



Publication Alert Newsletter

A recent review has looked at the use of recombinant tissue plasminogen activator (rtPA) for acute ischaemic stroke (AIS) and concluded that,

'In nearly 2 decades since the publication of the transformative National Institute of Neurological Disorders and Stroke trials, the efficacy and safety of IV rtPA has been consistently verified in international real-world clinical practice'.¹

The authors suggest that optimal care of patients with AIS should include community education and standardised protocols to guide immediate patient assessment and triage to medical centres with capability for efficient neurological assessment, brain imaging, drug administration, and specialised post-thrombolysis care.

This issue of the Actilyse® Publication Alert Newsletter highlights papers that cover the range of pre-hospital and in-hospital care for AIS patients, including suggestions on how stroke care should be measured in order to track the impact on outcomes of organisational improvements.

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 not all aspects may be covered by the label. Please always refer to the current prescribing information as in force in your country

Improving stroke outcomes is a multidisciplinary affair

Emergency and neurology/stroke physicians in New Zealand have joined forces to issue a consensus statement on the use of intravenous (IV) rtPA in AIS.²

This statement includes many of the points regularly highlighted in these newsletters:

- Agreed protocols should be available to help identify patients eligible for thrombolysis
- Emergency physicians, neurologists, and stroke physicians should work collaboratively to minimise treatment delays
- Stroke team pre-notification is encouraged, to assist rapid and efficient triage
- Appropriate infrastructure, including timely access to neuroimaging and scan interpretation, should be present
- Regular audits should be performed to monitor safety and measure outcomes in stroke patients receiving thrombolysis, with the results being made available to clinicians (ideally via a national database) and used to refine the ongoing use of thrombolysis

Stroke service audits should include in-hospital and post-discharge outcomes

Further consensus recommendations, this time on auditing stroke services, have been provided by a global forum of stroke experts.³ They highlight that metrics for assessing improvements in stroke care need to include measures of how changes in process translate into patient outcomes. To this end, the metrics recommended include both hospital-based measures, e.g. percentage of eligible patients receiving IV rtPA, and post-discharge patient outcomes, e.g. modified Rankin Scale (mRS) score at 30 and/or 90 days. When noting the need to measure and increase rtPA use, the authors remind us that,

'The full potential of rtPA therapy has yet to be realised'.

| Access-to-care metric | Outcome metric |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> • Volume of cases arriving within IV rtPA treatment time window • Volume of cases arriving by EMS transport • Percentage of eligible patients treated with IV rtPA • Percentage of stroke cases for which a cause for the stroke is identified • Percentage of discharged cases of stroke where: <ul style="list-style-type: none"> ○ Target BP is defined and treatment initiated ○ Statin is initiated in appropriate cases ○ Smoking cessation is addressed ○ Antithrombotic therapy is initiated | <ul style="list-style-type: none"> • Neurological status at 24 hours and discharge, compared with baseline, measured by NIHSS score or another validated scale • Discharge disposition • Ambulatory status at discharge • Communication status at discharge • mRS score at 30 and/or 90 days • Quality of life metric (country specific) |

The authors conclude that it is important to continually strive to improve stroke care provision, while ensuring that improvements in process lead to corresponding improvements in patient outcomes.

Reducing post-imaging delays is critically important for achieving optimal DNT

A US analysis of door-to-needle time (DNT) found that imaging-to-needle times, rather than door-to-imaging times, explained most of the variation in DNT between hospitals.⁴

The authors note that although timely brain imaging is clearly important for optimal rtPA delivery and further improvement in door-to-imaging time is desirable, prolonged imaging-to-needle time was a much greater problem. Post-imaging delays were largely responsible for the inability of hospitals to achieve DNT ≤60 min.

Study details

- Cohort analysis of 1193 patients with AIS treated with rtPA within 4.5 hours of arrival (Jan 2009–Dec 2012)
 - Data from 25 US hospitals, collected by the Michigan Stroke Registry
 - Primary outcome variable: DNT (sum of door-to-imaging time and imaging-to-needle time)
- Between 2009 and 2012, reductions were seen in median:
 - Door-to-imaging time: from 21 to 18 min
 - Imaging-to-needle time: from 55 to 51 min
 - DNT: from 77 to 72 min
- >68% of patients had a door-to-imaging time of ≤25 min, but only 29% of patients had a DNT of ≤60 min
- Imaging-to-needle time was strongly correlated with DNT (but not with door-to-imaging time)
 - For every additional minute of imaging-to-needle time, DNT increased by 0.95 min ($p < 0.001$)
- After adjustment for patient-level factors, door-to-imaging time explained 10.8% of the variation in hospital risk-adjusted DNT, while imaging-to-needle time explained 64.6%

| Variable | Outcome |
|--------------------------------------------|--------------|
| Onset-to-arrival time, median (range), min | 59.0 (0–252) |
| Door-to-needle time, mean (SD), min | 82.9 (35.4) |
| Door-to-needle time ≤60 min, % | 28.7 |
| Door-to-imaging time, mean (SD), min | 22.8 (15.9) |
| Door-to-imaging time ≤25 min, % | 68.4 |
| Imaging-to-needle time, mean (SD), min | 60.1 (32.3) |
| Imaging-to-needle time ≤35 min, % | 20.5 |
| Onset-to-treatment time, mean (SD), min | 153.2 (50.0) |

'More attention is needed to determine systems changes that can decrease imaging-to-needle time for patients with acute ischaemic stroke'¹⁴

Using performance measures may contribute to improvements in DNT

Improvements in thrombolysis treatment rates and DNT over a 7-year period may be explained by the combined impact of a series of structural and logistical interventions.⁵

The following interventions were introduced in a large university hospital between 2006 and 2012:

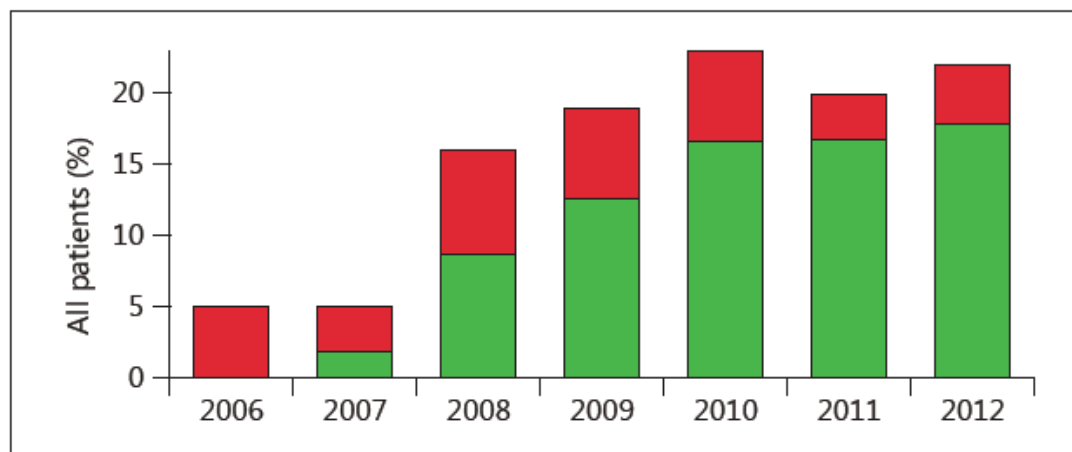
- Yearly training of residents and nursing staff
- Regularly updated pocket flowcharts with protocol summaries
- Pre-notification single-call activation system
- Emergency department (ED) triage protocol; computerised tomography (CT) scanner placed in the ED; treatment started in the CT room
- 24/7 neurologist availability
- DNT reported for every patient, and feedback given to doctors who exceeded the 1-hour threshold

The proportions of patients receiving rtPA and being treated within 60 min improved steadily over the study period. Median DNT decreased by 30 min and was not associated with any specific intervention.

The authors advocate the measurement and reporting of median DNT outcomes on a monthly or quarterly basis, to inform all professionals treating stroke patients of their achievements.

Study details

- Retrospective analysis of data from 1703 patients admitted with AIS to a large university hospital in the Netherlands (Jan 2006 to Dec 2012), to examine the trend in rtPA treatment rates and DNT
- Proportion of patients receiving rtPA improved from 5% in 2006 to 22% in 2012
- Proportion of patients with DNT ≤60 min improved from 0 in 2006 to 81% in 2012
 - Median DNT decreased from 75 min in 2006 to 45 mins in 2012



Percentage of patients with AIS treated with thrombolysis (red/green bars) and fraction treated within 1 hour (green), per year

'Measuring and reporting DNT could be helpful in keeping professionals focused and in improving performance'⁵

Hospital readiness to administer rtPA can be assessed using a simple survey

A condensed instrument has been developed to assess hospital readiness for rapid rtPA administration to eligible patients, and might also be used by institutions to discover areas for improvement.⁶

The survey instrument is divided into 4 factors:

1. **Stability:** 10 items that address reducing practice or process variation through standard protocols, ongoing education, and review of the team's performance to optimise patient care
2. **Shared goals:** 9 items that incorporate elements from communication, teamwork and organisational culture (such as institution-wide agreement on goals, team meetings to review whether goals are met, coordination across departments, and responsibility to the team)

3. **Preparedness:** 9 items that describe the ability to quickly and easily move the patient through the stroke process, beginning with the emergency services (EMS) encounter. This factor focusses on having an integrated pre-hospital plan, but also includes performance monitoring and feedback.
4. **Family:** 1 item that addresses allowing and encouraging the inclusion of family

The authors conclude that their analysis supports the validity of the instrument to assess components of care associated with the early administration of thrombolytic therapy for patients with AIS. This single tool could help clinicians identify the reasons that underpin treatment delays.

'This instrument will be essential for hospitals that wish to efficiently identify specific areas for quality improvement'⁶

rtPA use is increased by having a neurology residence programme

Hospitals with a neurology residency training programme have higher thrombolysis rates than other teaching and non-teaching hospitals.⁷ The disparity in rtPA treatment rates increased with increasing patient age.

The authors conclude that efforts to increase thrombolysis use, especially among elderly patients, in hospitals without a neurology residency programme could have a large impact on stroke care.

In an accompanying editorial, Lorenzano observed that, 'the study by Moradiya et al. provides a new point of view for further evaluation of barriers to thrombolysis delivery in ischaemic stroke patients'.⁸

| | |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>Study details</p> <ul style="list-style-type: none"> • Retrospective cohort study of 712 433 adult patients with AIS (US Nationwide Inpatient Sample; 2000–2010) • Thrombolysis rates for 298 hospitals with neurology residencies (NR) were compared with 1063 other teaching (OT) and 5478 non-teaching (NT) hospitals • Thrombolysis rates increased over time at all three institution types; NR had the greatest increase and the highest rates (significantly higher than OT and NT) <ul style="list-style-type: none"> ○ Disparities in thrombolysis rates increased with advancing patient age • In multivariate analysis, NR was an independent predictor of higher thrombolysis rates <ul style="list-style-type: none"> ○ Adjusted OR (95% CI): <ul style="list-style-type: none"> NR vs OT = 1.51 (1.44–1.59) NR vs NT = 1.82 (1.73–1.91) | <p style="font-size: small;">Temporal trends in thrombolysis rates based on hospital academic status; $p < 0.001$ for all trends</p> |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|

Admission direct to a stroke centre reduces delays and improves outcomes

Admitting patients with AIS directly to a stroke centre, rather than referring them from community hospitals, is associated with shorter onset-to-door time (61 vs 120 min) and onset-to-rtPA time (103 vs 155 min) and better odds of a favourable 90-day outcome (odds ratio [OR]: 2.03; 95% confidence interval [CI]: 1.051–3.917).⁹ Interestingly, DNT was shortened by 5 min among patients admitted by referral, as in-hospital processing time was reduced by pre-notification during patient transfer.

The authors emphasise the need to improve the EMS system and stroke education for both the public and paramedics. Both are required for the rapid and direct transfer of patients with AIS to hospitals where thrombolysis therapy is available.

'Thrombolysis after direct admission to a hospital offering intravenous thrombolysis therapy could shorten onset-to-rtPA time and improve stroke outcome in patients with AIS'⁹

Stroke care facilities with CSC characteristics carry out more interventions

The J-ASPECT study surveyed 1369 neurology and stroke training institutions in Japan in 2011. Based on 749 responses, 85% of hospitals had written protocols for rtPA administration. Facilities with rtPA protocols were more likely to provide comprehensive stroke centre (CSC)-criteria services. The number of CSC criteria met was positively associated with the number of interventions, including rtPA infusions, performed each year.¹⁰

Stroke systems of care can improve rtPA use in rural China

Implementing a stroke system of care in rural China led to more patients with stroke receiving thrombolytic treatment and also to more favourable patient outcomes.¹¹

Study details

- Prospective analysis comparing outcomes before and after implementation of a stroke system of care in 3 rural townships (vs 3 rural control townships)
 - Stroke care evidence-based guidelines were implemented, a stroke unit was designated as the referral centre for rural hospitals, and an educational campaign was begun (public and healthcare professionals)
- Implementation of a stroke system of care led to more patients being transferred to the stroke unit within 3 hours of symptom onset and receiving thrombolytic treatment:

| Indicators | Pre-intervention | | Post-intervention | |
|----------------------------|------------------|----------------------|-------------------|----------------------|
| | Control (n=471) | Intervention (n=468) | Control (n=471) | Intervention (n=468) |
| Admitted within 3 hours, % | 7.9 | 6.8 | 8.7 | 13.6* |
| CT scan within 24 hours, % | 54.8 | 56.2 | 58.5 | 65.3* |
| Thrombolysis, % | 1.1 | 1.4 | 1.7 | 3.9* |
| Disability, % | 52.8 | 54.6 | 48.1 | 38.4** |
| 1-year mortality, % | 9.6 | 11.4 | 10.1 | 6.5* |

* $p < 0.05$ and ** $p = 0.001$ vs post-intervention control

'The education campaign targeted at the public and health professionals clearly played a role in reducing time delays and increasing the number of patients who received timely treatment of acute stroke'¹¹

Telemedicine improves appropriate use of thrombolysis for AIS patients

Two studies have described evaluating outcomes in telestroke networks.

Over a 7-year period (2006–2012), thrombolysis rates in 13 US hospitals improved from 4.4% before telemedicine implementation to 6.9% post implementation.¹² The authors conclude that 'telemedicine improves appropriate use of thrombolytic treatment for AIS patients'.

Returning to the topic of metrics of care, a study in Germany has looked at using routine clinical data to assess quality of care in a telestroke network.¹³ Over a 4-year period (2006–2009), thrombolysis rates improved (from 1.1% to 5.9% in primary hospitals; from 4.2% to 7.7% in CSCs). The gap in thrombolysis rates between primary hospitals and CSCs was therefore reduced, while AIS mortality rates decreased in both settings (from 10.3% to 7.3% in primary hospitals; from 6.6% to 5.9% in CSCs).

Use of rtPA is highly cost-effective in the treatment of AIS

A model based on a recent meta-analysis shows that use of rtPA within 3 hours of stroke onset, compared to no use, is associated with improved quality of life (quality-adjusted life-year [QALY] increase of 0.14–0.46) and lifetime healthcare cost savings (\$2700–25 000 per QALY gained) across different scenarios.¹⁴

'rtPA is highly cost-effective in [the] treatment of AIS across numerous efficacy, safety, and mortality estimates'¹⁴

The long-term cost-effectiveness of rtPA was also described by Fugate and Rabinstein in the review article that was mentioned at the beginning of this newsletter. They note that:

'Intravenous thrombolysis is not only effective in clinical trials and in real-world practice but also produces economic benefits by reducing societal and health care costs'.

BP, blood pressure; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation.

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