



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

‘Why don’t more patients receive intravenous rtPA for acute stroke?’

This question was posed by the US author of a recent review article wondering why recombinant tissue plasminogen activator (rtPA) isn’t used more, despite:

- demonstrating clear, persuasive and long-term benefits across multiple patient populations
- being proven effective and cost-effective
- being approved in the USA for almost a decade
- being endorsed by the American Heart Association (AHA), the American Academy of Neurology, and the National Stroke Association since 1997.¹

He argues that now the promising initial data have been confirmed and supplemented:

‘...we must do no harm...by withholding a proven therapy through inaction.’

In this issue of the Actilyse® Publication Alert Newsletter we look at ways to increase rapid access to rtPA, through multifaceted approaches that require teamwork, decisiveness, and good organisation. We also highlight barriers to timely thrombolysis, and review studies assessing efforts to improve thrombolysis rates without compromising patient safety.

A multifaceted approach is needed to maximise the benefits of thrombolysis

A review examining the evolution of stroke thrombolysis emphasises the importance not just of giving rtPA to all eligible patients, but also of optimising efficient delivery to achieve the best possible outcomes.²

‘...to truly maximise the benefit of thrombolysis, we need to not just give rtPA but give it fast.’²

By giving rtPA to more patients, and giving it faster, the benefits of thrombolysis can be maximised. Even at well-organised centres, less than a third of patients with acute ischaemic stroke (AIS) receive rtPA. Improving the total proportion of patients treated with rtPA worldwide remains a major challenge that requires a multifaceted response involving telemedicine, ambulance services, and non-stroke physicians.

Reduction in door-to-needle time (DNT) can significantly improve patient outcomes and DNTs below 20 min are achievable. However, as in-hospital treatment times grow ever shorter, pre-hospital delays are becoming a bigger factor in the overall onset-to-needle time. The aim must be to reduce the time from symptom onset to reperfusion, by educating the public to recognise stroke and act without delay, and by minimising hospital transfer times.

‘...faster treatment is possible without compromising safety and outcomes.’²

The need for a coordinated approach to improve all links in the stroke care chain is similarly emphasised by Li and Johnson, who recommend that shortening onset-to-treatment time should be considered an indicator of quality improvement in acute stroke care.³

Treatment of acute ischaemic stroke must be fast and decisive

For AIS, as for acute coronary syndrome (ACS),

‘Two unifying concepts are that treatments must be fast and decisive and that organisation of care is critical to good outcomes.’⁴

Masuka *et al.* explore the parallels between AIS and ACS, and conclude that, in both conditions, good outcomes are dependent on timely treatment and coordinated systems of care. Successful treatment programmes require specialised treatment units, provision of care by teams of healthcare providers, and the ‘chain of survival’ from symptom onset to reperfusion.

Accurate assessment of speed of rtPA delivery requires routine and timely performance feedback

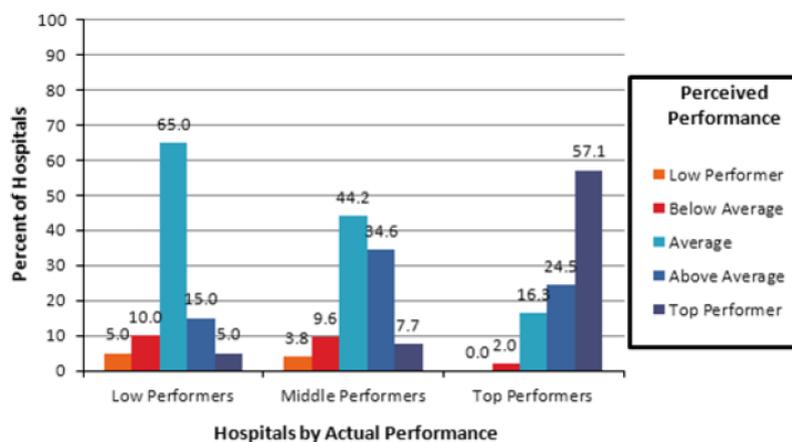
If stroke care providers believe their hospital is already performing well, they may not investigate treatment barriers or initiate changes in procedures, and no further improvements will be made.

A recent survey found that staff had optimistic perceptions of their hospital’s ability to deliver timely thrombolysis, and that the slowest hospitals had the biggest gap between perception and reality.⁵

By routinely analysing performance data and providing timely feedback, the true situation can be understood and resources directed to areas that would most improve the quality of stroke care.

Study details

- Survey of 141 US Get With The Guidelines-Stroke registry hospitals that treated 48 201 stroke patients (Oct 2009–Sep 2010), to compare stroke teams’ perceptions of their performance against known metrics associated with rtPA administration
 - One representative, was interviewed per institution, generally a stroke team nurse
 - Hospitals were classed as top, middle or low performers based on the proportion of rtPA-treated patients with DNT ≤60 min (top performers were taken from the 100 highest performing hospitals in the registry, low performers were taken from the 100 lowest performing hospitals, middle performers were taken from hospitals around the median level in the registry)
- Overall, only 29.1% of hospitals correctly estimated the proportion of their patients with DNT ≤60 min
 - 67.4% of top-performing hospitals estimated that >60% of their thrombolysed patients had DNT ≤60 min, when the median rate in this group was 57.1%
 - 67.5% of low-performing hospitals estimated that >20% of their thrombolysed patients had DNT ≤60 min, when the median rate in this group was 0.0%
- The majority (81.6%) of top performing hospitals correctly estimated themselves as above average or top in their ability to deliver timely rtPA compared with other hospitals nationwide (figure)
- In contrast, 85.0% of low performing hospitals estimated their performance as average or better compared with other hospitals, thus overestimating their performance (figure). Almost 5% of low-performing hospitals actually rated themselves as a top performer in comparison with other hospitals nationwide
- Top-performing hospitals tended to have more AIS admissions, higher volumes of rtPA administration, and higher proportions of patients with DNT ≤60 min, and were less likely to overestimate their performance



Hospitals often overestimate their ability to deliver timely rtPA to treated patients. Our findings indicate the need to routinely provide comparative provider performance rates as a key step to improving the quality of acute stroke care⁵

Initiating thrombolysis in the CT laboratory rather than in the ER reduces DNT

Valuable time can be lost when transferring a patient with AIS from one room to another for scanning and treatment, even when the computed tomography (CT) laboratory and emergency room (ER) are near each other.⁶

Starting intravenous (IV) thrombolysis immediately after performing the CT scan, without taking the patient back to the ER, can shorten DNT by more than 10 minutes and increase the proportion of patients with DNT <30 min, without adversely affecting safety.

Study details

- Retrospective review of SITS data from 243 patients who received rtPA in a general local hospital in Norway (Jan 2007–Dec 2011) to determine the impact on treatment times and safety outcomes of several new organisational routines – such as starting thrombolysis in the CT laboratory – introduced in March 2009
- Moving IV rtPA treatment initiation from the ER to the CT laboratory reduced DNT and increased the proportion of patients with DNT <30 min, while incidence of symptomatic ICH remained low
 - In multivariable analysis, treatment start in the CT laboratory was independently associated with decreased DNT (10.2-min reduction of median DNT, $p=0.007$)
- Seven patients with symptoms mimicking stroke received rtPA, perhaps because treatment was initiated before causes other than AIS could be ruled out, but none experienced serious side effects of thrombolysis

Variables	Jan 2007–Feb 2009 (n=82)	Apr 2009–Dec 2011 (n=156)	p value
DNT, median min	36	28	<0.001
DNT <30 min, %	23.2	55.1	<0.001
Onset-to-arrival time, median min	87	84	0.69
Symptomatic ICH, n (%)	4 (4.9)	2 (1.3)	
Stroke mimics treated, n (%)	0	7 (4.5)	

'Streamlining of IV rtPA logistics can reduce median DNT to <30 min in a general local hospital⁶

Acute care nurse practitioner first responders can reduce thrombolysis delays

Round-the-clock neurocritical care coverage provided by acute care nurse practitioners (ACNPs) can reduce treatment delays and improve functional outcomes among patients receiving rtPA.⁷

Adding 24/7 coverage by an ACNP stroke-code first-responder in a single primary stroke centre (PSC) significantly reduced DNT from 68.5 to 49.5 minutes, without affecting other time parameters or the proportion of patients with AIS receiving rtPA (31%).

Stroke patients need priority triage to overcome barriers to timely thrombolysis

Poor recognition of stroke symptoms, inaccessible emergency medical services (EMS), and lack of priority stroke triage remain significant barriers to thrombolysis, according to the authors of a retrospective study at a tertiary care hospital in India.⁸

Of 695 patients admitted with suspected AIS (Jan 2011–Nov 2013), only 148 (21%) arrived within 4.5 hours of symptom onset.

Among the 44 patients who received rtPA, door-to-imaging time (mean 58 min) and DNT (mean 104 min) were longer than recommended by the AHA; only seven patients had a DNT \leq 60 min. These findings emphasise the importance of a co-ordinated multidisciplinary stroke care team who can work together to prioritise the recognition, transport, imaging, and treatment of stroke patients.

Transfer of patients with AIS directly to stroke centres by EMS may improve care

There is opportunity to improve AIS outcomes by increasing the number of patients cared for at specialist stroke centres. One way to achieve this is for EMS personnel to transfer patients with AIS preferentially to approved stroke centres rather than to the nearest emergency department.⁹

A US study found that the proportion of patients with AIS cared for at a PSC increased from 10% to >90% after a regional system of preferential routing was introduced.¹⁰ Overall pre-hospital care times were not adversely affected and thrombolysis rates were high (42%).

...the impact of EMS regional stroke care organisation is immediate and profound, [and] has the potential to improve patient outcomes⁹

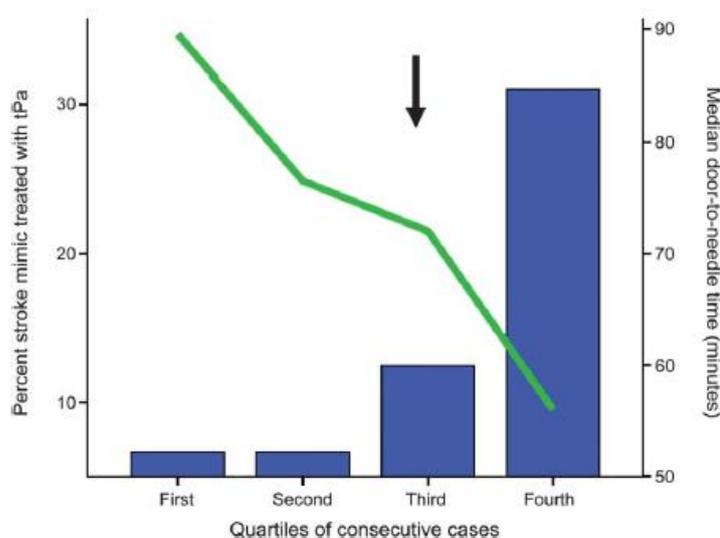
Efforts to decrease DNT may increase the treatment of stroke mimics

As more centres introduce initiatives to reduce DNT, there is a potential risk that patients with conditions that mimic stroke could receive thrombolytic treatment.¹¹

An association between decreases in DNT and increases in thrombolytic treatment of stroke mimic patients was observed at a Chicago hospital. The authors note that as we seek to achieve timely thrombolysis, it is important that rates of stroke mimic treatment are carefully monitored.

Study details

- Retrospective analysis of data from 121 patients who received IV thrombolysis at a single centre (Jan 2010–Feb 2014), to explore the relationship between DNT and thrombolysis of stroke-mimic patients
- Over the 4-year period, median DNT decreased (from 89 to 56 min), primarily driven by decreases in stroke code activation-to-treatment time (from 77 to 41 min) (figure)
- The proportion of treated patients with stroke mimics increased from 6.7% to 30% (figure)
 - Six of the 17 treated stroke-mimic patients had migraine
 - None of the stroke-mimic patients had a symptomatic ICH after thrombolysis



Relationship between treated stroke-mimic patients (left y-axis, blue bars) and door-to-needle time (right y-axis, green line) by quartiles of consecutive cases (x-axis). The black arrow depicts the start of a multidisciplinary initiative to improve acute stroke treatment times that began in April 2013.

'As global efforts are made to reduce DNTs, it is important that stroke mimic treatment is monitored to ensure an optimal balance of risk exposure in stroke mimic patients with the benefits of decreased DNT in confirmed stroke patients.'¹¹

Thrombolysis via telestroke can achieve outcomes equivalent to rtPA administration by an on-site neurologist

Telemedicine is being used increasingly to provide round-the-clock stroke care. Fong *et al.* demonstrate that experienced on-site clinicians can deliver thrombolysis successfully when guided remotely via telemedicine, with similar safety and functional outcomes to those achieved by on-site neurologists.¹²

Study details

- Prospective cohort study of 152 patients treated with IV thrombolysis at a single hospital, to compare efficacy and safety of rtPA administered by an on-site neurologist or via telemedicine (Jan 2009–Dec 2012)
 - Patients were treated by an on-site neurologist when available (e.g. during office hours) (n=102)
 - At other times, patients were treated by an internist experienced in stroke diagnosis and assessment, with the remote support of a neurologist via telephone consultation and teleradiology (n=50)
- In-hospital treatment times were prolonged in the telemedical group, yet safety and functional outcomes were similar in both groups

Variable	Neurologist on site	Telemedical	p value
Onset-to-door time, median (IQR)	54 (43–70)	44 (33–65)	0.015
Door-to-CT time, median (IQR)	26 (20–38)	30 (25–43)	0.29
CT-to-needle time, median (IQR)	41 (32–57)	67 (50–82)	<0.001
Door-to-needle time, median (IQR)	71 (60–89)	97 (85–119)	<0.001
Onset-to-needle time, median (IQR)	133 (109–154)	148 (134–170)	0.012
mRS 0–1, %	43.0	52.1	0.30
mRS 0–2, %	54.0	58.3	0.62
Symptomatic ICH, %	4.9	4.0	1.00
3-month mortality, %	12.0	8.3	0.58

Using Google Glass for telestroke consultations may be convenient and reliable

Yuan *et al.* describe a patient who successfully received rtPA following a Google Glass teleconsultation.¹³

Telestroke consultations may require the local physician to examine the patient while simultaneously holding a smartphone to communicate with the consulting expert. By using Google Glass, a local physician was able to perform their examination unencumbered while the remote neurologist gained a first-person perspective of the patient via the transmitted image.

ACNPs, acute care nurse practitioners; ACS, acute coronary syndrome; AHA, American Heart Association; AIS, acute ischaemic stroke; ASA, American Stroke Association; CT, computed tomography; DNT, door-to-needle time; EMS, emergency medical services; ER, emergency room; ICH, intracranial haemorrhage; IQR, interquartile range; IV, intravenous; mRS, modified Rankin Scale; PSC, primary stroke centre; rtPA, recombinant tissue plasminogen activator; SITS, Safe Implementation of Treatments in Stroke.

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