



## Publication Alert Newsletter

A recent review has looked at ways to increase the use of intravenous (IV) recombinant tissue plasminogen activator (rtPA) among patients with acute ischaemic stroke (AIS), highlighting that:

**‘rtPA changed the world, not just of stroke treatment, but of neurology in general’<sup>1</sup>**

The authors summarize the accumulating evidence that rtPA may benefit patients who lie outside of current treatment parameters and advocate increased efforts to broaden the range of eligible patients.

**‘More research will hopefully lead to the identification and inclusion of a greater number of suitable patients for thrombolysis, maximizing the number benefiting from rtPA’**

However, many patients who are eligible by *existing* criteria are still not receiving thrombolysis, mainly due to pre- and in-hospital delays. This issue of the Actilyse® Publication Alert Newsletter focusses on the importance of emergency medical services (EMS) in reducing delays within the stroke care pathway, together with other ways in which the proportion of AIS patients receiving timely thrombolytic therapy can be improved.

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**‘Save a Minute, Save a Day’: Small reductions in treatment delays lead to robust health benefits for patients**

Realistically achievable small reductions in stroke thrombolysis delays would result in significant and robust health benefits over patients’ lifetimes, according to modelled data.<sup>2</sup> The analysis found that an additional 2 days of healthy life were gained for *each minute* that onset-to-treatment time (OTT) was reduced. The authors conclude that **‘all attempts should be made to reduce treatment delays.’**

**Study details**

- Model based on: observational registry data (1998–2011; n=2258; stroke patients treated with rtPA in Australian and Finnish centres); pooled analysis of thrombolysis trials to determine effect of rtPA over time; general population survival data; disability weights for mRS categories
- Each minute of OTT saved granted on average 1.8 days of extra healthy life
  - Benefits were observed across age groups and stroke severity groups
  - Greatest benefits were seen in younger patients and women, over their longer lifetimes
  - Except for the oldest patients with the most severe strokes, patients gained at least a day of healthy life for each minute saved

Outcome	Patient age and stroke severity				Whole cohort
	Young (50 years)		Old (83 years)		
	Mild	Severe	Mild	Severe	
Number of days of extra healthy life (DALY) gained per 1-minute reduction in OTT	2.7	3.5	0.9	0.6	1.8

Mild, NIHSS score=4; severe, NIHSS score=20

*‘a few minutes saved in delivering intravenous rtPA translates to significant benefits*

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*equivalent to days, weeks, and even months of disability-free life<sup>2</sup>*

### **Many factors that cause treatment delays occur in the prehospital setting**

Factors that cause delays in thrombolytic treatment of AIS and actions that can reduce OTT are summarized in a recent review.<sup>3</sup> The authors emphasize the significant contribution of prehospital factors, the role that patients and EMS can play to reduce hospital admission delays, and describe several prehospital strategies that improve timely access to IV rtPA.

*'There remains an urgent need to adopt better strategies to optimize pre-hospital and in-hospital systems to achieve shorter DNT and OTT<sup>3</sup>*

In a similar review, Ragoschke-Schumm et al. describe five areas in the prehospital setting that can be targeted to reduce treatment delays.<sup>4</sup>

- *Continual public awareness campaigns* aimed at specific groups
- *EMS training* on the use of tools for stroke recognition
- *Prioritized transport* to hospitals with stroke expertise
- *Prenotification* to activate the stroke team and reserve the computerized tomography (CT) scanner
- *Prehospital stroke management* in a specialized ambulance, potentially using telemedicine to liaise with the receiving stroke team

*'Stroke educational campaigns could...be a solution for improving patients' and families' awareness of the correct response in case of stroke'<sup>4</sup>*

Results from a telephone survey in Italy support the view that a lack of public awareness of acute stroke care and available treatment options may limit access to stroke services.<sup>5</sup> Only 15% of participating adults were aware of stroke units and only 26% were aware of rtPA. The authors urge hospitals to provide ongoing stroke awareness campaigns that include information about rtPA.

### **EMS can use prehospital tools to identify potential rtPA candidates**

Berglund et al. compared the use of the Face Arm Speech Time (FAST) test by different prehospital personnel. On-scene ambulance crew were better than dispatchers at identifying stroke using FAST, but false positives and false negatives were frequent in both groups. The authors conclude that FAST may be a useful tool, but better identification tools are needed for the prehospital care setting.<sup>6</sup>

When used by emergency medical technicians in the Emergency Department (ED) to assess patients with AIS/TIA, the Kurashiki Prehospital Stroke Scale (KPSS) showed excellent correlation with the NIHSS, and a KPSS score  $\geq 3$  was significantly associated with administration of IV rtPA.<sup>7</sup> A cut-off KPSS score of 3 provided 98% sensitivity and 71% specificity for administration of IV rtPA within 3 hours of stroke onset. Thus, the KPSS could be used in the prehospital setting to identify candidates for rtPA

### **A prehospital stroke alert protocol reduces delays in patients identified by EMS**

A prehospital stroke alert protocol has been shown to decrease in-hospital delays and increase rates of rtPA use. In addition to prenotification, the protocol allows the patient to bypass the ED and be taken directly to a neurological emergency team for a CT scan<sup>8</sup>

- EMS stroke identification was accurate 66% of the time
- Mean door-to-CT time was reduced by 67% (11.8 mins vs historical mean of 35 mins)
- Thrombolysis treatment rate was 18%, compared with 5% over the previous 3 years
- Mean door-to-needle time (DNT) was reduced by 44% (56.5 mins vs historical mean of 99 mins)

*'EMS training in addition to the prehospital stroke alert system is effective in delivering*

*patients to our comprehensive stroke centre in a timely fashion*<sup>8</sup>

**On-scene care by a stroke specialist reduces delays and increases rtPA use**

In-hospital delays are substantially reduced, and rtPA rates significantly increased, by on-scene physician assessment and a triage of stroke patients – termed ‘prehospital medicalization’.<sup>9</sup> Patients assessed this way can bypass the ED and be admitted directly to radiology, dramatically reducing door-to-imaging time and increasing the window for rtPA therapy.

*‘Prehospital transfer medicalization, in stroke patients calling within 6 h, promotes high rtPA administration rate’<sup>9</sup>*

**Study details**

- Analysis of processing time and treatment rates in stroke patients transported by fire department ambulance or by a mobile medical team (SAMU) that provides first acute care on location (Jul 2007 to Dec 2009)
- Patients transported by SAMU had significantly shorter door-to-image times and higher thrombolysis rates than patients arriving by fire department ambulance

	<b>SAMU (n=193)</b>	<b>Fire department (n=120)</b>	<b>p value</b>
Call-to-door time, mean min	89	82	0.04
Admission MRI, n (%)	168 (87)	88 (73)	0.01
Door-to-image time, mean min	52	159	<0.0001
Door-to-image <25 min, n (%)	97 (50)	17 (14)	<0.0001
rtPA administration, n (%)	71 (37)	30 (25)	0.04
Image-to-thrombolysis, mean min	59	55	n.s.
Onset-to-needle time, mean min	215	234	n.s.
Intracerebral haematoma, n (%)	23 (12)	12 (10)	n.s.

**EMS-reported stroke onset times are similar to neurologist-reported times**

Prospectively collected last-known normal (LKN; stroke onset) times reported by EMS were generally in agreement with neurologist-determined times at a tertiary-care hospital and comprehensive stroke centre in Missouri, USA.<sup>10</sup>

Among patients who received rtPA, use of EMS (rather than neurologist) LKN times to determine treatment eligibility would not have incorrectly excluded any patients; 6% of patients who *did not* receive rtPA would have been incorrectly *included* for rtPA treatment had the EMS time been used.

The authors conclude that if these results are confirmed in larger studies then:

*‘EMS-reported LKN times could be used more frequently to avoid prolonged DNT and excluding patients from treatment who should have been included’<sup>10</sup>*

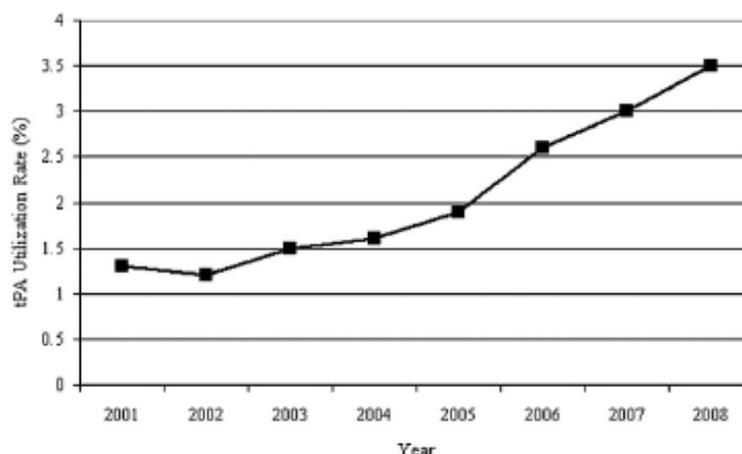
**rtPA use is increasing in the USA, but remains low in some subgroups**

The use of rtPA to treat AIS in the USA has increased in recent years, from 1.3% in 2001 to 3.5% in 2008.<sup>11</sup> However, the rate of rtPA use was lower in females and older patients.

The authors attribute the rise in rtPA use to increased public awareness of stroke symptoms and improved protocols in EDs allowing for timely administration of rtPA.

### Study details

- Retrospective analysis of discharge data from almost 3 million US patients with acute stroke, recorded in the National Inpatient Sample database between 2001 and 2008
- Overall rtPA utilization rates increased over time



- rtPA treatment rates decreased with increasing age, were lower in females than in males (across all age groups), and were influenced by hospital characteristics and admission route

Subpopulation	% rtPA
<b>Age &lt;65 years</b>	<b>2.7</b>
Age 65–79 years	2.2
Age 80+ years	1.6
<b>Male</b>	<b>2.4</b>
Female	1.9

All  $p < 0.0001$  vs reference group (in italics)

Hospital variable	% rtPA
<b>Rural</b>	<b>0.9</b>
Urban non-teaching	1.7
Urban teaching	3.0
<b>Emergency admission</b>	<b>2.2</b>
Transfer	1.6
Long-term care	1.1
Routine admission	1.0

### ***rtPA use and the quality of stroke care has increased in Sweden***

Improvements in stroke care quality have been achieved in a relatively short time in Sweden.<sup>12</sup> Notably, rtPA treatment rates increased from 0.4% in 2001 to 8.6% in 2010.

**Study details**

- Retrospective analysis of data from 320 181 patients in the Swedish stroke register (1995–2010)
- The proportion of patients treated in stroke units, receiving CT scans, and receiving rtPA all increased significantly. More patients in later years were discharged home, living at home at 3 months and had functional outcomes at 3 months

	1995 (N=10 287)	2001 (N=21 273)	2005 (N=25 240)	2010 (N=25 558)
Care in stroke unit, %	53.9	72.5	89.8	87.5
CT scan, %	87.5	96.5	97.5	98.0
<b>Thrombolysis, %</b>	<b>0</b>	<b>0.4</b>	<b>3.3</b>	<b>8.6</b>
Number of days in hospital		18	17	15
Discharge to in-hospital rehabilitation, %		23.6	17.2	13.4
Discharge home, %		44.2	49.5	52.4
Living at home after 3 months, %	68.1	75.0	77.8	80.0
Functional outcomes at 3 months, %				
Independent walking		83.8	84.3	85.6
Independent toileting		81.2	81.9	84.1
Independent dressing		78.0	79.1	80.4

All outcomes  $p < 0.001$  for trends over time, except % CT scan ( $p = 0.003$ ) and receiving home help service ( $p = 0.04$ )

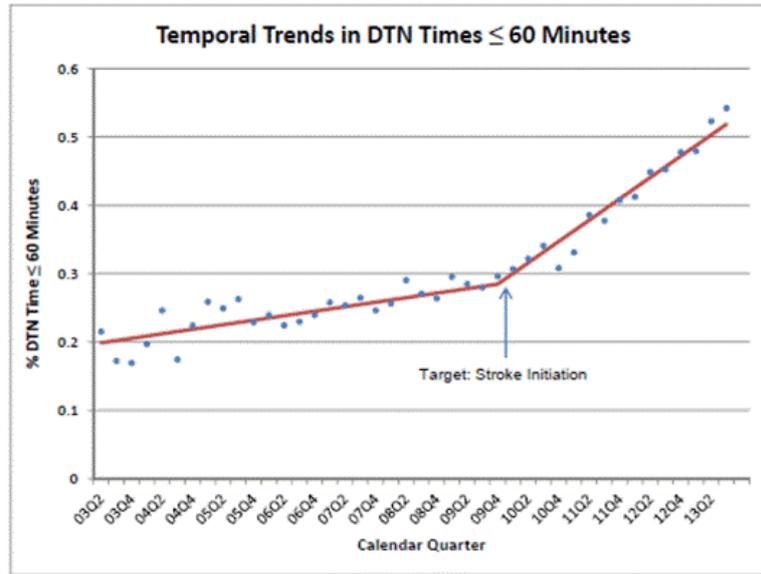
***The Target:Stroke initiative is associated with rapid improvements in stroke care***

A presentation at the recent International Stroke Conference in San Diego, USA, showed that since its introduction in 2010, the Target: Stroke initiative has had a significant and positive impact on timely rtPA administration and clinical outcomes in the USA.<sup>13</sup>

Analysis of data from >70 000 patients showed:

- A significant decrease in DNT and a significant increase in patients with DNT ≤60 mins
  - Median DNT: 74 min in Q4 2009; 59 min in Q3 2013
  - DNT ≤60 min: 29.6% in Q4 2009; 53.3% in Q3 2013
- Faster DNT was accompanied by improvements in clinical outcomes between 2009 and 2013
  - Decreased in-hospital mortality rates and symptomatic intracranial haemorrhage (ICH) rates
  - Increased discharge home rates and independent ambulatory status rates
  - Decrease in rtPA complications

**Figure: Time Trend in DTN Times within 60 Minutes Pre- and Post-Target: Stroke**



**Table: Clinical Outcomes Pre- and Post-Target Stroke Implementation**

Outcome	Pre-Target Stroke (n=27,303)	Post-Target Stroke (n=42,743)	P value	Adjusted Harzard Ratios (95% CI)*	P value*
In-Hospital Mortality	9.93%	8.25%	<0.0001	0.89 (0.83-0.95)	0.0004
Discharge Home	37.7%	42.6%	<0.0001	1.13 (1.08-1.19)	<0.0001
Ambulatory Status Independent	42.2%	45.3%	<0.0001	1.03 (0.97-1.09)	0.3957
Symptomatic ICH	5.68%	4.70%	<0.0001	0.84 (0.77-0.91)	<0.0001
tPA Complications	6.68%	5.51%	<0.0001	0.83 (0.77-0.90)	<0.0001

\*adjusted for patient characteristics, including stroke severity (NIHSS), and hospital characteristics

*'...our findings suggest that more rapid reperfusion therapy in acute ischemic stroke is not only feasible, but can be achieved with actual reductions in complications and improved outcomes'<sup>13</sup>*

**CTP imaging may help to identify patients who would benefit from thrombolysis**

Incorporating CT perfusion (CTP) imaging into stroke care protocols may facilitate thrombolysis treatment decisions, based on experiences in the USA and Malaysia.<sup>14,15</sup>

A prospective analysis of the effect on clinical management of a new imaging protocol incorporating CTP and CT angiography was conducted by Noorian et al.<sup>14</sup> During the 6-month study period, 83 patients presented within 4.5 hours of stroke onset and had CTP, and 30 (36%) of these received IV thrombolysis. The imaging protocol was reported to aid stroke team decision-making in nearly half of cases.

A retrospective review of 272 AIS patients admitted to a tertiary referral hospital over a 2-year period identified 44 patients who arrived within 4.5 hours of stroke onset and had CTP imaging<sup>15</sup>. Five patients received IV thrombolysis due to significant penumbra seen on CTP (one was treated >4.5 hours after stroke onset). Patient outcomes were favourable, with modified Rankin Scale (mRS) scores of 1 or 2 at

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follow-up.

### **Telestroke implementation is associated with an increase in rtPA treatment rates**

A retrospective medical records review of AIS admissions before and after implementation of a US community hospital telestroke network revealed an increase in overall IV rtPA use in the post-telemedicine period.<sup>16</sup> Telemedicine had no effect on OTT or DNT.

*'the implementation of telestroke support was associated with an incremental increase in the use of IV rtPA.'*<sup>16</sup>

	Pretelestroke (n=919)	Post-telestroke (n=1669)
Overall IV rtPA use	26 (2.8%)	113 (6.8%)**
IV rtPA protocol violations	2 (0.2%)	5 (0.3%)
Onset-arrival time <3 hours	55 (6%)	159 (9.5%)*
Symptomatic ICH in patients receiving rtPA	1/27 (3.7%)	1/113 (0.9%)

\* $p < 0.01$  and \*\* $p < 0.001$  vs pretelestroke

### **Telestroke can improve access to rtPA treatment in depopulated rural areas**

After installing a telemedicine system in a depopulated region of rural France, 53 patients were examined via telestroke between Oct 2010 and Feb 2012; 21 patients with confirmed AIS (mean age 72 years; range 38–88 years) received rtPA.<sup>17</sup> Mean OTT was 169 min and mean DNT was 69 min. Patient outcomes at 3 months were favourable and the authors conclude that:

**'In rural areas, for elderly patients with severe ischaemic strokes, telemedicine appears to be a way of improving accessibility and benefits of rt-PA treatment'**

CI, confidence interval; DALY, disability-adjusted life year; MRI, magnetic resonance imaging; NIHSS, National Institute of Health Stroke Scale n.s., not significant; TIA, transient ischaemic attack

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