Impact of the Extended Thrombolysis Time Window on the Proportion of Recombinant Tissue-Type Plasminogen Activator-Treated Stroke Patients and on Door-to-Needle Time

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Background and Purpose—The European Cooperative Acute Stroke Study (ECASS) III extended the thrombolysis time window for patients with stroke from 3 to 4.5 hours after symptom onset. We investigated the effect of the extended thrombolysis time window on the proportion of recombinant tissue-type plasminogen activator-treated stroke patients and on the time of treatment initiation after hospital arrival.

Methods—The present study was based on a prospective database of 93 hospitals of the Stroke Register of Northwestern Germany, which included 91 805 patients with ischemic stroke admitted between January 2007 and December 2009. Main outcome measures were the use of recombinant tissue-type plasminogen activator among patients with stroke and the door-to-needle time before and after the publication of ECASS III in September 2008 and subsequent changes of the German guidelines in May 2009.

Results—Overall, 9262 patients (10.1%) were treated with recombinant tissue-type plasminogen activator. The proportion of thrombolized patients increased from 8.6% in 2007 to 11.7% in 2009. This increase was pronounced for patients admitted between 3 and 6 hours after symptom onset after the third quarter of 2008 (OR, 1.88; 95% CI, 1.24 to 2.85) and after the second and third quarters of 2009 (OR, 2.50; 95% CI, 1.69 to 3.69 and OR, 3.02; 95% CI, 2.07 to 4.41) compared with the first half year 2007. The proportion of stroke patients with a stroke-to-door time <60 minutes increased after publication of ECASS III (OR, 1.49; 95% CI, 1.37 to 1.63).

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Stroke Register of Northwestern Germany: For the present study we used data from the neurological departments of Johannes Wesling Klinikum Minden; Klinikum Herford; St Josef-Hospital, Bochum; Knappschaftskrankenhaus, Bochum-Langendreer; BG Universitätsklinikum Bergmannsheil GmbH, Bochum; Evangelisches Krankenhaus, Hattingen; Evangelisches Krankenhaus GmbH, Gelsenkirchen; Evangelisches Krankenhaus, Herne; Universität Münster; Herz-Jesu-Krankenhaus, Münster-Hiltrup; Klinikum Ibbenbüren; LWL-Klinik; St Marien-Hospital, Hamm; St Johannes Hospital, Hagen; Klinikum Lüdenscheid; Kreisklinikum Siegen; Klinikum Lippe-Lemgo; Ev Krankenhaus Bielefeld Biegel, Bielefeld, Germany.

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Conclusions—Results of ECASS III were rapidly implemented in routine stroke care. Concerns of a delay in recombinant tissue-type plasminogen activator treatment initiation after the extension of the thrombolysis time window were not confirmed. (Stroke. 2011;42:2838-2843.)

Key Words: ECASS III • guidelines • stroke • thrombolysis

Thrombolysis with recombinant tissue-type plasminogen activator (rtPA) for the treatment of acute ischemic stroke was approved by the Food and Drug Administration in 1996 and by the European Medicines Agency in 2002.1 The European Medicines Agency approval was subject to 2 requests. First, an observational safety study had to be initiated. Subsequently, the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) was conducted showing a similar safety profile of rtPA in routine clinical practice compared with that shown in clinical trials.2 Second, a randomized controlled trial was requested in which the therapeutic time window should be extended beyond the so far proven 3 hours. The European Cooperative Acute Stroke Study (ECASS) III trial enrolled 821 patients who were randomized to receive either rtPA or placebo within 3 to 4.5 hours after the onset of symptoms.3 Thrombolysis was associated with a significant improvement in the clinical outcome in this study that was published in September 2008. Subsequently, in May 2009, the recommendation of rtPA use in patients with stroke within 4.5 hours of symptom onset was included into the German guidelines.4 Because the majority of patients with stroke arrive at the hospital later than 3 hours after symptom onset and because the narrow therapeutic time window is a main reason for the overall small proportion of patients with stroke receiving thrombolysis, the results of ECASS III raised hope that considerably more patients will be treated with rtPA.5–7 Recently, the Safe Implementation of Treatment in Stroke-International Stroke Thrombolysis Registry (SITS-ISTR) observational study reported a rapid increase of rtPA-treated stroke patients after publication of ECASS III.8 However, the interpretation of this finding is limited because the overall number of patients with ischemic stroke was not surveyed but only stroke patients treated with thrombolysis were included. There is a general trend of a rising number of patients with stroke, which was even increased in the SITS-ISTR study due to the successive participation of additional hospitals during the study period.9 Thus, the important information regarding the proportion of patients treated with thrombolysis could not be obtained in this trial. Moreover, the SITS-ISTR analysis only considered the subgroup of rtPA-treated patients who were compliant with the European Summary of Product Characteristics criteria, thus not reflecting the stroke population routinely accessible for thrombolysis.

The beneficial effects of thrombolysis in patients with stroke are strongly time-dependent with the highest therapeutic yield after early treatment initiation.9 Therefore, the door-to-needle (DTN) time, which indicates the time between hospital arrival and treatment initiation, is required to be as short as possible. Despite the well-known importance of rapid rtPA administration, an inverse relation between time from symptom onset to hospital arrival and DTN time was reported.10,11 The DTN time was shorter in patients arriving late after symptom onset compared with patients arriving early, raising concerns about a “loss of time” if the interval until the end of the 3 hours window is still large. Because ECASS III extended the therapeutic time window to 4.5 hours, there were concerns whether this would cause a further delay in treatment initiation of early-arriving patients.

The aim of this analysis was to study changes in the proportion of patients with stroke treated with rtPA after the publication of ECASS III and the subsequent guideline modification as well as the rapidity with which these changes were implemented in routine stroke care. We further investigated the effects of the extended time window on the DTN time. Data of a large German stroke register for the years 2007 to 2009 were used.

Methods

All data were collected within the regional Stroke Register of Northwestern Germany.12,13 This registration is part of a legal act implemented in Germany through which hospitals participate in programs for quality assurance of acute clinical stroke care. The registry is not population-based and participation is open to all hospitals that treat patients with acute stroke. Although registration is optional, for reasons of quality assurance, hospitals with a stroke unit need to prove participation in a registry to be certified by the German Stroke Society. Participation in the registry is subject to a fee for data management and benchmarking reports. Participating hospitals cover the whole variation of hospitals that provide acute stroke care in Germany, including hospitals in urban and rural regions as well as departments of neurology and internal medicine from academic and community hospitals. Of 149 participating hospitals, we considered those 93 hospitals that continuously documented their patients with stroke during the study period between January 1, 2007, and December 31, 2009. All patients with ischemic stroke admitted to the participating hospitals during the study period were considered in the present analysis; sampling of cases was not allowed. Data were collected prospectively by the treating hospital physician. Information gathered for each patient included sociodemographic characteristics, comorbidities, neurological deficits, stroke type, complications, diagnostic procedures, admission procedures, and treatment strategies during the in-hospital period. In addition, details concerning the treating institution were documented. Data collection was standardized and the documented forms were sent to the coordinating center of the Stroke Register of Northwestern Germany at the University of Muenster. Forms were scanned and checked for completeness and plausibility.

The following definitions were used.

Hypertension was defined as systolic blood pressure of ≥160 mm Hg, diastolic blood pressure of ≥95 mm Hg, or patient self-report of treated arterial hypertension. Diabetes mellitus was defined as elevated fasting blood glucose level, patients’ self-report of a physician’s diagnosis of diabetes, or use of antidiabetic drugs. Atrial fibrillation was documented by electrocardiogram. Previous stroke was defined as a neurological deficit ≥24 hours before the current event.

Stroke was defined according to the World Health Organization criteria.14 The stroke subtype (ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, transient ischemic attack, undefined) was diagnosed from the results of CT or MRI scan. Stroke severity was assessed using an ordinal score reflecting the number of major stroke-related symptoms, that is, presence or absence of upper and/or lower limb paresis, presence or absence of diminished vigilance, presence or absence of dysarthria, and presence or absence of aphasia. Treatment with rtPA intravenously, intra-arterial...
thrombolysis, or no thrombolysis was recorded. The onset-to-door (OTD) time was categorized into <2 hours, 2 to 3 hours, 3 to 6 hours, and >6 hours. Because the stroke register was designed before the publication of ECASS III, the OTD times did not include a separate category of a 3- to 4.5-hour time window. The DTN time was categorized into <30 minutes, 30 to 60 minutes, 60 to 120 minutes, 120 to 180 minutes, and >180 minutes. Following prior analyses, we defined the total number of patients with stroke treated in an individual hospital per year as the hospital expertise with acute stroke treatment. To investigate whether the hospital expertise influences the time until the extended thrombolysis time window was implemented in clinical practice, hospitals were categorized according to the number of patients that were treated on average per year during the study period: (1) <500; (2) 500 to 749; and (3) ≥750 patients.

### Statistical Analysis

Means were compared using Student t test; for medians, Wilcoxon rank sum test was used. For comparison of frequencies, we used Fisher exact test and for trend analyses Maentel-Haenszel χ² test. Multivariable logistic regression was applied to identify the impact of the publication of ECASS III in September 2008 and the German guideline changes in May 2009 on thrombolysis frequency for the different OTD time categories. All models were adjusted for age, sex, Rankin Scale, stroke severity, and history of diabetes mellitus. We included 2 time variables in the regression models: (1) 3-month periods from January 2007 to December 2009 with the first 2 quarters combined to a 6-month time period under study. However, there was a significant decrease in the prevalence of diabetes in patients with stroke across quarters (P=0.002). In-hospital mortality of all patients with ischemic stroke was 5.13% before and 5.25% after publication of ECASS III (P=0.41). Overall, 9262 patients (10.1%) were treated with rtPA intravenously for acute ischemic stroke during the 3 years: 41.5% of patients admitted within 2 hours, 19.2% of patients admitted within 2 to 3 hours, 2.7% of patients admitted within 3 to 6 hours, and 0.6% of patients admitted >6 hours after symptom onset received intravenous thrombolysis. The proportion of patients treated with rtPA intravenously significantly increased over time from 8.6% in 2007 to 11.7% in 2009 (P<0.0001). Figure 1 shows the increase in the overall proportion of intravenous rtPA-treated patients and the increases in proportions of patients who received thrombolysis with OTD times <3 and between 3 and 6 hours according to quarters. The total number of patients treated with rtPA

### Results

During the 3-year observation period, a total of 93 245 patients with ischemic stroke were registered within the 93 included hospitals of the Stroke Register of Northwestern Germany. Of those, 1440 were excluded from further analysis because of missing values for thrombolysis-related variables. Mean age of the remaining 91 805 patients was 71.6 years; 46.6% were women. Comorbid conditions of patients with ischemic stroke and OTD times are given in the Table. There was no significant difference in the prevalence of arterial hypertension, atrial fibrillation, and prior stroke across the time period under study. However, there was a significant decrease in the presence of diabetes in patients with stroke across quarters (P trend=0.002). In-hospital mortality of all patients with ischemic stroke was 5.13% before and 5.25% after publication of ECASS III (P=0.41). Overall, 9262 patients (10.1%) were treated with rtPA intravenously for acute ischemic stroke during the 3 years: 41.5% of patients admitted within 2 hours, 19.2% of patients admitted within 2 to 3 hours, 2.7% of patients admitted within 3 to 6 hours, and 0.6% of patients admitted >6 hours after symptom onset received intravenous thrombolysis. The proportion of patients treated with rtPA intravenously significantly increased over time from 8.6% in 2007 to 11.7% in 2009 (P<0.0001). Figure 1 shows the increase in the overall proportion of intravenous rtPA-treated patients and the increases in proportions of patients who received thrombolysis with OTD times <3 and between 3 and 6 hours according to quarters. The total number of patients treated with rtPA

### Figure 1

The proportion of rtPA-treated patients of all patients with stroke, the proportion of rtPA-treated patients of those who arrived at hospital within 3 hours, and the proportion of rtPA-treated patients of those who arrived between 3 and 6 hours after symptom onset. rtPA indicates recombinant tissue-type plasminogen activator; OTD, onset-to-door.
intravenously increased from 451 in the first 3 months of 2007 to 1033 in the last 3 months of 2009 (Figure 2).

When analyzing the increase in the proportion of intravenous rtPA-treated patients (Figure 2), the strongest effect was observed for patients admitted between 3 and 6 hours after symptom onset between the third and the fourth quarters of 2008 (88.9% relative increase in IV 2008 compared with the first half year 2007, OR, 1.88; 95% CI, 1.24 to 2.85) and after the second and third quarters of 2009 (144.4% relative increase in III 2009 and 194.4% relative increase in IV 2009 compared with the first half year of 2007, OR, 2.50; 95% CI, 1.69 to 3.69 and OR, 3.02; 95% CI, 2.07 to 4.41). After adjustment for important confounders (age, gender, diabetes, number of neurological symptoms, Rankin Scale), this increase in the proportions of intravenous rtPA-treated patients after the third quarter of 2008 and after the second quarter of 2009 remained significant (P<0.0001 and P=0.004, respectively). The increase in the proportion of rtPA-treated patients with an OTD time between 3 and 6 hours was independent from the hospital expertise with acute stroke treatment (data not shown).

Among the patients with stroke treated with intravenous rtPA, the largest proportion received thrombolysis within 30 to 60 minutes after hospital admission (48.9%; Figure 3). The proportion of stroke patients with a DTN time <60 minutes increased after publication of ECASS III (OR, 1.49; 95% CI, 1.37 to 1.63), whereas the proportion of patients with a DTN time of 60 to 180 minutes decreased after publication of ECASS III (OR, 0.74; 95% CI, 0.67 to 0.81). Within the fourth quarter of 2008, the proportion of patients treated with rtPA intravenously within 30 minutes exceeded the proportion of patients who received thrombolysis within 60 to 120 minutes after hospital admission (Figure 3). When analyzing the DTN time separately for different OTD times, the trend of a decreased time to rtPA treatment after admission was pronounced within the group of patients with an OTD time between 3 and 6 hours (data not shown).
We additionally investigated the proportion of patients treated with intra-arterial thrombolysis. During the study period, 929 patients (1.02%) received rtPA intra-arterially (0.71% in 2007, 0.97% in 2008, and 1.29% in 2009, \( P \) for trend <0.0001). Of all patients admitted within 2 hours, 2.66% were treated with intra-arterial rtPA while the proportions were 1.80% between 2 and 3 hours, 0.86% between 3 and 6 hours, and 0.29% of the patients admitted >6 hours. There was no significant effect of ECASS III or guideline publication on the proportion of intra-arterially treated patients when analyzed for the overall study population and stratified for OTD times.

**Discussion**

In this large stroke register, we examined if the publication of ECASS III and the subsequent new guideline recommendations to extend the thrombolysis time window from 3 to 4.5 hours increased the number of patients with acute ischemic stroke receiving rtPA and how fast this increase occurred. The time period chosen sufficiently covered the period before trial publication and after guideline changes. The overall proportion of patients with ischemic stroke treated with intravenous thrombolysis increased from 8% to 11% during the study period. The increase was particularly evident in the 3-month period after the publication of the ECASS III trial in September 2008 among patients admitted between 3 and 6 hours after symptom onset and in the 3-month period after the publication of the new German guidelines. This rapid implementation into clinical practice was independent from the hospital expertise with acute stroke treatment as indicated by the number of patients with stroke admitted to an individual hospital per year. In-hospital mortality did not change during the implementation period. Extension of the time window for intravenous thrombolysis had no significant effect on intra-arterial thrombolysis rates. There was no increase in the DTN time after the publication of ECASS III and the subsequent guideline changes indicating that the extension of the thrombolysis time window did not result in a “laissez-faire” approach for those patients admitted early. In contrast, the proportion of patients who received rtPA early after admission was even increased, whereas the proportion of patients treated later after admission decreased after the publication of ECASS III.

Previous studies reported an increasing use of rtPA in patients with stroke over time.\textsuperscript{16–18} However, the impact of the extension of the thrombolysis time window to 4.5 hours on routine clinical practice was not reported so far. Factors previously reported to be associated with the proportion of patients with ischemic stroke receiving thrombolysis were the number of beds per hospital, admission to a stroke unit compared with admission to general wards, the population density of the area served by the hospital, and the education of the emergency department staff.\textsuperscript{16,19–21}

The adoption of results from landmark clinical trials into clinical practice and the adherence to new guidelines was extensively investigated for cardiovascular diseases.\textsuperscript{22–25} In contrast, only 1 recent study evaluated the transferral of clinical trial results into routine stroke care.\textsuperscript{8} However, the impact of guideline changes was not included. It has been shown that the speed of this transferral into clinical practice varies in studies evaluating different drug effects in cardiovascular diseases. Comparable to our finding, an immediate adoption of positive results from clinical trials was reported for the use of spironolactone in heart failure.\textsuperscript{26} However, other therapies shown to be effective in large clinical trials such as angiotensin-converting enzyme inhibitors in heart failure were incorporated only slowly in clinical routine.\textsuperscript{27,28} No temporal impact of guideline publication on clinical management was reported for early mechanical revascularization after myocardial infarction.\textsuperscript{25} Overall, the factors that determine the promptness with which evidence-based therapies influence clinical practice are not well understood so far.

The SITS-ISTR study found an overall similar DTN time before and after September 2008, the date of ECASS III publication.\textsuperscript{8} However, after the publication of ECASS III, it reported an increased DTN time for patients arriving >60 minutes.\textsuperscript{8} In our study, the proportion of early treated patients was increased after September 2008. This effect was present also when we stratified the analysis for different OTD times. Several factors were reported to be associated with the DTN time. Larger experience with thrombolysis, the use of a prehospital notification system, and a protocol-driven assessment of patients with stroke led to a decreased DTN time.\textsuperscript{10,29,30} In contrast, delays in neuroimaging and its interpretation, processing of laboratory results, and stabilization of blood pressure were identified to extend the DTN time.\textsuperscript{31}

We cannot rule out that changes in these factors might account for the increased proportion of early treated patients in our study. However, the rapid increase of early treated patients within the last quarter of 2008 in our study suggests that the results of ECASS III strengthened the overall confidence in thrombolysis as a stroke therapy and thus contributed to achieve faster treatment consensus in individual patients.

Our study has strengths and limitations. Information was collected in a uniform, prospective way over a study period of 3 years in 93 hospitals across Germany, thus enabling the analysis of temporal trends. In contrast to one prior study, our analysis was restricted to hospitals that participated during the entire study period because changes in treatment patterns can only be evaluated in this group. Due to the large number of patients, subgroup analyses among rtPA-treated patients could be performed with sufficient power. However, it is possible that changes in rtPA use reflect several influences including the overall trend of an increased proportion of patients receiving thrombolysis or unobserved variations in patient characteristics. Thus, a definitive causal relationship between ECASS III and guideline publications with the frequency of thrombolysis as well as with the DTN times cannot be made. However, statistical analyses were adjusted for relevant factors such as demographic characteristics, stroke severity, and comorbid conditions. Moreover, the sudden changes in rtPA use in the last quarter of 2008 and the first quarter of 2009 clearly suggest an impact of ECASS III. Although our analysis includes a large number of hospitals of northwestern Germany, the Northwestern Germany Stroke Registry is not population-based, thus limiting the generalizability of our findings.

The findings of ECASS III extended the thrombolysis time window from 3 to 4.5 hours. Because the data of our stroke register were collected prospectively and the register was...
designed before the publication of ECASS III, the OTD times were categorized into 3 to 6 hours and not recorded separately as a 3- to 4.5- and a 4.5- to 6-hour time window. However, on the basis of the recently completed 2010 data, we demonstrated that the largest proportion of rtPA-treated patients with OTD times between 3 and 6 hours were within the subgroup with OTD times of 3 to 4 hours (data not shown). Our observational study did not aim to show a benefit of the extended thrombolysis time window on patient outcome. The significantly improved clinical outcome of patients with stroke treated with rtPA between 3 and 4.5 hours after the onset of symptoms has been demonstrated by the ECASS III publication.3

Conclusions
In our study, we observed a rapid implementation of the results of the ECASS III study and the following guideline changes into routine stroke care. Within 3 months after publication of ECASS III, the proportion of patients who received thrombolysis among patients with ischemic stroke who arrived at the hospital within 3 to 6 hours after symptom onset was significantly increased. Previous concerns that the DTN time would increase after the extension of the thrombolysis time window were not confirmed. The proportion of early treated patients was even increased after publication of ECASS III.

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Disclosures
None.

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