



## 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 vital to impress upon physicians, healthcare providers, and the public the message that ‘time is brain’, to ensure that as many as possible patients with acute ischaemic stroke (AIS) receive thrombolysis without delay in order to maximize the likelihood of better outcomes.

This issue of the Actilyse® Publication Alert Newsletter features a study that highlights the biology behind this message, and which shows that timeliness of treatment is linked to the degree of thrombus resolution, as well as the extent to which brain tissue might be salvaged. In the authors words:

**‘Time is clot as well as brain’<sup>1</sup>**

We also highlight barriers to timely thrombolysis that exist in clinical practice, studies assessing efforts to improve stroke detection and treatment, and initiatives to improve access to optimal stroke care.

### Earlier administration of rtPA is associated with better thrombus reduction

Time between stroke onset and administration of recombinant tissue plasminogen activator (rtPA) is important, because faster restoration of blood flow to the brain leads to better patient recovery.

Resolution of the thrombus is necessary to restore blood flow, but this may become more difficult as time passes.

In patients with AIS treated within 3 hours of symptom onset, earlier thrombolysis with intravenous (IV) rtPA was associated with better thrombus resolution.<sup>1</sup>

*...the likelihood of a thrombus being resolved by rtPA treatment decreases with increasing time from thrombus formation.<sup>1</sup>*

#### Study details

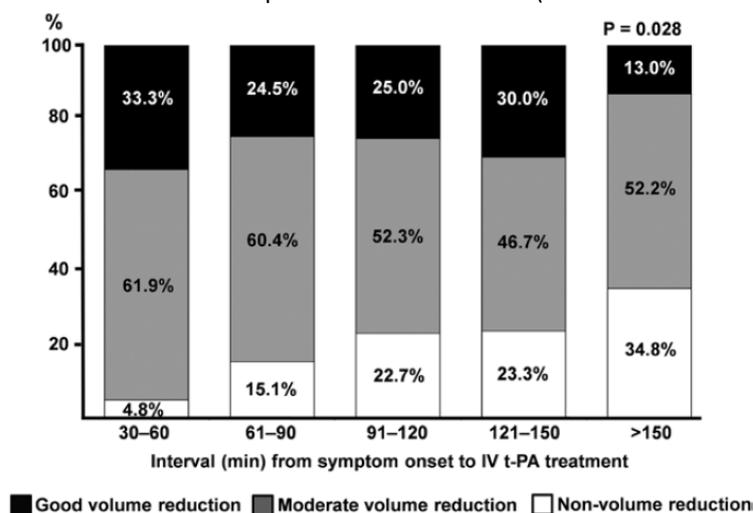
- Analysis of data from 243 patients with AIS who received rtPA within 3 hours of symptom onset at university hospitals in Korea (Nov 2006–Jun 2013), to evaluate whether time to rtPA affected thrombus resolution
  - Thrombi were detected in 171/243 patients and were reassessed 1 hour after rtPA administration
  - Thrombus volume reduction ≥50% was classed as good; <50% reduction as moderate
- 80% of patients had good/moderate reduction in thrombus volume
  - Although 20% of patients had no reduction, a single assessment at a time when rtPA was still exerting its fibrinolytic action, may have been insufficient to assess the entire process of thrombus dissolution after rtPA therapy

Variable	Outcomes
Stroke onset to rtPA administration, median (IQR) min	100 (75–133)
rtPA administration to follow-up CT scan, mean (SD) min	58.7 (18.0)
Thrombus volume reduction on follow-up CT scan, % of patients	
Any/none	80.1/19.9
Good (median [IQR] volume reduction 86.2% [60.1–100%])	25.1
Moderate (median [IQR] volume reduction 17.9% [8.5–30.5%])	55.0

- As time (in intervals of 30 minutes) from onset to rtPA increased, the proportion of patients with good/moderate thrombus reduction decreased (figure)

## Study details (continued)

- Thrombus reduction was independently associated with shorter time interval from onset to IV rtPA:
  - Good volume reduction: OR per minute saved: 0.986 (95% CI: 0.974–0.999),  $p=0.035$
  - Moderate volume reduction: OR per minute saved: 0.988 (95% CI: 0.978–0.999),  $p=0.038$



Proportions of patients in each category of thrombus resolution according to time from symptom onset to IV rtPA treatment

*'Earlier administration of rtPA after stroke onset is important not only for brain salvage but also for better thrombus resolution.'*<sup>1</sup>

### **Delayed hospital presentation after symptom onset is still the biggest barrier to timely thrombolysis**

A survey to evaluate potential barriers to thrombolysis in the emergency room (ER) setting found that stroke onset-to-admission delay was commonly felt to be the biggest obstacle in administering rtPA to patients with AIS.<sup>2</sup>

Based on responses from 37 stroke centres in the southwest USA, typically administering rtPA 2–5 times/month, **the most common obstacle to timely thrombolysis was patients presenting outside the time window for rtPA** (cited by 39% of respondents).

Other barriers included:

- Physician reluctance (19%)
- Emergency department (ED)–neurology communication time (14%)
- Difficulty identifying stroke in presenting patients (6%)
- Lack of urgency in the ED (6%)
- Blood pressure control (6%)

One respondent noted that physicians would wait until the end of the time window to see if the patient's symptoms improved prior to giving rtPA.

Additional assessment of nursing, clinical pharmacy and hospital practices in the ER setting showed considerable differences between hospitals, which may account for variability in door-to-needle times (DNT):

- Consent prior to administering rtPA required: always (44%), in some cases (28%), never (25%)
- Weight (for rtPA dose) determined by: scales (43%), family report (30%), healthcare professional estimate (27%)
- Stroke pagers carried by: stroke coordinator (62%), ER physician (30%), ED nurse (19%)

**Time to CT is longer for in-hospital stroke vs stroke patients presenting to the ER**

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

An analysis of stroke alert activations highlighted that in-patients took longer than newly admitted patients to have a computed tomography (CT) scan, and this resulted in delays to rtPA use.<sup>3</sup>

Locating the CT scanner within the ER makes it quicker and easier to obtain scans for patients admitted via the emergency medical services (EMS), but patients with in-hospital stroke need to be transported some distance to have their scan and this delay may adversely affect treatment rates and outcomes.

**Study details**

- Retrospective analysis of data from 122 stroke code activations that ended successfully in patients receiving rtPA or endovascular intervention at a single PSC in the US (Jan 2010–Jan 2013), to determine whether treatment times differ in the ER and in-patient settings
- In-patients experienced significant delays from stroke code activation to CT scan, and from stroke code activation to rtPA treatment, compared with ER patients (who in many cases had EMS pre-notification)
  - Mean time to CT scan was outside the AHA/ASA recommended time of 25 min
  - Longer time to CT scan was the main source of delay from stroke code activation to rtPA use

Variables	ER (n=106)	In-patient (n=16)	p value
Received rtPA	96	10	
Stroke code to neurological evaluation, mean (CI) min	2.8 (2.2–3.4)	4.4 (0.5–8.4)	0.19
Stroke code to CT scan, mean (CI) min	14.9 (12.7–17.1)	32.3 (23.1–41.4)	<0.001
Stroke code to rtPA administration, mean (CI) min	59.3 (54.7–64.0)	80.3 (63.4–97.2)	0.01
CT scan to rtPA administration, mean (CI) min	44.4 (39.2–49.6)	53.3 (39.7–66.9)	0.09

*‘...in the in-patient setting, there was a significant delay during stroke codes specifically in the time from stroke code to CT scan’<sup>3</sup>*

**Round-the-clock presence of an in-house stroke neurologist reduces door-to-needle times, throughout the whole 24-hour period**

Round-the-clock stroke neurologist care has a significant impact in reducing treatment delays.<sup>4</sup>

Introducing 24/7 stroke neurologist presence in a single US centre more than halved DNT, from 102 to 38 minutes, while the number of patients with AIS receiving rtPA more than trebled. This improvement was seen both during working hours (DNT ~33 minutes) and out-of-office hours (DNT ~44 minutes).

**Reductions in treatment delays serve as targets for quality improvement efforts**

Delivery of thrombolysis treatment in a timely manner remains a significant challenge to stroke physicians, as evidenced by results from a retrospective study at a tertiary hospital stroke unit in Australia.<sup>5</sup>

Of 490 patients admitted with AIS (Jan 2010–Dec 2012), 11.6% of eligible patients received rtPA, with a median onset-to-treatment time (OTT) of 175 min and a median DNT of 97 min.

This study provides a template for data collection to review treatment delay and outcome measurement in detail and the authors encourage all stroke units to prospectively collect thrombolysis data for purposes of peer comparisons and shared learning.

*‘More accurate patient selection and reductions in treatment delays serve as targets for quality improvement efforts that have broad applicability’<sup>5</sup>*

## Accurate pre-hospital stroke recognition improves the delivery of high-quality stroke care

There is opportunity for improving pre-hospital care by reducing both the over- and under-recognition of stroke by EMS providers.

In a retrospective records analysis, EMS transporters accurately detected AIS in 141 out of 186 patients (76%), but half of EMS-suspected strokes were false positives.<sup>6</sup>

*Stroke recognition by EMS providers in the field is a crucial step in the stroke chain of recovery<sup>6</sup>*

For EMS-recognized stroke patients, door-to-CT times were significantly faster (35 vs 85 min;  $p < 0.001$ ) and thrombolysis rates were higher (14.9% vs 4.4%;  $p = 0.074$ ) than for patients with stroke not recognized by the EMS.

## With educational support, more than 40% of patients recognize recurrent stroke and arrive at hospital within 3 hours of symptom onset

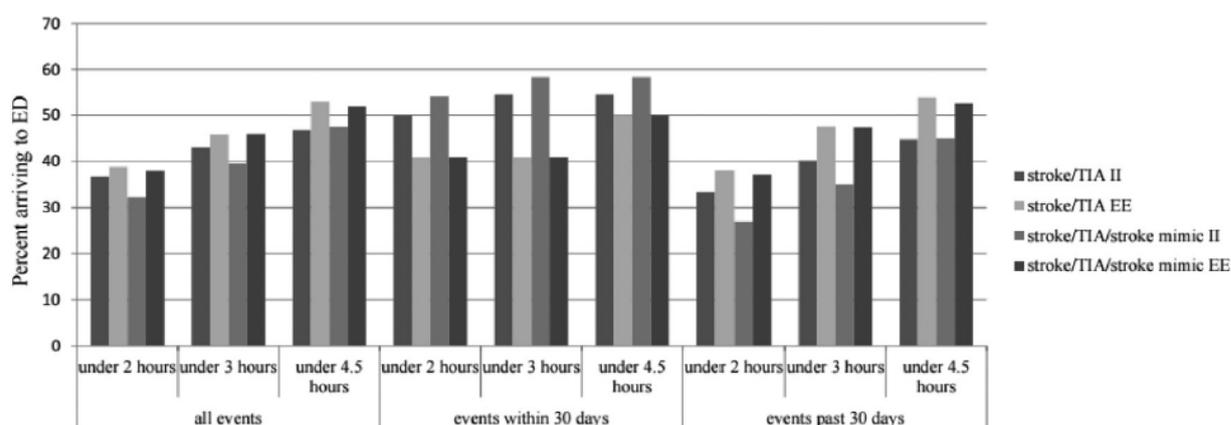
After receiving educational materials following a previous stroke, almost half of patients experiencing recurrent stroke arrived at hospital within 3 hours of symptom onset.<sup>7</sup> This compares with 27% of patients arriving within 3 hours of symptoms onset for their first stroke.

Interactive intervention and enhanced education were both associated with similar proportions of patients arriving within 3 hours of symptom onset.

The authors do not discuss whether the increase seen in the study might simply be due to the fact that patients were more familiar with stroke symptoms having experienced them before, but they do acknowledge the lack of a 'true placebo arm' as a study limitation.

### Study details

- Prospective, randomized, controlled, single-centre trial ('SWIFT') to compare the effect on recurrent stroke onset-to-arrival times of two different post-stroke educational interventions (2005–2011)
- 1193 stroke patients were randomized to receive either an interactive intervention or enhanced education
  - Both groups received a standard pack of educational materials, with educational reinforcement by telephone 1 and 12 months later
  - The interactive group additionally received in-hospital sessions consisting of a community placed preparedness PowerPoint presentation; a stroke survivor preparedness narrative video; and the use of role-playing techniques to describe stroke symptoms
- At baseline, onset-to-arrival time was within 3 hours in 27% of patients and 4.3% received rtPA
- After randomization, 224 patients experienced a recurrent stroke/TIA or stroke mimic within 12 months
  - Onset-to-arrival time was within 3 hours in 42% of patients, with no significant difference between intervention strategies (40% interactive intervention vs 46% enhanced education)
  - 4% received rtPA, with no difference between interventions



EE indicates enhanced educational; and II, interactive intervention.

*'...even modest educational efforts can significantly and realistically increase awareness and action'<sup>7</sup>*

### **Specific legislation may improve access to stroke care**

Access to stroke care may be improved by introducing regional legislation for stroke centre designation as well as standard policies relating to pre-hospital stroke care.<sup>8</sup> At the end of 2013, 18 US states had legislation relating to stroke triage and stroke centre designation, and these states had a higher proportion of primary stroke centres than the remainder (median 43% vs 13%).

### **Legislation can play an important role in increasing the adoption of telestroke**

State legislation can play an important role in increasing the adoption of telestroke in the USA, by addressing barriers to telemedicine practice and helping to establish telestroke programmes.<sup>9</sup>

For example, the requirement for physicians to be licensed by the state in which they are practising medicine is a barrier to telestroke, but this can be overcome with special telemedicine licenses.

As of June 2012, 44 states had enacted more than 250 statutes and regulations addressing telemedicine, many of which enacted policies and practices that facilitate telestroke access.

### **Practice-based telestroke care can deliver rtPA and achieve outcomes equivalent to academic-based telestroke care**

Telestroke care can be delivered successfully by practice-based general neurologists, with similar clinical outcomes to those achieved in academic-based stroke care systems.<sup>10</sup>

#### **Study details**

- Analysis of data from emergency stroke patients treated by the AcuteCare Telemedicine (ACT) network of seven US hospitals to evaluate clinical outcomes of practice-based telestroke care (Oct 2010–Oct 2012)
  - 54/202 patients (26.7%) received rtPA; 8 of these were stroke mimics but did not have complications
  - Of the patients who received rtPA, 57% were discharged home and 28% to rehabilitation facilities
- Clinical outcomes were generally comparable with two previous telestroke studies, Pittsburgh and TEMPIS:

Variable	ACT (n=54)	Pittsburgh (n=83)	TEMPIS (n=115)
Onset-to-treatment time, average mins	179.4		
Arrival-to-treatment time, average mins	103.0	89.9*	
Duration of hospital stay, average days	5.2		10.3**
In-hospital mortality, %	14.8		3.5*
SICH, %	3.7	1.2	7.8

\* $p < 0.05$  and \*\* $p < 0.01$  vs ACT outcomes

### **'Time is brain' applies to young and old alike when treated by telestroke**

For the elderly, as for younger patients, time seems to be critical for favourable outcome after AIS.<sup>10</sup>

Among 542 patients treated with rtPA within a telestroke network in Germany:

- Earlier onset-to-treatment time was associated with favourable outcomes (modified Rankin Scale score 0–2 at discharge) in patients aged <80 years (adjusted OR: 1.18; 95% CI: 1.03–1.34;  $p=0.01$ ) and tended to be associated with favourable outcomes in patients aged >80 years (adjusted OR: 1.13; 95% CI: 0.92–1.38;  $p=0.25$ ).
- Patients aged >80 years had higher risks of symptomatic intracranial haemorrhage, less favourable outcomes and mortality than patients aged <80 years.
- Age was not associated with longer delivery times for thrombolysis in telestroke.

**Note:** Actilyse® is contraindicated in patients aged >80 years.

AHA, American Heart Association; ASA, American Stroke Association; CI, confidence interval; CT, computed tomography; IQR, interquartile range; OR, odds ratio; PSC, primary stroke centre; SD, standard deviation; SICH, symptomatic intracranial haemorrhage; TIA, transient ischaemic attack.

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