

Publication Alert Newsletter

Efforts to increase access to recombinant tissue plasminogen activator (rtPA) treatment by reducing delays in the stroke care pathway should begin before patients even reach hospital.

Yperzeele et al. have looked at pre-hospital stroke care and conclude that,

'timely initiation of treatment can effectively reduce the medical and economic burden of stroke and should begin in the pre-hospital phase'.¹

They highlight telestroke as a 'particularly attractive approach because it is a scalable solution that has the potential to rapidly optimise stroke care at limited cost'. In this issue of the Actilyse[®] Publication Alert Newsletter we report on telestroke studies that demonstrate how stroke care timeliness and quality can be improved, as well as the positive impact of local and regional protocols.

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

Timely initiation of treatment should begin with optimal pre-hospital stroke care

'Pre-hospital delay contributes significantly to delayed or missed treatment opportunities in acute stroke'¹

Yperzeele et al. review current strategies to reduce pre-hospital delays, and their limitations:

- Public education – campaigns do raise awareness of stroke symptoms, but often fail to reach key risk populations, and evidence is lacking on cost-effectiveness
- Education of Emergency Medical Services (EMS) dispatchers and paramedics – use of pre-hospital stroke scales and screening tools are useful; impact on treatment rates is, as yet, unknown
- Pre-hospital stroke code activation and priority transport – door-to-imaging times are reduced and rtPA administration rates are improved, though effect on door-to-needle time (DNT) varies between studies

The authors then outline proposed new options for reducing stroke care delays and improving patient outcomes. Some of these strategies have been reported on in previous issues of this newsletter:

- Telestroke – expansion of successful telestroke networks to the pre-hospital setting, enabling specialist stroke care to be provided at very early stages
- Mobile stroke units – deployment of a specialised ambulance and expert team to perform diagnostic tests and provide stroke care on the way to hospital
- Additional opportunities – non-invasive diagnostics (e.g. pre-hospital trans-cranial ultrasound) and pre-hospital neuroprotective strategies (e.g. field-initiated magnesium sulphate)

The authors conclude that, while several challenges still need to be tackled, pre-hospital telestroke is a promising concept that would allow specialist care throughout the entire stroke care pathway.

'Despite major efforts, pre-hospital delays for stroke patients have not reduced significantly over the years'¹

Shorter pre-hospital delays are associated with EMS use and knowledge of rtPA

A study among older stroke patients in Japan found that lifestyle factors significantly affected pre-hospital delays.² Shorter onset-to-arrival times were associated with use of EMS, having knowledge of rtPA, and living in a nursing home or with extended family (rather than alone or with a spouse). The authors conclude that older people tend to overlook the signs of stroke and respond inadequately. Therefore, elderly patients living alone or with a spouse should be the target of education initiatives.

Study details

- Retrospective analysis of 469 consecutive patients admitted to a single stroke centre in Japan within 2 weeks of stroke or transient ischaemic attack (TIA) onset (May 2007–Mar 2009)
- Knowledge of rtPA and use of EMS were independently associated with short pre-hospital delay ($p < 0.001$)
- Delays were significantly increased if the patient themselves or a local doctor (rather than a spouse, another relative, or someone else) recognised their symptoms
- Patients with prior stroke arrived at hospital no quicker than those experiencing a first stroke

Variable	n (%)	OR (95% CI) for arrival within 4 hours	p value
Knowledge of rtPA	36 (8)	4.21 (1.91–9.70)	<0.001
Use of EMS	251 (54)	3.67 (1.98–7.08)	<0.001
Pre-stroke mRS score ≤ 2	390 (83)	2.80 (1.44–5.61)	0.002
Symptoms recognised by the patient	288 (61)	0.50 (0.27–0.92)	0.025
Visited a local doctor prior to arrival	123 (26)	0.27 (0.10–0.66)	0.004
Living alone	91 (19)	0.40 (0.21–0.76)	0.005
Living with a spouse	160 (34)	0.51 (0.29–0.89)	0.017
Prior stroke	154 (33)	0.76 (0.45–1.27)	0.30

More patients are treated more quickly when using a rapid response protocol

Implementing a rapid response protocol in a Norwegian hospital led to an increase in the number of patients with acute ischaemic stroke (AIS) receiving rtPA (particularly within 1.5 hours of onset) and a 42-min reduction in DNT.³

The authors observe that progressive changes need to become part of routine practice to ensure that treatment improvements are sustained.

Study details

- Retrospective analysis of 320 patients with AIS treated with rtPA at a university hospital in Norway (2003–2012), to evaluate the impact of a rapid response treatment protocol implemented in 2009
 - After 2009, patients with suspected AIS were sent, via the EMS with pre-stroke notification, directly to the emergency room where they were triaged as a high priority and received rtPA if indicated
- The rapid response protocol was associated with an increase in the number of patients treated and with yearly improvements in treatment times, without significantly affecting pre-hospital transfer time
 - Extension of the rtPA treatment window to 4.5 hours in 2009 allowed more patients to receive rtPA, but the greatest increase occurred in the group treated within 1.5 hours of AIS onset

Variable	2003–2008	2009	2010	2011	2012
Received rtPA, n	31	45	74	86	84
≤ 1.5 hours after onset, n	0	5	12	30	25
1.5–3 hours after onset, n	29	31	40	36	38
3–4.5 hours after onset, n	2	9	22	20	21
DNT, median min	73		50*	45*	31**
Onset-to-needle time, median min	135		134	122	119

* $p < 0.05$ and ** $p < 0.001$ vs 2003–2008

‘The implementation of the rapid treatment protocol for acute onset ischaemic stroke patients led to a significant decrease in the DNT time’³

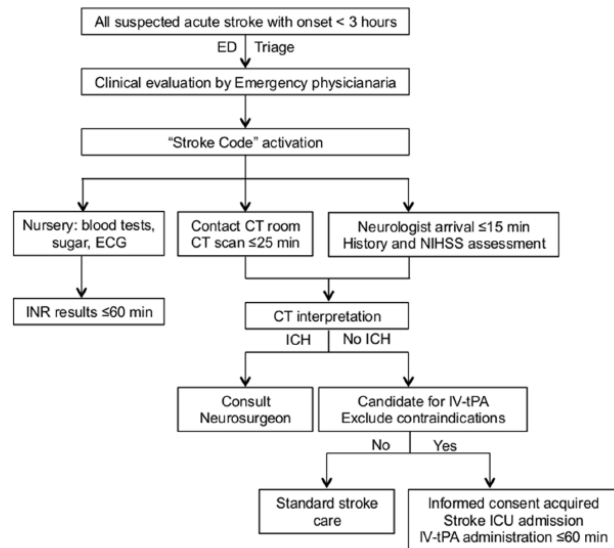
Stroke code protocol use increases thrombolysis rates and decreases DNT

Implementation of a stroke code protocol was associated with a 13-min reduction in door-to-computerised tomography (CT) time, a 37-min reduction in DNT, and a 5-fold increase in the proportion of patients with DNT ≤60 min.⁴

The authors conclude that use of the stroke code protocol reduces treatment delays and increases thrombolysis rates without increasing the incidence of symptomatic intracranial haemorrhage (ICH) or in-hospital mortality.

Study details

- Retrospective analysis of data from 5957 patients admitted with AIS to a university hospital in Taiwan (Jul 2006–Jul 2013)
- Outcomes compared pre- and post-stroke code protocol (figure) implementation in Aug 2010
- rtPA use increased from 2.6% to 8.6% after introduction of the stroke code protocol
- For patients with an onset-to-door time of ≤3 hours, rtPA use increased from 13.9% to 33.3% ($p < 0.001$)
- In-hospital delays were reduced in the stroke code era, particularly DNT and door-to-CT time
- Patients treated in the protocol era tended to be more likely to have good outcome (mRS ≤2) at discharge and at 3 months, with less symptomatic ICH or in-hospital mortality (though these differences did not reach statistical significance)
- Increasing age and increasing onset-to-door time were both significantly associated with DNT ≤60 min in all patients and in those treated in the protocol era (multivariate analysis):
 - Age – adjusted OR: 0.96; 95%CI: 0.94–0.99
 - Onset-to-door time – adjusted OR per 15-min increase: 1.27; 95%CI: 1.11–1.44



Time intervals and clinical outcomes	Pre-stroke code era (n=91)	Stroke code era (n=216)
Onset-to-door time, median (IQR) min	45 (30–65)	58 (32–94.5)
Door-to-CT time, median (IQR) min	24 (19–38.5)	11 (9–13)
Door-to-CT ≤25 min, %	52.7	91.7*
CT-to-needle time, median (IQR) min	61 (44–79)	40 (32–51)
DNT, median (IQR) min	88 (67–107)	51 (43–64)*
DNT ≤60 min, %	14.3	71.3*
Onset-to-needle time, median (IQR) min	145 (122–163)	125 (90.3–157)
Onset-to-needle 3–4.5 hours, %	7.7	10.6
Symptomatic ICH, %	7.7	4.6
Good outcome (mRS ≤2) at discharge, %	39.6	49.5
Good outcome (mRS ≤2) at 3 months, %	44.0	50.5
In-hospital mortality, %	6.6	3.2

* $p < 0.001$ vs pre-stroke code era

'The stroke code protocol increases the percentage of acute ischaemic stroke patients receiving intravenous rtPA and decreases door-to-needle time'⁴

An in-hospital organised clinical pathway attenuates the ‘out-of-hours’ effect on door-to-CT time and DNT

A systematic, computerised, team-wide stroke alert system already known to reduce DNT is effective whenever patients arrive at hospital – whether during normal working hours or at the weekend.⁵

The study authors conclude that an organised clinical pathway for AIS can achieve consistent in-hospital time intervals, regardless of patient arrival time at the emergency department, and may help to offset ‘out-of-hours’ effects.

Study details

- Retrospective analysis of data from 649 patients admitted to a tertiary academic hospital within 12 hours of AIS onset (Sept 2010–Sept 2012), to examine whether an organised clinical pathway can reduce treatment times and improve patient outcomes, regardless of admission time
- Patients were grouped based on emergency department arrival time (weekday or weekend, working hours, or ‘off-hours’ [18:00–09:00])
- At weekends and during weekdays, rates of rtPA use did not differ significantly between working hours and off-hours
- No significant between-group differences in time intervals among patients who received rtPA:
 - Median door-to-CT time and DNT did not differ significantly between working hours and off-hours
- Among all patients, those admitted during ‘off-hours’ at the weekend had a higher rate of 30-day mortality than other groups. However, this difference was not seen in patients who received rtPA

Time intervals and clinical outcomes	Weekday working hours	Weekday off-hours	Weekend working hours	Weekend off-hours
All patients, n	220	241	92	96
Onset-to-door time, median (range) min	150 (10–1294)	201 (11–1330)	145 (11–677)	167.5 (5–1481)
Door-to-CT time, median (range) min	25 (2–136)	28 (7–748)	28.5 (9–83)	27 (3–85)
30-day mortality, n (%)	25 (11)	29 (12)	14 (15)	23 (24)*
mRS score poor (3–6), n (%)	48 (22)	51 (21)	24 (26)	29 (30)
Received rtPA, n (%)	28 (12.7)	25 (10.4)	15 (16.3)	11 (11.5)
Onset-to-door time, median (range) min	50 (17–143)	58 (11–123)	46 (23–131)	42 (15–131)
Door-to-CT time, median (range) min	14 (5–29)	16 (7–34)	16 (9–36)	13 (3–28)
DNT, median (range) min	40.5 (18–77)	44 (21–76)	41 (24–81)	36 (29–63)
Length of stay, median (range) days	10 (4–71)	8 (4–74)	9 (2–79)	10 (5–98)
30-day mortality, n (%)	7 (25)	5 (20)	4 (27)	6 (55)
mRS score poor (3–6), n (%)	11 (39)	9 (36)	9 (60)	7 (64)

*p<0.01 vs weekday working hours and weekday off-hours

‘This pathway may also help to eliminate off-hour and weekend effects on outcomes from ischaemic stroke.’⁵

The order in which hospitals perform tests is important in determining DNT

Avoidable delays in DNT, created by performing other diagnostic tests before CT scans in patients with AIS, were identified by a detailed medical record review at a large hospital in the USA.⁶

Patients were more likely to have a DNT of ≤60 min if the electrocardiogram (ECG) was done after the head CT scan (and also if time since symptom onset was >90 min).

The authors conclude that the ordering of testing for patients with AIS is important in reducing the potential time to treatment with rtPA. Results such as this may help shape pathways and protocols and

‘hospitals should evaluate their own procedures and locate barriers to determine ways to reduce treatment times’.

Study details

- Retrospective record review of 79 patients presenting with AIS at a certified primary stroke centre in the USA (2007–2012)
 - 22 (28%) received rtPA within 60 min of arrival
- The order in which testing occurred affected treatment times
 - ECG before CT increased door-to-CT by 6 min
 - Chest X-ray before CT increased door-to-CT by 13 min
- **Fastest DNT (median 66 min) was achieved when CT was performed before both ECG and chest X-ray**
- Patients were more likely to receive rtPA within 60 min if:
 - they had CT before ECG (OR: 3.67; 95%CI: 1.29–10.5; $p < 0.02$)
 - they arrived >90 min after symptom onset (OR: 3.52; 95%CI: 1.03–12.1; $p < 0.05$)

Times by test order	Median (IQR) min
Door-to-CT time	20 (13–28)
ECG before CT	23 (15–36)
ECG after CT	17 (10–24)
Chest X-ray before CT	32 (21–38)
Chest X-ray after CT	19 (13–27)
DNT	84 (60–110)
ECG before CT	95 (75–111)
Chest X-ray before CT	105 (96–105)
CT before X-ray & ECG	66 (51–86)

ECG before CT: n=43; chest X-ray before CT: n=9

‘Testing should be prioritised with head CT and blood analysis being of the utmost importance. Other testing...should be delayed until the head CT is performed’⁶

Regional health policies can help to improve local thrombolysis rates

A large relative increase in rtPA treatment rates was achieved across 13 districts in Northern France following the implementation of a regional health policy.⁷

In 2009, 10 835 residents with AIS received rtPA (annual rate: 103 per million inhabitants); in 2012, after the addition of 4 more stroke units and a 5-hospital telestroke network, this proportion increased by 76% (to 181 per million inhabitants). The authors conclude that,

‘even when the proportion of patients receiving rtPA is already high, improvements in thrombolysis rates can still be achieved’.

Rural telestroke systems can sustain a high-quality thrombolysis service

Implementing a telestroke network in rural Germany in 2003 led to reduced treatment delays and more patients with stroke receiving thrombolysis over a 10-year period.⁸

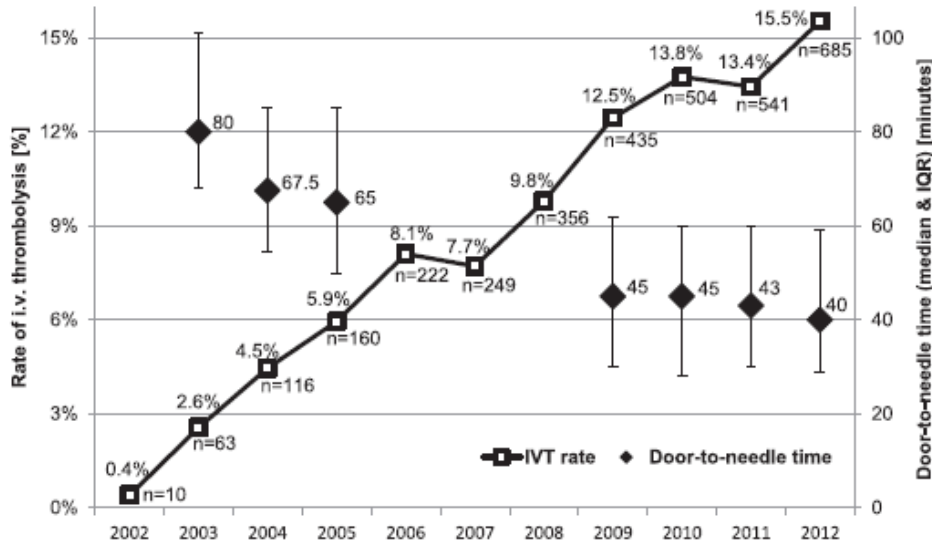
‘Eighty percent of all IV thrombolysis in the TEMPiS Stroke Units are delivered within 60 minutes of admission’⁸

Study details

- Retrospective analysis of data from 54 804 patients admitted with AIS or TIA to 15 spoke hospitals within a rural telestroke network in Germany (Feb 2003–Dec 2012), to examine changes in stroke care over time
 - A total of 31 864 teleconsultations were performed, increasing from 1928 in 2003 to 4513 in 2012
- Between 2003 and 2012, improvements were seen in: thrombolysis rates and DNT (see figure, below), onset-to-treatment time, proportion with DNT ≤60 min, length of in-hospital stay, and 7-day in-hospital mortality

Variable	2003	2012	p value
AIS patients receiving rtPA, %	2.6	15.5	<0.001
DNT, median (IQR), min	80 (68–101)	40 (29–59)	<0.001
DNT ≤60 min, %	26	80	<0.001
Onset-to-door time, median (IQR), min	60 (45–79)	68 (48–105)	0.63
Onset-to-treatment time, median (IQR), min	150 (127–163)	120 (90–160)	<0.001
7-day in-hospital mortality, %	5.0	3.1	Not stated

Study details continued



Numbers, rates, and DNT times (including IQR) of intravenous thrombolysis (IVT) performed in all patients with AIS.

The IVT rate in 2002 indicates the status before network implementation. DNTs were not available for 2002 and 2006–2008.

The authors conclude that this type of telestroke network offers increased access to thrombolysis and is associated with long-term sustained improvements in acute stroke care.

‘TeleStroke units can provide sustained high-quality stroke care in rural areas’⁸

Thrombolysis rates as high as 25% can be achieved in urban telestroke systems

The successful implementation of telestroke in an urban practice setting has been demonstrated by improved thrombolysis rates (compared with pre-telestroke) in four Chicago spoke hospitals.⁹

Over a 2-year period (Mar 2011–Mar 2013), 498 patients were admitted with suspected AIS and assessed via telestroke: 281 patients (56% of teleconsults) were determined to have AIS/TIA and 72 patients (26% of those with AIS/TIA) were recommended rtPA. The authors conclude that telestroke use in an urban setting may increase access to neurologists and improve thrombolysis rates.

‘A telestroke partnership with dedicated 24/7 staff improves stroke care (by increasing rtPA utilisation)’⁹

Pre-hospital telestroke decreases delays and increases thrombolysis rates

The reliability and feasibility of in-ambulance telestroke, as suggested in the review by Yyperzeele et al., has been demonstrated using actors simulating acute stroke in the PURSUIT study.¹⁰

- A full National Institutes of Health Stroke Score examination was performed remotely with EMS assistance, in a mean time of 10 min
- In 34/40 scenarios (85%), teleconsultation was completed without major technical complications
- Patient transportation was reportedly not delayed by the remote consultation

The authors conclude that **‘mobile telemedicine is reliable and feasible in assessing actors simulating acute stroke in the pre-hospital setting’**.

‘Pre-hospital evaluation using telemedicine may accelerate acute stroke treatment with tissue-type plasminogen activator’¹⁰

CI, confidence interval; IQR, interquartile range; IV, intravenous; mRS, modified Rankin Scale; OR, odds ratio.

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