

Publication Alert Newsletter

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

It is often said that ‘time is brain’ for patients with acute ischaemic stroke (AIS). A recent review article summarises the accumulation of evidence that led to the ‘time is brain’ concept and looks at the development of pharmacological recanalisation therapy in AIS.¹ The article highlights that, to date:

‘Intravenous thrombolysis with tissue plasminogen activator up to 4.5 hours after symptom onset is the only proven reperfusion therapy for AIS.’

The authors also consider future perspectives and how modern imaging techniques might help to identify patients who may benefit from thrombolysis based on determining potentially salvageable tissue; this is being studied in the EXTEND and ECASS 4 studies.

This issue of the Actilyse® Publication Alert Newsletter looks at the impact that individual members of the stroke care team, patients and their families can have on timely and effective AIS management.

Less experienced neurologists should not be excluded from rtPA programmes

Among neurologists, greater thrombolysis experience may increase the positive effects of intravenous (IV) recombinant tissue plasminogen activator (rtPA).²

A French study found that patients treated by the most rtPA-experienced neurologists are more likely to be functionally independent at 3 months, even though these patients were older and had lower modified Rankin Scale (mRS) scores on admission.

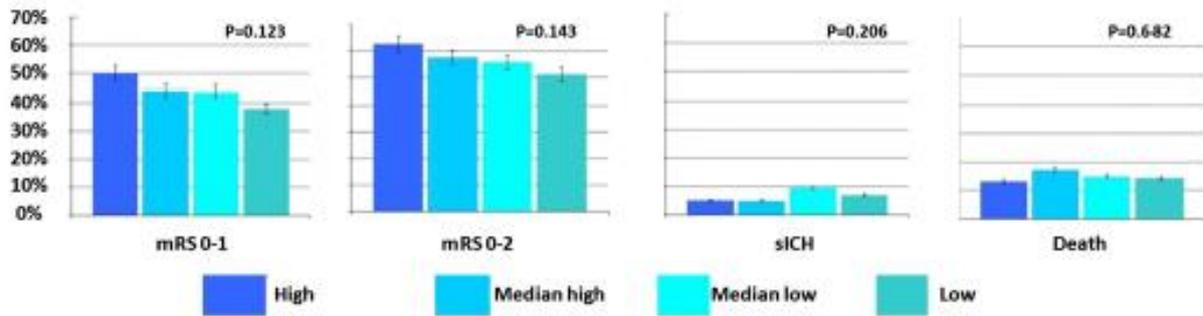
Importantly, risk of intracranial haemorrhage (ICH) or death was **not** influenced by neurologist experience. The authors note that patients treated by less experienced neurologists have similar outcomes to those in clinical trials, and thus still benefit from thrombolysis. Therefore, less experienced neurologists should not be excluded from rtPA programmes.

‘The benefit of rtPA is still present in patients treated by less experienced neurologists’²

Study details

- Analysis of data from 800 consecutive patients with AIS treated with IV rtPA at Lille University Hospital (2003–2014), to evaluate the influence of treating neurologist experience on patient outcomes
 - Each neurologist had 4–5 years in training, 6–12 months in a stroke unit, and 100–125 days with senior neurologist supervision before being permitted to take thrombolysis decisions
 - At study end, neurologist experience ranged from 0 to 131 previous decisions to administer rtPA
- Patients treated by the most experienced neurologists were older, more likely to have a pre-stroke mRS score of 0–1, and more likely to have unknown onset time
- rtPA treatment times did not vary significantly across neurologist experience groups
 - Median OTT 145–160 min; median DNT 54–56 min
- Unadjusted analysis showed no difference in outcome measures between experience groups (Figure)
- After logistic regression analysis, neurologist experience (continuous variable) was an independent predictor of mRS 0–1 and mRS 0–2 at 3 months, **but not death or SICH**:
 - OR (95% CI) for 10 patients more with mRS 0–1: 1.062 (1.008–1.120)
 - OR (95% CI) for 10 patients more with mRS 0–2: 1.076 (1.016–1.140)

Study details (continued)



Unadjusted patient outcomes according to neurologist experience (number of previous decisions to administer rtPA): high (35–131 decisions); median high (14–34 decisions); median low: 5–13 (decisions); low (0–4 decisions)

This finding strongly encourages not restricting the prescription of IV rtPA for cerebral ischaemia to the most experienced neurologists, provided they have a minimum level of training²

Stroke alerts in the ER lead to quicker CT scans and higher rtPA rates than alerts that originate in other hospital locations

Hospital processes have been put in place to provide timely care to patients admitted to the emergency room (ER) with AIS, but similar consideration should be given to patients with in-hospital stroke.

A retrospective analysis of stroke alert activations highlights that patients who have a suspected stroke in the intensive care unit or on the medical/surgical ward take longer to have a computerised tomography (CT) scan and are less likely to receive rtPA than patients in the ER.³

The rate of rtPA administration was lower for stroke alerts called from medical/surgical floors than from the ER.³

Study details

- Chart review of 983 stroke alert activations within a US general hospital (Jan 2011–Mar 2013), to determine the effect of hospital location and time of the stroke alert on patient management
 - A low threshold to activate the stroke alert was encouraged: 41% of alerts had a final diagnosis of stroke
- Most stroke alerts originated in the ER: these patients had the highest rate of thrombolysis (16%)
- Time to CT scan was the only performance time affected by stroke alert location
 - ER alerts were associated with the fastest time to CT scan
 - ICU alerts had the longest time to CT scan, due to the physical distance between the ICU and the scanner
- Stroke alerts were most frequent between 9 am and 6 pm
 - From 5 to 7 am, the medical/surgical floor originated the majority of stroke alerts and the ER the least
 - There was no effect on time of day on rtPA rate or treatment times

Variables	ER	Medical/ surgical	Neuro floor	ICU	p value
% of all stroke alerts	67	21	1	6	–
Stroke diagnosis, % of alerts	49.4	34.0	0	55.8	<0.001
Thrombolysis rate	8.8	3.1	0	3.9	0.05
% of all patients					
% of stroke patients	16.2	2.1	0	9.1	0.07
Alert to CT scan, mean (SD) mins	25.3 (0.87)	38.5 (1.6)	32.4 (6.4)	50.1 (3.5)	<0.0001

Patient companions may facilitate more effective ED management of stroke

Family members of stroke patients play a key role in the decision to seek early medical attention and to act as facilitators of care in the emergency department (ED). Their importance should be recognised in ED care protocols.

Patients admitted to the ED with companions were more likely to arrive by emergency medical services (EMS), with prenotification, and had shorter door-to-CT times and higher rates of stroke recognition by the triage nurse, compared with unaccompanied patients.⁴

The presence of one companion reduced time to CT by 15 minutes, and the presence of a second companion decreased this time by a further 20 minutes.

The authors conclude that two companions are optimal in the case of a stroke patient, and may assist the medical emergency system in achieving a better quality of care.

Study details

- Prospective study of 724 consecutive stroke patients admitted to the ED of a tertiary referral hospital in Israel (Aug 2011 – Oct 2012), to evaluate the effect of patient companion number on ED diagnosis efficiency
 - Admitted patients had AIS (n=585), TIA (n=75) or ICH (n=64)
 - Most patients were accompanied by 1 (40.2%) or 2 (20.3%) people
- In multivariate analysis, number of companions was independently associated with shorter time to CT scanning and with higher rates of stroke recognition by the triage nurse
 - Time to CT scan: RR=0.82, 0.73, and 0.70 for 1, 2, and ≥3 companions, respectively, vs none
 - Stroke recognition: OR=2.11, 2.62, and 4.11 for 1, 2, and ≥3 companions, respectively, vs none
- Number of companions was not significantly associated with DNT or thrombolysis rate
- Women and the elderly gained the largest benefit from the presence of companions

Variable	Number of ED companions				p value
	0 (n=73)	1 (n=291)	2 (n=147)	3–6 (n=99)	
Onset-to-arrival time <3 hours, %	28.8	33.3	36.1	36.4	0.68
Arrival via EMS, %	33.3	50.5	54.1	69.7	<0.001
EMS prenotification, %	8.3	21.3	27.9	33.3	0.001
ED triage recognition, %	22.2	37.8	47.6	54.5	<0.001
Door-to-CT time, median (IQR) min	137 (89–251)	122 (75–212)	102 (56.5–164)	101.5 (55.25–152.25)	0.001
Thrombolysis, % of pts with AIS	9.1	7.7	8.9	8.8	0.96
CT-to-needle time, median (IQR) mins	131 (48–131)	45 (24.5–71)	51 (27–69)	51 (42–60)	0.25
DNT, median (IQR) mins	270 (145–270)	90 (73–153.25)	100 (77–117)	92 (83–177)	0.10
In-hospital mortality, %	8.3	4.1	10.3	14.1	0.006

'Family members and other companions could serve as facilitators of faster and more effective ED management of stroke patients, possibly improving their outcome'⁴

'Drip and ship' thrombolysis may facilitate widespread rtPA use in AIS

Analysis of data from the US Get With The Guidelines-Stroke programme has shown that 'drip and ship', interhospital transfer after IV rtPA use, is an important, frequently used strategy for rtPA administration.⁵

Between Apr 2003 and Oct 2010, this method was used for 1 in 4 patients with AIS who received IV rtPA within 3 hours of symptom onset. Over the study period, overall rtPA use increased in patients with AIS. The authors conclude that the drip and ship approach has been an important contributor to this increase.

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The drip and ship paradigm may facilitate widespread rtPA use in patients with acute stroke.⁵

rtPA use is feasible and effective in developing countries

Nikkhah et al. evaluated thrombolysis implementation in a region of Iran and found that rates of use were lower than in most developed countries, but comparable with other developing ones.⁶

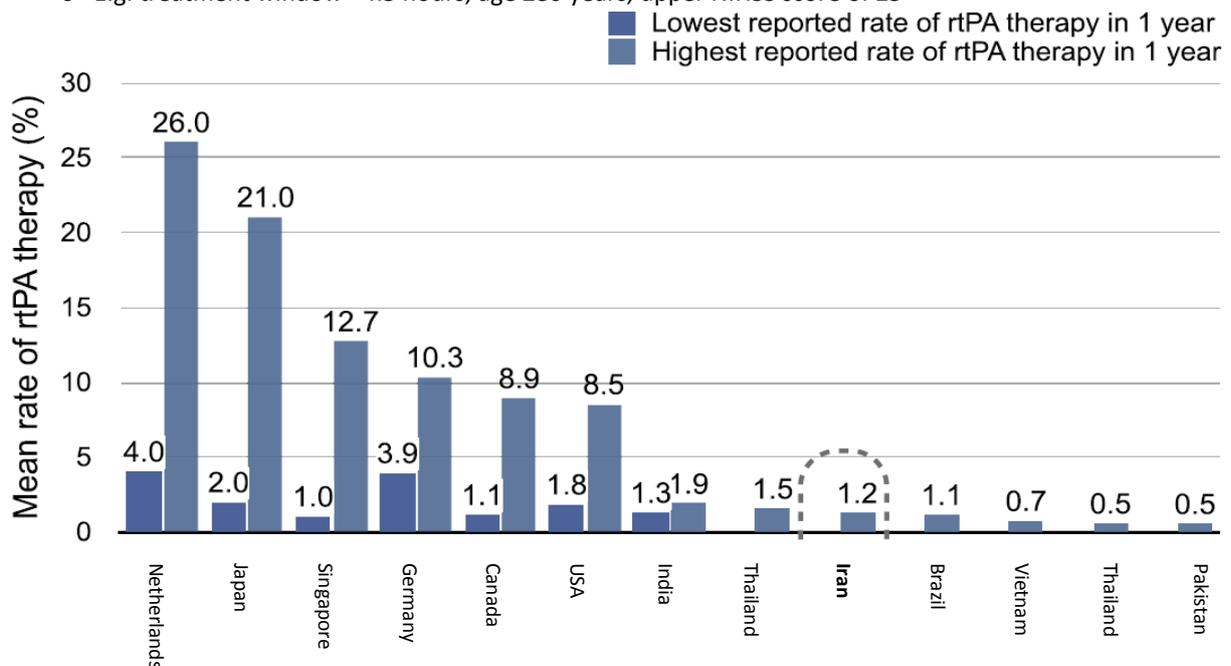
The thrombolysis rate was low (1.2%) because the vast majority of patients arrived at hospital more than 3 hours after symptom onset, and neurologists were cautious in their decisions to use rtPA.

The authors conclude that public campaigns and teamwork including healthcare professionals and policy makers with the support of scientific organisations would help to improve stroke care delivery in Iran as a developing country.

The results of this preliminary study suggest that rtPA is feasible and effective in a developing country like Iran.⁶

Study details

- 1-year cohort study of 1144 patients with AIS admitted to a tertiary neurological referral clinic in Iran (Sep 2011–Sep 2012), to assess implementation of thrombolysis
 - rtPA was administered at a lower dose (0.6 mg/kg) than recommended by the AHA/ASA (0.9 mg/kg)
 - Exclusion criteria were more stringent than in developed countries
- Only 14 patients (1.2%) received rtPA
 - Mean (range) door-to-CT time 14.3 (10–25) mins; DNT 57.6 (48–66) mins; OTT 172.1 (135–180) mins
 - At 3 months, all patients were alive and 7/14 had an mRS score of 0 or 1
- Of the 1130 patients deemed ineligible for rtPA:
 - 980 (86%) arrived >3 hours after symptom onset; another 18 passed the 3-hour window while being evaluated
 - 42 were excluded based on age (>75 years)
 - 90 were excluded based on NIHSS score (<4 or >20), hypertension, recent MI, or other contraindications
- A thrombolysis rate of 5.1% could have been achieved if typical rtPA eligibility criteria had been applied
 - E.g. treatment window <4.5 hours, age ≤80 years, upper NIHSS score of 25



Mean rate of rtPA use during treatment period (among all eligible patients with AIS admitted within 3 hours of symptom onset) in different studies in developed and developing countries, including the present study

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The need to avoid delays in administering rtPA, the only FDA-approved treatment for AIS, is emphasised in continuing medical education materials

An educational paper based around a theoretical case study highlights that alteplase is the only US Food and Drug Administration (FDA) approved treatment for AIS.⁷

The article emphasises that identifying a clear time of symptom onset is critical in determining whether IV thrombolytic therapy is indicated.

*'One of the most important aspects of the initial evaluation of a patient with suspected stroke is identifying the exact time of symptom onset, if possible.'*⁷

Prehospital delay is negatively correlated with NIHSS score

Patients or bystanders act quickly in response to certain stroke symptoms, but not to others and this can contribute to prehospital delays.⁸

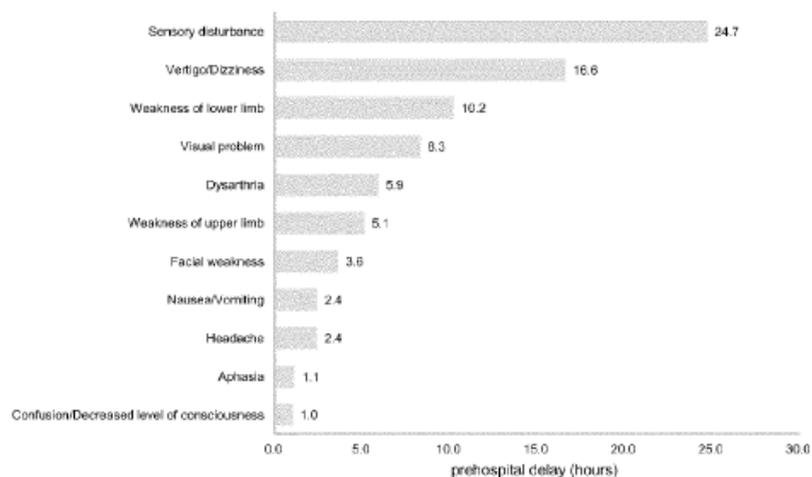
In an analysis conducted at an urban hospital in Japan, stroke patients with confusion/decreased consciousness, aphasia, headache, or nausea/vomiting visited hospital earlier than patients without these symptoms. In contrast, patients with sensory disturbance or vertigo/dizziness delayed visiting hospital compared with patients without these symptoms. There was a significant negative correlation between prehospital delay and overall National Institutes of Health Stroke Scale (NIHSS) score.

The authors conclude that public education is necessary to encourage early hospital visitation even with mild symptoms.

Study details

- Single-centre observational study of 469 consecutive patients hospitalised within 2 weeks of acute stroke / TIA onset (May 2007–Mar 2009), to assess the effect of symptom recognition on prehospital delay
 - 342 patients (73%) had AIS, 30 (6%) had TIA; the remainder had haemorrhagic stroke
 - Median NIHSS score was 4 (IQR 1–8)
 - Median prehospital delay was 6.6 hours (IQR 1.2–43.6 hours)
 - IV rtPA was given to 9.7% of patients with AIS or TIA
- Lower/upper limb weakness and confusion/decreased level of consciousness were well recognised by patients/bystanders. Facial weakness, aphasia, visual problems and sensory disturbances were poorly recognised
- Confusion/decreased level of consciousness, aphasia, headache, and nausea/vomiting were associated with shorter prehospital delay compared with stroke in the absence of these symptoms
- Sensory disturbance and vertigo/dizziness were associated with a significant delay in hospital visitation compared with stroke in the absence of these symptoms
- Higher NIHSS scores were associated with shorter prehospital delays ($p < 0.001$)

Median prehospital delay associated with each stroke symptom



*'Public education to promote early hospital visitation, even with milder symptoms, is critical.'*⁸

Delivering thrombolysis using a telephone advice system is effective

Remote thrombolysis using telephone advice and teleradiology was as effective as standard thrombolysis, with no significant increase in symptomatic ICH or mortality, based on a retrospective analysis of data from 586 consecutive patients treated within a regional UK network of five stroke hospitals (Jan 2012 to Dec 2013).⁹

Although telephone advice delayed treatment by ~22 minutes, some of this delay could be attributed to the majority of the remote group (94%) being treated out-of-hours.

Variable	Standard thrombolysis (n=366)	Remote thrombolysis (n=220)	p value
Door-to-needle time, mean (95% CI) mins	53.7 (50.9–56.5)	76.6 (72.2–80.9)	<0.001
Onset-to-treatment time, mean (95% CI) mins	139.5 (134.5–144.4)	161.6 (154.9–168.3)	<0.001
NIHSS change at 7 days/discharge, median	-8.5 (7.5–9.0)	-8.5 (8–9.5)	0.835
Symptomatic ICH, %	4.6	3.6	0.7085
7-day mortality, %	7.1	6.4	0.8612
3-month mortality, %	17.5	15.0	0.5032
3-month functional outcome, good (mRS 0–2), %	46.1	46.0	1

*'Telephone advice and teleradiology, within an organised system of care, can be an effective method of delivery of intravenous thrombolysis'*⁹

rtPA use varies across spoke hospitals within telestroke networks

Although telestroke networks increase access to a stroke specialist, particularly in remote locations, they do not automatically mean a uniformly higher rate of rtPA use.¹⁰

Analysis of data from two large, longstanding US telestroke networks found that rtPA treatment rates varied by up to 10-fold across their 32 spoke hospitals. Higher rates of thrombolysis occurred in spoke hospitals with stroke nurse coordinators. The hospital with the highest thrombolysis rate had an in-house neurohospitalist on duty 7 days a week, from 8 am to 6 pm, and used telestroke for after-hours consultation.

The authors conclude that rtPA usage varies significantly across spokes within telestroke networks. Specific strategies to maximise rtPA use within the telestroke network model are needed, and might include combining the use of in-house neurohospitalists by day with telestroke support at night.

AHA/ASA, American Heart Association/American Stroke Association; CI, confidence interval; DNT, door-to-needle time; IQR, interquartile range; MI, myocardial infarction; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; OTT, onset-to-treatment time; RR, relative risk; SICH, symptomatic intracranial haemorrhage; TIA, transient ischaemic attack.

References

1. Hlavica M, Diepers M, Garcia-Esperon C et al. Pharmacological recanalization therapy in acute ischemic stroke - Evolution, current state and perspectives of intravenous and intra-arterial thrombolysis. *J Neuroradiol* 2015;42:30-46.
[PubMed Link](#) [Journal link](#)
2. Tuffal A, Moulin S, Dequatre-Ponchelle N et al. Influence of neurologists' experience on the outcome of patients treated by intravenous thrombolysis for cerebral ischaemia. *J Neurol* 2015.
[PubMed Link](#) [Journal link](#)
3. Stecker MM, Michel K, Antaky K et al. Characteristics of the stroke alert process in a general hospital. *Surg Neurol Int* 2015;6:5.
[PubMed Link](#) [Journal link](#)
4. Ashkenazi L, Toledano R, Novack V et al. Emergency department companions of stroke patients: implications on quality of care. *Medicine (Baltimore)* 2015;94:e520.
[PubMed Link](#) [Journal link](#)
5. Sheth KN, Smith EE, Grau-Sepulveda MV et al. Drip and ship thrombolytic therapy for acute ischemic stroke: use, temporal trends, and outcomes. *Stroke* 2015;46:732-9.
[PubMed Link](#) [Journal link](#)
6. Nikkhah K, Avan A, Shoeibi A et al. Gaps and hurdles deter against following stroke guidelines for thrombolytic therapy in Iran: exploring the problem. *J Stroke Cerebrovasc Dis* 2015;24:408-15.
[PubMed Link](#) [Journal link](#)
7. Kelly AG. Patient management problem. *Continuum (Minneap Minn)* 2014;20:476-93.
[PubMed Link](#) [Journal link](#)
8. Yanagida T, Fujimoto S, Inoue T et al. Prehospital delay and stroke-related symptoms. *Intern Med* 2015;54:171-7.
[PubMed Link](#) [Journal link](#)
9. Dutta D, Kendall J, Holmes C et al. Evaluation of a telephone advice system for remote intravenous thrombolysis in ischemic stroke: data from a United Kingdom network. *Stroke* 2015;46:867-9.
[PubMed Link](#) [Journal link](#)
10. Switzer JA, Singh R, Mathiassen L et al. Telestroke: Variations in intravenous thrombolysis by spoke hospitals. *J Stroke Cerebrovasc Dis* 2015.
[PubMed Link](#) [Journal link](#)

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