



Publication Alert Newsletter

The significant benefits of intravenous (IV) recombinant tissue plasminogen activator (rtPA) have been demonstrated repeatedly in randomized clinical trials (RCTs). In addition, there is now substantial evidence of the efficacy and safety of thrombolysis in clinical practice, from sources such as the Safe Implementation of Treatments in Stroke (SITS) registry – the largest data source for thrombolysis in stroke, which currently includes more than 100 000 patients worldwide (<https://sitsinternational.org/>).

This issue of the Actilyse® Publication Alert Newsletter discusses a study of more than 10 000 patients that confirms that thrombolysis in clinical practice has a similar treatment effect to that seen in RCTs.¹ It also reiterates the association between quicker treatment and better outcomes:

‘Early treatment was associated with favourable outcome in daily clinical practice, which underlines the importance of speeding up the process for thrombolytic therapy.’

Please be aware that the purpose of this Newsletter is to make you familiar with the most recent publications, and you must keep in mind that not all aspects are covered by the label. Please always refer to the current prescribing information as in force in your country

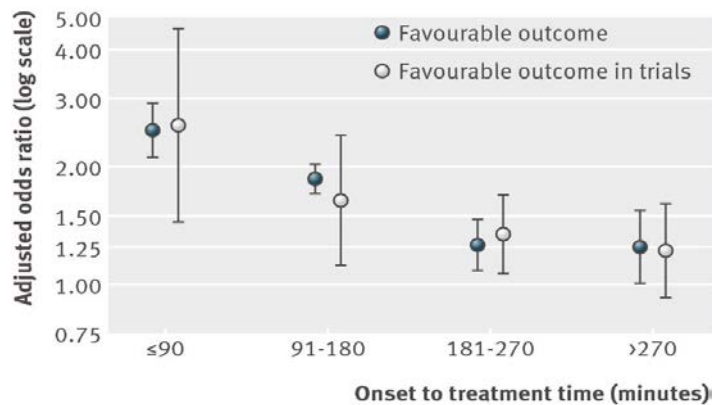
Earlier thrombolysis is associated with better outcomes in clinical practice and the effectiveness of thrombolysis is comparable to that shown in clinical trials

An analysis of an unselected cohort of more than 10 000 patients with acute ischaemic stroke (AIS) treated with rtPA (at hospitals with different levels of stroke expertise) showed a clear association between shorter treatment delay and better functional outcome.¹ The benefit:risk ratio was similar to that in a pooled analysis of RCTs, suggesting a similar magnitude of treatment effect.

The authors concluded that the effectiveness of thrombolysis in everyday practice might be comparable to that shown in clinical trials. The findings also support the implementation of initiatives to raise public awareness of stroke symptoms and to shorten the time from onset to treatment.

Study details

- Retrospective analysis of prospectively collected stroke registry data (Jan 2008–Dec 2012) from 84 439 patients with AIS admitted to 148 hospitals in Germany; 10 263 (12%) patients were treated with rtPA
- rtPA treatment was associated with an overall favourable early outcome (mRS score 0–1 at discharge; $p < 0.001$)
- Chances of a favourable outcome decreased with increasing onset-to-treatment time
- Odds of, and NNT for, a favourable outcome were similar to those in randomized clinical trials
- In-hospital mortality after rtPA was <8.5% in all groups treated up to 4.5 hours after stroke onset



Odds for favourable outcome (mRS score 0–1) vs time to rtPA treatment after onset
 Control group in present analysis = patients without rtPA treatment
 Control group in pooled clinical trial analysis = placebo-treated patients

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*'Our results support the relation between short time to treatment and better functional outcome in everyday practice.'*¹

Employing multiple strategies leads to cumulative reductions in DNT

Xian et al. surveyed more than 300 US hospitals to analyse the adoption and efficacy of Target: Stroke strategies in reducing door-to-needle times (DNT).²

Incremental reductions in DNT were observed for all analysed strategies, with a potential total of 14 minutes saved if all strategies were used all of the time. However, few hospitals were employing the most effective strategies.

*'...rapid treatment is a critical factor in the outcomes of patients with acute stroke who are treated with intravenous rtPA.'*²

Study details

- Survey of 304 Get With The Guidelines-Stroke hospitals treating 5460 patients with AIS with rtPA within 3 hours of symptom onset (Jan 2008–Dec 2009); median DNT =72 min; 34% of patients had DNT ≤60 min
- Hospitals that implemented a greater number of strategies had shorter DNTs
- For each strategy implemented, an adjusted mean of 1.3 minutes would be saved
- The strategies most strongly associated with shorter DNT were among those least frequently used: rapid triage protocol with stroke team notification; single-call activation systems; rtPA being stored in the ED

| Strategy | Adjusted mean difference in DNT (95% CI), min | Association between strategy and DNT ≤60 min: adjusted OR (95% CI) |
|---|---|--|
| Advance hospital notification by EMS ^a | | |
| Some of the time | 2.1 (-3.8 to 7.9) | 0.96 (0.67 to 1.37) |
| All of the time | -0.5 (9.2 to 5.3) | 1.07 (0.75 to 1.54) |
| Rapid triage protocol + stroke team notification ^a | | |
| Some of the time | -7.0 (-13.6 to -0.5)* | 1.10 (0.59 to 2.04) |
| All of the time | -8.1 (-14.1 to -2.1)** | 1.41 (0.80 to 2.51) |
| Single-call activation system ^a | | |
| Some of the time | -2.2 (-7.9 to 3.5) | 0.96 (0.59 to 1.56) |
| All of the time | -4.3 (-7.8 to -0.7)* | 1.32 (0.97 to 1.80) |
| 24/7 access to in-house stroke expertise ^a | | |
| Some of the time | 1.7 (-8.8 to 12.3) | 0.86 (0.32 to 2.25) |
| All of the time | 0.9 (-9.1 to 11.0) | 1.04 (0.41 to 2.62) |
| Trainees involved in stroke team ^a | | |
| Some of the time | 4.8 (0.6 to 9.0)* | 0.66 (0.44 to 0.98)* |
| All of the time | -3.6 (-7.0 to -0.3)* | 1.37 (1.04 to 1.80)* |
| Rapid brain imaging protocol ^b | -3.8 (-11.1 to 3.4) | 1.16 (0.73 to 1.84) |
| Rapid laboratory testing protocol ^b | -0.9 (-6.7 to 4.9) | 0.96 (0.60 to 1.54) |
| rtPA administration protocol ^b | -2.7 (-8.3 to 2.9) | 1.48 (0.86 to 2.53) |
| Routine premixing of rtPA ahead of time ^b | -2.2 (-6.8 to 2.4) | 1.33 (0.93 to 1.91) |
| Team-based approach to stroke care ^b | -3.7 (-16.4 to 9.0) | 0.91 (0.38 to 2.15) |
| rtPA stored in the emergency department ^b | -3.5 (-6.7 to -0.4)* | 1.32 (1.02 to 1.71)* |
| Regular feedback on DNT provided ^b | -1.4 (-5.0 to 2.1) | 1.23 (0.93 to 1.64) |

*p<0.05 and **p<0.01 vs reference categories: ^aNone of the time; ^bNo

The authors concluded that there is considerable variation in the application of strategies to reduce delays in rtPA administration, and most hospitals were not using the most effective strategies.

*'Future efforts are needed to facilitate the integration of evidence into clinical practice and disseminate the most effective strategies for improving timeliness of acute stroke thrombolysis.'*²

In an accompanying editorial, Ozark and Jauch commended the insightful analysis by Xian et al. and observed that a 14-minute saving would bring average DNTs to within the recommended 60 minutes.³ They noted the importance of advance notification in reducing treatment times and emphasized that efforts to improve the quality of stroke care should not be limited to provision within the hospital. The editorial concluded that hospitals already active in improving stroke care are those most likely to adhere to new interventions and to reap the greatest benefits, and yet further efforts are needed to change use of a positive initiative from ‘some of the time’ to ‘all of the time’.

In-ambulance thrombolysis reduces treatment delays without increasing AEs

Trying to improve stroke care outside the hospital can indeed realise rewards, according to a study showing that initiating rtPA in a specialized ambulance (Stroke Emergency Mobile, STEMO) reduces treatment delays and increases thrombolysis rates, without increasing adverse events.⁴

Study details

- Prehospital Acute Neurological Treatment and Optimization of Medical care in Stroke (PHANTOM-S) study: randomized-week, open-label clinical trial conducted in Berlin, Germany (May 2011–Jan 2013)
 - Specialized ambulance (STEMO) equipped and staffed to administer rtPA in eligible patients
 - STEMO weeks (n=3213) and STEMO deployment (n=1804) compared with routine care (n=2969)
 - Primary outcome measure: time from dispatcher activation of alarm to rtPA administration
- STEMO deployment reduced alarm-to-treatment time by 25 minutes, due to faster alarm-to-imaging and imaging-to-treatment intervals (all $p < 0.001$ vs routine care)
- Thrombolysis rates with STEMO deployment (33%) were higher than with routine care (21%) ($p < 0.001$)
- STEMO deployment incurred no increased risk for ICH or 7-day mortality compared with routine care

| Outcome | Patients during control weeks | Patients during STEMO weeks | Patients with STEMO deployment ^a |
|--|-------------------------------|-----------------------------|---|
| Patients with AIS treated with rtPA, n | 220 | 310 | 200 |
| Treatment times, mean (95%CI) min | | | |
| OTT | 119 (112 to 125) | 110 (103 to 117)* | 103 (94 to 112)** |
| OTT ≤90 min, n (%) | 82 (37.4) | 149 (48.1)* | 115 (57.5)** |
| Alarm to imaging ^b | 52.4 (50.3 to 54.4) | 44.0 (42.0 to 46.0)** | 37.7 (35.6 to 39.7)** |
| Imaging to treatment ^b | 23.8 (21.6 to 26.1) | 17.4 (15.7 to 19.0)** | 14.1 (12.4 to 15.8)** |
| Alarm to treatment (primary endpoint) ^b | 76.3 (73.2 to 79.3) | 61.4 (58.7 to 64.0)** | 51.8 (49.0 to 54.6)** |

^aSubset of STEMO weeks: patients for whom STEMO was available and deployed;

^bAnalysis excludes 20 patients (2 from control, 8 from STEMO weeks, and 10 from STEMO deployment)

* $p < 0.05$ and ** $p < 0.001$ vs control

‘Compared with usual care, the use of ambulance-based thrombolysis resulted in decreased time to treatment without an increase in adverse events.’⁴

An editorial commenting on the study stressed the primary importance of reducing time from stroke onset to rtPA treatment, to improve patient outcomes after AIS.⁵

More rapid treatment may result in better clinical outcomes for patients with AIS in two broad ways.

- More patients will be treated with rtPA.
- More patients will be treated within 60 minutes of stroke onset, when rtPA is likely to have its greatest benefit.

‘The studies... indicate exactly where and how to direct efforts in improving treatment outcomes for patients with AIS – namely by reducing time from symptom onset to treatment.’⁵

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Targeted stroke preparedness initiatives aim to reduce stroke treatment disparities in multi-ethnic communities

The US Acute Stroke Program of Interventions Addressing Racial and Ethnic Disparities (ASPIRE) will use strategies targeted both within and outside the hospital, including emergency medical services and community strategies, to increase acute stroke preparedness.⁶ The impact of this multilevel intervention on treatment delays and rtPA utilization rates in black urban populations will be reported.

Thrombolysis outcomes are not affected by patient admission outside regular working hours

Admission to Polish stroke centres outside regular hours does not appear to adversely affect rtPA treatment times and clinical outcomes, although prehospital delays may limit the number of patients receiving treatment within 90 minutes of stroke onset.⁷

The authors concluded that stroke centres should feel confident about administering rtPA outside regular working hours, while endeavouring to shorten prehospital delays during these periods.

Study details

- Retrospective analysis of data from 1330 patients with AIS treated with IV rtPA (Oct 2003–Dec 2010) at 27 Polish stroke centres included in the SITS registry
- The proportion of patients with OTT ≤90 min was lower during non-regular hours, due to prehospital delays
- In multivariate logistic regression, none of the evaluated periods showed any differences in median OTT or DNT, nor any association with SICH, 7-day mortality, or neurological outcomes, with one exception:
 - Patients admitted during night hours were less likely to achieve a favourable outcome (mRS score 0–2 at 3 months) (adjusted OR: 0.53; 95% CI: 0.29–0.95)

| Outcome | Regular hours (n=462) | Out-of-office hours (n=867) | Non-working days (n=448) | Night hours (n=105) |
|----------------------|--------------------------|--------------------------------|-----------------------------|------------------------|
| OTT, median min | 150 | 150 | 148 | 150 |
| OTT ≤90 min, % | 12.1 | 7.3** | 6.7** | 7.6 |
| DNT, median min | 75 | 72 | 70 | 76 |
| DNT ≤60 min, % | 35 | 35 | 37 | 30 |
| SICH, % | 5.3 | 4.6 | 5.9 | 2.9 |
| 7-day mortality, % | 7.4 | 7.7 | 9.2 | 6.8 |
| 3-month mRS 0–1, % | 35 | 36 | 35 | 29 |
| 3-month mRS 0–2, % | 53 | 52 | 51 | 42 |
| 3-month mortality, % | 18 | 19 | 20 | 18 |

**p<0.01 vs regular hours

‘There is no such thing as a bad time for intravenous thrombolysis.’⁷

Patients admitted outside of regular working hours have longer treatment delays but similar clinical outcomes

In a similar but smaller study by Fang et al., stroke patients admitted to an Australian comprehensive stroke centre outside of regular working hours and treated with rtPA had longer DNT, but did not have worse clinical outcomes.⁸

The authors believe that the study highlights the importance of continued improvement to hospital systems and medical education for neurologists, to overcome the effect of out of hours delivery on thrombolysis therapy. The authors conclude that centres should audit non-working hours and incorporate system improvements to negate treatment delays.

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Study details

- Retrospective analysis of prospectively collected data from 388 consecutive patients with AIS treated with IV rtPA (Jan 2003–Dec 2011) at a single Australian comprehensive stroke centre
- Thrombolysis treatment times were longer in patients admitted outside of normal working hours, due to prehospital and in-hospital delays (e.g. the neurologist was off site)
- There was no difference in functional outcomes or mortality at 3 months, although the sample size is small
- Despite increasing numbers of patients treated over time, the out-of-hours effect remained consistent

| Outcome | Working hours (n=162) | Non-working hours (n=226) | Median difference (95% CI) |
|--------------------------------|--------------------------|------------------------------|-------------------------------|
| Onset-to-door time, median min | 66 | 71 | 5 (-1.9 to 11.9) |
| Door-to-CT time, median min | 23.5 | 28 | 4 (-1.16 to 9.2) |
| DNT, median min | 64.5 | 80* | 15 (6.4 to 23.6) |
| OTT, median min | 140 | 165** | 25 (13.2 to 36.1) |
| 3-month mRS 0–1, % | 33 | 35 | |
| 3-month mRS 0–2, % | 49 | 49 | |
| 3-month mortality, % | 17 | 20 | |

* $p=0.01$ and ** $p<0.01$ vs working hours

Patient transfer within a telemedicine network allows receipt of specialist care

A retrospective 2-year analysis of 1413 consultations within a telemedicine network in Germany revealed that 270 patients (39% of all AIS cases) received IV rtPA at a Spoke site, and 240 patients with a stroke diagnosis were transferred to the main Hub site to receive care not available at Spoke sites.⁹ Almost a third of transferred stroke patients had a favourable functional outcome at discharge.

The authors conclude that, '...a remarkable number of stroke patients can be transferred within a telemedical network, enabling delivery of specific stroke therapies that require advanced multispecialty expertise.'

Telestroke networks allow acute stroke therapies to be accessible to all

Bladin and Cadilhac provide a short review of the current position of telemedicine in acute stroke care.¹⁰

- Telemedicine assessment of stroke (NIHSS) is comparable with inpatient assessment.
- Teleradiology systems are recommended for timely review of brain CT and MRI scans.
- **Telemedicine can enable rural hospitals to deliver rtPA onsite** instead of transferring patients to specialized stroke centres.
- **Telemedicine can increase thrombolysis rates and reduce time to treatment in rural hospitals.**
- Telemedicine can enable remote specialists to supervise stroke care through to rehabilitation.
- Telestroke networks seem to be cost-effective from a long-term, societal perspective.
- Successful and efficient use of telestroke requires appropriate policies and guidelines.

The authors conclude that, 'With improvements in technologies and systems of care, telemedicine can encompass all aspects of care from prehospital to stroke rehabilitation.'

*'The ground is fertile for stroke telemedicine to flourish and to improve the quality of care for patients with stroke, no matter the geographic location.'*¹⁰

The legal, ethical, and clinical challenges of acute stroke telephone consultations are discussed by Sattin.¹¹ He highlights that providing such consultations can help to address geographical disparities in access to timely care, but correct recommendations are reliant on accurate clinical information, an appropriate informed consent process, and correct execution of treatment.

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July 2014

CI, confidence interval; CT, computed tomography; ED, emergency department; EMS, emergency medical services; ICH, intracranial haemorrhage; MRI, magnetic resonance imaging; mRS, modified Rankin scale; NIHSS, National Institute of Health Stroke Scale; NNT, number needed to treat; OR, odds ratio; OTT, onset to treatment time; SICH, symptomatic intracranial haemorrhage.

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