. If stroke is suspected a CT scan excludes intracranial haemorrhage. The CT-scans are telemetrically transmitted to the neuroradiologist on-call. If coagulation status of the patient is normal and patient's medical history reveals no contraindication, pre-hospital thrombolysis is applied according to current guidelines (intravenous recombinant tissue plasminogen activator, iv rtPA, alteplase, Actilyse).

Thereafter patients are transported to the nearest hospital with a certified stroke unit for further treatment and assessment of stroke aetiology. After a pilot-phase, weeks were randomized into blocks either with or without STEMO care. Primary end-point of this study is time from alarm to the initiation of thrombolysis. We hypothesized that alarm-to-treatment time can be reduced by at least 20 minutes compared to regular care.

Introduction

Thrombolysis with intravenous recombinant tissue Plasminogen Activator (rtPA) is the only proven effective treatment in acute ischemic stroke. The benefits of thrombolysis are time-dependent. Efficacy of thrombolytic therapy for ischemic stroke decreases with time elapsed from symptom onset (1). Therefore, delays until initiation of treatment must be avoided. However, there are pre-hospital and in-hospital reasons for delays in treatment initiation. Patients' decision time to call emergency services and the time from emergency call to arrival at the hospital are factors in the pre-hospital delay. In hospital, reductions of both the time to CT scanning and of the time between CT scan and start of thrombolysis remain challenging (2). Stroke awareness campaigns shorten patient related times to emergency call (3), but effects are only temporary and require repetition of such campaigns. While there are successful examples of reducing in-hospital delays (4,5) many centres struggle to remain within the required 60 minutes from door to needle. One way to avoid these delays may be a start of specific stroke treatment at the emergency site, i.e. pre-hospital thrombolysis. Until recently, several requirements made this unfeasible. First, only physicians experienced in stroke care are qualified to make acute treatment decisions. Second, computed tomography (CT) is necessary to rule out intracranial haemorrhage. Third, laboratory tests should be available to exclude coagulation disorders (6). In order to overcome these challenges, a stroke emergency mobile (STEMO) was constructed. This special ambulance is equipped with a CT scanner, a point-of-care laboratory and an infrastructure for teleradiological support (7). It is operated by a highly specialized crew consisting of experienced neurologists, paramedics of the Berlin Fire Brigade and radiology technicians (8). To meet the legal requirements and the requirements of the Berlin Medical Board, each neurologist involved completed an additional training in emergency medicine. Radiology technicians completed a three month formal training in emergency care (9,10). STEMO has been integrated in public emergency medical services (EMS) provided by the Berlin Fire Brigade. For the identification of eligible patients with suspected stroke during the emergency call, a special interview algorithm was developed and integrated at the dispatcher level (11). During a three months pilot-study, we demonstrated safety and feasibility (12). Our colleagues from Homburg, Germany, recently published their experience with the first 12 pre-hospital thrombolysis in the Saarland State (13). We believe that pre-hospital stroke care using STEMO can reduce the alarm-to-needle time compared to regular care ultimately leading to improved patients care. However, prior to implementation final results of sufficiently powered studies need to confirm safety and efficacy of this approach. Here we present the methods used in the "pre-hospital acute neurological therapy and optimization of medical care in stroke patients" study (PHANTOM-S).

Protocol

1. Emergency response at the dispatch center of the Berlin Fire Brigade

1.1. Answer an incoming „112" emergency call.

1.2. Gather information about the emergency site, such as address, floor, name on the doorbell and phone number. Type the data directly into the worksheet of the computer-controlled emergency dispatch system (called Ignis)

1.3. Identify the medical emergency as a stroke emergency, using the newly developed Dispatcher Identification Algorithm for Stroke Emergencies (DIASE).

1.4. Verify that the emergency site is within the operating area of STEMO via Ignis.

1.5. Communicate alarm to STEMO via a radio-based alarm system. (In Berlin, currently, a regular care ambulance is alarmed simultaneously.) Available information concerning the emergency is automatically transmitted via fax.

2. Receipt of the alarm transmission at the fire station

2.1. A personal pager signals the alert by audible tone. Go immediately to the fax machine and take the fax containing the detailed emergency information.

2.2. Go to the STEMO vehicle, press the status button 3 on the on-board radio, thus confirming a receipt for alert to the dispatch center. The GPS-based navigation system has automatically received a routing to the patient's location.

2.3. When complete crew is on board (Paramedic, Neurologist and Radiology technician) drive the STEMO vehicle to the emergency site. CAUTION: Approach with blue lights flashing and siren to the scene. Therefore, pay particular attention to other road users and observe the regulations of the German traffic law concerning the use of blue lights and siren (14).

2.4. Upon arrival at the emergency site, press the status button 4 on the on-board radio, thus giving a confirmation to the dispatch center.

2.5. Pay extra attention to safety before leaving the STEMO vehicle at the emergency site. CAUTION: Watch out for potential hazards, such as unsecured scene of an accident, violent people, risk of fire, moving traffic or hazardous substances.

3. Examination of the patient at the emergency site

3.1. Check consciousness using the Glasgow Coma Scale (GCS).

3.2. Follow the structured "ABCDE algorithm" for the initial assessment of the patient's status: Airways, Breathing, Circulation, Disability, Exposure (15).

3.3. Explore medical history of the patient. If stroke is suspected clinically assess severity of symptoms using the National Institutes of Health Stroke Scale (NIHSS).

3.4. Determine the exact onset of symptoms by questioning the patient/witnesses.

3.5. Ask for current medication with a main focus on anticoagulation therapy.

3.6. Measure and log the vital signs, such as heart rate, blood pressure, blood sugar concentration and oxygen saturation.

4. Insert a peripheral intravenous (iv) line and perfom blood withdrawals.

4.1. Apply a tourniquet around the upper arm.

4.2. Search for a suitable hand, forearm or antecubital vein. The best choice for the iv line is a vein on the dorsum of the hand.

4.3. Disinfect the skin.

4.4. Remove needle sheath from the indwelling venous catheter. Ensure needle bevel is upwards.

4.5. Apply traction distal to the vein to prevent vein from rolling during cannulation.

4.6. Insert the needle into the vein at 20-40°. The flashback of blood confirms that the needle tip is inside the vein. Advance the catheter off the needle into the vein.

4.7. Fix the catheter using adhesive tape.

4.8. Remove the needle, discard it to a sharps container and connect a plastic adapter containing a shrouded needle, which enables to start with a blood draw from the indwelling venous catheter.

4.9. Perform blood draw using several Vacutainer blood test tubes. Some of these blood tubes contain different anticoagulatory additives, such as EDTA, citrate and heparine. The type of blood test tube is color-coded: 1. Purple for complete blood counts; 2. Blue for coagulatory assays; 3. Green for electrolytes, BUN and other basic blood parameters; 4. Orange for specialized serum analysis)

4.10. Push a Vacutainer blood test tube into the plastic holder, so that its rubber cap is pierced by the shrouded needle. (The negative pressure in the Vacutainer tubes forces blood into the blood test tubes.)

4.11. Remove the Vacutainer tube after it was filled with blood and repeat this procedure with the other Vacutainer tubes

4.12. After the last Vacutainer tube was filled, remove the tourniquet, flush the indwelling venous catheter with normal saline solution and close the catheter using a closing cone.

5. Determine the International Normalized Ratio (INR), using a bedside point-of-care analyzer.

5.1. Take a test strip from its container. Slide it into the guide in the direction indicated by the arrows.

5.2. Take a lancet and twist the protective cap off. Press the tip of the lancet against the side of the fingertip and press the trigger button.

5.3. Apply the blood sample on the target area of the test strip within 15 seconds of sticking the fingertip. After a few seconds the result (INR) is displayed.

5.4. Place the used strip and the lancet into containers for biohazards and sharps, respectively.

6. Advanced diagnostics and intervention

6.1. Immediately transfer the patient into the STEMO vehicle.

6.2. Position the patient on a stretcher.

6.3. Insert the purple Vacutainer blood test tube into the point-of-care laboratory (Horiba ABX Micros 60). Measure additional blood parameters such as platelet count, total leukocyte count, erythrocyte count, haemoglobin concentration, haematocrit, electrolytes.

6.4. Insert the patient's insurance card into the card reader (installed in the control room).

6.5. Call the neuroradiologist on-call to discuss the indication for CT scanning and prepare for examination.

6.6. Explain benefits and risks of CT scanning to the patient. Afterwards, obtain informed consent from the patient, if possible.

6.7. Start the CT. CAUTION: X-ray radiation is released from the CT scanner. Radiology technician has to be in the shielded control room. The rest of the STEMO staff is requested to leave the vehicle during the examination in order to avoid unnecessary exposure to x-ray radiation (STEMO vehicle is lead covered). Furthermore, protective measures (eye protection) should be applied to the patient.

6.8. Transmit the CT image via on-board telemetric infrastructure and request teleradiological support for decision making regarding diagnosis and therapy. (Parallel analysis of images in the STEMO by the neurologist.)

6.9. Ask the patient for contraindications against thrombolytic therapy using a standardized check list.

6.10. Explain benefits and possible risks of thrombolysis. Inform the patient that the treatment is part of a clinical study and obtain informed consent, if possible.

7. Administration of recombinant tissue plasminogen activator (rtPA or alteplase)

7.1. Calculate the dose of alteplase (trade name: Actilyse) based on the best approximation of bodyweight available. The recommended dose is 0.9 mg/kg bodyweight. Maximum dose is 90 mg (6).

7.2. Reconstitute the dry solid alteplase using the solvent provided. Use the transfer cannula, which must be introduced vertically into the rubber stopper of the phials and through the mark at its centre.

7.3. Dissolve the dry solid by gentle agitation.

7.4. Initiate thrombolysis by administering 10% of the calculated total dose as a bolus injection over 1 minute. Keep record of the point in time, when alteplase bolus is injected. CAUTION: Pay attention to immediate allergic responses following administration. Be prepared to administer anti-allergic drugs (i.e. antihistaminics, high-dose glucocorticoids, catecholamines) in case of an acute allergic response. In general, alteplase should be used only by a physician experienced in the treatment of ischemic stroke (6).

7.5. Inject the remaining dose via an injection pump syringe continuously over 60 minutes (after evacuation of the tubing to avoid the injection of air bubbles).

8. Transportation of the patient to a suitable hospital

8.1. Make an advanced notification to the emergency room of the closest hospital with a certified stroke unit.

8.2. Start the transportation immediately. Communicate the selected hospital to the dispatch center via radio.

8.3. Monitor neurological deficits and vital signs during transfer to the hospital.

8.4. Print-out and sign the admission letter (using Vimed software) including diagnosis, history, results of neurological examination, neuroradiological report (sent by the neuroradiologist on call via UMTS), results of laboratory investigations and description of actions taken. Copy CT-scan on a CD for the hospital.

8.5. On arrival at the hospital (press status button 8) provide concise present and past medical histories of the patient to the neurologist on-call and to the primary team in the Emergency Room. Hand over printed report, CD containing CT images (cp 8.4), and the blood-filled blue, green and orange Vacutainer blood test tubes (cp 4.9).

9. Restoring the operational readiness

9.1. Clean and disinfect hands and all equipment that has been used during the EMS response.

9.2. Report operational stand-by status to the dispatch center using button 1 on the on-board radio. Return to the local fire station.

Representative Results

From February 8 to April 30, 2011, a total of 152 subjects were treated in the STEMO vehicle. Informed consent was obtained from 77 patients. Forty-five patient's (58%) had an acute ischemic stroke and 23 (51%) of these patients received rtPA. The mean alarm-to-needle time using STEMO was 62 minutes compared to 98 minutes in a control cohort of 50 consecutive patients thrombolysed in Berlin in 2010. Two (9%) of the rtPA-treated patients suffered a symptomatic intracranial haemorrhage and one of these patients (4%) died in hospital. Technical failures comprised one CT dysfunction and two delayed CT-image transmissions. (12)

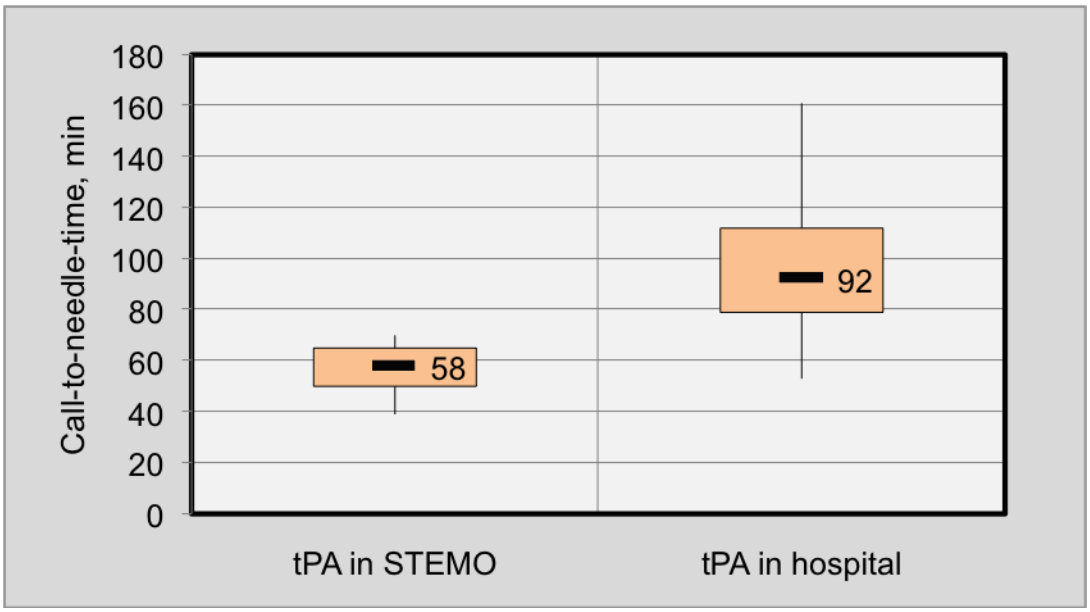

Fig. 1 Call-to-needle-time. Comparison of acute ischemic stroke patients who received tissue-Plasminogen Activator (tPA). STEMO-treated patients (n=23) vs. in-hospital treated patients in 2010 (n=50). Boxes show interquartile range (IQR) with the line representing the median call-to-needle time (58 minutes vs. 92 minutes); whiskers indicate the distribution width within 1.5 x IQR. Based on data from Weber *et al.* (12).

Tables and Figures

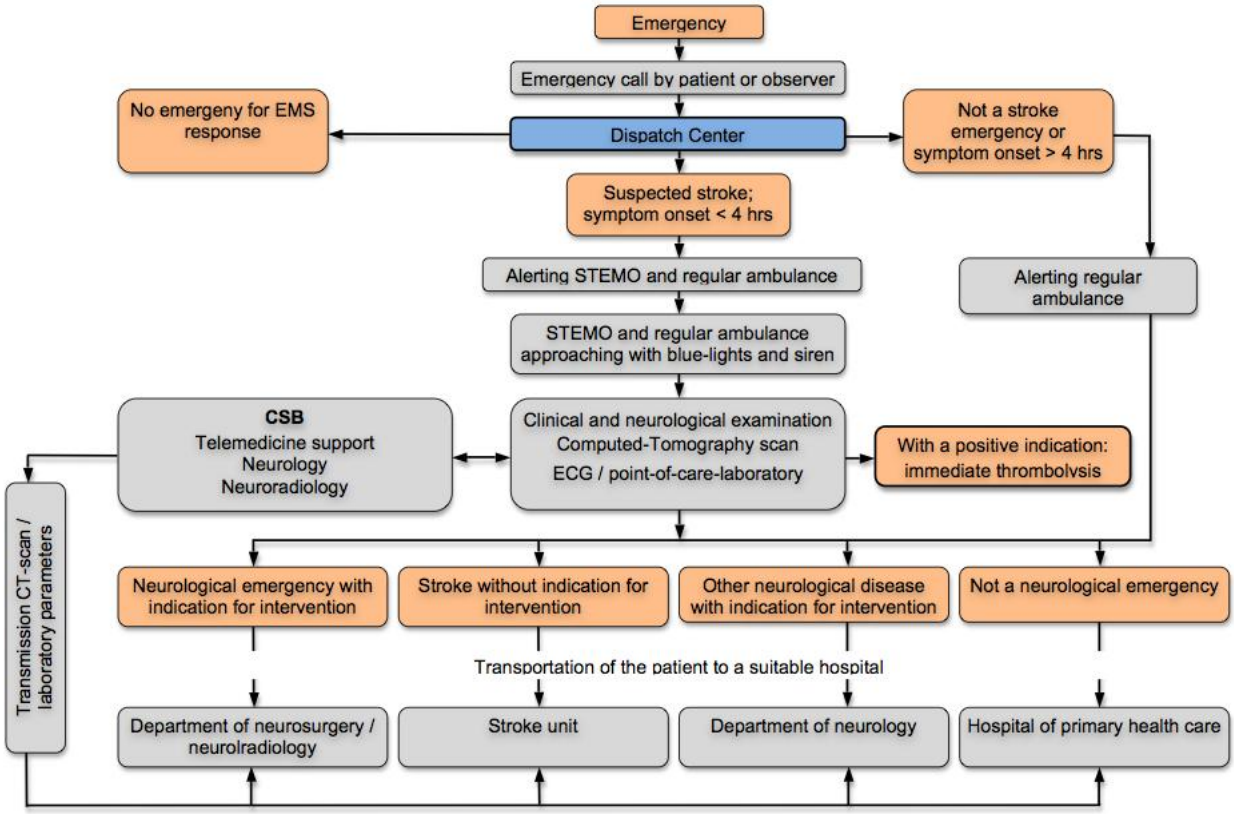

Fig. 2 STEMO overall concept. Flow diagram of EMS response with main focus on stroke emergencies responded by STEMO. Modified according to an original design by Audebert, H. J. STEMO (Stroke-Einsatz-Mobil). http://tsb-berlin.de /media/uploads/zukunfsfonds/STEMO_(Stroke-Einsatz-Mobil).pdf

Discussion

Pre-hospital thrombolysis may be able to revolutionize acute specific stroke treatment. However, it is a cost and resource consuming way of treatment delivery. In general, a 'stay-and-play' rather than a 'load-and-go' approach needs to be justified by specific characteristics of the emergency at hand. Ischemic stroke has distinctive features that warrant a 'treat-and-run' compromise: The benefits of acute stroke treatment are enormously time dependent. During an ischemic stroke approximately 2.000.000 neurons die per minute (16). Intravenous treatment with rtPA enhances the chances of reperfusion and favourable functional outcome in stroke patients (17). Treatment should be started as soon as possible. By now, it is the only evidence-based, effective and approved treatment for acute ischemic stroke. Associated with the risk of severe bleeding, the exclusion of intracranial bleeds and other contraindications is mandatory prior to thrombolysis.
STEMO is set up to prove that this specific treatment can be safely administered in a pre-hospital setting and actually safes time compared to regular care (8, 12). First results from 12 pre-hospital thrombolyses in the Saarland State, Germany, seem promising in this respect (13). In this study, Walter and colleagues reported that after randomized weeks between November, 2008, and July, 2011 and an interim analysis at 100 of 200 planned patients (53 in the prehospital setting, 47 in the control group), the median time from alarm to therapy decision (primary end-point) was substantially reduced in the 12 cases of pre-hospital thrombolysis: 35 min (IQR 31-39) versus 76 min (63-94), p<0•0001; median difference 41 min (95% CI 36-48 min). Overall, the additional costs have to be weighed

against benefits that patients may experience. For this, the final results of the ongoing PHANTOM-S will be crucial. In this prospective study (http://clinicaltrials.gov/ct2/show/ NCT01382862), weeks with and without STEMO on duty are randomized until 228 patients have received iv rtPA in both treatment arms. Primary end-point of the study is time from alarm to thrombolysis. Secondary end-points include modified Rankin Scale score after three months, symptomatic intracranial haemorrhage, mortality and cost effectiveness. Results of this study will help decision makers whether to implement pre-hospital thrombolysis of acute ischemic stroke patients with specialized ambulances in their emergency systems. Site specific adaptations may be necessary. For instance, in regions with a shortage of neurologists telemedicine may provide the expertise to the emergency physician on board. Similarly, the results of the PHANTOM-S study may help to identify regions with the most likely benefit for patients and cost effectiveness for authorities. So far, it is not known whether pre-hospital thrombolysis is the most appropriate approach in mega-cities, urban or rural settings (18). Taken together, pre-hospital thrombolysis seems to be a logical step when the need of shortening time to treatment is taken seriously. Only a sufficiently powered study may provide the evidence of actual benefit to stroke patients.

Disclosures

The authors declare that they have no competing financial interests.

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Table of specific reagents

Name of the Drug	Company	Comments (optional)
Alteplase (rtPA)	Boehringer-Ingelheim	Licensed drug

Tab. 1 Alteplase. Alteplase (tissue-Plasminogen Activator) is the only licensed drug for acute ischemic stroke that has proven effectiveness within 4.5 hours of symptom onset in randomized controlled trials.

Table of specific equipment

Name of the device	Company	Comments (optional)
ABX micros 60	Horiba Medical	Point-of-care laboratory
CereTom	NeuroLogica	CT-Scanner
CoaguChek XSPlus	Roche	Handheld blood analyzer
EBA 20	HettichLab	centrifuge
FastPack System	Qualigen	Point-of-care immunoassay
i-STAT	Abbot	Handheld blood analyzer
OptiStat	Siemens	Contrast agent delivery system
Pilot A2	Fresenius	Infusion pump
TGL 12.250 4x2 BL	MAN	Vehicle chassis
Van body	Fahrtec Systeme GmbH	Custom-built
Vimed COMM	MEYTEC GmbH	Video communication system
Vimed GATEWAY	MEYTEC GmbH	Network solution
Vimed STEMO-DOC	MEYTEC GmbH	Documentation software
Vimed TELEMED	MEYTEC GmbH	Equipment for telemedicine
Vimed WEB-ENTRY	MEYTEC GmbH	Teleradiology

Tab. 2 Table of specific equipment. The software solution used in the ambulance was developed by a partner of the STEMO-consortium, MEYTEC GmbH, Germany.

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*Figure
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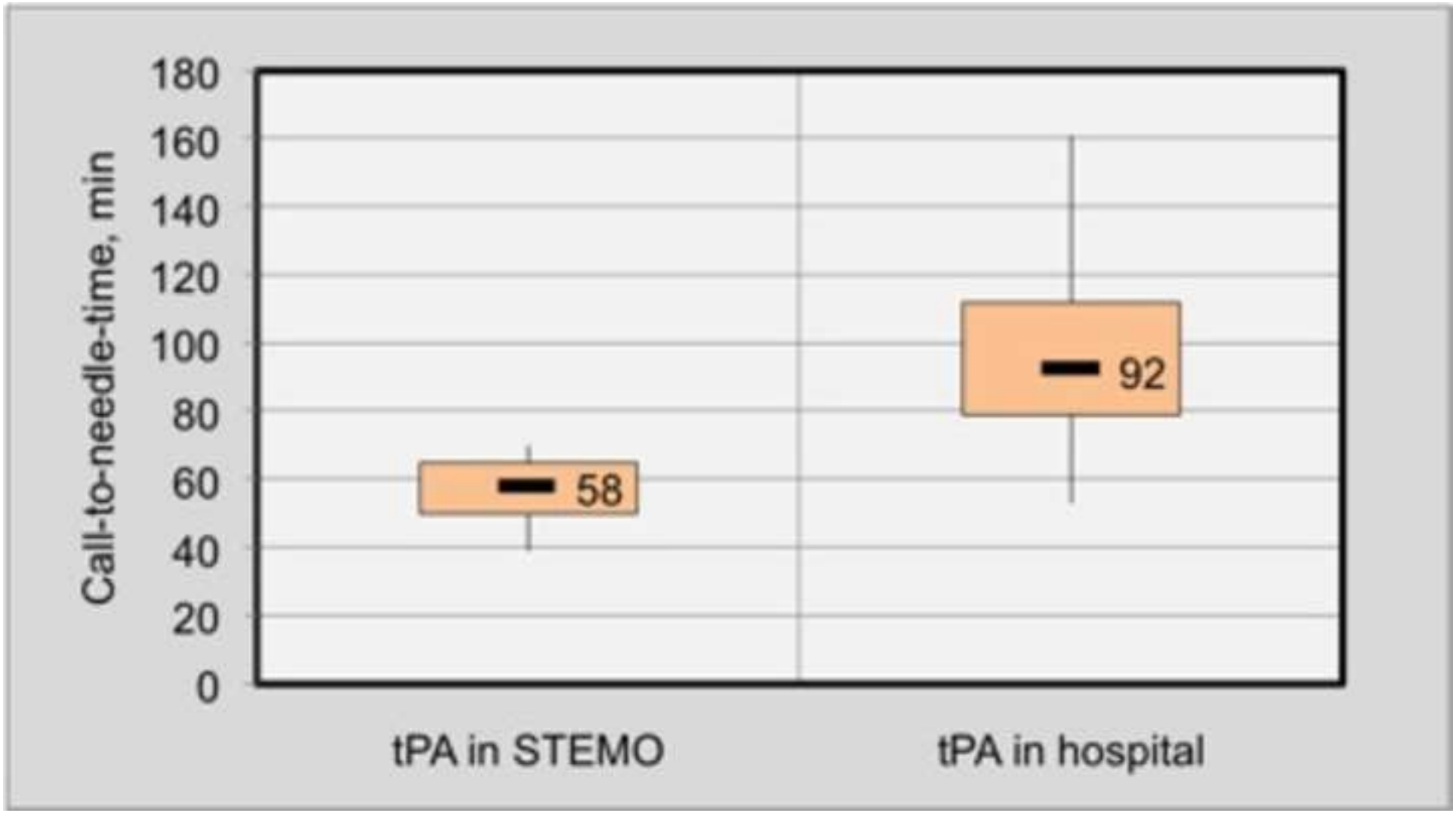

*Figure
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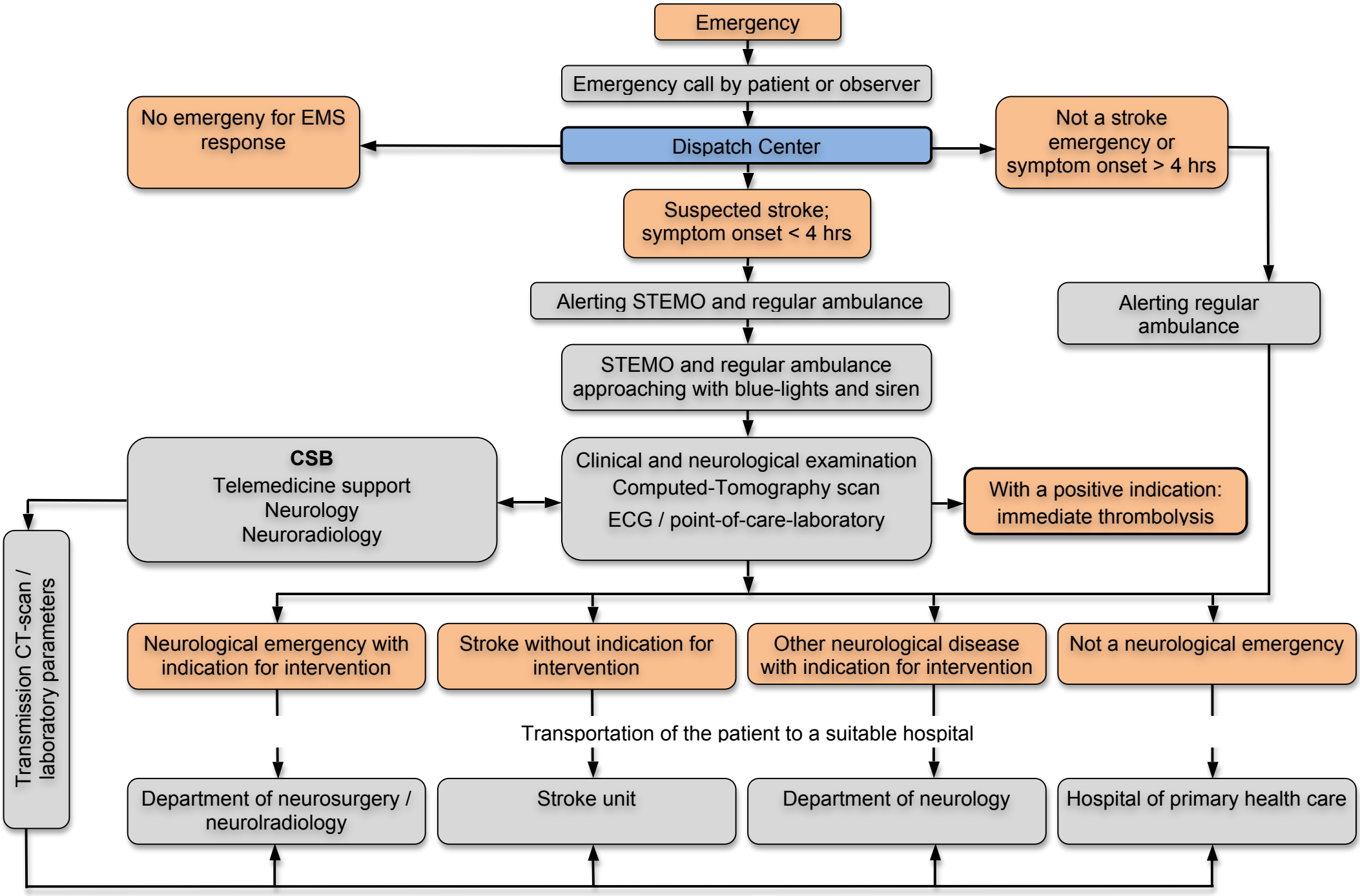

*Table of Reagents/ Materials Used

Click here to download Excel Spreadsheet- Table of Materials/Equipment: Table1.xls

Name of the Drug	Company	Comments (optional)
Alteplase (rtPA)	Boehringer-Ingelheim	Licensed drug
Name of the device	**Company**	**Comments (optional)**
ABX micros 60	Horiba Medical	Point-of-care laboratory
CereTom	NeuroLogica	CT-Scanner
CoaguChek XSPlus	Roche	Handheld blood analyzer
EBA 20	HettichLab	centrifuge
FastPack System	Qualigen	Point-of-care immunoassay
i-STAT	Abbot	Handheld blood analyzer
OptiStat	Siemens	Contrast agent delivery system
Pilot A2	Fresenius	Infusion pump
TGL 12.250 4x2 BL	MAN	Vehicle chassis
Van body	Fahrtec Systeme GmbH	Custom-built
Vimed COMM	MEYTEC GmbH	Video communication system
Vimed GATEWAY	MEYTEC GmbH	Network solution
Vimed STEMO-DOC	MEYTEC GmbH	Documentation software
Vimed TELEMED	MEYTEC GmbH	Equipment for telemedicine
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The Journal of Visualized Experiments (JoVE)

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Response to Reviewers

We would like to thank the reviewers for their comments and suggestions and hope we could handle all issues raised in a satisfactory manner.

Responses to comments by **Reviewer #1:**

Reviewer:

“The authors provide a methods paper for the STEMO vehicle use in acute stroke thrombolysis, utilizing mobile CT. The methods are clear and the work is undoubtedly innovative. The inherent focus is on shortening time to thrombolysis with the ultimate goal of improving patient outcomes, hinging on the mantra of "time is brain". This unique methodological approach and the preliminary results however, refute such a relationship and expected outcomes. Even in a limited cohort, the hemorrhagic transformation rate and mortality are substantial despite much faster treatment. In other words, this resource-intensive approach may speed up delivery of thrombolysis, but it may not improve patient outcomes, at all.”

Response:

We thank the reviewer for his time and comments. Indeed, this manuscript is supposed to describe the methods used in PHANTOM-S, the study powered to demonstrate safety and a reduction in alarm-to-thrombolysis time. This study will show if symptomatic bleeds or mortality are unacceptably high despite faster treatment times. Please cp. our Discussion: ”Overall, the additional costs have to be weighed against benefits that patients may experience. For this, the final results of the ongoing “pre-hospital acute neurological therapy and optimization of medical care in stroke patients” (PHANTOM-S) study will be crucial. In this prospective study (http://clinicaltrials.gov/ct2/show/NCT01382862), weeks with and without STEMO on duty are randomized until 228 patients have received iv rtPA in both treatment arms. Primary end-point of the study is time from alarm to thrombolysis. Secondary end-points include modified Rankin Scale score after three months, symptomatic intracranial haemorrhage, mortality and cost effectiveness. Results of this study will

help decision makers whether to implement pre-hospital thrombolysis of acute ischemic stroke patients with specialized ambulances in their emergency systems."
No changes were made to the manuscript in regard to this comment.

Responses to comments by **Reviewer #2:**

Reviewer:
The paper of Ebinger et al. describes the concept of stroke treatment delivery in the field with a detailed protocol to be used in a complex ambulance and by a specially trained team. This appears to be a methodological description of a procedure studied in an ongoing trial. The paper is interesting and well written but could be improved if more details regarding the concept and the protocol could be provided and if the scope of this paper could be more clearly outlined.

Response:
We thank the reviewer for his time and comments. Indeed, this is a methodological description for a video publication in *JoVE*. The pertinent study (PHANTOM-S) is mentioned in the Discussion. We apologize in case this wasn't made clear enough. However, the manuscript is supplementary to the video to be produced and will not be published outside the context of this video. So, in the end it will be clear to any potential reader that this is a 'screen-play' rather than a paper presenting results of a currently active trial.
In order to avoid misunderstandings we added the following sentences to the end of the Introduction: "…However, prior to implementation final results of sufficiently powered studies need to confirm safety and efficacy of this approach. Here we present the methods used in the "pre-hospital acute neurological therapy and optimization of medical care in stroke patients" study (PHANTOM-S)."

Reviewer:
1. The differences of practical work-up by EMS in the field compared to routine work-up (e.g. blood sampling, prenotification) should be outlined in more detail.

Response:
The prenotification will be visualized by an incoming emergency call in the dispatch center (Protocol item 1.) and the receipt of the alarm at the site where the STEMO and its team are stationed (Protocol item 2.) handling of blood samples including determination of INR (Protocol item 5) and further point-of-care laboratory (Protocol item 6) are also described in the script. Every step will be visualized in the video making the difference to regular care obvious.
No changes were made to the manuscript in regard to this comment.

Reviewer:
2. Given that there is earlier work on this topic, this should be cited in the text in detail (study design, primary endpoints, number of patients, etc.; see Walter et al.). Further literature available in Medline on pre-hospital stroke thombolysis should also be cited.

Response:
We thank the reviewer for this suggestion. So far, we mentioned “First results from 12 pre-hospital thrombolyses in the Saarland State, Germany, seem promising in this respect.” And quoted this landmark paper in Lancet Neurology.
We now added behind this sentence: “In this stud, Walter and colleagues reported that after randomized weeks between November, 2008, and July, 2011 and an interim analysis at 100 of 200 planned patients (53 in the prehospital setting, 47 in the control group), the median time from alarm to therapy decision (primary end-point) was substantially reduced in the12 cases of pre-hospital thrombolysis: 35 min (IQR 31-39) versus 76 min (63-94), p<0·0001; median difference 41 min (95% CI 36-48 min).”
Since this is the highest-impact publication available (as of March 12, 2013) and we are not aware of any further groups publishing original results on pre-hospital thrombolysis in stroke we quoted no further literature.

Reviewer:
3. The additional information provided in this paper, compared to their earlier papers, should be highlighted.

Response:
There is no additional information provided in this methodological paper other than the planned video-visualization compared to our earlier papers.
No changes were made to the manuscript in regard to this comment.

Reviewer:
4. The title of the paper suggests the presentation of a protocol for delivery of stroke treatment in the field. The presentation of initial data of an ongoing randomized trial might be out of the scope of this paper. The author should either consider not to present such data at this time or to redefine the aims (and title).

Response:
Unfortunately, we are not yet able to present data of our trial. However, we do not perceive our title as misleading. This is *‘a’* video-manual describing one optional way of how you could deliver pre-hospital thrombolysis. We made it more clear at the end of the introduction that the decision to implement this approach to stroke care is open to debate and final results of the PHANTOM-S should be awaited.
We added the following sentences: “However, prior to implementation final results of sufficiently powered studies need to confirm safety and efficacy of this approach. Here we present the methods used in the “pre-hospital acute neurological therapy and optimization of medical care in stroke patients” study (PHANTOM-S).”