Fast Protocol for Treating Acute Ischemic Stroke by Emergency Physicians

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Study objective: Thrombolysis with tissue plasminogen activator should occur promptly after ischemic stroke onset. Various strategies have attempted to improve door-to-needle time. Our objective is to evaluate a strategy that uses an emergency physician–based protocol when no stroke neurologist is available.

Methods: This was a retrospective before-after intervention analysis in an urban hospital. Reorganization of the acute ischemic stroke treatment process was carried out in 2013. We evaluated time delay, symptomatic intracerebral hemorrhage, and clinical recovery of patients before and after the reorganization. We used multivariable linear regression to estimate the change in door-to-needle time before and after the reorganization.

Results: A total of 107 patients with comparable data were treated with tissue plasminogen activator in 2009 to 2012 (group 1) and 46 patients were treated during 12 months in 2013 to 2014 (group 2). Median door-to-needle time was 54 minutes before the reorganization and 20 minutes after it (statistical estimate of difference 32 minutes; 95% confidence interval 26 to 38 minutes). After adjusting for several potential cofounders in multivariable regression analysis, the only factor contributing to a significant reduction in delay was group (after reorganization versus before). Median onset-to-treatment times were 135 and 119 minutes, respectively (statistical estimate of difference 23 minutes; 95% confidence interval 6 to 39 minutes). The rates of symptomatic intracerebral hemorrhage were 4.7% (5/107) and 2.2% (1/46), respectively (difference 2.5%; 95% confidence interval –8.7% to 9.2%). Approximately 70% of treated patients were functionally independent (modified Rankin Scale score 0 to 2) when treated after the reorganization.

Conclusion: Implementation of a stroke protocol with emergency physician–directed acute care decreased both door-to-needle time and onset-to-treatment time without increasing the rate of symptomatic intracerebral hemorrhage. [Ann Emerg Med. 2019;73:105-112.]

Please see page 106 for the Editor's Capsule Summary of this article.

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INTRODUCTION
Background

Thrombolysis with tissue plasminogen activator (tPA) is a cornerstone in treating a patient with acute ischemic stroke.[1,2] This treatment should be given as soon as possible, preferably within 4.5 hours after symptom onset and within 60 minutes after patient arrival at the hospital.[1] Previous studies have shown that a median door-to-needle (DNT) time of 20 minutes is achievable.[3] Each minute saved from the time to treatment can produce significant improvement in a patient's poststroke life.[4]

Various strategies for improving door-to-needle time have been presented previously.[5] After having begun postgraduate training in the nationally new specialty of emergency medicine in our hospital,[6] we changed the treatment of acute ischemic stroke from the use of telestroke to a model based on a strong contribution of emergency physicians. We recently reported the basic principles and preliminary results of this new model.[7]

The primary aim of this study was to analyze median door-to-needle time together with safety data of tPA-treated acute ischemic stroke patients during the first 12 months of the emergency physician–based protocol. These results are compared with those in 2009 to 2012, preceding reorganization of the acute ischemic stroke protocol. Secondarily, we aimed to reveal whether onset-to-treatment (OTT) time was affected after the reorganization. Safety data are compared with international data as well.

Editor's Capsule Summary

What is already known on this topic

Most stroke teams are led by neurologists, whereas emergency physicians typically are the first to evaluate and treat patients with acute neurologic deficits.

What question this study addressed

What was the effect of a reorganization of the acute stroke process to focus on emergency physicians guiding acute stroke care?

What this study adds to our knowledge

Stroke patients were treated faster after the reorganization. Although complications were similar before and after the change, the study was not powered to confirm their equivalency.

How this is relevant to clinical practice

With training and a well-defined protocol, emergency physicians quickly treated patients with acute stroke.

MATERIALS AND METHODS

This was a before-after intervention analysis, and its design was approved by the local ethics committee. The study included all patients with acute ischemic stroke who were treated with tPA in our emergency department (ED) in 2009 to 2012 (group 1, ie, "before") and from October 1, 2013, to September 30, 2014 (group 2, ie, "after"). In 2009 to 2012, before the implementation of the emergency medicine specialty, the treatment protocol of patients with acute ischemic stroke varied slightly, as described in one of our earlier studies.[7] Thereafter, stroke education for emergency physician trainees took place during the 9-month reorganization period preceding October 1, 2013.[7] It consisted of training in the stroke unit at the neurology ward, theoretical teaching and practical training in diagnosing and treating patients with acute ischemic stroke (eg, diagnosis and differential diagnosis of acute ischemic stroke, National Institutes of Health Stroke Scale [NIHSS] scoring with indications and contraindications of tPA administration), preparation with the electronic patient record after the prenotification given by emergency medical services (EMS), shadowing of an experienced neurologist in acute neurologic emergencies, and finally with the diagnosis and treatment of their own patients with clinical acute ischemic stroke, under the supervision of the specialist in the ED. Radiologists taught emergency physicians the evaluation of head computed tomography (CT) of patients with acute ischemic stroke. After training, radiologists

remained on call and available continuously to evaluate head CT images. Finally, we emphasized the importance of the acute ischemic stroke process without extra delays in our ED.[7]

Depending on the day of the week or the time of day, the physician on call taking care of patients with acute ischemic stroke was either a neurologist (or resident) or internist resident working with the aid of telestroke before the reorganization. Since October 1, 2013, the responsible physician in the ED has been a stroke-educated emergency physician in 97.5% of all out-of-hour shifts during the first year after the reorganization.[7] The neurologist on call was always reachable by telephone if needed. Every emergency physician trainee in our ED became stroke educated during the 9-month reorganization period before October 1, 2013 (ie, the official start of our program). However, because of the relatively small number (n=9) of our trainees, on a few occasions we had to rely on experienced physicians who were not specifically stroke educated. In these situations, the role of the senior neurologist on call was emphasized.

The data were collected from patient files retrospectively by using the relevant primary source data. The written patient records consisted of 3 sources: the report from EMS by paramedics; a paper form filled out in the ED by nurses, which contained information from the clinical care delivered and described during the stroke activation (time of arrival and time of initiation of tPA); and the electronic patient record generated by the responsible physician. The paper form was considered a primary source if there were any conflicts concerning the data that occurred after patient arrival. For example, the time of patient entrance and that of tPA bolus are primarily recorded on this paper. Physicians usually later dictate the same information into the electronic record. On the other hand, the onset of symptoms is usually confirmed by a physician and stored in the electronic patient record. If there was any discrepancy in the time of onset between data sources, the notation of the attending physician in the ED was considered the true value. The data were abstracted by the first author (I.H.). He read all patient records of tPA-treated patients and collected the numeric information into the electronic abstraction form. These data included precisely defined variables such as sex, age, NIHSS score, intervals (door-to-needle and onset-to-treatment time), and presence of intracerebral hemorrhages in both groups (intracerebral hemorrhage at this point: yes or no). Missing data were coded as such. Conflicting or ambiguous chart elements had to be discussed with the senior researcher. However, in our setting such data did not exist. This investigator was not blinded to the period (pre- versus postintervention).

We calculated the annual proportion of stroke patients treated with thrombolysis. Then, the numbers of adverse hospital outcomes (inhospital mortality or impaired recovery leading the patient to become permanently bedridden) were abstracted from the electronic Effica patient database (version 1.5; Tieto Oy, Helsinki, Finland) and other hospital sources by using the Web-based database program Exreport (version 2.0; Neotide Oy, Vaasa, Finland). The crucial data of each hospital stay are nationally coded uniformly and can be accessed without entering confidential individual patient records. Furthermore, the calculation of the 30-day mortality of all patients with acute ischemic stroke was based on data obtained from the Statistical Office of Finland. The annual results before the reorganization (ie, 2009 to 2012) are presented as such, and the average mortality of these 4 years is compared with that of 12 months after the reorganization. For patients who received tPA treatment, we collected individual data, including sex, age, NIHSS score, intervals (door-to-needle and onset-to-treatment time), and presence of intracerebral hemorrhages in both groups.

The modified Rankin Scale is commonly used to measure disability in tPA-treated patients.[8] It is a 7-level, ordinal, noninterval scale in which 0 corresponds to no symptoms; 5, to severe disability; and 6, to death. Evaluation of clinical recovery by using the modified Rankin Scale was not routine practice in our hospital until 2013. Since then, it has been used in all cases 3 months after acute ischemic stroke[9] by way of the modified Rankin Scale–9Q questionnaire.[10] So in this study, the modified Rankin Scale score was recorded clinically in patient files (only after reorganization) at 3 months after the tPA treatment and collected from the patient files retrospectively with the other data by investigators.

All tPA-treated patients were included in the analysis. Exclusion criteria were as follows: symptomatic stroke in an inhospital patient, symptom fluctuation (ie, no evident time for the start of index stroke symptoms), basilar artery occlusion, discontinuation of tPA infusion before a full dose (for example, because of low hemoglobin level), and missing data on crucial times.

The safety of the new protocol was assessed by using the European Cooperative Acute Stroke Study (ECASS II) criteria.[11] During the study periods, routine reimaging of the brain by way of CT was carried out approximately 24 hours after tPA treatment if there were no patient-related reasons for reimaging before that. Brain hemorrhages were classified by using slightly modified ECASS II criteria: intracerebral hemorrhage was defined as symptomatic if there was blood at any site in the brain on the CT scan according to the radiologist and significant clinical

worsening of the situation occurred; for example, drowsiness and deepening of hemiparesis or an increase in NIHSS score by 4 or more points. Other findings concerning blood at any site of the brain but without clinical effect were classified as asymptomatic. This practical slight modification was carried out because of the retrospective setting: radiologists' reports presented CT reading panels and patient record notes indicated "documentation by the investigator."[11] The interrater reliability assessment was used when the intracerebral hemorrhages were classified as asymptomatic and symptomatic hemorrhages. This was accomplished in 2 phases. First, I.H. classified the patients without blinding according to the information that was available from the patient records (eg, the radiologist report of the head CT, the clinical situation in the ED or in the stroke unit). ECASS II criteria were used as described. Thereafter, before further evaluation, each patient file was blinded so that the group, date, and name of the patient or physician could not be identified. Finally, an experienced neurologist (H.K.) conducted the classification for the same patients, using the identical but blinded information.

Methods of Measurement

Statistical analyses were performed by using IBM SPSS Statistics (version 22; IBM, Chicago, IL). Differences of dichotomous variables with 95% confidence intervals (CIs) with a correction for continuity were analyzed by using public statistical software (http://vassarstats.net/prop2_ind.html) according to a method described by Newcombe[12] and derived from the procedure outlined by Wilson.[13] Data are presented as median (minimum–maximum) if not mentioned otherwise. We made a priori a sample size calculation for the door-to-needle time (SD 40%), with the presumed sampling ratio of 4:1. For the effect of 30% (α=.05, 2 tailed), we would have needed approximately 20 patients in group 2 to yield power of 80%.

Before we compared results before and after the reorganization, we tested the homogeneity of the results during 2009 to 2012. Dichotomous variables such as proportions of stroke patients treated with tPA and the 30-day mortality of all patients with acute ischemic stroke before and after the reorganization were compared by χ^2 test. Because of small numbers, comparisons of adverse hospital outcome of all ischemic stroke patients, all intracerebral hemorrhages, and symptomatic versus asymptomatic intracerebral hemorrhages were conducted with Fisher's exact test. The estimated differences of door-to-needle time and onset-to-treatment time before and after reorganization, with 95% CIs, were calculated by using the

independent-samples Hodges-Lehman median difference test. Differences in continuous variables were assessed by using the Mann-Whitney U test.

To analyze whether the reorganization as such had an effect on door-to-needle time, our preplanned analysis was to perform multivariable regression analysis including collinearity statistics with the group and 9 well-known biologically relevant variables possibly affecting door-to-needle time. Factors used in the analysis were entered as predictors as follows: age in years, sex (male or female), year (from 2009 to 2014), home municipality (3 groups based on the distance to the hospital), prenotification (from the EMS before patient arrival: yes or no), use of telestroke consultation (yes or no), day of the week (Saturday/Sunday versus other, ie, weekend [yes or no]), hour of the day (office hours versus out-of-office hours), NIHSS score at patient arrival to the ED, and the group (1 versus 2). Here, we were interested in the comparative effects of these factors on door-to-needle time instead of conducting any estimation or general modeling based on our results.

In statistical analyses, $P<.05$ was considered significant.

RESULTS

Before the reorganization, 1,581 patients with acute ischemic stroke were treated in our ED in 2009 to 2012. Furthermore, 355 patients were treated during the 12 months after the reorganization. The proportions of patients treated yearly with tPA were 7.9% (n=29), 7.9% (n=33), 8.1% (n=27), and 7.6% (n=35) in 2009 to 2012, respectively. Taken together, the proportions of tPA-treated patients with acute ischemic stroke before and after the reorganization were 7.8% (n=124) and 14.4% (n=51), respectively (difference 6.5%; 95% CI 2.8% to 10.9%). Of the 124 of patients in group 1, 17 were

excluded, 8 because of basilar artery occlusion or because of an inhospital stroke and 9 because of insufficient time data. In group 2, the total number of patients was 51. Five of them were excluded, 1 because of missing data, 1 because tPA was started after symptom fluctuation, 1 because the tPA infusion was discontinued because of low hemoglobin level, and 2 because of basilar artery occlusion.

When only tPA-treated patients without exclusion criteria were counted, the yearly numbers were 25, 30, 21, and 31 in 2009 to 2012, respectively. During these 4 years, the percentage of tPA treatment varied from 6.3% to 7.2%, without any temporal trend. Hence, the mean proportion of this period could be compared with that of the 12-month period after the reorganization. As a result, the total numbers of patients included in further analyses were 107 in group 1 (2009 to 2012) and 46 in group 2 (2013 to 2014) (Figure 1). Proportions of tPA-treated patients with acute ischemic stroke and without exclusion criteria before (group 1) and after (group 2) the reorganization were 6.8% and 13.0%, respectively (difference 6.2%; 95% CI 2.7% to 10.4%). The characteristics of the groups are presented in the Table.

The median door-to-needle time was 54 minutes in group 1 and 20 minutes in group 2 (statistical estimate of difference 32 minutes; 95% CI 26 to 38 minutes) (Figure 2A and B). According to multivariable regression analysis, the only factor explaining door-to-needle time was group. All assessed variance inflation factors were less than 10, so we did not find evidence of multicollinearity. Results of the model with all 10 of the potentially biologically relevant predictors are given in Table E1, available online at http://www.annemergmed.com.

The median onset-to-treatment time in group 1 was 135 minutes, whereas it was 119 minutes in group 2 (statistical estimate of difference 23 minutes; 95% CI 6 to 39 minutes) (Figure 3).
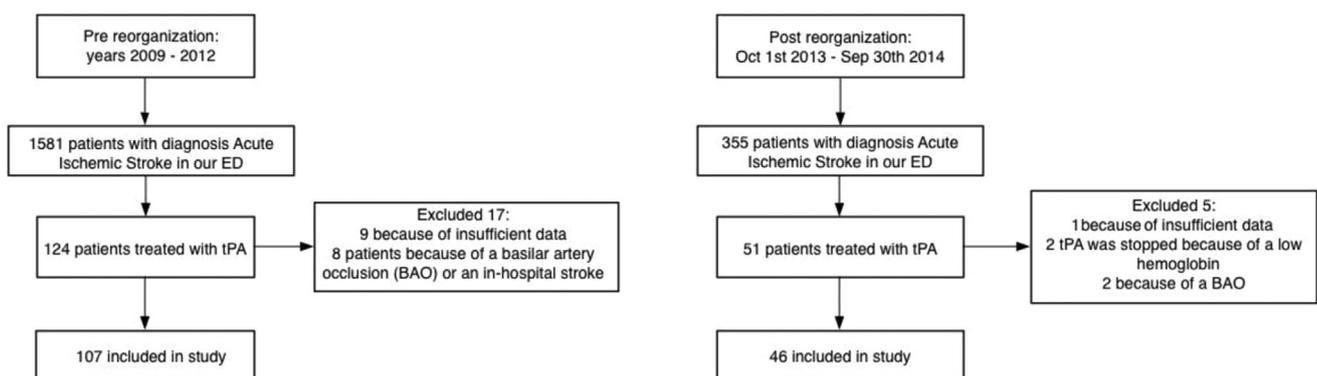
Figure 1. The trial profile was a before-after intervention analysis. Group 1 (ie, "before") represents 2009 to 2012; and group 2, 1 year (from October 1, 2013, until September 30, 2014).

Table. Study population and the main findings.

Study Population and Main Findings	Group 1	Group 2
Patients included	107	46
Men (%)	50 (47)	28 (61)
NIHSS score, median (IQR)	7 (4–12)	5 (4–9)
DNT median, min	54	20
OTT median, min	135	119
Hospital mortality, No. patients	4	0
Mortality at 3 mo, No. patients	NA	1
mRS 3 mo, median (IQR)	NA	1 (0–3)
sICH, No. patients (%)	5 (4.7)	1 (2.2)

IQR, Interquartile range; *OTT*, onset-to-treatment time; *NA*, not applicable before the reorganization; *mRS*, modified Rankin Scale score; *sICH*, symptomatic intracerebral hemorrhage.

Figure 3. Median OTT was 135 minutes before reorganization (group 1). After implementation of the new stroke protocol, it was 119 minutes (group 2). The difference (statistical estimate 23 minutes; 95% CI 6 to 39 minutes) was significant (*P*=.006).

In group 2, the median modified Rankin Scale score 3 months after treatment was 1.0 (mean 1.6; data available from 44 patients). Thirty-two of the 46 patients were functionally independent, with a modified Rankin Scale score of 0 to 2. These data were not available for group 1 because our hospital did not have a standard practice to systematically assess outcomes at 90 days before the reorganization.

Six cases of symptomatic intracerebral hemorrhages after tPA treatment were detected, 5 of 107 (4.7%) in group 1 and 1 of 46 (2.2%) in group 2 (difference 2.5%; 95% CI –8.7% to 9.2%) (Table). For the assessment of classifying the intracerebral hemorrhages as asymptomatic and symptomatic, I.H. and H.K. obtained the same results so that the agreement of the symptomatic intracerebral hemorrhages in both groups was 100%.
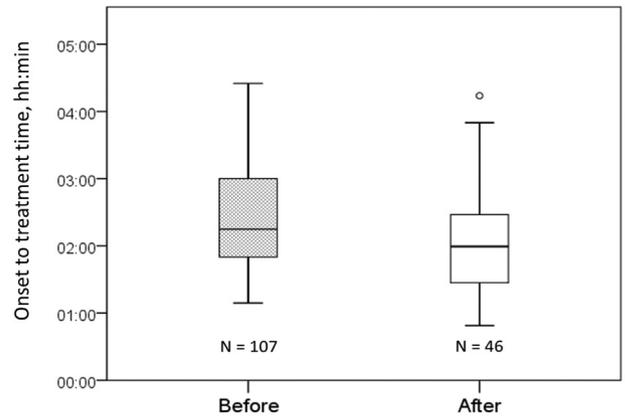
Of tPA-treated patients with acute ischemic stroke, 4 (3.7%) in group 1 died during the hospital stay, whereas none did in group 2 (difference 3.7%; 95% CI –6.2% to 9.9%) (Table). After the hospital stay, 57.9% (62 of 107) and 63.0% (29 of 46) of patients with acute ischemic stroke and tPA treatment were discharged home in groups 1 and 2, respectively (difference 5.1%; 95% CI –13.0% to 21.8%). The 30-day mortality of all ischemic stroke patients (both tPA treated and untreated) was 8.1% before and 7.5% after the reorganization of the stroke protocol in our ED (difference 0.6%; 95% CI –0.4% to 1.6%). In tPA-treated patients with acute ischemic stroke, the 3-month mortality rate in group 2 was 2.2% (ie, only 1 patient of 46 died after treatment) (Table). Because there were no reliable data on 3-month modified Rankin Scale
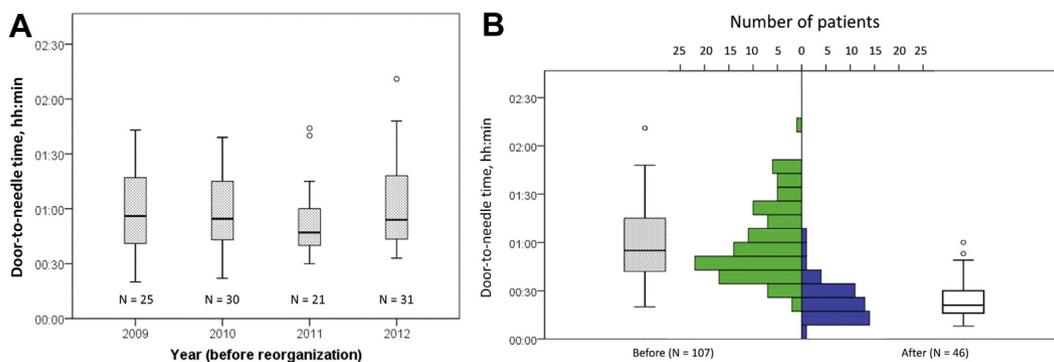

Figure 2. *A*, Before the reorganization (group 1, 2009 to 2012), in median DNTs there were no trends either to decrease or increase (NS). *B*, In group 1 (ie, "before," 2009 to 2012), median DNT was 54 minutes. After reorganization, it was 20 minutes (group 2 [ie, "after," 12 months from October 1, 2013]). The difference (statistical estimate 32 minutes; 95% CI 26 to 38 minutes) was significant. DNT as in *A*. Also shown is a back-to-back histogram representing same results. Box plots represent medians and interquartile range. Whiskers and outliers (open circles) represent the whole range of DNTs. In group 1, minimum and maximum DNTs were 20 minutes and 2 hours, 11 minutes, respectively. In group 2, they were 8 and 60 minutes, respectively.

scores available in group 1, the mortality rate in this group was unavailable.

The diagnosis at discharge from the stroke unit in the neurology department was associated with acute ischemic stroke in all of the cases in group 2.

LIMITATIONS

A limitation of our study is that it was retrospective and modified Rankin Scale score data on patients treated before 2013 were available only in a limited number of cases. Therefore, we were able to compare our modified Rankin Scale score data from group 2 only with international findings.[14] Since 2013, modified Rankin Scale score evaluation using the modified Rankin Scale–9Q[10] has been routine practice. As is well known, the modified Rankin Scale has its own limitations,[15] but it is still probably the most relevant scale.[9]

A further limitation of this study is that as a single-center study carried out in a medium-sized hospital, the total number of tPA-treated patients was relatively low. However, the number of tPA-treated patients during the 12-month observation period was 51 (46 included in the study) of 355 patients with acute ischemic stroke, so the proportion of patients with thrombolysis (14.4; 13.0%) was relatively good compared with results published earlier.[16] After the reorganization, not only did door-to-needle time and onset-to-treatment time decrease but also the number of stroke patients per year who were treated with tPA increased compared with that in previous years. Because the median NIHSS score of the patients decreased (Table) and simultaneously no stroke mimics were treated, our study implies that, overall, reorganization of the stroke protocol improved the treatment of patients with acute ischemic stroke.

An important methodological limitation is similar to that of many other studies in the field of emergency medicine.[17] Retrospective studies are always challenging and susceptible to biases. Especially the chart-reviewing process in this study was not perfect because the data abstracting and chart reviewing were conducted by the authors. However, especially when evaluating symptomatic intracerebral hemorrhages, we tried to avoid biases by using blinded double-check after an open evaluation. There was no discrepancy between the open and blinded evaluations in regard to symptomatic or asymptomatic intracerebral hemorrhages. We did not find the retrospective nature of this study a major problem because the most important data (for example, time and mortality data) are numeric and thus not sensitive to subjective biases. Still, we are well aware of the possibility of failure to train and monitor data abstractors, as

described in a review article by Vassar and Holzmann according the considerations of retrospective chart review.[18]

DISCUSSION

On the basis of our results in this single-center study, emergency physicians were able to treat acute ischemic stroke with tPA rapidly, without increasing intracerebral hemorrhage, with the aid of neurologists on call over the telephone if needed. Shortening of median door-to-needle time to 20 minutes and onset-to-treatment time to 119 minutes was statistically significant, and there was no increase in the rate of symptomatic intracerebral hemorrhages. Because we did not evaluate the subintervals of door-to-needle time, we are not able to exactly show where time saving actually occurred. One of the key points is that the treatment protocol is always the same, without any variations, and that the patient is examined immediately after entrance to the ED.

Patient selection was adequate because no stroke mimics were treated with tPA in group 1 nor 2, although small sample size limits the generalization of our results. More important, there is no evidence that any patient with acute ischemic stroke during the latter study period would have been left without tPA when indicated: according to the systematic quality assurance in the neurology department (including the stroke unit), no patient was missed in the latter period (group 2). The use of the telestroke was interrupted on September 30, 2013, so that it was not available in the latter period (group 2).

There are ways to improve capacity efficiency in EDs through, for example, optimizing work spaces; education; cooperation of staff between EMS, EDs, and neurology and radiology departments; reorganizing processes; and implementation of bedside diagnostics.[19-22] Our acute ischemic stroke process represents a combination of these (Figure 4).[7]

There is marked regional variation in thrombolysis treatment.[23] Some potential external and internal barriers to the emergency use of tPA for acute ischemic stroke has been recognized, including, for example, environmental factors and outcome expectancy.[24] Scott et al[16] reported the findings of an important Increasing Stroke Treatment through Interventional behavioral Change Tactics (INSTINCT) trial, in which they made an intervention designed to alter systems and behavior at an institutional level and individual staff level. In that study, the use of tPA remained below 3% after having increased in both groups, and the intervention had no significant effect on alteplase use in patients with acute ischemic stroke. The original aim of our new protocol was to decrease the delay of treatment.
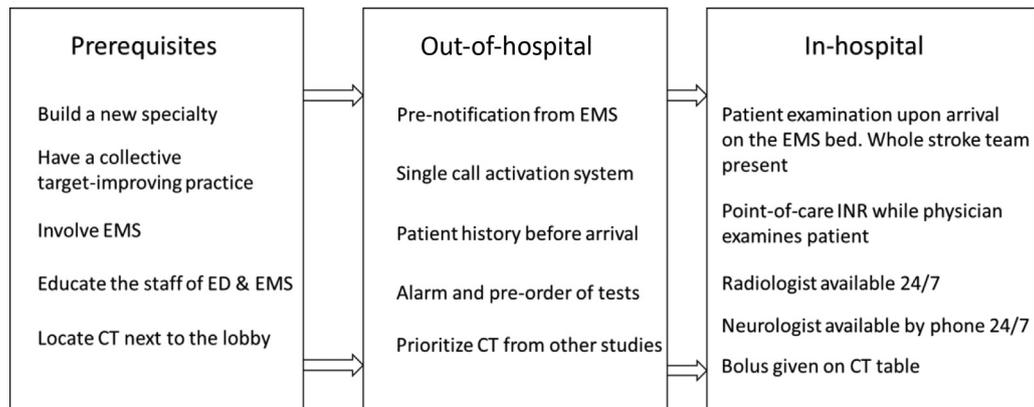
Figure 4. Main prerequisites and elements of the intervention. Modified from our earlier publication.[7] *INR*, International normalized ratio.

Simultaneously, we succeeded in significantly increasing the proportion of tPA-treated patients with acute ischemic stroke.

Comparison of the intracerebral hemorrhage and recovery data with the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) shows that our protocol had comparable safety and efficacy. In our study, symptomatic intracerebral hemorrhage in group 2 was found in only 2.2% of the whole population, according to ECASS II,[11] whereas the percentage varies between 1.6% and 7.3% in SITS-MOST, depending on the particular criteria.[14] Again, 70% of our patients had modified Rankin Scale scores of 0 to 2 after 3 months compared with 54.8% to 56.0% in SITS-MOST.[14]

To our knowledge, this study is the first in which the role of emergency physicians as important executors of a stroke protocol with a very short median door-to-needle time has been confirmed. Greenberg et al[25] presented results in which emergency physicians trained in neuroscience could achieve better results than their colleagues without such training, with door-to-needle times of 35 and 83 minutes, respectively. We carried out a search in PubMed (2007 to November 2016; search terms "Emergency physician" [Title/Abstract] OR "Emergency physicians" [Title/Abstract] AND "stroke" [Title/Abstract] AND "thrombolysis" [Title/Abstract]) that revealed a total of 19 publications, including an earlier study of ours.[7] Of these, 15 were based on clinical studies, but only 2 reported door-to-needle or onset-to-treatment times.[26,27]

An article by Ferrari et al[26] focused on Austrian stroke protocols and inhospital delays. They found that door-to-needle times ranged between 30 and 78 minutes in Austrian stroke centers in April 2004 to November 2012. The study did not include emergency physician–led protocols because the specialty of emergency medicine does not exist in the country. Another clinical study concerned thrombolysis for acute ischemic stroke in a district general hospital in the United Kingdom with an emergency physician–led stroke team.[27] The main finding of this study was that thrombolysis is both safe and possible in a nonspecialist center led by emergency physicians compared with SITS-MOST register data.[28] This study involved not door-to-needle times but onset-to-treatment times. Their finding of an onset-to-treatment time of 142 minutes is in line with our results in group 1 (ie, before the reorganization). In a third study, onset-to-treatment time was available in only 4 cases, and it was focused mainly on CT angiography in basilar artery occlusion with intubated patients.[29] One educational study revealed that the Canadian system provided detailed stroke protocol education for trainees in emergency medicine.[30]

To conclude, we found that implementation of a stroke protocol based on the central role of emergency physicians decreased both door-to-needle time and onset-to-treatment time. Emergency physicians are able to treat stroke patients quickly and efficiently once the acute ischemic stroke protocol has been created, with cooperation between neurologists, radiologists, and emergency physicians.

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