

Publication Alert Newsletter

Patients with acute ischaemic stroke (AIS) may benefit most from care initiatives that comprehensively target all aspects of the stroke pathway. In particular, to increase the use of intravenous recombinant tissue plasminogen activator (IV rtPA), it is important to target pre- and in-hospital processes.

This issue of the Actilyse® Publication Alert Newsletter begins with a study reporting improvements in rtPA use and patient outcomes after introducing a comprehensive stroke-management programme that covered pre-hospital, in-hospital, and post-hospital phases.¹ An accompanying editorial highlights the significance of the findings:

'Lessons can be learned here for all personnel and hospitals that treat patients with acute stroke and who want to improve thrombolytic use and patients' outcomes.'²

We also look at articles showing a shift towards assessing and treating AIS in the emergency room (ER).

Please be aware that the purpose of this Newsletter is to make you familiar with the most recent scientific publications, and you must keep in mind that all aspects may not be covered by the label. Please always refer to the current prescribing information as in force in your country

A comprehensive stroke-management programme increases rtPA use and improves patient functional outcome

Implementing a multifaceted stroke-care pathway, covering pre-hospital, in-hospital, and post-hospital phases, led to improved rtPA delivery rates and times, and better 3-month functional outcomes in patients with AIS.¹

The aim of the programme was to standardise all aspects of stroke care across all hospitals in the Tyrol region of Austria.

*'Use of this programme achieved high thrombolysis administration rates and significant improvement in clinical outcome... thrombolysis administration rates in patients with acute ischaemic stroke as high as 16.8% are feasible.'*¹

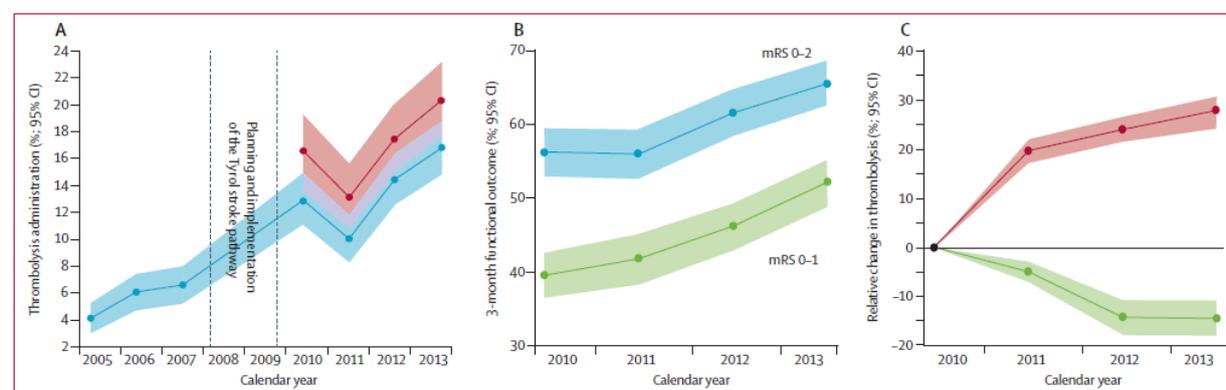
The pathway comprised four consecutive phases:

Pre-hospital	<ul style="list-style-type: none"> • Public education and efforts to reduce delays and ensure information transfer • One emergency medical services (EMS) protocol and one triage algorithm for suspected stroke <ul style="list-style-type: none"> ○ Referral guidelines for thrombolysis ○ Pre-notification system ○ Potentially eligible patients directed to a hospital offering thrombolysis
Hospital	<ul style="list-style-type: none"> • Local multidisciplinary stroke teams to identify local barriers
Inpatient rehabilitation	<ul style="list-style-type: none"> • Immediate access to brain imaging (prioritisation for patients with stroke) • Stroke neurologists always available via a telephone hotline • Discussion of yearly data reports with each hospital
Outpatient rehabilitation	<ul style="list-style-type: none"> • Establish quality-controlled outpatient rehabilitation

Study details

- Retrospective analysis of data from 4947 patients with AIS admitted to all eight hospitals in Tyrol (2010–2013), to investigate the impact of a statewide routine stroke-care pathway on use of rtPA and patient outcomes
 - 47% female; median age =75 years; median NIHSS score =4 (IQR 2–10)
- rtPA use increased significantly from 12.9% to 16.8%
 - Variability in rtPA use across the region decreased, from 2.2–22.6% in 2010 to 12.1–22.5% in 2013
- DNT was significantly reduced and 3-month functional outcome significantly improved
- Symptomatic ICH after thrombolysis was uncommon – 4.1% of patients (2010–2013)
- 3-month mortality was unchanged (13% in both 2010 and 2013)

Variable	2010 (n=1238)	2013 (n=1266)	p value
Onset-to-arrival <4.5 hours, n (%)	517 (42)	505 (40)	
rtPA administration, n (%) [95% CI]	160 (12.9 [11.1–14.9])	213 (16.8 [14.8–19.0])	<0.0001
DNT, median (IQR) mins	49 (35–60)	44 (29–60)	0.03
3-month functional outcome, % (95% CI)			
Excellent (mRS score 0–1)	39.7 (36.6–42.8)	52.5 (49.0–55.3)	<0.0001
Good (mRS score 0–2)	56.3 (53.1–59.5)	65.5 (62.5–68.5)	<0.0001



(A) Trends in thrombolysis administration in all patients with AIS (blue) and in patients with first-ever strokes and an NIHSS score >0 (red) (2005–2007 data included to allow estimation of long-term trends)
 (B) Trends in excellent and good clinical outcome (3-month mRS 0–1 [green] and 0–2 [blue], respectively)
 (C) Change in rtPA use for AIS in states with (red) or without (green) ongoing integrative comprehensive stroke care programmes

The authors conclude that their pathway is the first routine stroke-care programme to comprise the entire journey from stroke onset to outpatient rehabilitation, and that similar programmes could benefit all patients with AIS.

In the accompanying editorial, Levine notes that the programme was successful because it systematically addressed different types of barrier to the use of rtPA and acute stroke care.²

[this] approach could have an important public health effect... it represents the method for which there is the strongest evidence of potential to optimise acute stroke treatment.²

A systemised stroke code reduces delays in rtPA use

Sohn *et al.* have shown that implementation of a computerised stroke-code programme improves the timeliness of rtPA therapy in patients with AIS.³ In certain cases, use of the programme was also associated with improved clinical outcomes.

Activation of the programme initiates a pre-set chain of events, including notification of the stroke team and patient information being sent to relevant departments (e.g. radiology to prepare for imaging, pharmacy to prepare the rtPA). Magnetic resonance imaging (MRI) was used to screen patients for thrombolysis. Computerised tomography (CT) was used if MRI was unavailable.

Overall, implementation of the programme was associated with increased use of IV rtPA and decreased door-to-needle time (DNT), door-to-imaging time, and onset-to-needle time. The proportion of patients with a favourable outcome (modified Rankin scale [mRS] score 0–2) also increased (though significance was lost after regression analysis).

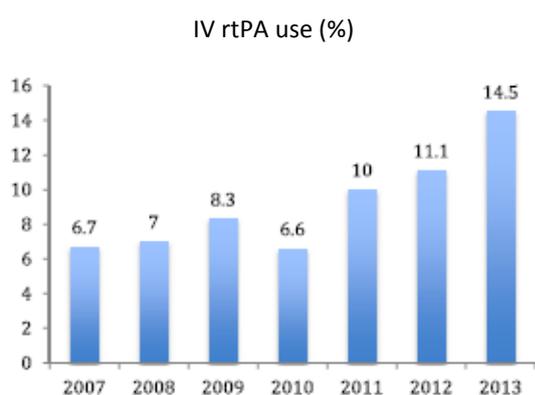
Significant reductions in delays were observed regardless of whether patients were screened by MRI or by CT scan. Interestingly, the proportion of patients with a favourable outcome significantly increased among those screened by MRI but not among those screened by CT scan.

The authors recommend further study into the prospect that a systemised stroke code with MRI screening might enhance the efficacy of thrombolysis.

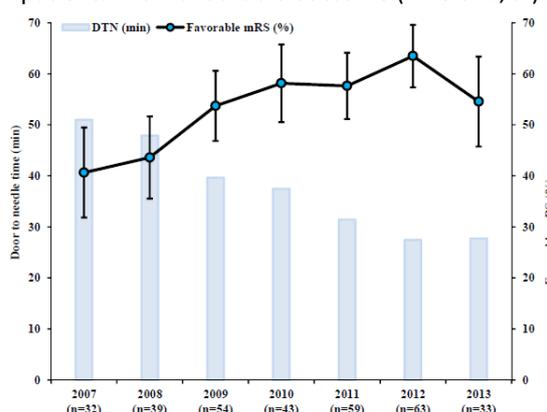
Study details

- Retrospective study of 377 patients with AIS who received IV rtPA <3 hours after symptom onset at a tertiary care hospital in Korea (January 2007–May 2013)
 - Outcomes compared before and after systemised stroke code implementation in January 2009
 - Outcomes reported overall and for patients screened by MRI (n=261) and by CT scan (n=62)
- IV rtPA use significantly increased from 6.9% (pre-code, 2007–08) to 9.6% (post-code, 2009–13)
- In-hospital delays decreased and the proportion of patients with favourable outcomes improved after implementation of the code (association between the code and favourable outcome was not significant after correction for age, sex, and NIHSS score)

Variable	Pre-stroke code (n=71)	Post-stroke code (n=252)	p value
Age (IQR) years	64 (52–73)	67 (58–76)	0.03
Baseline NIHSS (IQR)	12 (8–15)	10 (7–16)	0.34
MRI screen, n (%)	53 (74.6)	208 (82.5)	0.14
Onset-to-arrival time, median (IQR) mins	98 (62–114)	86.5 (47.5–120.5)	0.32
Door-to-imaging time, median (IQR) mins	27 (17–35)	13 (9–20.5)	<0.01
Door-to-needle time, median (IQR) mins	48 (32–62)	30.5 (22–40)	<0.01
Door-to-needle time <60 mins, %	67.6	95.3	<0.01
Onset-to-needle time, median (IQR) mins	142 (120–170)	122.5 (87.5–151.5)	<0.01
Symptomatic ICH, n (%)	5 (7.1)	7 (2.8)	0.02
mRS score 0–2 at 90 days, n (%)	30 (42.3)	146 (57.9)	0.02



Median door-to-needle time (mins) and proportion of patients with favourable outcome (mRS 0–2, %)



- In-hospital delays were significantly reduced for MRI-screened patients and CT-screened patients after implementation of the code (data not shown here)
- Proportion of patients with mRS score 0–2 significantly increased in MRI-screened patients (from 41.5% to 60.1%; $p=0.02$) but not CT-screened patients (44.4% to 47.7%; $p=0.81$), though there was no significant association between code and outcome in either population after regression analysis

...the systemised stroke code reduced the time necessary for thrombolysis and enhanced its effectiveness when screened by MRI.³

Timely access to rtPA requires accurate pre-hospital stroke identification

There is a call for improved methods for EMS identification of stroke after a systematic review estimated that some pre-hospital stroke scales are 'no better than a coin toss'.⁴

Brandler *et al.* emphasise that all efforts to improve in-hospital systems of care, shorten treatment times, and introduce innovations such as telestroke or mobile stroke units, are in vain if EMS personnel and first responders can't recognise and accurately identify the acute stroke patient.

***'Whether we use an existing pre-hospital system of stroke recognition or implement new models ... this critical first step should not be left to chance.'*⁴**

As an accompanying editorial notes, pre-hospital recognition of patients with AIS is a key determinant of the effectiveness of stroke care. Identifying stroke allows pre-notification, which in turn decreases DNT and increases rtPA use, each of which lead to better patient outcomes. As EMS personnel can't perform detailed examinations, they rely on screening tools to identify suspected stroke.⁵

Brandler *et al.* undertook the first systematic review of pre-hospital stroke scales, to determine which has the best operating characteristics for use by EMS to identify stroke in the field.

- Seven scales were assessed: FAST, CPSS, ROSIER, Med PACS, OPSS, LAPSS, MASS
- The scales varied in accuracy and missed up to 30% of acute strokes in the field
- LAPSS appeared to be the best and most reliable scale, but still missed 22% of strokes

The authors conclude that more study is required to identify the best current approach and find new tools for accurate and reliable pre-hospital stroke identification.

*'The primary reason for pre-hospital identification is to speed access to rtPA.'*⁴

Pre-hospital use of NIHSS may facilitate triage to the appropriate hospital

An analysis of the US Get With The Guidelines database has shown that the National Institutes of Health Stroke Scale (NIHSS) may be a suitable pre-hospital stroke screening tool.⁶ After NIHSS training, pre-hospital nurse/paramedic helicopter crews administered the scale to 305 patients with AIS during 2010. The scores given by the helicopter EMS team showed moderate to good agreement with scores given by the receiving stroke team at a comprehensive stroke centre. Of the cases of disagreement, only 16 (5.2%) were undertriaged by the EMS.

The authors conclude that the EMS can accurately perform the NIHSS and use it to triage patients with stroke to appropriate care.

An EMS assessment-based transportation protocol reduces pre-hospital delays

A citywide transportation protocol that includes EMS stroke assessment (Maria Prehospital Stroke Scale, MPSS), pre-notification, and repeated quality assurance monitoring, reduced pre-hospital delays without a weekend effect.⁷

Detection-to-door time was reduced and the proportion of patients with a good functional outcome after thrombolysis (30-day mRS score 0–2) increased, even though in-hospital times were unchanged by the transportation protocol.

The authors conclude that quality assurance programmes for acute stroke therapy may improve the process and outcome of IV rtPA therapy.

Study details

- Analysis of 2049 patients transported by EMS directly to 11 stroke centre hospitals in Kawasaki, Japan, based on MPSS assessment (April 2009–March 2013), to determine the effect of quality assurance monitoring
 - A citywide transportation protocol was launched in 2009, using the MPSS to determine patient transfer destination, with pre-notification to the receiving hospital
- Ambulance call-to-door time decreased by 3.6 mins over 4 years; there were no reductions in OTT or DNT
- Proportion of patients with good functional outcome after thrombolysis increased steadily over time
- No differences between weekday and weekend admissions on any clinical indicators

Quality indicators	2009 (n=380)	2010 (n=544)	2011 (n=529)	2012 (n=596)	p value
Time parameter, mean (range) mins					
Detection-to-door	37.5 (16–126)	36.1 (14–119)	35.5 (10–136)	33.9 (13–117)	0.000
Onset-to-needle	132.4 (75–180)	117.4 (71–170)	138.0 (60–210)	117.4 (49–282)	0.168
Door-to-needle	75.3 (33–128)	80.3 (14–165)	77.4 (27–145)	78.1 (27–195)	0.457
Received rtPA, n (%)	51 (13.4)	67 (12.3)	62 (11.7)	66 (11.1)	0.633
30-day mRS score 0–2, %	23.5	23.9	27.4	34.8	0.454

*'A citywide MPSS-based transportation protocol significantly decreased the delay in the ambulance call-to-door time.'*⁷

Strategies that target ER physicians could improve rtPA rates

Results of an online survey of 429 Australian ER physicians suggest up to a third feel unable to interpret brain imaging scans and identify stroke patients eligible for thrombolysis, and the majority stated they do not receive assessment, performance monitoring, or feedback regarding rtPA use.⁸

The authors conclude that targeting ER physicians' knowledge and skills while monitoring rtPA use and providing feedback may increase thrombolysis use in patients with AIS.

*'As emergency physicians are commonly the first point of contact for the in-hospital care of stroke patients, their perceptions towards rtPA use, and the system processes to support its use, in acute stroke, may be a critical factor in the adoption and guideline use of this treatment.'*⁸

AIS treatment can begin in the emergency department

More advanced and efficient care of stroke patients can be achieved by providing ER physicians with specialist neuroscience training, and dedicating a section of the emergency department (ED) to identifying, triaging, and treating patients with neurological emergencies.⁹

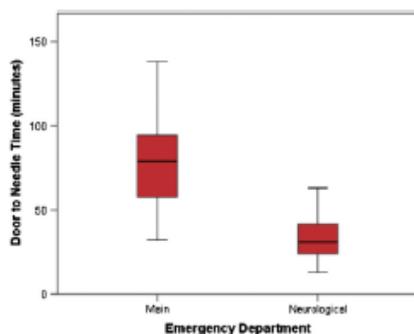
When ER physicians were trained to administer rtPA to patients with AIS without consulting a specialist, a substantially shorter DNT was achieved (compared with out-of-hours treatment requiring specialist consultation), with no apparent compromise on safety and better functional outcomes.

The authors conclude that these outcomes suggest utility in training ER physicians to administer rtPA independently, based on clinical practice guidelines.

*'Trained neurologic emergency physicians can safely give IV rtPA independently for AIS patients with improved door-to-needle times, lower discharge NIHSS scores, and a higher likelihood of being discharged to home compared to the main emergency department physicians who used teleneurology consultation.'*⁹

Study details

- Retrospective analysis of 67 patients with AIS who received IV rtPA at a comprehensive stroke centre, 35 in the neuro ED and 32 in the main ED (August 2012–2014), to compare outcomes in the two groups
 - Neuro ED physicians received specialist training and were able to administer IV rtPA independently, without specialist consultation, between 7 am and 6 pm each day
 - From 6 pm to 7 am, patients with AIS were treated in the main ED: telestroke or specialist consultation was required before rtPA could be administered
- In the neuro ED group compared with the main ED group, mean DNT was significantly faster (figure), discharge NIHSS score was significantly lower, and more patients were discharged to home (table)
 - There were no cases of symptomatic ICH in either group



	Main ED (n=32)	Neuro ED (n=35)	p value
Mean presenting NIHSS	10	8	0.14
Mean DNT, mins	83	35	<0.0001
DNT <60 mins, %	31	89	
Average discharge NIHSS	6	2	0.049
Discharged to home, n	15	25	0.04

Safety and feasibility of rtPA administration in an ED setting has been shown

Training ED physicians in AIS management and rtPA treatment can reduce delays and increase the proportion of patients potentially eligible for thrombolysis.¹⁰

When thrombolysis assessment and administration are carried out by trained ED physicians in a general hospital, thrombolysis rate and clinical outcomes compare favourably with the SITS-MOST study and national averages in specialist stroke units.

The authors conclude that the study supports the safety and feasibility of administering rtPA in an ED setting without a specialised neurological stroke unit, and providing ED physicians with thrombolysis training may increase the geographical distribution and availability of treatment-capable centres.

Study details

- Prospective observational study of 43 patients with AIS who received IV rtPA (thrombolysis rate 5.9%) in an ED setting without a specialist neurological stroke team (May 2010–Dec 2013), to evaluate safety outcomes
 - Administration of IV rtPA within 3 hours of stroke onset permitted after implementation of staff training, triage, and EMS pre-hospital assessment protocols
- Treatment rates, times and outcomes were comparable with those of the SITS-MOST study

Variable	ED rtPA (n=43)	SITS-MOST (n=6483)
Age, median (range) years	68 (22–82)	68
Female, %	37.2	39.8
NIHSS, % mild/moderate/severe	13.9/39.6/46.5	23/37/40
Onset-to-door time, median (range) mins	43 (0–90)	N/A
Door-to-needle time, median (range) mins	59 (17–120)	68
Onset-to-treatment time, mean (range) mins	110 (17–60)	140
Treated within 90 mins, %	25.5	10.6
Symptomatic ICH (SITS-MOST definition)	4.6	1.7
3-month mortality, %	9.3	11.3
3-month functional outcome, %		
Excellent (mRS 0–1)	55.0	38.9
Good (mRS 0–2)	72.0	55.0

*'Our study seems to support the safety, efficacy and feasibility of thrombolysis when delivered in an ED setting of a district general hospital without a specialised neurological stroke unit.'*¹⁰

Mobile stroke units may enable earlier evaluation and treatment with rtPA

Use of mobile stroke units may result in earlier patient evaluation and treatment with rtPA, particularly in the first hour after onset, leading to substantially better clinical outcomes.¹¹ Costs may then be offset by reduction in care costs and increase in quality-adjusted life-years. Using telemedicine consultation rather than carrying an on-board vascular neurologist may reduce costs further without affecting patient outcomes.

To evaluate the logistics, outcomes, and cost-effectiveness of mobile stroke unit deployment in the USA, a prospective study (BEST-MSU) is being conducted in Houston, Texas.

*'The mobile stroke unit strategy could dramatically transform the way acute stroke is managed in the United States.'*¹¹

The widespread success of telestroke has led to expansion of teleneurology

Telemedicine is now used widely to provide stroke care expertise when in-person consultations are not possible. Its potential application to other neurology disciplines is reviewed by Wechsler.¹²

Teleneurology is now being used or piloted for acute care, intensive care unit monitoring, outpatient consultations, and home care in conditions such as stroke, Parkinson's disease, multiple sclerosis, and epilepsy.

*'Outcomes after intravenous tissue plasminogen activator treatment via telemedicine (telestroke) are similar to those achieved with in-person evaluations.'*¹²

Robotic telepresence-supervised stroke assessment can be used to determine thrombolysis eligibility

A retrospective analysis of 196 stroke alert assessments at a US primary stroke centre (2009–2012) found that, although robotic telepresence assessments took several minutes longer than those conducted in person, safety outcomes after thrombolysis were excellent.¹³

The authors note the comparison groups differed in several respects and these factors could have influenced robotic assessment time. They conclude that, 'robotic telepresence may be preferable in situations where no stroke specialist is available in-house.'

CI, confidence interval; CPSS, Cincinnati Pre-Hospital Stroke Scale; DNT, door-to-needle time; FAST, Face Arm Speech Test; ICH, intracranial haemorrhage; IQR, inter quartile range; LAPSS, Los Angeles Pre-Hospital Stroke Screen; MASS, Melbourne Ambulance Stroke Screen; Med PACS, Medic Prehospital Assessment for Code Stroke; MPSS, Maria Prehospital Stroke Scale; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OPSS, Ontario Prehospital Stroke Screening Tool; OTT, onset-to-treatment time; ROSIER, Recognition of Stroke in the Emergency Room

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