Promoting Thrombolysis in Acute Ischemic Stroke

Maaike Dirks, MD; Louis W. Niessen, MD, Reg PH, PhD; Jeroen D.H. van Wijngaarden, PhD; Peter J. Koudstaal, MD, PhD; Cees L. Franke, MD, PhD; Robert J. van Oostenbrugge, MD, PhD; Robbert Huijsman, PhD; Hester F. Lingsma, MSc; Mirella M.N. Minkman, MSc; Diederik W.J. Dippel, MD, PhD; for the PROMoting ACute Thrombolysis in Ischemic StrokE (PRACTISE) Investigators

Background and Purpose—Thrombolysis with intravenous recombinant tissue plasminogen activator is an effective treatment for acute ischemic stroke, but the number of treatable patients is limited. The PROMoting ACute Thrombolysis in Ischemic StrokE (PRACTISE) trial evaluated the effectiveness of a multidimensional implementation strategy for thrombolysis with intravenous recombinant tissue plasminogen activator in acute ischemic stroke.

Methods—The PRACTISE trial was a national multicenter cluster-randomized controlled trial with randomization after pairwise matching. Twelve hospitals, both urban and community, academic and nonacademic, in the Netherlands participated. All patients admitted with stroke within 24 hours from onset of symptoms were registered. The intervention included 5 implementation meetings based on the Breakthrough Series model. The primary outcome was treatment with thrombolysis. Secondary outcomes were admission within 4 hours after onset of symptoms, death or disability at 3 months, and quality of life.

Results—Overall 5515 patients were included in the study, 308 patients (12.2%) in the control centers and 393 patients (13.1%) in the intervention centers were treated with thrombolysis (adjusted OR, 1.25; 95% CI, 0.93 to 1.68). Among the 1657 patients with ischemic stroke admitted within 4 hours from onset, 391 (44.5%) of 880 in the intervention centers were treated with thrombolysis and 305 (39.3%) of 777 in the control centers; the adjusted OR for treatment with thrombolysis was 1.58 (95% CI, 1.11 to 2.27).

Conclusions—An intensive implementation strategy increases the proportion of patients with acute stroke treated with thrombolysis in real-life settings. An apparently pivotal factor in the improvement of the treatment rate is better application of contraindications for thrombolysis.

Key Words: cluster-randomized controlled trial ▪ implementation ▪ stroke ▪ thrombolysis

Thrombolysis with intravenous recombinant tissue plasminogen activator (rtPA) is widely accepted as an effective treatment for patients with acute ischemic stroke if treatment can be started within 4.5 hours after onset. Although up to 25% of the patients might be eligible for thrombolysis, in most Western countries, only a relatively small proportion of patients (3% to 7%) is actually treated. To tackle the problem of undertreatment, we developed intervention strategies to remove barriers in the application of thrombolysis. We adapted a list of observed treatment obstacles by Kwan et al and grouped them into 4 categories: interorganizational, intragorganizational, medical, and psychological, which served as pretexts for targeted intervention strategies. Interorganizational barriers relate to the proportion of patients arriving in time for treatment. Intraorganizational barriers concern the availability of on-demand laborato-

Materials and Methods
PROMoting ACute Thrombolysis in Ischemic StrokE (PRACTISE) is a national cluster-randomized controlled trial for the evaluation of an intensive multidimensional implementation strategy for thrombolysis. The medical ethics committees in each participating center approved the study. The study was registered at the Clinical Trials Register (ISRCTN79204515). The online-only Data Supplement is available at http://stroke.ahajournals.org/cgi/content/full/STROKEAHA.110.596940/DC1.

From the Department of Neurology (M.D., P.J.K., D.W.J.D.), Erasmus MC University Hospital Rotterdam, Rotterdam, the Netherlands; the Institute for Health Policy and Management (L.W.N., J.D.H.v.W., R.H.), Erasmus University Rotterdam, Rotterdam, the Netherlands; the School of Medicine, Health Policy and Practice (L.W.N.), University of East Anglia, Norwich, UK; the Department of International Health (L.W.N.), Johns Hopkins School of Public Health, Baltimore, MD; the Department of Neurology (C.L.F.), Atrium Medical Center Parkstad, Heerlen, the Netherlands; the Department of Neurology (R.J.v.O.), Maastricht University Medical Center, Maastricht, the Netherlands; the Department of Public Health (H.F.L.), Erasmus MC University Medical Center, Rotterdam, the Netherlands; and the Dutch Institute for Healthcare Improvement CBO (M.M.N.M.), Utrecht, the Netherlands.

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Correspondence to Maaike Dirks, MD, Erasmus MC, Department of Neurology, Room H-673, PO Box 2040, 3000 CA Rotterdam, the Netherlands. E-mail m.dirks@erasmusmc.nl

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center assessed the study protocol. The protocol has been set up according to the revised Consolidated Standards of Reporting Trials (CONSORT) statement for cluster-randomized trials and has been published earlier. Twelve hospitals participated and were assigned to the intervention or control group by random allocation after pairwise matching. Pairing was based on hospital type, previous thrombolysis rate, and size (number of patients with stroke admitted per year).

**Participating Centers and Patient Population**

Stroke service characteristics of the 12 hospitals were assessed to determine a "situation score" in line with the barriers mentioned before and to identify potentially successful implementation actions. We collected these data through interviews with key providers of care in each center using prestructured questionnaires. These included the presence and content of protocols, the level of formal education, and the infrastructure around and within the hospital (for instance, the number of ambulance services, specialists, and residents). All single items received a rating between 0 and 1. The standardized sum scores were calculated by adding all single items per category, divided by the maximum score, and multiplied by 10 so that all sum scores had a standardized rating between 0 and 10. All patients >18 years with acute stroke who were admitted to the hospital within 24 hours from onset of symptoms were included in the trial. Patients admitted within 4 hours were assessed in detail and were followed up to 3 months after onset by telephone. The 4-hour time window was used because in the trial period, the generally accepted time window for treatment with alteplase was 3 hours. The 4-hour time window was chosen not to miss patients who were, for instance, treated just outside the 3-hour time window and to have more information on the patients not arriving in time for treatment. Patients had to give consent for follow-up visits.

**Intervention**

The implementation strategy for thrombolysis consisted of intervention meetings based on the Breakthrough Series model. We formed local teams that included a stroke neurologist and a stroke nurse. We asked the teams to note specific local barriers to further implementation in their hospital, to set goals, and to plan actions to reach these goals in a reasonable timeframe, and we monitored the results of their actions. Each team was asked to evaluate and update their acute stroke guideline. The intervention continued for 2 years and comprised 5 half-day intervention meetings and 1 closing session. The meetings started in May 2005, almost 6 months before the start of data collection.

**Data Collection, Blinding, and Safety**

Trained, local personnel not involved in the patient's treatment collected the data, which were entered into Web-based forms. The central trial office provided the 3-month follow-up assessment and used simple questions to record the patient's dependency and health-related quality of life. The 2 researchers who assessed outcome data were blinded to the intervention assignment. Local neurologists and paramedical personnel in intervention hospitals were aware that they participated in a program to enhance the rate of thrombolysis. Their colleagues in the control hospitals were only notified that they participated in a registration project. During the period of recruitment, interim analyses of in-hospital mortality, intracranial hemorrhages, and other serious adverse events believed to be due to treatment were confidentially reported to a data monitoring committee. The data monitoring committee met 4 times and advised the steering committee on continuation of the study.

**Outcome Measures**

The primary outcome was treatment with rtPA in the total stroke population and in the subgroup of patients with an ischemic stroke admitted within 4 hours. Secondary outcomes were admission within 4 hours after onset of symptoms, death or disability at 3 months measured with the modified Rankin Scale (mRS), and quality of life measured with the EuroQol. The mRS and EuroQol were assessed only in the subgroup of patients with ischemic stroke who were admitted within 4 hours. Tertiary outcomes were onset-to-door time and door-to-needle time as process indicators of the timelines of acute stroke care.

**Clinical Definitions**

Symptomatic intracranial bleeding was defined as a hemorrhage confirmed by CT scan preceded by an increased deficit on the National Institutes of Health Stroke Scale (NIHSS). Contraindications were identified by the treating physicians and checked retrospectively from source data by the investigators. Unambiguous contraindications refer to contraindications used in guidelines for thrombolysis on, for instance, blood pressure and laboratory findings. The thrombolysis rate was calculated by dividing the total number of patients treated with rtPA by all patients with stroke patients within 24 hours of symptom onset (including intracerebral hemorrhage).

**Sample Size**

With adjustments for randomization at the center level, the expected size of our study (12 hospitals, 5000 registered patients) was considered to be sufficient to detect a statistically significant (\(\alpha=0.05\)) increase in thrombolysis rate in the intervention hospitals with a power of 80%. This calculation was based on the assumption of a relative increase of 50% in thrombolysis rate in the intervention hospitals superimposed on an secular, increasing trend, leading to an estimated thrombolysis rate of 7.5% in the control hospitals and 11.3% in intervention hospitals.

**Statistical Analysis**

Statistical analysis was carried out on an intention-to-treat basis. In the analysis of the primary and secondary outcome, we used a multilevel logistic regression model to adjust for potential clustering effects. In the analysis of the tertiary outcome, which are continuous outcome variables, we used a multilevel linear regression model. In addition, we adjusted for hospital size, type of hospital, and previous thrombolysis rates at the hospital level. At the individual patient level, we adjusted for age and sex. In the group of patients admitted within 4 hours, we also adjusted for stroke severity and comorbidity. Intervention effects were reported as ORs with 95% CI. We used STATA Version 10 to analyze the data (STATA Corp, College Station, TX).

**Results**

Patient registration ran from October 2005 until October 2007. The follow-up period was closed in January 2008. The overall participation in the intervention meetings was good. One hospital team dropped out of the intervention halfway during the trial due to a change in medical staff. Members of the central trial office completed data collection in that hospital. Hospital size ranged from 100 to 500 stroke admissions a year (Table 1). Some of the larger hospitals were allocated to the intervention group and more patients were registered in that group. The extramural education score was better in the intervention hospitals, whereas the intramural protocol score was higher in the control group. At the end of the study, only the intramural protocol score had increased substantially in the intervention hospitals.

Overall, 5515 patients were registered, 2990 in the intervention hospitals and 2525 in the control hospitals (Figure 1). There were no missing data in the minimal set of baseline data. Twenty-nine percent (880) of the patients in the intervention hospitals and 31% (777) in the control hospitals were admitted within 4 hours. In total, 892 (16%) patients had an intracranial hemorrhage (Table 2). Follow-up assessment was complete in 1589 of the 1657 patients; 68 patients (4%) were lost to follow-up or refused informed consent. The mean age in both arms was 72 years, sex was equally distributed, and the mean NIHSS score at admittance did not differ between...
intervention and controls. The intracluster correlation from the actual analysis of the primary outcome was 0.0154.

**Outcomes**

**Primary Outcome and Safety**

In the intervention hospitals, 393 patients (13% of all patients with acute stroke) were treated with thrombolysis and 308 (12%) in the control hospitals (adjusted OR, 1.25; 95% CI, 0.93 to 1.68; Table 3). In the group of 1657 patients with ischemic stroke who were admitted within 4 hours from onset, 391 (44%) of 880 patients in the intervention centers were treated with rtPA and 305 (39%) of 777 patients in control centers (adjusted OR, 1.58; 95% CI, 1.11 to 2.27). Per hospital, the thrombolysis rate ranged between 9% and 22% in the intervention hospitals and between 7% and 16% in the control hospitals (Figure 3, supplemental data, Table 1. Baseline and End Hospital Characteristics).

**Table 1. Baseline and End Hospital Characteristics**

<table>
<thead>
<tr>
<th>Characteristic, Mean (Range)</th>
<th>Intervention (n=6)</th>
<th>Control (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size (stroke admissions in 2003)</td>
<td>332 (125–500)</td>
<td>264 (100–400)</td>
</tr>
<tr>
<td>Academic/nonacademic</td>
<td>1/5</td>
<td>1/5</td>
</tr>
<tr>
<td>Teaching hospital/no teaching hospital</td>
<td>3/3</td>
<td>2/4</td>
</tr>
<tr>
<td>Prior thrombolysis rate 2003</td>
<td>6.3 (3–10)</td>
<td>5 (0–10)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Organizational Structure</th>
<th>Baseline</th>
<th>End</th>
<th>Baseline</th>
<th>End</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extramural protocols (0–10)</td>
<td>2.3 (2.1–2.9)</td>
<td>2.4 (0.4–4.2)</td>
<td>2.3 (1.3–2.9)</td>
<td>2.4 (1.3–3.8)</td>
</tr>
<tr>
<td>Extramural education (0–10)</td>
<td>4.8 (1.7–8.2)</td>
<td>4.3 (1.5–7.0)</td>
<td>3.6 (0.3–7.0)</td>
<td>3.6 (0.7–5.3)</td>
</tr>
<tr>
<td>Extramural infrastructure (0–10)</td>
<td>4.1 (2.5–5.7)</td>
<td>4.1 (2.5–5.7)</td>
<td>4.3 (3.3–5.0)</td>
<td>4.3 (3.4–5.0)</td>
</tr>
<tr>
<td>Intramural protocols (0–10)</td>
<td>1.9 (1.0–2.7)</td>
<td>3.2 (2.2–3.8)</td>
<td>2.8 (1.6–3.8)</td>
<td>3.2 (2.4–3.8)</td>
</tr>
<tr>
<td>Intramural education (0–10)</td>
<td>2.6 (1.5–4.0)</td>
<td>2.5 (0–6.9)</td>
<td>2.9 (1.0–6.0)</td>
<td>2.1 (1.8–2.8)</td>
</tr>
<tr>
<td>Intramural infrastructure (0–10)</td>
<td>4.5 (2.4–6.0)</td>
<td>4.5 (2.4–6.0)</td>
<td>4.3 (2.2–6.2)</td>
<td>4.3 (2.2–6.2)</td>
</tr>
</tbody>
</table>

**Figure 1. Flow chart of the study.**
Contraindications

There was no clear difference in the proportion of patients with unambiguous contraindications, 21% in the intervention hospitals and 23% in the control hospitals. However, “mild or rapidly improving symptoms” as a contraindication was less frequent in the intervention hospitals, 17% versus 26%. The median NIHSS score in this group was 2 in both arms. Unconventional contraindications like hemorrhoids, menstruation, or “bumped his head” were also less frequent in the intervention hospitals, 17% versus 26%. The onset-to-door time in all registered patients with stroke was 7 hours 4 minutes in the intervention hospitals and 6 hours 32 minutes in the control hospitals. The mean door-to-needle time was 70 minutes versus 73 minutes in the control hospitals, an adjusted difference of −3 minutes (95% CI, −15 to 10).

Secondary and Tertiary Outcomes

Good clinical outcome at 3 months (mRs <3) was observed in 441 (52%) patients treated in the intervention hospitals, slightly less than in the control hospitals (429 [58%]; adjusted OR, 0.56; 95% CI, 0.42 to 0.74). Of the patients treated with rtPA, 51% had a good outcome in the intervention versus 49% in the control hospitals. The mortality rate was 17% in both groups, and the mean NIHSS score at discharge was 4 in the patients treated in intervention hospitals and 5 in control hospitals; the mean EuroQol-derived utility weight was 0.56 versus 0.58 (adjusted difference, 0.01; 95% CI, −0.05 to 0.08; Table 3). The mean onset-to-door time in all registered patients with stroke was 7 hours 4 minutes in the intervention hospitals and 6 hours 32 minutes in the control hospitals. The mean door-to-needle time was 70 minutes versus 73 minutes in the control hospitals, an adjusted difference of −3 minutes (95% CI, −15 to 10).

Table 3. Patient Outcomes and Intervention Effect

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Control</th>
<th>Effect (95% CI)</th>
<th>Effect (95% CI)</th>
<th>Effect (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>Unadjusted</td>
<td>Cluster-Adjusted</td>
<td>Cluster-Adjusted</td>
</tr>
<tr>
<td>All patients</td>
<td>2990</td>
<td>2525</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombolysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onset–to–door time, minutes</td>
<td>393 (13%)</td>
<td>308 (12%)</td>
<td>1.08 (0.93–1.28)</td>
<td>1.28 (0.87–1.89)</td>
<td>1.25 (0.93–1.68)</td>
</tr>
<tr>
<td>Patients with ischemic stroke</td>
<td>880</td>
<td>777</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>admitted within 4 hours</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombolysis*</td>
<td>391 (44%)</td>
<td>305 (39%)</td>
<td>1.24 (1.02–1.51)</td>
<td>1.44 (0.93–2.22)</td>
<td>1.58 (1.11–2.27)†</td>
</tr>
<tr>
<td>mRS &lt;3 at 3 months‡</td>
<td>441 (52%)</td>
<td>429 (58%)</td>
<td>0.79 (0.65–0.96)</td>
<td>0.78 (0.63–0.98)</td>
<td>0.56 (0.42–0.74)†</td>
</tr>
<tr>
<td>Mortality at 3 months‡</td>
<td>141 (17%)</td>
<td>127 (17%)</td>
<td>0.96 (0.74–1.25)</td>
<td>0.96 (0.74–1.25)</td>
<td>1.05 (0.74–1.48)†</td>
</tr>
<tr>
<td>EQ5D§</td>
<td>0.56</td>
<td>0.58</td>
<td>−0.01 (−0.05–0.03)</td>
<td>−0.02 (−0.16–0.12)</td>
<td>0.01 (−0.05–0.08)†</td>
</tr>
<tr>
<td>Onset–to–door time, minutes</td>
<td>91</td>
<td>90</td>
<td>1 (−4–6)</td>
<td>1 (−5–6)</td>
<td>−1 (−7–5)†</td>
</tr>
<tr>
<td>Door–to–needle time, minutes</td>
<td>70</td>
<td>73</td>
<td>−2 (−13–9)</td>
<td>−1 (−13–11)</td>
<td>−3 (−15–10)†</td>
</tr>
</tbody>
</table>

Values are numbers and effects in ORs. In continuous variables, values are means and effects are differences between mean values.

mRS indicates modified Rankin Scale.

*Five patients were treated with recombinant tissue plasminogen activator outside the 4-hour window.
†Adjusted for hospital size, academic vs nonacademic and previous thrombolysis rate at hospital level. Adjusted for age, sex, stroke severity, history of ischemic stroke, myocardial infarction, heart failure or peripheral artery disease, diabetes mellitus, and atrial fibrillation at patient level.
‡Data not available in 68 patients (4%).
§Data not available in 166 patients (10%).
Discussion

In this study, we found that the proportion of patients treated with rtPA increased through an intensive implementation strategy in real-life settings. Among the patients admitted within 4 hours after onset, the likelihood of treatment with rtPA was higher in the intervention centers also after adjustment for prespecified center and patient characteristics. The rate of symptomatic intracranial bleeding complications was nonsignificantly higher in the intervention group and an important increase in bleeding rate is not ruled out. However, the complication rate was similar to the rate in clinical trials and registries, indicating that our implementation actions did not lead to increased adverse health effects.\textsuperscript{1,12}

We observed a significant effect of the intervention on only 1 of the 2 primary outcome measures. The first outcome measure, treatment with rtPA in the whole registered stroke population, was chosen mainly to be able to detect a shift in onset-to-door time and to compare it with previous numbers. The second primary outcome measure, treatment with rtPA inpatients with ischemic stroke admitted within 4 hours of symptom onset, was chosen because it is easier to interpret. The size and direction of the effect were similar in both primary outcomes. The intracluster correlation we used in the sample sized estimation (0.0032) was larger than the intracluster correlation from the actual analysis of the primary outcome (0.0154), which led to a larger design effect (ie, 7.35 instead of the assumed 2.34). This means that the study will have had lower than expected power to identify the estimated 50% relative effect. The intervention did not have an effect on the timelines of admission and therefore there was no significant effect on thrombolysis rate in all patients registered. Our study lacked sufficient power to detect changes in clinical outcomes; such an outcome study would need to be much larger. The proportion of patients with dependency according to the mRS was higher in the intervention group. The mortality rate, mean NIHSS score at discharge, and the mean quality of life measured on the EuroQol at 3 months were similar in both groups. The statistically nonsignificant difference in complication rates between the intervention and control hospitals could not explain the higher mRS scores in the intervention hospitals. Within the patient group treated with rtPA, good clinical outcome was similar in both study arms. The effect on mRS was not consistent with the effect of intervention on other clinical outcomes and may be due to chance or to unregistered comorbidity other than cardiovascular comorbidity or cardiovascular risk factors.

The strength of the study is the extent of blinding and lack of contamination risk; the neurologists (except for the principal investigator) and paramedical personnel in the control group were not made aware of the treatment allocation. Patients with a stroke were transported to the nearest hospital and were unaware of the study. All patients with acute stroke were registered and most outcome measures were routine data collected by local personnel not involved in the patient’s treatment. In the intervention hospitals, more healthcare professionals (stroke nurses, all neurologists) were aware of the study because the intervention is a deliberate implementation that needed cooperation of these professionals. A more conservative design would be unrealistic and the intervention effect would then be artificial. Additional outcome measures were assessed blinded for treatment allocation. The participating hospitals are representative of a large spectrum of hospital types: from small urban and regional hospitals to the larger academic hospitals. Intervention adherence varied from very active to doing as little as possible, probably a good reflection of daily practice. The number of centers involved is a limitation of the study; only 12 hospitals of the approximately 110 hospitals in the Netherlands (11%) participated. This makes the study more sensitive to noncompliance on center level. The hospital that dropped out of the intervention did not participate in the intervention meetings and did not perform any implementation assignments. However, members of the central trial office completed data collection in that hospital and the statistical analysis was carried out on an intention-to-treat basis. Despite this dilution of possible effect, we observed an overall significant effect in thrombolysis rate in patients with an ischemic stroke admitted within 4 hours of symptom onset. In the hospital that stopped participating in the intervention strategy, we observed an initial increase in thrombolysis rate during active participation in the study and a decrease in thrombolysis rate after the hospital dropped out. This suggests that implementation needs to be a continuous process of measuring, adaptation, and feedback. In addition, the time period between the

![Figure 2. Thrombolysis rate in time. Mean of thrombolysis percentages in the 6 hospitals of each arm by half-year periods.](http://stroke.ahajournals.org/DownloadedFrom/380x725)
breakthrough sessions may have been too long, which may have led to lower compliance and loss of motivation.

Dissemination of simple thrombolysis referral guidelines to primary care and local emergency departments increases the proportion of intravenous thrombolysis.\textsuperscript{11} In the Get With The Guidelines (GWTG) stroke project, participation was associated with increased adherence to several stroke care performance measures,\textsuperscript{14} and the use of rtPA increased dramatically over time. However, the GWTG stroke project is an uncontrolled study, which could not distinguish between an autonomous time trend and an intervention effect. To our knowledge, there are no published randomized trials evaluating active implementation strategies in acute stroke care. In the treatment of acute myocardial infarction, a randomized controlled trial evaluated guideline implementation through clinician education by local opinion leaders and performance feedback in 37 community hospitals in Minnesota. It showed that guided quality improvement interventions could accelerate adoption of effective treatments in community practice in the treatment of acute myocardial infarction.\textsuperscript{15}

The evaluation of a complex multifaceted intervention is difficult. Further research is needed to examine whether this benefit can be maintained and increased by implementing a structured and ongoing audit of thrombolysis practice. We found no single component or combination of components in the structure of the stroke service that could explain the intervention effect. However, we did observe that in the intervention hospitals, more patients were treated with alteplase with a lower NIHSS score and there were less ambiguous contraindications. These 2 particular items were emphasized during the intervention meetings when the neurologists were instructed to update their treatment protocol that resulted in an increase in intramural protocol score. The mean onset-to-door time was even longer in the intervention hospitals reflecting that there was no improvement in the extramural organization of stroke care. This finding can probably be attributed to the generally short distances between homes and hospitals in the Netherlands. The patient composition within the subgroup of patients with an ischemic stroke admitted within 4 hours of symptom onset might be influenced by the intervention itself. If the intervention had affected the onset-to-door time, the analysis of those admitted within 4 hours would not have been easily interpretable. Also, the intervention effect of our study was small in comparison with the autonomous time trend. This emphasizes the need for better implementation methods.

Conclusions

This study shows that an intensive implementation strategy can increase the proportion of patients treated with rtPA. A major component of the intervention effect we found was more appropriate application of contraindications of thrombolysis. Critical assessment of justified contraindications in our study reveals that if all patients who were eligible for treatment with rtPA in this study were actually treated, an overall thrombolysis rate of 18% of all patients with stroke could have been achieved. Naturally, the ultimate goal of an improved implementation of thrombolysis would be an increase in patients with a good outcome.

Acknowledgments

We extend our gratitude to all stroke care teams who participated in this study and to the PRACTISE investigators. The PRACTISE investigators and their affiliations are listed in the published trial protocol.

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Disclosures

None.

References

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