

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

A recent historical perspective on stroke and recombinant tissue plasminogen activator (rtPA) notes:

'...the decisive benefit of tPA was the establishment of new treatment paradigms requiring patients with stroke to obtain specialized care as quickly as possible.'¹

Various targets have been set in order to try and improve the timeliness of acute ischaemic stroke (AIS) care. One of the most well-known is a door-to-needle time (DNT) of less than 60 minutes. To achieve this target, stroke teams need to assess their performance regularly and to identify where improvements can be made. However, when looking at the factors that affect treatment timeliness, it may be important to consider which are intrinsic and which can be modified.

This issue of the Actilyse® Publication Alert Newsletter features a paper that highlights that when assessing care standards factors that are unavoidable need to be taken into account, but also notes that most patients – including some with unavoidable delays – can still be treated within 60 minutes.

Unavoidable patient-related reasons for delay does not always mean that treatment targets cannot be met

Unfortunately, a variety of patient-related factors can cause unavoidable treatment delays. Choi *et al.* found recently that 30% of patients with AIS had medical or eligibility-related delays that may be legitimate reasons for providing rtPA later than the benchmark time of 60 minutes.

However, half of these patients still received rtPA within 60 minutes.²

The authors conclude that 70% of patients did not have patient-related reasons for delay and certainly should be treated within the benchmark time of 60 minutes or less.

*'Stroke centers should be able to treat at least 70% of alteplase eligible patients within 1 hour of arrival to the ED.'*²

They also note that patient delays were not predominantly caused by any specific reason, so the focus on further shortening DNT should be on improving multiple hospital and systemic processes that individually and cumulatively may be responsible for delays in rtPA administration.

Study details

- Data from 102 consecutive patients with AIS who received rtPA at a single academic medical centre (Jun 2012–Jun 2013) within 4.5 h of onset, to identify potential reasons for DNT delays and their impact
 - Potential reasons were collected prospectively and divided into 'unavoidable' (patient and eligibility reasons) and 'potentially avoidable' (hospital and systems) factors
 - Overall, median DNT was 53 mins and 63 patients (62%) were treated within 60 mins of symptom onset
- Patients with *potentially avoidable* (systems-related) reasons for delay had longer DNT than those with no reasons for delay, and a smaller proportion were treated within 60 mins
 - Median DNT: 60 mins vs 45 mins ($p=0.03$)
 - Treated within 60 mins: 54% vs 72% ($p=0.11$)
- The same was true for patients with *unavoidable* reasons for delay
 - Median DNT: 61 mins vs 45 mins ($p<0.001$)
 - Treated within 60 mins: 48% vs absent 72% ($p=0.05$)

Study details continued

Potential reasons for delay	N (%)	Median DNT, mins	Difference in geometric means vs no delays (95% CI), mins	p value
Patient-related (unavoidable)	31 (30)	61	22 (10 to 36)	<0.001
Required antihypertensive	14 (14)	56	11 (-1 to 27)	0.07
Emergent medical condition	7 (7)	90	34 (14 to 60)	<0.001
Unable to determine eligibility*	7 (7)	60	29 (10 to 55)	0.002
Seizure	4 (4)	100	52 (22 to 94)	<0.001
Unclear time of onset	3 (3)	75	26 (2 to 61)	0.03
Hospital and systems factors (avoidable)	41 (40)	60	11 (2 to 21)	0.02
Delay in diagnosis	9 (9)	60	21 (5 to 41)	0.007
Reviewed advance imaging prior to rtPA decision	7 (7)	64	17 (4 to 35)	0.02

*Reasons other than time of onset

In addition, given that many of the patients with unavoidable reasons for delay were still treated within 60 minutes of arrival at hospital, it can be argued that these factors are not necessarily a barrier to achieving target DNT.

By focusing on improving hospital and systemic processes that are associated with *avoidable* delays, hospitals can achieve treatment targets even among patients with *unavoidable* delays.

*'...good ED care pathways might mitigate some of the effect of these <unavoidable> delays and still allow some patients to be treated within the benchmark 60 minute time.'*²

In-hospital processes can be optimized to reduce rtPA treatment delays and strategies for improvement should be shared between stroke centres

Differences in in-hospital processes can result in considerable variability in DNT between stroke centres. These unnecessary delays should be identified and modified to enable optimal patient care.

Based on an analysis of data from more than 6000 patients with AIS receiving rtPA in Austria over an 8-year period, various adjustments to in-hospital processes were identified that could reduce DNT, including:³

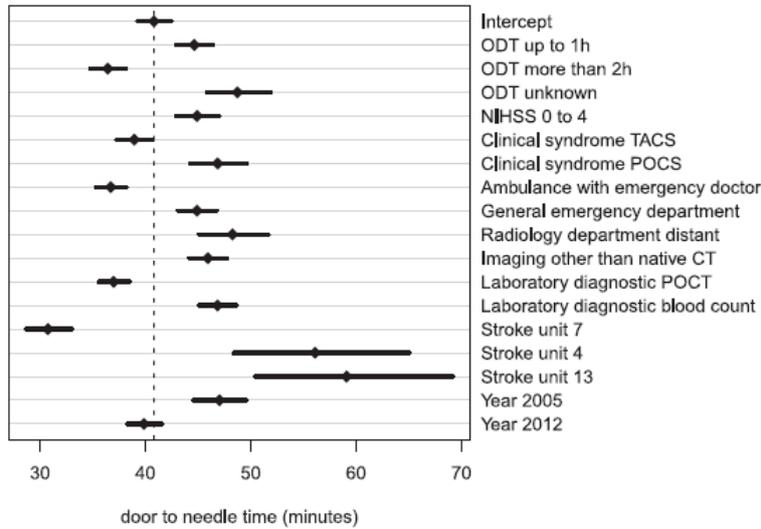
- Direct admission (via emergency medical services [EMS]) to specialist stroke unit or neurological ED
- Reducing time to CT scan
- Using point-of care devices to avoid delays waiting for lab results
- Developing standardized protocols for selected patient subgroups

The authors, 'highly recommend a continuous quality assessment in the context of acute stroke treatment and a regular lively intra- and intercenter discussion of possibilities to optimize processes and patient care.'

Study details

- Data from 6246 patients with AIS treated with rtPA at 34 Austrian stroke units (Apr 2004–Nov 2012) within 4 h of onset, to identify patient and in-hospital process factors that influence DNT
- Median DNT in 2005–2012 was 48 mins (range 30 to 78 mins across 34 centres)
 - Proportion of patients treated within 60 mins of stroke onset increased from 59% in 2005 to 76% in 2012
- A *longer* DNT was associated with (see figure):
 - Patient factors: onset-to-door time ≤60 mins or unknown; NIHSS ≤4; posterior circulation stroke
 - Process factors: admission to general ED; distant radiology department; primary imaging other than CT; waiting for blood test results
- A *shorter* DNT was associated with (see figure):
 - Patient factors: ODT >120 mins; total anterior circulation stroke
 - Process factors: EMS transport; recent year of admission; point-of-care testing

Study details continued



Multiple regression model of the effect of case-level and centre-specific factors on DNT across 34 Austrian stroke centres.

*'...it seems crucial that every single stroke center documents and critically reviews possibilities of optimizing practice strategies in acute stroke care.'*³

Transporting patients directly to stroke centres offering rtPA, even if it is not the nearest hospital, reduces treatment delays and improves clinical outcome

Patients with AIS should be admitted as quickly as possible to a hospital with rtPA capability. Initial admission to a hospital that is nearer but unable to deliver rtPA can result in treatment delays and poor clinical outcomes.⁴

*'...direct admission to organized stroke centers offering IV rtPA treatment around the clock is associated with improved patient outcome'*⁴

A Korean study showed that patients admitted directly to stroke centres have shorter treatment times and better clinical outcomes after IV thrombolysis than do patients transferred in from hospitals without rtPA capability.

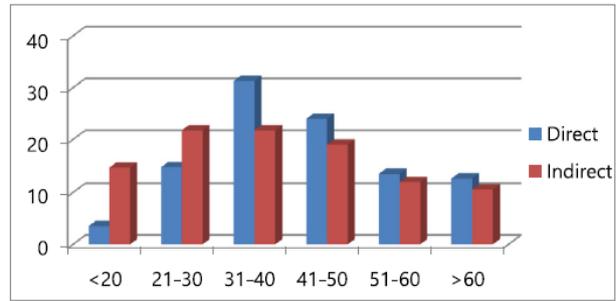
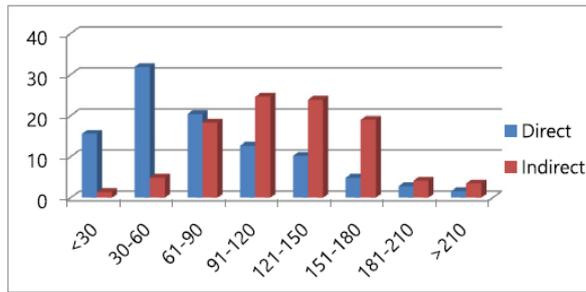
The authors conclude that a preferential routing system together with EMS/public education could substantially contribute to faster rtPA administration times in Korea.

Study details

- Prospective registry data from 820 patients with AIS admitted to 12 hospitals in Korea with 24/7 thrombolysis capability (Jan 2011–Dec 2012) and treated with rtPA within 4.5 h of onset, to evaluate the impact on functional outcomes of direct admission vs transfer from hospitals unable to administer rtPA
 - 142 patients (17%) were first admitted to nearer hospitals and then transferred
- ODTs and ONTs were shorter in the direct admission group (table, figure)
 - Slightly faster DNT in the indirect group may have been achieved by pre-notification and sharing of scan results with the receiving hospital, but this was more than offset by transport delays
- Direct admission to a stroke centre was independently associated with good functional outcome (mRS score 0–2) at 90 days: OR 1.57 (95% CI: 1.02–2.39), $p=0.04$

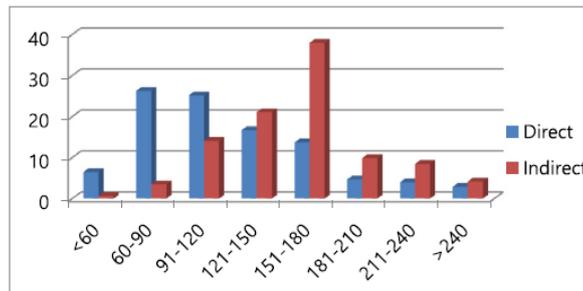
	Direct admission (n=678)	Indirect admission (n=142)	p value
ODT, median (IQR) mins	63 (39–105)	121 (98–152)	<0.001
DNT, median (IQR) mins	41 (33–51)	37 (25–49)	<0.001
ONT, median (IQR) mins	110 (81–154)	161 (138–180)	<0.001
SICH, n (%)	26 (4)	5 (4)	0.85
90-day mortality, n (%)	62 (9)	18 (13)	0.19
90-day mRS 0–2, n (%)	394 (58)	69 (49)	0.04

Study details continued



(A) Onset to emergency room arrival time

(B) Door to needle time



(C) Onset to needle time

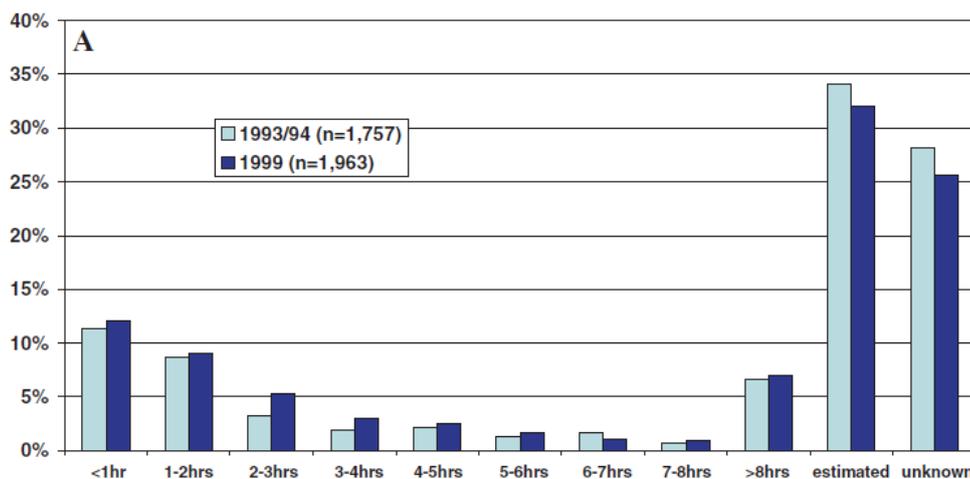
Emergency room arrival time according to admission route in patients with stroke onset

More work is needed to ensure patients arrive at the ED soon after stroke onset

The time between stroke onset and ED admission is crucial for determining whether a patient with AIS can receive rtPA: if the time of onset is too long ago or not known, the patient will be ineligible.

During the 1990s, despite numerous national and local public campaigns about stroke awareness, there was only a slight improvement in how quickly after AIS onset patients arrived at the ED in selected US hospitals (see figure).⁵ In 1999, only 26% of patients presented within 3 h of symptom onset (21% within 2 h); the remainder had lengthy, unknown (26%) or estimated (32%) onset-to-arrival times that meant they would not be considered for rtPA treatment.

Interventions are needed to raise public awareness of stroke and improve the speed of response of patients and their families.



Time from symptom onset to arrival in ED, comparison between 1993/94 and 1999, exact times only

*'the delayed arrival of patients to the ED imposes a very low theoretical limit on how many patients may be eligible for rt-PA.'*⁵

More can be done to facilitate rapid transport of patients with suspected stroke

The AHA/ASA guidelines recommend adopting EMS routing protocols for the rapid identification of patients with AIS and preferential transfer to the nearest specialist stroke unit. However, adoption of these protocols may be limited by available stroke care infrastructure.⁶

A survey carried out in California, USA, in September 2013 found that only 45% of local EMS agencies had stroke routing protocols, covering just 68% of the state population. Scarcely populated regions were less likely to have routing protocols.

In areas that lack a nearby specialist stroke unit, adopting a routing protocol may still improve the efficiency of stroke care, and could be achieved by adjusting the protocol to match available resources.

Stroke patients may seek help sooner if they know more about symptoms and treatment

Identifying factors that stop people having a stroke seeking urgent treatment may help to inform education initiatives.

A survey of 103 African-American stroke patients carried out between 1997 and 1999 found that only 49% sought medical attention within 3 h of symptom onset, and the average delay was 25 h.⁷ Three factors were identified as possible reasons for the lack of prompt action: lack of information about treatment options; inability to recognize stroke symptoms; denial of illness.

The authors speculate that, 'A multifaceted public education program that utilizes mass media and other public forums would help'.

Having a pharmacist in the ED can improve rtPA treatment times

Including pharmacists in ED stroke teams may provide rapid access to rtPA and improve patient care. Pharmacists can acquire and prepare rtPA, enabling physicians to focus on the patient. They may also facilitate efficient lowering of blood pressure by selecting the most appropriate agent and dose, thus reducing treatment delays.

In a study by Gosser *et al.*, the presence of a pharmacist in the ED during office hours was associated with a significant reduction in DNT. ED pharmacists are now included on their stroke team.⁸

Study details

- Retrospective analysis of data from 105 patients receiving rtPA at a US stroke centre (Jan 2008–Oct 2012) within 4.5 h of AIS onset, to examine rtPA dosing accuracy and DNT when a pharmacist was present in the ED
 - Pharmacists staffed the ED between 10.00 am and 6.30 pm
 - Most of the 'pharmacist absent' comparator group is from the out-of-hours overnight period
- Dosing accuracy was similar and median DNT was 20 minutes shorter when a pharmacist was present (table)

	Overall (n=105)	Pharmacist present (n=67)	Pharmacist absent (n=38)
DNT, median (IQR) mins	75.0	69.5 (59–87.5)*	89.5 (70–104)
DNT ≤60 mins, n (%)	26 (24.8)	20 (29.9)	6 (15.8)
Dosing accuracy, %		96.6	95.6

*p=0.003

Shorter treatment times in telestroke systems may best be achieved by targeting in-hospital delays in 'spoke' hospitals

Actions to reduce in-hospital delays at 'spoke' hospitals may have a large impact on overall treatment times – and patient outcomes – within telestroke hub and spoke networks.

Telestroke systems can save time for patients with AIS, particularly during the pre-hospital phase (provided the spoke hospital is at least 30 mins closer than the hub stroke unit). However, these pre-hospital gains may be offset by in-hospital delays.⁹

A retrospective study in France found that rtPA administration at a spoke hospital via telestroke was as safe and effective as bedside evaluation and administration at an experienced hub stroke unit (table). However, while ONT and patient outcomes were similar in each group, DNT was 31 minutes longer in the telestroke system. This represents a key target for improvement.

	Telemedicine (n=27) Spoke hospital	Bedside (n=70) Hub stroke unit	p value
Door-to-videoconference time, median (IQR) mins	11 (7–19)	–	
Imaging-to-needle time, median (IQR) mins	40 (31–51)	40 (30–49)	0.67
DNT, median (IQR) mins	86 (63–94)	55 (45–64)	<0.001
Onset-to-needle time, median (IQR) mins	180 (158–208)	170 (135–199)	0.35
3-month mortality, n (%)	8 (30)	14 (20)	0.42
3-month mRS 0–1, n (%)	8 (30)	22 (31)	1.00

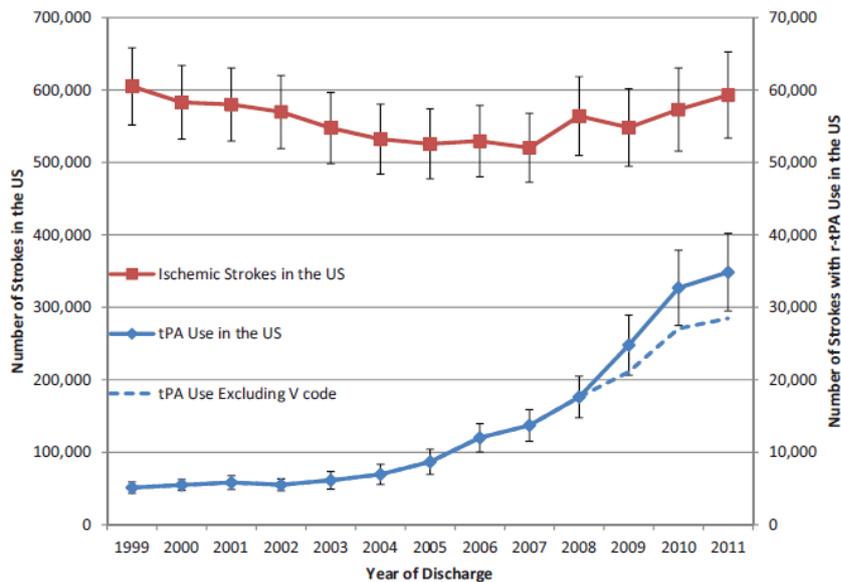
Mobile stroke units improve the rate and timeliness of rtPA treatment

To date, three studies have demonstrated the safety and feasibility of using mobile stroke units (MSUs) to deliver rtPA in a pre-hospital setting. A review of these studies highlights that despatching teams in ambulances equipped with a mobile CT scanner, point-of-care laboratory system, and telemedicine support leads to increased rates of rtPA use and shorter treatment times than conventional care, and improved triage to specialist hospitals.¹⁰

rtPA treatment of AIS improves patient life expectancy and quality of life

Compared with no thrombolysis, rtPA treatment of AIS results in reduced post-stroke disability and improved functioning, which in turn leads to gains in quality-adjusted life-years (QALYs).

Discharge data from a nationwide sample of US hospitals show that use of rtPA increased from 1% of patients with AIS in the year of its approval (1998) to over 4% in 2011 (figure).¹¹



Frequency of acute ischaemic stroke and rtPA utilization*, nationwide inpatient sample, 1998–2011.

*rtPA utilization excluding V code reflects enumeration of ‘Drip and Ship’.

Patients treated with rtPA were more likely than those not treated to be discharged to home or short-term care and have a greater likelihood of long-term functioning. In a population model based on these outcomes, rtPA treatment was associated with gains in life expectancy and QALYs.

‘Overall, treatment with rtPA for AIS has resulted in substantial reduction in disability and improvement in functioning since its US approval introduction.’¹¹

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AIS, acute ischaemic stroke; AHA/ASA, American Heart Association/American Stroke Association; CI, confidence interval; CT, computed tomography; DNT, door-to-needle time; ED, emergency department; EMS, emergency medical services; IQR, interquartile range; IV, intravenous; mRS, modified Rankin scale; MSU, mobile stroke unit; NIHSS, National Institutes of Health Stroke Scale; ODT, onset-to-door time; ONT, onset-to-needle time; OR, odds ratio; POCS, posterior circulation stroke; POCT, CT with oral contrast; QALY, quality-adjusted life-year; rtPA, recombinant tissue plasminogen activator; SICH, symptomatic intracranial haemorrhage; TACS, total anterior circulation stroke.

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