Original Contribution

Improving Access to Thrombolysis and Inhospital Management Times in Ischemic Stroke

A Stepped-Wedge Randomized Trial

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Background and Purpose—A suboptimal number of ischemic stroke patients eligible for thrombolysis actually receive it, partly because of extended inhospital delays. We developed a comprehensive program designed for emergency unit staff and evaluated its effectiveness for reducing intrahospital times and improving access to thrombolysis.

Methods—We conducted a randomized stepped-wedge controlled trial in 18 emergency unit. The sequentially implemented training intervention, targeting emergency physicians and nurses, was based on specifically designed videos and interactive simulation workshops on intrahospital management optimization. The effectiveness was assessed on intrahospital times and thrombolysis proportion. During the study period, all consecutive patients with confirmed ischemic stroke and no contraindications to thrombolysis were included.

Results—A total of 328 patients were enrolled in the control group and 363 in the intervention group. Mean age was 73.6 years. Overall thrombolysis proportion was 34.2% in the intervention group versus 25.6% in the control group (adjusted odds ratio, 1.42; 95% confidence interval, 1.01–2.01), thrombolysis proportion within 4 hours 30 minutes almost doubled (adjusted odds ratio, 1.9; 95% confidence interval, 1.32–2.73). Although imaging-to-stroke unit time was significantly decreased in the intervention group (39 versus 53 minutes; P=0.03), median door-to-imaging and door-to-needle times were not different between groups (P=0.70 and P=0.40, respectively).

Conclusions—An interactive and multifaceted training program targeting emergency professionals was significantly associated with an increased access to thrombolysis, especially within 4 hours and 30 minutes.

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Key Words: emergency unit ■ interactive training ■ ischemic stroke ■ stepped-wedge design ■ stroke ■ thrombolysis

Thrombolysis and endovascular treatments constitute the main effective therapeutic options for ischemic stroke (IS).[1–3] Both treatments should be administered after ischemia has been confirmed by cerebral imaging, within a short therapeutic window, and as early as possible for an increased benefit/risk ratio.[4,5] Although 24% of stroke patients would be eligible to thrombolysis,[6] published thrombolysis rates remain <15% in most countries.[7–10] Major limitations to thrombolysis are extended management times. Stroke registries have revealed that more than half of the delays were attributable to inhospital procedures, that is, the door-to-needle time, defined as the time from emergency unit (EU) arrival to thrombolysis administration.[11] It is known that delays significantly increase morbidity and mortality.[4,5,12] Guidelines for optimal management recommend that cerebral imaging should be performed within 25 minutes and a door-to-needle time <1 hour.[13,14] In a previous comprehensive cohort of 1306 cases of suspected stroke, we observed that 80% of patients were managed in EU instead of being admitted directly to a stroke unit (SU). Eventually <10% of patients were thrombolysed, because of too long delays.[15] This study showed that improving practices of EU professionals in acute stroke management is a real

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*A list of all AVC II Trial group members is given in the Appendix.

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issue. Many actions designed to improve thrombolysis rates have been published; however, a recent review pointed out that only a limited number of interventions have been assessed with a high level of evidence.[16]

We, therefore, aimed to assess the efficacy of a multifaceted interactive intervention targeting EU professionals for decreasing inhospital management times and increasing the proportion of thrombolysed IS in a stepped-wedge randomized trial.

Methods

Study Design

We conducted a multicenter cluster randomized stepped-wedge trial in 18 EUs in the Rhône-Alpes and Bourgogne regions of France. Each EU was considered as a cluster (ie, 18 clusters). The 18 EUs were arranged into 4 groups based on their geographical proximity. Each group, thus, composed of 4 to 5 EUs. The trial was performed in 4 steps, and each group of clusters was randomly assigned to one step (steps 1–4). After a preintervention period (control), the intervention was sequentially implemented in the groups at different times, according to a random allocation sequence generated by computer by the biostatistical team in charge of data analysis blind to group composition (Figure 1). All clusters eventually received the intervention. The control group composed of patients included in the preintervention period, and the intervention group composed of patients included after the implementation of the intervention. No patient was included during the transition periods corresponding to the 2 months after the implementation of the intervention, during which the trainees had to teach back the intervention to their team.

Eligibility Criteria for Clusters

All EU and SU from public hospitals on the studied territory were eligible for study participation.

Eligibility Criteria for Participants

All patients >18 years of age admitted to one of the participating units for an IS suspicion within 4 hours of symptom onset were considered as eligible. Among them, only patients with a confirmed IS and without thrombolysis contraindication[17] were included in the study.

Intervention

The intervention was a multifaceted and interactive training program on acute stroke management. The aim of this program was to decrease management times at the early acute phase for patients presenting with a suspicion of IS in EU and to improve access to thrombolysis. The program content was collaboratively designed by a multidisciplinary group composed of emergency physicians, neurologists, and nurses from SU, radiologists, and public health physicians. SU neurologists and nurses involved in the intervention were working in the 10 SUs related to the 18 participating EUs.

The program was based on a train the trainer approach. In each participating center, 1 EU physician and 1 EU nurse, representing their teams, received the intervention and had to teach it to the other staff members in their unit with the help of the training package they received. We also asked for the participation of 1 radiologist and 1 neurologist of the referral SU for each EU.

The intervention was designed with 2 parts and implemented during a 1-day training session in each cluster. The first part was designed to improve knowledge and skills of triage nurses regarding stroke detection and identification and to increase the use of the National Institutes of Health Stroke Scale (NIHSS) score by the emergency physicians. The second part aimed at improving the local organization of stroke management up to thrombolysis. During the first part, information was given on physiopathological mechanisms of stroke, symptom recognition, diagnostic imaging, appropriate treatments, and impact of these treatments on consequent disability. Participants watched a film specifically made for the project to show the consequences of an optimized versus suboptimal EU management of stroke patient. Nurses were then trained to the FAST tool (Face Arm Speech Time) for stroke detection through interactive simulation with clinical cases played by 2 SU nurses. Physicians were trained to perform the NIHSS scoring by watching the French national neurovascular society video and performing NIHSS scoring on simulated patients. The second part of the program was the elaboration by each EU team of a clinical pathway for IS management in their particular setting. This was developed in each group of clusters by the EU physicians and nurses with the local neurologist and radiologist in accordance with the methodology recommended by the national health authority[18] and the French national IS

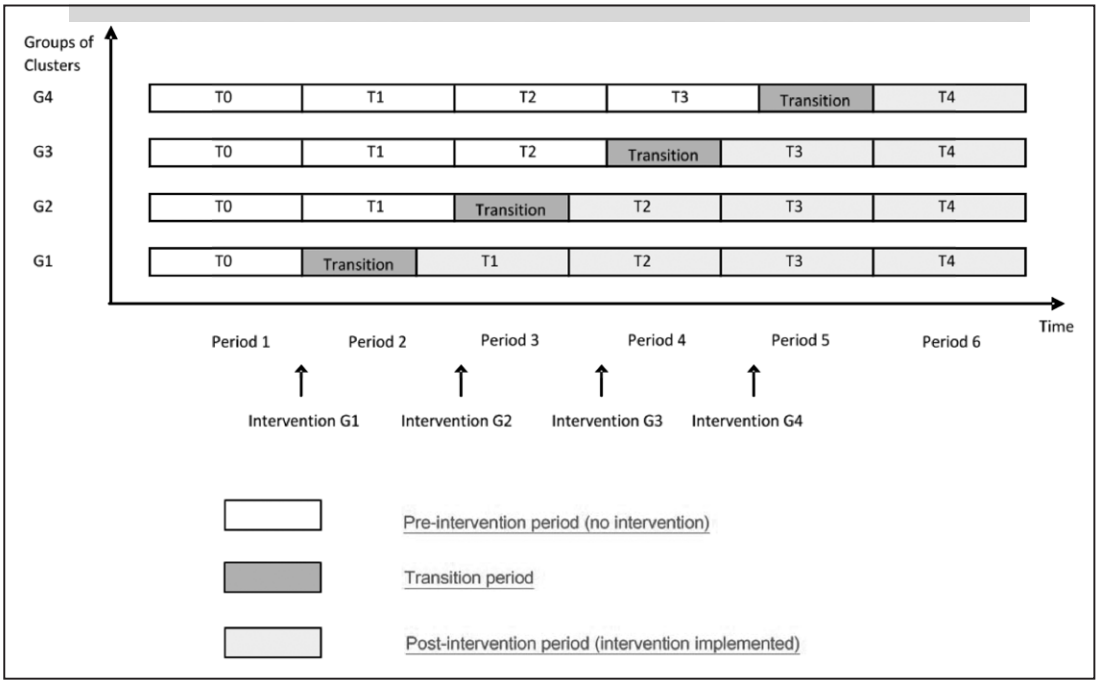

Figure 1. Study design and clusters randomization according to the different time periods. TIA indicates transient ischemic attack.

management clinical guidelines.[17] It described for each step of patient management the tests to perform, the decisions to make, the name and telephone number of the professionals involved in their local setting, especially for imaging and biology, and the Alteplase location and availability. The clinical pathway acted as a reminder and a decision-making tool aiming at decreasing management times and practice variability. A training toolkit (video, posters, and leaflets) was given to the participants who were expected to train other professionals of their EU.

Outcomes

The outcomes of interest were initially inhospital management times, separated in door-to-imaging time (between admission in the EU and cerebral imaging), door-to-SU (from arrival in the EU to arrival in the SU), imaging-to-SU (from cerebral imaging to arrival in the SU), and door-to-needle (from arrival in the EU to thrombolysis). Furthermore, a higher-than-expected statistical power enabled us to consider the percentage of patients receiving thrombolysis as primary outcome. Secondary outcomes were complications during hospitalization, death, stroke recurrence, hemorrhage, pneumonia, and other complications and the performance of FAST by EU nurses and NIHSS by EU physicians. All outcomes were measured at individual level.

Data Collection

All eligible patients were identified prospectively by the research staff with EU nurses and physicians and also with a systematic screening of EU registries. IS was confirmed by the neurologist based on cerebral imaging. Data were collected in medical charts. All times were collected in hours and minutes. Complications were collected from admission until discharge of SU.

Statistical Analysis

In the previous study in the Rhône-Alpes region, the thrombolysis rate was ≈8%. Thus, sample size calculation was initially based on the inhospital times because they were described as strong predictors of access to thrombolysis. Sample size was calculated using the Hussey and Hughes[19] method. Considering 4 randomization steps, an expected decrease of 15% of the time between EU admission and cerebral imaging, 18 clusters with intercluster coefficient of variation expected between 0.15 and 0.4, and an α risk of 5%, it was estimated that a total number of 900 patients with suspected stroke would provide 95% power. Many more subjects presenting with a stroke suspicion than expected were screened for eligibility during the study period (3238 patients). This increased statistical power allowed thrombolysis proportion to be considered as a main outcome.

Quantitative data were described using mean and SD or median and interquartile range (IQR), depending on distribution. Qualitative data were described using absolute and relative frequencies. Comparisons between groups were performed using Student *t* test or nonparametric Wilcoxon rank-sum test for quantitative characteristics and χ^2 test or Fisher exact test for qualitative characteristics.

A stepped-wedge design is a unidirectional crossover trial. As recommended by Hussey and Hughes,[19] the analyses of the intervention effect on the outcomes were performed using mixed regression models with a random intercept, to take into account the within-cluster correlation, to use both within-cluster and between-cluster information, and to take into account any evolution of the intervention effect over time. A log transformation was previously applied to normalize the distribution of the time outcomes. Univariate and multivariate analyses were performed to adjust the effect of the intervention for the main confounding factors, that is, age, admission after emergency medical services (EMS) call (yes/no), and time of admission (night versus day). The intracluster correlation coefficient was estimated for the 3 main outcomes: door-to-imaging time, thrombolysis, and thrombolysis within 4.5 hours, using the variances estimated by the univariate mixed regression models; the intercluster coefficient of variation was also estimated for the door-to-imaging time (Table I in the online-only Data Supplement). Analyses were performed using SAS (version 9.2; SAS Corporation, Cary, NC) by the biostatistics unit of the University of Lyon, independently from the coordinating center.

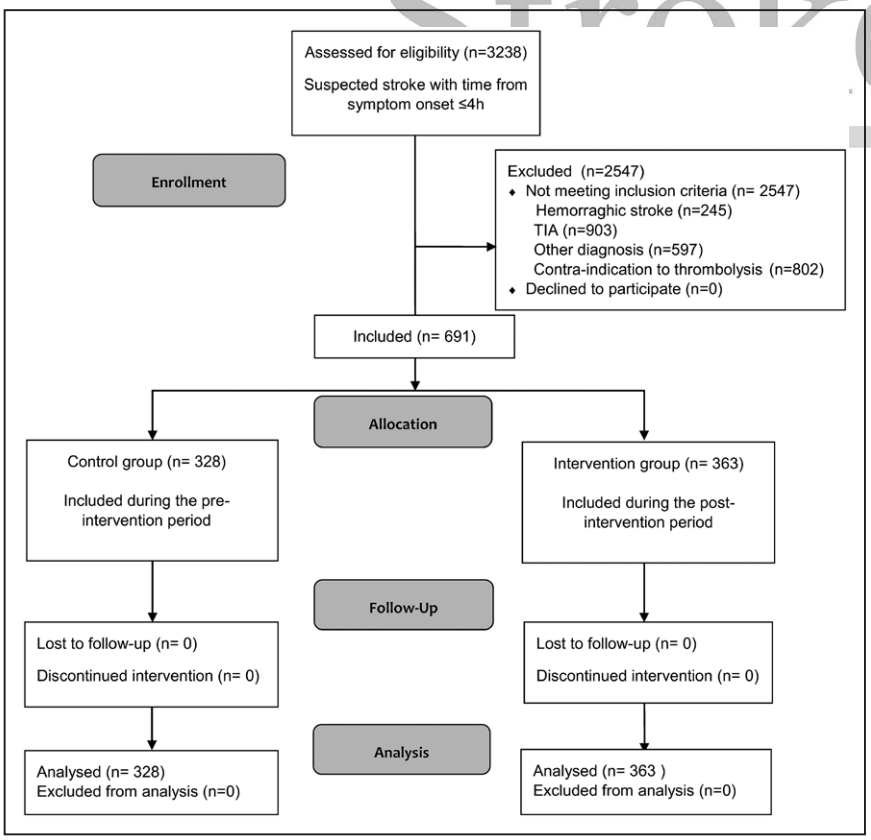

Figure 2. Study flow chart.

To be conservative, all patients with missing data on thrombolysis were considered as not thrombolysed (n=1).

Data, analytic methods, and study materials are available to other researchers at the Hospices Civils de Lyon on request to the corresponding author who is responsible for maintaining availability.

Ethics

The study received ethics committee approval according to French legislation in place at the time of the study. The board waived the need for consent because of the nature of the study intervention.

Results

A total of 3238 patients were screened in the 18 participating EUs. Among those, 1745 had a diagnosis other than IS and were not included in the study. Of the 1493 patients who were considered as having confirmed IS, 691 arrived within 4 hours from symptom onset and had no thrombolysis contraindication and, therefore, were included in the study. There were 328 patients included during the preintervention period (control group) and 363 during the postintervention period (intervention group; Figure 2). Among the total population, approximately half of patients were male (53.7%), and mean age was 73.6 years. Overall, most patients (53.7%) were admitted to EU after calling EMS; this was the case for a significantly higher proportion of patients in the control group (59.3%) than in the intervention group (48.7%; *P*=0.007). Cerebral imaging was performed with computed tomographic scan in 79.0% of patients in the control group and 70.8% of patients in the intervention group; magnetic resonance imaging was performed in 22.0% of the control group and 29.5% of the intervention group. In total, 62.0% of patients were transferred to an SU (Table 1).

A total of 254 patients were thrombolysed (37% of the total population). The overall thrombolysis proportion was significantly higher in the intervention group (38.6%) than in the control group (34.8%). Patients in the intervention group were also more likely to be thrombolysed within 4 hours and 30 minutes, as recommended (124 patients, ie, 34.2% of the total population) than patients during the control period (84 patients, ie, 25.6%; Table 2). After adjustment for age, time of admission, and referral patterns (EMS call yes/no), the intervention was significantly associated with the overall thrombolysis proportion (adjusted odds ratio [OR], 1.4; 95% confidence interval [CI], 1.01–2.02; *P*=0.04) and within 4 hours and 30 minutes (adjusted OR, 1.9; 95% CI, 1.3–2.7; *P*=0.0006). Proportion of patients thrombolysed before 4 hours and 30 minutes increased in all clusters except 4 in which no patient was thrombolysed during the intervention period (Table II in the online-only Data Supplement). Patients were mostly thrombolysed in SU (93% in the control group and 90% in the intervention group). In the control and intervention groups, only 3 (2.6%) and 11 (7.9%) patients, respectively, were thrombolysed in EU and 5 (4.4%) and 2 (1.4%), respectively, in imaging unit or ICU.

Median door-to-imaging time was not significantly different between the 2 groups (Table 3). Median imaging-to-SU time was significantly reduced in the intervention group (0.65 hours; IQR, 0.44–1.38, ie, 39 minutes; IQR, 26–83) compared with the control group (0.88 hours; IQR,

Table 1. Patient Characteristics

	Control (n=328)	Intervention (n=363)	Total (N=691)
Sex			
Female	143 (43.6)	177 (48.8)	320 (46.3)
Male	185 (56.4)	186 (51.2)	371 (53.7)
Age, mean±SD	72.2±15.9	74.8±15.2	73.6±15.5
Provenance			
Home	261 (84.5)	301 (88.8)	562 (86.7)
Medical center	3 (1.0)	0 (0.0)	3 (0.5)
Healthcare institution	7 (2.3)	9 (2.7)	16 (2.5)
Street or public place	29 (9.4)	22 (6.5)	51 (7.9)
Other	9 (2.9)	7 (2.1)	16 (2.5)
Means of transport			
Mobile emergency unit	30 (9.5)	21 (5.9)	51 (7.6)
Ambulance	122 (38.6)	113 (31.7)	235 (35.0)
Fire service	113 (35.8)	163 (45.8)	276 (41.1)
Private/own	50 (15.8)	55 (15.4)	105 (15.6)
Other	1 (0.3)	4 (1.1)	5 (0.7)
Sent by			
None	75 (24.6)	123 (36.5)	198 (30.8)
EMS	181 (59.3)	164 (48.7)	345 (53.7)
GP	38 (12.5)	37 (11.0)	75 (11.7)
GP on duty	9 (3.0)	10 (3.0)	19 (3.0)
Other	2 (0.7)	3 (0.9)	5 (0.8)
Day of admission			
Weekend (Saturday/Sunday)	91 (27.7)	90 (24.8)	181 (26.2)
Week (Monday–Friday)	237 (72.3)	273 (75.2)	510 (73.8)
Time of admission			
Day (8:00 AM to 7:00 PM)	235 (71.6)	248 (68.3)	483 (69.9)
Night (7:00 PM to 8:00 AM)	93 (28.4)	115 (31.7)	208 (30.1)
Cerebral imaging			
CT	259 (79.0)	257 (70.8)	516 (74.7)
MRI	72 (22.0)	107 (29.5)	179 (25.9)
Transfer to SU	202 (61.6)	227 (62.5)	429 (62.0)
Overall thrombolysis	114 (34.8)	140 (38.6)	254 (36.8)
Thrombolysis within 4.5 h	84 (25.6)	124 (34.2)	208 (30.1)
Place of administration of thrombolysis*			
SU	106 (93.0)	127 (90.7)	233 (91.7)
EU	3 (2.6)	11 (7.9)	14 (5.5)
Other (imaging unit, ICU)	5 (4.4)	2 (1.4)	7 (2.8)
Follow-up, median (IQR), d	3 (1–9)	4 (2–11)	4 (2–10)

Results are presented as n (%). CT indicates computed tomography; EMS, emergency medical services; EU, emergency unit; GP, general practitioner; MRI, magnetic resonance imaging; and SU, stroke unit.

*Percent are presented on the 254 thrombolysed patients.

Table 2. Impact of the Intervention on Thrombolysis Proportion

	Control Group (n=328)	Intervention Group (n=363)	OR (95% CI)	aOR (95% CI)	*P* Value
Overall thrombolysis	114 (34.8)	140 (38.6)	1.39 (0.99–1.97)	1.43 (1.01–2.02)*	0.04*
Thrombolysis within 4.5 h	84 (25.6)	124 (34.2)	1.83 (1.28–2.62)*	1.90 (1.32–2.73)*	<0.001*

Results are presented as n (%). OR represents OR for the intervention effect in the univariate analyses. aOR represents adjusted OR in the multivariate analyses. Adjustment was for age, admission during the night vs day, and admission after EMS call vs no EMS call. aOR indicates adjusted odds ratio; CI, confidence interval; EMS, emergency medical services; and OR, odds ratio.

*Significant results (P<0.05).

0.48–2.02, ie, 53 minutes; IQR, 29–122; P=0.03). Overall median door-to-needle time was not different between control and intervention groups.

Results of the complete multivariate models are presented in Table III in the online-only Data Supplement. The variable that had the strongest effect on thrombolysis proportion and on intrahospital times was admission after EMS call, which increased the overall proportion of thrombolyzed patients (adjusted OR, 1.5; 95% CI, 1.0–2.1; P=0.04) and before 4.5 hours (adjusted OR, 1.6; 95% CI, 1.1–2.3; P=0.02) and was associated with a significant reduction of door-to-imaging time of 1 hour and 16 minutes. Age had a negative impact on inhospital times with an increase of 5 minutes of the door-to-imaging time for every 10-year increase (P<0.001). Admission during the night was associated with a decreased time from EU to SU arrival (P=0.04) without impact on thrombolysis.

In the control group, FAST evaluation was never used in the control period. In the intervention group, it was performed in 17% of IS patients at EU admission (P<0.001). The NIHSS scoring was performed for 12.8% of patients in the control group and 20% in the intervention group (P=0.005). The median (IQR) duration of the follow-up for complications was 4 (2–10) days. During hospitalization, 36 patients died, and major complication occurred in 58 patients, with no significant difference between the 2 groups regarding each type of complication (Table 4).

Discussion

The multifaceted intervention investigated here was associated with a significant improvement of thrombolysis proportion, particularly within 4 hours and 30 minutes of symptom onset. However, this was not accompanied with a decrease of median door-to-imaging, door-to-SU, or door-to-needle times. Nevertheless, after radiological confirmation of the diagnosis, patients were transferred more rapidly to the SU in the intervention group as the time from imaging to SU significantly decreased. This could reflect a higher reactivity of emergency professionals when faced with confirmed acute IS and a better cooperation between EU and SU. The clinical pathway, developed in co-construction between EU and SU professionals during the intervention, was designed in this way, to improve the patient's pathway efficiency and reduce time losses in transitions. The absence of improvement in the door-to-imaging time might be because of difficulties in obtaining imaging. We encountered difficulties during the study in mobilizing radiologists. Only one radiologist was present in the training sessions and participated to the clinical pathway elaboration with EU staff and neurologists. Cerebral imaging is a key point in acute stroke management, and its unavailability constitutes a blocking factor for transfer to SU and thrombolysis.[20] Moreover, if our intervention improved the use of stroke-specific tools, FAST and NIHSS, their use remains very low. A generalization of the use of the FAST test at admission would improve the stroke identification and the use of fast-track pathway with priority imaging. Acute stroke management is a complex concatenation of multiple actions that requires a significant commitment of actors at each step to ensure that the patient is thrombolysed in time. Various other interventions have been set up to increase access to thrombolysis. Programs that were assessed were often broader, including other components and professionals, such as EMS,[21–23] SU team,[24] or community educational campaigns.[23,25] The evaluation of the impact of these programs is complex because of the heterogeneity of interventions, settings, and designs. However, the effect size for thrombolysis is within the range of that reported in other interventional studies,[23–27] with a pooled OR of 2.1 (1.0–4.5) in a recent review.[16]

Table 3. Impact of the Intervention on Management Times

	Control (n=328)	Intervention (n=363)	β (Log)	*P* Value	aβ (Log)	*P* Value
Door to imaging	1.19 (0.67–2.27)	1.33 (0.78–2.55)	−0.003	0.96	−0.020	0.77
Door to SU	1.88 (1.23–3.53)	1.77 (1.30–2.95)	−0.077	0.38	−0.131	0.14
Imaging to SU	0.88 (0.48–2.02)	0.65 (0.44–1.38)	−0.207	0.12	−0.293*	0.03*
Door to needle	1.58 (1.23–2.13)	1.60 (1.25–2.07)	−0.048	0.36	−0.043	0.40

Results are presented as median (IQR); times are presented in hours. β represents regression coefficient for the intervention effect in the univariate analyses. aβ represents adjusted coefficients in the multivariate analyses. Adjustment was for age, admission during the night vs day, and admission after EMS call vs no EMS call. IQR indicates interquartile range; and SU, stroke unit.

*Significant results (P<0.05).

Table 4. Occurrence of Deaths and Adverse Events in the Control and Intervention Groups

	Control (n=328)	Intervention (n=363)	*P* Value
Death	22 (6.1)	14 (4.3)	0.289
Complication	40 (12.2)	44 (12.1)	0.976
Hemorrhage	17 (5.2)	20 (5.5)	0.925
Pneumonia	6 (1.8)	11 (3.0)	0.309
Stroke recurrence	3 (0.9)	1 (0.3)	0.350
Coma	3 (0.9)	2 (0.6)	0.672
Other complication*	12 (3.7)	10 (2.8)	0.499

Results are presented as n (%).

*Miscellaneous including, for example, depression, dementia symptoms, or other complications occurring utmost once.

The results also highlight the importance of EMS call that was strongly associated with increased thrombolysis proportion and decreased management times. However, only half of patients called EMS despite national and local campaigns on stroke awareness pointing out the importance to immediately call EMS in case of evocative symptoms. Increase in EMS call may reduce management times and improve access to thrombolysis through direct transfer of patients in SU and prenotification.[27] Additional efforts should be made on the prehospital level to sensitize the population.

Strengths and Limitations

Some limitations should be addressed. The intervention was implemented on a train the trainer approach, and this had several limitations. First, the impact of such a teaching method could be limited if the trainers did not forward the intervention to the all staff members. Second, the choice of the professionals who were identified to represent their team was based on volunteers but should have been based more on their leadership capacities. Third, a stronger long-term support of the trainer may have been needed as well as a formal evaluation of the training process of the whole EU staff. However, results over a 1-day training session are encouraging and suggest that repetition of the training would improve the outcomes. Adjusting for stroke severity in the multivariate models would also have been interesting, but it was not feasible because the NIHSS scoring was little performed. The study does also have strengths. Unlike most studies on stroke management effectiveness, which use a before and after design or are performed in a unique tertiary center,[16] we conducted a multicenter stepped-wedge randomized trial, reducing the risk of bias, including contamination bias that is frequent in the field of health services research. The intervention was designed based on a territorial and pragmatic approach, supported by results of a previous study on our territory.[15] The participating centers were from various settings and volumes, and the intervention was coconstructed with nurses and physicians to be easily implemented in practices and to meet their needs. These aspects may increase the acceptability and the reproducibility of the intervention and make the intervention more generalizable.

Conclusions

Increasing EU professionals' awareness and skills significantly increased thrombolysis proportion although we observed effects on only 1 of the 4 measured management times. The optimal strategy to reduce delays and improve access to stroke treatment should associate several complementary measures to act at each step of the chain and reach all professionals involved.

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Disclosures

None.

Appendix

The AVC II Trial investigators are Elisabeth Saligari, Samira Cailler, Adeline Hénniche, Sylvain Prost, Carole Fournier, Jean-Baptiste Le Loch, Cécile Roncoroni, Frédéric Verbois, Olivier Debas, Marc Tesniere, Béatrice Bontemps, Jean-Pierre Lavignon, Mathilde Rimet, Patricia Trinquet, Thomas Millot, Odile Dumont, Samir Tabyaoui, Elie Ziade, Olivier Detante, Maurice Giroud, Serkan Cakmak, Sébastien Marcel, Karine Blanc-Lasserre, Dominique Minier, Gilles Rodier, Frédéric Philippeau, and Anne-Evelyne Vallet.

References

1. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995;333:1581–1587.
2. Wardlaw JM, Murray V, Berge E, del Zoppo G, Sandercock P, Lindley RL, et al. Recombinant tissue plasminogen activator for acute ischaemic stroke: an updated systematic review and meta-analysis. *Lancet*. 2012;379:2364–2372. doi: 10.1016/S0140-6736(12)60738-7.
3. Sardar P, Chatterjee S, Giri J, Kundu A, Tandar A, Sen P, et al. Endovascular therapy for acute ischaemic stroke: a systematic review and meta-analysis of randomized trials. *Eur Heart J*. 2015;36:2373–2380. doi: 10.1093/eurheartj/ehv270.
4. Lees KR, Bluhmki E, von Kummer R, Brott TG, Toni D, Grotta JC, et al; ECASS, ATLANTIS, NINDS and EPITHET rt-PA Study Group. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet*. 2010;375:1695–1703. doi: 10.1016/S0140-6736(10)60491-6.
5. Lansberg MG, Schrooten M, Bluhmki E, Thijs VN, Saver JL. Treatment time-specific number needed to treat estimates for tissue plasminogen activator therapy in acute stroke based on shifts over the entire range of the modified Rankin Scale. *Stroke*. 2009;40:2079–2084. doi: 10.1161/STROKEAHA.108.540708.
6. Boode B, Welzen V, Franke C, van Oostenbrugge R. Estimating the number of stroke patients eligible for thrombolytic treatment if delay could be avoided. *Cerebrovasc Dis*. 2007;23:294–298. doi: 10.1159/000098330.
7. Eriksson M, Jonsson F, Appelros P, Asberg KH, Norrving B, Stegmayr B, et al; Riks-Stroke Collaboration. Dissemination of thrombolysis for acute ischemic stroke across a nation: experiences from the Swedish stroke register, 2003 to 2008. *Stroke*. 2010;41:1115–1122. doi: 10.1161/STROKEAHA.109.577106.
8. Singer OC, Hamann GF, Misselwitz B, Steinmetz H, Foerch C; Arbeitsgruppe Schlaganfall Hessen. Time trends in systemic thrombolysis in a large hospital-based stroke registry. *Cerebrovasc Dis*. 2012;33:316–321. doi: 10.1159/000335816.
9. Fang MC, Cutler DM, Rosen AB. Trends in thrombolytic use for ischemic stroke in the United States. *J Hosp Med*. 2010;5:406–409. doi: 10.1002/jhm.689.
10. Scherf S, Limburg M, Wimmers R, Middelkoop I, Lingsma H. Increase in national intravenous thrombolysis rates for ischaemic stroke between 2005 and 2012: is bigger better? *BMC Neurol*. 2016;16:53. doi: 10.1186/s12883-016-0574-7.

11. Fonarow GC, Smith EE, Saver JL, Reeves MJ, Bhatt DL, Grau-Sepulveda MV, et al. Timeliness of tissue-type plasminogen activator therapy in acute ischemic stroke: patient characteristics, hospital factors, and outcomes associated with door-to-needle times within 60 minutes. *Circulation*. 2011;123:750–758. doi: 10.1161/CIRCULATIONAHA.110.974675.
12. Saver JL, Fonarow GC, Smith EE, Reeves MJ, Grau-Sepulveda MV, Pan W, et al. Time to treatment with intravenous tissue plasminogen activator and outcome from acute ischemic stroke. *JAMA*. 2013;309:2480–2488. doi: 10.1001/jama.2013.6959.
13. Jauch EC, Saver JL, Adams HP Jr, Bruno A, Connors JJ, Demaerschalk BM, et al; American Heart Association Stroke Council; Council on Cardiovascular Nursing; Council on Peripheral Vascular Disease; Council on Clinical Cardiology. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013;44:870–947. doi: 10.1161/STR.0b013e318284056a.
14. Summers D, Leonard A, Wentworth D, Saver JL, Simpson J, Spilker JA, et al; American Heart Association Council on Cardiovascular Nursing and the Stroke Council. Comprehensive overview of nursing and interdisciplinary care of the acute ischemic stroke patient: a scientific statement from the American Heart Association. *Stroke*. 2009;40:2911–2944. doi: 10.1161/STROKEAHA.109.192362.
15. Porthault-Chatard S, Termoz A, Derex L, Polazzi S, Cakmak S, Nighoghossian N, et al. Effectiveness of thrombolysis in the Rhône region, France: a prospective population-based study. *Int J Stroke*. 2012;7:E13. doi: 10.1111/j.1747-4949.2012.00887.x.
16. Paul CL, Ryan A, Rose S, Attia JR, Kerr E, Koller C, et al. How can we improve stroke thrombolysis rates? A review of health system factors and approaches associated with thrombolysis administration rates in acute stroke care. *Implement Sci*. 2016;11:51. doi: 10.1186/s13012-016-0414-6.
17. Haute autorité de santé. Recommandations de bonne pratique: Accident vasculaire cérébral: prise en charge précoce (alerte, phase préhospitalière, phase hospitalière initiale, indications de la thrombolyse). http://www.has-sante.fr/portail/upload/docs/application/pdf/2009-07/avc_prise_en_charge_precoce_-_recommandations.pdf. 2009. Accessed May 24, 2016.
18. Haute autorité de santé. Développement professionnel continu, Fiche méthode chemin clinique. http://www.has-sante.fr/portail/upload/docs/application/pdf/2013-02/chemin_clinique_fiche_technique_2013_01_31.pdf. 2014. Accessed May 24, 2016.
19. Hussey MA, Hughes JP. Design and analysis of stepped wedge cluster randomized trials. *Contemp Clin Trials*. 2007;28:182–191. doi: 10.1016/j.cct.2006.05.007.
20. Johnson M, Bakas T. A review of barriers to thrombolytic therapy: implications for nursing care in the emergency department. *J Neurosci Nurs*. 2010;42:88–94.
21. Fonarow GC, Zhao X, Smith EE, Saver JL, Reeves MJ, Bhatt DL, et al. Door-to-needle times for tissue plasminogen activator administration and clinical outcomes in acute ischemic stroke before and after a quality improvement initiative. *JAMA*. 2014;311:1632–1640. doi: 10.1001/jama.2014.3203.
22. Schwamm LH, Fonarow GC, Reeves MJ, Pan W, Frankel MR, Smith EE, et al. Get With The Guidelines-Stroke is associated with sustained improvement in care for patients hospitalized with acute stroke or transient ischemic attack. *Circulation*. 2009;119:107–115. doi: 10.1161/CIRCULATIONAHA.108.783688.
23. Huang Q, Song HQ, Ji XM, Cheng WY, Feng J, Wu J, et al. Generalization of the right acute stroke prevention strategies in reducing in-hospital delays. *PLoS One*. 2016;11:e0154972. doi: 10.1371/journal.pone.0154972.
24. Dirks M, Niessen LW, van Wijngaarden JD, Koudstaal PJ, Franke CL, van Oostenbrugge RJ, et al; PRomoting ACute Thrombolysis in Ischemic StrokE (PRACTISE) Investigators. Promoting thrombolysis in acute ischemic stroke. *Stroke*. 2011;42:1325–1330. doi: 10.1161/STROKEAHA.110.596940.
25. Morgenstern LB, Bartholomew LK, Grotta JC, Staub L, King M, Chan W. Sustained benefit of a community and professional intervention to increase acute stroke therapy. *Arch Intern Med*. 2003;163:2198–2202. doi: 10.1001/archinte.163.18.2198.
26. Scott PA, Meurer WJ, Frederiksen SM, Kalbfleisch JD, Xu Z, Haan MN, et al; INSTINCT Investigators. A multilevel intervention to increase community hospital use of alteplase for acute stroke (INSTINCT): a cluster-randomised controlled trial. *Lancet Neurol*. 2013;12:139–148. doi: 10.1016/S1474-4422(12)70311-3.
27. Ragoschke-Schumm A, Walter S, Haass A, Balucani C, Lesmeister M, Nasreldein A, et al. Translation of the 'time is brain' concept into clinical practice: focus on prehospital stroke management. *Int J Stroke*. 2014;9:333–340. doi: 10.1111/ijs.12252.

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Improving Access to Thrombolysis and Inhospital Management Times in Ischemic Stroke: A Stepped-Wedge Randomized Trial

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SUPPLEMENTAL MATERIAL

Table I: Intra-cluster correlation coefficient and Inter-cluster coefficient of variation estimates in our study

Table II: Thrombolysis rate and door-to-imaging time by centre and arm

Table III: Effect of the intervention on thrombolysis rate and stroke management times adjusted for potential confounders in multivariate analyses

Table I: Intra-cluster correlation coefficient and Inter-cluster coefficient of variation estimates in our study

Variable	Intra-cluster correlation estimate	Inter-cluster coefficient of variation estimate
Door-to-imaging time	0.023	0.53
Thrombolysis	0.24	
Thrombolysis within 4.5 hours	0.22	

The intra-cluster correlation coefficient was estimated using the variances estimated by the univariate mixed regression models.

Table II: Thrombolysis rate and door-to-imaging time by centre and arm

			Thrombolysis within 4.5h		Door-to-imaging time (h)		
Cluster	Arm	Total*	N	(%)	N	Median	(Q1-Q3)
G1-1	Control	10	1	(10%)	10	1.73	(1.23-2.57)
G1-1	Intervention	23	5	(22%)	23	2.53	(1.43-3.38)
G1-2	Control	20	3	(15%)	20	2.26	(1.82-4.38)
G1-2	Intervention	58	16	(28%)	57	2.20	(1.33-3.47)
G1-3	Control	15	2	(13%)	12	1.71	(1.13-2.93)
G1-3	Intervention	29	6	(21%)	28	2.78	(1.61-3.63)
G1-4	Control	4	0	(0.0%)	4	5.95	(2.35-8.50)
G1-4	Intervention	34	21	(62%)	23	0.97	(0.55-2.10)
G1-5	Control	15	7	(47%)	14	0.59	(0.32-0.98)
G1-5	Intervention	21	12	(57%)	16	0.48	(0.25-0.85)
G2-1	Control	71	20	(28%)	68	1.24	(0.79-2.21)
G2-1	Intervention	69	25	(36%)	65	1.13	(0.88-2.08)
G2-2	Control	12	0	(0.0%)	6	1.57	(0.97-1.97)
G2-2	Intervention	8	3	(38%)	4	0.99	(0.60-2.12)
G2-3	Control	8	1	(13%)	7	1.73	(0.65-3.93)
G2-3	Intervention	6	0	(0.0%)	5	1.57	(1.10-1.93)
G2-4	Control	7	0	(0.0%)	7	0.90	(0.85-2.30)
G2-4	Intervention	24	1	(4.0%)	21	1.28	(0.98-2.52)
G3-1	Control	67	33	(49%)	65	0.57	(0.35-1.25)
G3-1	Intervention	34	18	(53%)	34	0.73	(0.55-1.20)
G3-2	Control	2	0	(0.0%)	2	0.99	(0.43-1.55)
G3-2	Intervention	1	0	(0.0%)	1	1.38	(1.38-1.38)
G3-3	Control	13	1	(8.0%)	12	0.87	(0.43-2.10)
G3-3	Intervention	15	3	(20%)	15	0.83	(0.53-1.67)
G3-4	Control	15	2	(13%)	15	1.17	(0.73-1.87)
G3-4	Intervention	10	2	(20%)	8	1.19	(0.83-2.05)
G3-5	Control	10	0	(0.0%)	3	0.88	(0.73-1.03)
G4-1	Control	10	3	(30%)	9	0.75	(0.43-1.07)
G4-1	Intervention	7	3	(43%)	7	1.02	(0.62-1.48)
G4-2	Control	34	11	(32%)	27	1.82	(0.73-3.52)

			Thrombolysis within 4.5h		Door-to-imaging time (h)		
Cluster	Arm	Total*	N	(%)	N	Median	(Q1-Q3)
G4-2	Intervention	15	9	(60%)	12	0.89	(0.54-2.09)
G4-3	Control	6	0	(0.0%)	6	3.26	(2.67-3.57)
G4-3	Intervention	4	0	(0.0%)	4	1.11	(0.92-1.47)
G4-4	Control	9	0	(0.0%)	7	1.63	(1.38-1.95)
G4-4	Intervention	5	0	(0.0%)	4	0.81	(0.53-0.98)

**Total number of patients included in the centre during the control or intervention phase of the study, h: hours, Q: quartile, G; Randomization group.*

Table III: Effect of the intervention on thrombolysis rate and stroke management times adjusted for potential confounders in multivariate analyses

	Overall thrombolysis		Thrombolysis within 4.5h		Door-to-imaging		Admission-to-SU		Imaging-to-SU		Door-to-needle	
	OR (95%CI)	p value	OR (95%CI)	p value	Beta (log)	p value	Beta (log)	p value	Beta (log)	p value	Beta (log)	p value
Intervention vs. control group	**1.43 (1.01-2.02)**	**0.04**	**1.90 (1.32-2.73)**	**0.0006**	-0.020	0.774	-0.131	0.136	**-0.293**	**0.03**	-0.043	0.4
Age (10-year increase)	0.99 (0.98-1.00)	0.2	0.99 (0.98-1.00)	0.08	**0.07**	**0.001**	0.01	0.663	0.003	0.9	-0.001	0.7
Admission during the night (Yes vs. No)	0.87 (0.61-1.24)	0.4	1.01 (0.70-1.47)	0.9	-0.109	0.1	-0.189	**0.044**	-0.233	0.12	0.056	0.3
Admission after EMS call (Yes vs. No)	**1.46 (1.02-2.09)**	**0.04**	**1.57 (1.08-2.29)**	**0.02**	**-0.235**	**0.002**	**-0.362**	**<0.001**	**-0.398**	**0.004**	**-0.164**	**0.004**

All ORs are adjusted for age, admission during the night vs. day and admission after EMS call vs. no EMS call