

Publication Alert Newsletter

Intravenous recombinant tissue plasminogen activator (IV rt-PA) remains the only approved medical intervention for the treatment of acute ischaemic stroke (AIS) within the first hours of symptom onset. Achieving timely treatment of patients with AIS crucially involves every person in the stroke care team.¹ Putting stroke treatment guidelines into practice can only be achieved successfully with multidisciplinary cooperation.

‘Treatment of stroke is a multidisciplinary approach involving the EMS [emergency medical services], emergency department physicians, neurologists, nurses, radiology, and laboratory technicians. Every person involved in this multidisciplinary team is crucial to evaluate the stroke patient in a timely fashion and administer rt-PA for eligible patients.’¹

In this issue of the Actilyse[®] Publication Alert Newsletter we highlight the use of protocols to aid multidisciplinary cooperation and timely intervention, as well as other papers on stroke care.

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 multidisciplinary stroke protocol improves the provision of rt-PA treatment

Use of a system-wide, fully accountable, multidisciplinary stroke care protocol (‘Code Stroke’) is associated with better than average times to treatment and rt-PA delivery rates.² In a recent review article, Fessler et al. report that US institutions that have adopted the Code Stroke protocol have rt-PA delivery rates, door-to-needle times (DNT), and computed tomography (CT)-to-needle times that are many times better than the national average and are still improving 4 years after implementation.

An important feature of the implementation of the protocol is regular multidisciplinary meetings to look at quality metrics and identify opportunities for improvement.

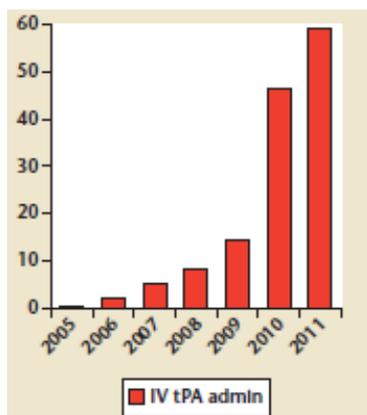
Code Stroke Process

- Automated stroke alert sent to multidisciplinary stroke team: on-call stroke neurologist, neuroendovascular surgeon, CT technician, radiologist, ED operational manager, bed coordinator
- Activated within 15 min of patient with stroke presenting at the ED, if time of onset unknown or within 8 hours.
- Stroke alert packet placed on suspect stroke charts in ED triage: contents include recommended timeline (Table), reference sheet for healthcare providers, NIHSS worksheet, IV rt-PA criteria checklist and dosing chart

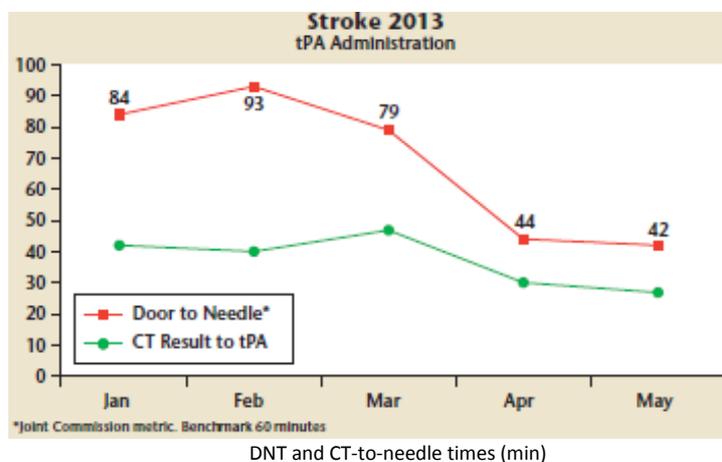
| Timeline | | | |
|----------|--|----------------------------|--------------------|
| 0 min | Patient arrives at ED with stroke symptoms | | |
| 5 min | Registered nurse assessment completed | | |
| 10 min | Physician assessment completed | <i>ED physician</i> | <i>ED nurse</i> |
| 15 min | Activate stroke alert | <i>Rapid response team</i> | <i>Staff nurse</i> |
| 25 min | Brain imaging completed | | |
| 45 min | Brain imaging and lab results reported | | |
| 60 min | Initiate treatment option | | |

Code Stroke process (continued)

- Multidisciplinary quality assurance meetings held regularly
 - Representatives from neurology, emergency medicine, radiology, and endovascular surgery
- Evaluate treatment timelines, identify trends, and provide opportunities for improvement
- In institutions that have adopted the Code Stroke protocol, rt-PA delivery rates and benchmark treatment times are many times better than the national average, and are still improving 4 years after implementation



rt-PA administration rates over time (%)



DNT and CT-to-needle times (min)

*'...times to treatment and overall IV rt-PA delivery rates are several times faster than the national average.'*²

The authors conclude that by creating the Code Stroke protocol, the process of identifying and subsequently providing appropriate treatments for patients with ischaemic stroke in a timely and effective manner has been streamlined.

Real-time team feedback via text message improves DNT

A text-messaging quality improvement intervention was associated with a 15-min reduction in DNT in an academic medical centre.³ For each Code Stroke activation, the entire team were sent a text on whether IV rt-PA was administered and the DNT. Any cases with DNT >60 min were reviewed within 24–72 hours to identify any systemic barriers to timely rt-PA treatment. Performance data were shared with the team on a biweekly basis.

- Median (interquartile range [IQR]) DNT decreased from 82 (68–103) min in the 3 years before the text-messaging intervention (n=94), to 56 (44–71) min in the 3 years afterwards (n=108) (Jan 2008–Apr 2014).
- The proportion of patients with DNT ≤60 min increased from 16% to 61%.

The authors observe that a real-time reporting mechanism allows for a tighter feedback loop while the clinical details of a particular case are still fresh in the minds of team members.

*'A simple real-time text-messaging intervention was associated with significant improvements in door-to-needle times for AIS... A significantly higher proportion of patients were treated within 60 minutes (61% versus 16%)'*³

A computerised triage system in the ED can facilitate acute stroke care

The validity of a computerised ED triage system to sort patients with AIS appropriately has been shown by a retrospective review of patients admitted to a community hospital in Taiwan.⁴ Use of the triage system led to Code Stroke activation in 224 cases, and there was good correlation between triage priority levels and stroke severity, length of hospital stay, and functional outcome in patients with AIS.

The authors note the important role played by ED staff in helping to achieve timely treatment of AIS.

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*'It is important to triage stroke patients according to their need for thrombolysis as quickly as possible in order to deliver timely treatment.'*⁴

In-hospital stroke care response times are improved by expedited EMS transport and hospital pre-notification

Pre-hospital recognition and management of patients with AIS is a key determinant of the timeliness of stroke care, and can influence in-hospital treatment timelines.

Oostema et al. found that compliance with pre-hospital guideline recommendations for patients with suspected stroke was suboptimal at two primary stroke centres in the USA.⁵ Highest-priority transportation and hospital pre-notification were both associated with significantly faster in-hospital stroke care response (door-to-CT time), and are logical targets for EMS quality improvement.

Study details

- Prospective observational study of 186 patients with confirmed AIS, transported by EMS to two primary stroke centre hospitals (April 2012–March 2013), to quantify compliance with guideline-recommended pre-hospital practices and examine associations between EMS performance and in-hospital stroke care
- Compliance with pre-hospital guideline recommendations was variable, and below 50% on some measures
 - EMS suspected stroke in 141 patients (76%): 94% of whom were screened for stroke by EMS, but only 68% were transported as highest priority and only 62% had hospital pre-notification
 - EMS missed stroke in 45 patients: 31% of these had been screened for stroke by EMS; 16% were transported as highest priority and 38% had hospital pre-notification (all $p < 0.05$ vs suspected stroke)
- Door-to-CT time ≤ 25 min was achieved in 78 patients (42%)
 - Highest priority transport and hospital pre-notification were independently predictive of CT ≤ 25 min
- 23 patients (12.4%) received rt-PA, with a median (IQR) DNT of 97 (68–106) min
 - Study was underpowered to detect associations between pre-hospital care and thrombolysis rates

| EMS performance measure | Adjusted odds ratio (95% CI) | | | |
|-------------------------------------|------------------------------|-------------------|------------------|------------------|
| | Door-to-CT ≤ 25 min | rt-PA delivery | Discharge home | Alive |
| Dispatched highest priority | 1.80 (0.76–4.28) | 1.14 (0.29–4.47) | 1.14 (0.47–2.77) | 0.74 (0.16–3.38) |
| Response time ≤ 8 min | 0.67 (0.36–1.26) | 0.43 (0.17–1.10) | 0.94 (0.45–1.94) | 2.52 (0.97–6.54) |
| Cincinnati prehospital stroke scale | 3.18 (1.35–7.52) | 4.99 (0.63–39.74) | 0.63 (0.28–1.45) | 1.60 (0.53–4.80) |
| On-scene time ≤ 15 min | 2.09 (1.12–3.90) | 0.78 (0.30–2.02) | 1.18 (0.58–2.43) | 0.76 (0.30–1.92) |
| Glucose level recorded | 1.15 (0.48–2.76) | 0.53 (0.16–1.73) | 0.58 (0.23–1.47) | 0.91 (0.22–3.78) |
| Last known well time recorded | 2.57 (1.28–5.17) | 0.80 (0.29–2.20) | 0.54 (0.26–1.14) | 0.87 (0.32–2.36) |
| Hospital pre-notification | 3.75 (1.93–7.30) | 1.24 (0.48–3.23) | 0.73 (0.36–1.48) | 0.91 (0.35–2.33) |
| Transported highest priority | 13.45 (5.94–30.47) | 2.89 (0.88–9.45) | 1.12 (0.54–2.35) | 0.81 (0.30–2.18) |

Statistically significant results are in bold; in-hospital mortality was 12.4% (n=23); 32% patients (n=60) were discharged home

*'Our data indicate that improving high priority transportation and hospital pre-notification for suspected stroke cases are promising targets for quality improvement efforts.'*⁵

Administering thrombolysis in a mobile stroke unit shortens time to treatment and increases the proportion of patients receiving rt-PA within the 'golden hour'

The effectiveness of IV rt-PA is likely to be highest if it is given within an hour of stroke symptom onset (the 'golden hour').⁶ The proportion of patients receiving thrombolysis within the golden hour increased six-fold when a stroke emergency mobile unit (STEMO) – including CT scanner, stroke care team, and thrombolysis administration capabilities – is deployed compared with conventional care.⁶

Furthermore, patients who received thrombolysis within the golden hour had no higher risk of mortality and were more likely to be discharged home than patients with longer time from symptom

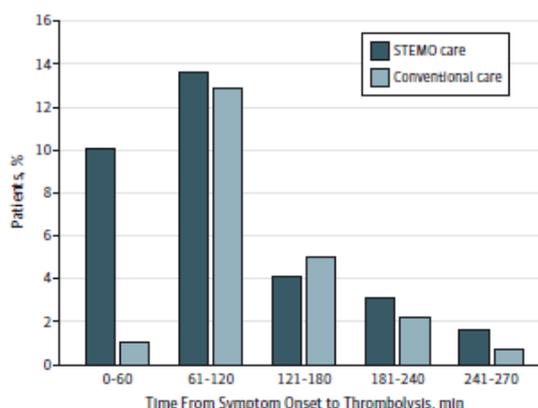
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onset to treatment. The authors note how these findings support the ‘time is brain’ concept.

‘The use of STEMO increases the percentage of patients receiving thrombolysis within the golden hour... Golden hour thrombolysis was associated with better short-term outcomes.’⁶

Study details

- *Post hoc* analysis of the PHANTOM-S study of 2111 patients with AIS (May 2011–Jan 2013) comparing rt-PA use and outcomes when a STEMO was deployed vs conventional care
- Thrombolysis was started in the STEMO if a stroke was confirmed and no contraindication was found
- 530 patients (25.1%) received thrombolysis; 78 within 60 min of symptom onset
- Thrombolysis rate was higher with STEMO than with conventional care
 - 32.6% vs 22.0%; $p < 0.001$
- Golden hour thrombolysis rate was higher with STEMO than with conventional care
 - 31.0% vs 4.9%; $p < 0.01$
- Patients who received golden-hour thrombolysis had no higher risks of 7- or 90-day mortality, and were more likely to be discharged home, than patients with an onset-to-thrombolysis time (OTT) >60 min



| Variable | OTT >60 min (n=451) | OTT ≤60 min (n=78) | p value |
|---------------------------------|---------------------|-------------------------|-------------|
| OTT, median (IQR) min | 105 (85–155) | 50 (43–55) | <0.001 |
| Secondary ICH, n (%) | 23 (5.1) | 6 (7.7) | |
| Adjusted OR | | 1.35 (0.52–3.49) | 0.54 |
| Discharge to home, n (%) | 200 (44.3) | 39 (50.0) | |
| Adjusted OR | | 1.93 (1.09–3.41) | 0.02 |
| Mortality within 7 days, n (%) | 22 (4.9) | 2 (2.6) | |
| Adjusted OR | | 0.38 (0.09–1.70) | 0.21 |
| Mortality within 90 days, n (%) | 64 (14.3) | 11 (14.3) | |
| Adjusted OR | | 0.69 (0.32–1.53) | 0.36 |

An associated editorial says pre-hospital thrombolysis for stroke is ‘an idea whose golden hour has arrived’.⁷

‘STEMO significantly shortened the time to thrombolytic treatment, which may translate to clinical benefits.’⁷

Patients with in-hospital stroke have better outcomes when referred within 3 hours

‘Time is brain’ applies to all patients with AIS, including those experiencing a stroke while in hospital.

A UK study has found that early symptom recognition, referral and specialist management of in-hospital stroke leads to more patients being eligible for thrombolysis and better clinical outcomes.⁸

Study details

- Retrospective analysis of data from 84 patients with in-hospital stroke (Jan 2009–Dec 2010) at an academic hospital in South London, UK
- Outcomes were compared between patients referred for specialist management early (within 3 hours of onset) and those referred later

Study details (continued)

- 53 (63%) in-hospital strokes were recognized and referred within 3 hours of onset; 26 of these received rt-PA
 - Seven patients had symptoms recognized within 3 hours of onset, but specialist referral was delayed beyond 4.5 hours
- Early referral improved functional outcomes and was an independent predictor of mRS 0–2 at 90 days
OR: 1.13 (95% CI: 1.10–1.27); $p=0.002$

| Clinical outcomes | Early referrals (n=53) | Later referrals (n=31) | Thrombolysed (n=29) |
|--|------------------------|------------------------|--|
| Eligible for thrombolysis, n | 27 | 10 | 26 early referrals* 3 later referrals |
| Good outcome (mRS 0–2) at 90 days, n (%) | 21 (40)* | 2 (7) | 10 (34.5) |
| 90-day stroke-related mortality, n (%) | 4 (8) | 7 (23) | 4 (14) |

* $p=0.001$ vs later referrals; three later referrals received rt-PA 'out of protocol', based on perfusion mismatch

*'The study highlights the need for implementing processes that facilitate early recognition, referral and specialist management of in-hospital stroke patients.'*⁸

Adopting guideline recommendations for the thrombolysis treatment window translates into improved patient outcomes

An analysis of thrombolysis rates over a 5-year period demonstrates that expansion of the time window, from ≤ 3 to ≤ 4.5 hours after stroke onset, has increased access to life-saving therapy.⁹ Increased use of IV thrombolysis was associated with greater proportions of patients with favourable clinical outcomes. The authors conclude that:

'...guideline recommendations on IV reperfusion after AIS in an expanded time window are slowly being adopted into community practice'

Study details

- Retrospective analysis of data from 182 235 patients with AIS in a US national stroke registry (2007–2012), comparing IV rt-PA use before and after 2009 AHA/ASA recommendations to expand the time window
- Proportion of all AIS patients receiving IV rt-PA increased significantly from 2007 to 2012
 - ≤ 3 -hour window: from 3.7% to 5.1%
 - 3–4.5-hour window: from 0.2% to 1.3%
- No evidence of reduced usage in the ≤ 3 -hour window in favour of the extended time window
- Increased use of IV thrombolysis was associated with greater proportions of patients with favourable clinical outcomes (Table)

| Variable | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | p value for trend |
|----------------------------------|-----------|------------|------------|------------|------------|------------|-------------------|
| Patients admitted with AIS | 13 499 | 22 086 | 27 963 | 35 289 | 40 148 | 43 250 | |
| Received IV rt-PA, n (%) | 576 (4.3) | 1028 (4.7) | 1482 (5.3) | 2162 (6.1) | 2434 (6.1) | 2923 (6.8) | <0.05 |
| Symptomatic ICH, % | | 5.8 | 5.1 | 3.9 | 4.4 | 3.7 | 0.003 |
| Life-threatening complication, % | | 1.4 | 0.8 | 0.9 | 0.7 | 0.8 | 0.13 |
| In-hospital mortality, % | 9.5 | 8.6 | 9.0 | 8.0 | 6.9 | 5.7 | <0.001 |
| Ambulating at discharge, % | 30.7 | 33.3 | 35.7 | 34.6 | 37.1 | 40.4 | <0.001 |
| Discharge home, % | 30.4 | 32.6 | 36.0 | 40.9 | 38.2 | 37.3 | 0.0005 |

*'There was a trend for increased utilisation of IV rt-PA in the 0–3 hours and the 3–4.5 hours time windows, which began around the same time as the publication of AHA/ASA recommendations in 2009.'*⁹

AHA/ASA, American Heart Association/American Stroke Association; CI, confidence interval; ICH, intracranial haemorrhage; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; OR, odds ratio

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References

1. Nagaraja N, Adams HP, Jr. Alteplase in acute ischemic stroke: putting the guidelines into practice. *CNS Drugs* 2014;28:1035-45.
[PubMed Link](#) [Journal link](#)
2. Fessler RD, To CY, Gordon V *et al.* An innovative, multidisciplinary, process-driven approach to acute stroke in a community health system network. *Rev Cardiovasc Med* 2014;15:252-65.
[PubMed Link](#)
3. Burnett MM, Zimmermann L, Coralic Z *et al.* Simple Text-Messaging Intervention Is Associated With Improved Door-to-Needle Times for Acute Ischemic Stroke. *Stroke* 2014;45:3714-6.
[PubMed Link](#) [Journal link](#)
4. Sung SF, Huang YC, Ong CT *et al.* Validity of a computerised five-level emergency triage system for patients with acute ischaemic stroke. *Emerg Med J* 2013;30:454-8.
[PubMed Link](#) [Journal link](#)
5. Oostema JA, Nasiri M, Chassee T *et al.* The Quality of Prehospital Ischemic Stroke Care: Compliance with Guidelines and Impact on In-hospital Stroke Response. *J Stroke Cerebrovasc Dis* 2014;23:2773-9
[PubMed Link](#) [Journal link](#)
6. Ebinger M, Kunz A, Wendt M *et al.* Effects of Golden Hour Thrombolysis: A Prehospital Acute Neurological Treatment and Optimization of Medical Care in Stroke (PHANTOM-S) Substudy. *JAMA Neurol* 2014. Nov 17. doi: 10.1001/jamaneurol.2014.3188. [Epub ahead of print]
[PubMed Link](#) [Journal link](#)
7. Warach S. Prehospital Thrombolysis for Stroke: An Idea Whose Golden Hour Has Arrived. *JAMA Neurol* 2014. Nov 17. doi: 10.1001/jamaneurol.2014.3389. [Epub ahead of print]
[PubMed Link](#) [Journal link](#)
8. Manawadu D, Choyi J, Kalra L. The impact of early specialist management on outcomes of patients with in-hospital stroke. *PLoS One* 2014;9:e104758.
[PubMed Link](#) [Journal link](#)
9. Asaithambi G, Tong X, George MG *et al.* Acute stroke reperfusion therapy trends in the expanded treatment window era. *J Stroke Cerebrovasc Dis* 2014;23:2316-21.
[PubMed Link](#) [Journal link](#)

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