

PUBLICATION ALERT NEWSLETTER

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.

The concept that ‘time is brain’ after an AIS* is well established. The earlier that thrombolysis with IV rtPA is given to a patient with AIS, the greater are the chances of a favourable outcome, because more brain tissue is saved from the devastating damage caused by stroke. An imaging study has recently identified that it is salvage of the penumbra specifically that is associated with reduced post-stroke disability.

“...earlier treatment results in less disability because it saves penumbra”¹

Eligible patients receiving rtPA within 60 minutes of hospital arrival is a common target, but even shorter treatment times are desirable. By implementing stroke care protocols that target multiple pre-hospital and in-hospital factors, it is possible to deliver thrombolysis more quickly, to more patients.

This issue of the Actilyse[®] Publication Alert Newsletter demonstrates the advances that can be made in acute stroke care, while also highlighting the importance of ensuring that these advances benefit all patients regardless of characteristics or location.

*Abbreviations are defined at the end of the newsletter.

EARLIER THROMBOLYSIS SALVAGES MORE PENUMBRA AND IMPROVES PATIENT OUTCOMES

Kawano and colleagues examined how effective perfusion CT imaging variables (e.g. penumbral volumes) were at predicting post-stroke disability in patients with AIS undergoing thrombolysis, compared with standard clinical predictors (e.g. OTT).¹

The results showed that each minute saved in OTT translated into an extra 4 days of disability-free life, while each mL of penumbra saved translated into an extra week of disability-free life. The impact of penumbral salvage was greater in younger patients (<70 years). Interestingly, the association between OTT and reduced disability was not observed after adjustment for imaging variables. Whereas, even after adjustment for clinical variables, extent of penumbra salvaged remained a strong predictor of longer disability-free life.

The authors conclude that greater penumbral salvage appears to explain why earlier treatment increases disability-free life.

Study details

- Analysis of data from 772 patients with AIS who received rtPA and who underwent perfusion CT scanning within 6 h of stroke onset (2011–2013), to examine the influence of imaging and clinical variables on long-term disability after stroke
 - Functional outcome was measured in DALYs, which comprises years of life lost due to premature death and years of life lost due to disability
 - Fewer DALYs equate to longer disability-free life after stroke
 - Median OTT was 152 minutes (IQR: 116–190)
- Stroke severity was related to ischaemic core volume and penumbral volume at baseline: for each 1-point increase in NIHSS score, ischaemic core volume increased by 2.3 mL and penumbral volume increased by 4.6 mL
- Baseline factors that negatively influenced functional outcome (more life-years lost) were: greater ischaemic core volume; greater penumbral volume; higher stroke severity (NIHSS score); older age
- Treatment factors that positively influenced functional outcome (fewer life-years lost) were: shorter OTT; greater salvage of penumbra; partial or complete recanalization achieved
- In patients with recanalization, each 1-min decrease in OTT saved 10.9 DALY-days and each 1 mL of salvaged penumbra saved 11.8 DALY days
 - For the median salvaged penumbra volume of 56.7 mL in patients with recanalization, 660 DALY days were gained
- The impact of penumbral salvage was greater in younger patients: each 1 mL of salvaged penumbra saved 3.0 DALY days in those ≥70 years of age and 10.5 DALY days in those <70 years of age

“Each minute of earlier onset-to-treatment time resulted in a saving of 4.4 disability-free days after stroke”

“For every millilitre of penumbra salvaged, 7.2 days of disability-adjusted life-year days were saved”¹

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THROMBOLYSIS WITHIN 1 HOUR OF AIS ONSET ACHIEVES THE MOST FAVOURABLE OUTCOMES

Reinforcing the benefits of rapid treatment, a recent study showed that patients who received rtPA within 60 minutes of stroke onset (the ‘golden hour’) had excellent functional outcomes.² At the time of discharge:

- nearly a half were walking independently
- nearly half could be sent home immediately
- more than a third were free of disability.

Treatment within the first 3 hours after onset was also important, because the chances of a good outcome declined most rapidly during this period. This emphasizes the importance of reducing pre- and in-hospital delays to achieve earliest possible treatment.

The authors conclude that their findings support intensive efforts to organize systems of stroke care to improve the timeliness of thrombolytic therapy in AIS, including greater use of telemedicine networks and, potentially, mobile stroke units.

Study details

- Analysis of data from 65 384 patients with AIS admitted to Get With The Guidelines-Stroke hospitals and treated with rtPA within 4.5 h of stroke onset (Jan 2009–Sep 2013), to explore the additional benefits of hyperacute treatment within 1 h
 - Median OTT was 141 min (IQR: 110–173); 878 (1.3%) patients had an OTT ≤60 min
- Patients treated within 60 min were more likely to be discharged home, have independent ambulation, and be disability free, than those treated later (see table)
 - For every 15-min delay in treatment, the number of patients with independent ambulation at discharge or discharged home decreased by approximately 10 per 1000 treated
 - Chance of being discharged home declined most rapidly in the first 170 min after stroke
- Rates of SICH and in-hospital death were similar across groups

OUTCOME (UNADJUSTED ANALYSIS)	OTT 0–60 min (n=828)	OTT 61–90 min (n=6120)	OTT 91–180 min (n=43,221)	OTT 181–270 min (n=10,721)	p VALUE (0–60 vs >60 min)
mRS score 0–1 at discharge	40%	31%	27%	30%	<0.001
Independent ambulation at discharge	47%	45%	41%	44%	0.008
Discharge to home	48%	45%	41%	46%	0.002
SICH	3.7%	3.9%	4.6%	4.5%	0.27
In-hospital mortality	8.0%	7.0%	7.7%	6.8%	0.57

“Thrombolysis started within the first 60 minutes after onset is associated with best outcomes for patients with acute ischemic stroke.”²

PHYSICIANS TAKE MORE TIME WITH PATIENTS WHO ARRIVE SOON AFTER STROKE ONSET

For patients who present soon after AIS onset, there may be a perception that extra time is available in the thrombolysis treatment window, resulting in longer delays to rtPA treatment than among patients who present later.

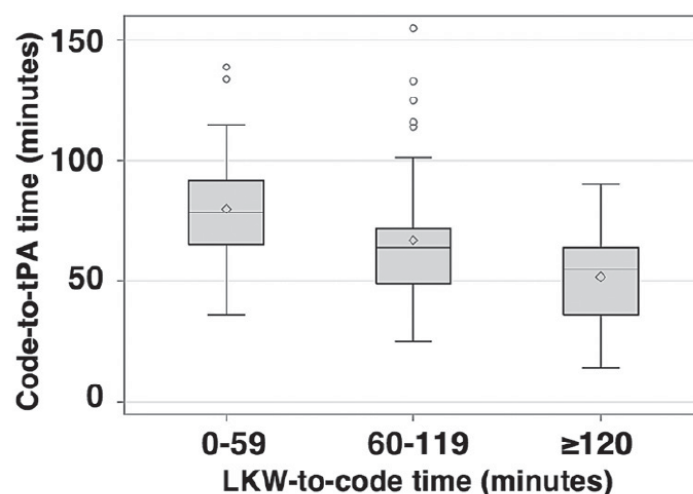
In a single US hospital, it took an extra 28 minutes to deliver rtPA to patients with AIS who presented within an hour of stroke onset versus those who presented more than 2 hours after onset.³

The authors observe that the 30 minutes of time lost in earlier-presenting patients could decrease the odds of a favourable outcome by 30%. To improve patient care and outcomes, it is important to continue educating medical staff and promoting the ‘time is brain’ message.

Study details

- Analysis of data from 122 patients who received rtPA at the Mount Sinai Hospital Stroke Registry, USA (Jan 2009–Dec 2015), grouped by time from last known well to stroke team activation (‘LKW-to-code’):
 - 0–59 min (n=38), 60–119 min (n=49), and ≥120 min (n=35)
- Mean LKW-to-code time was 91 min and mean code-to-rtPA time was 67 min
- Patients with shorter LKW-to-code times had longer code-to-rtPA times (figure)
 - Mean code-to-rtPA time was 28 min longer in the 0–59-min group than in the ≥120-min group
 - For every 4-min decrease in LKW-to-code time, code-to-rtPA time increased by 1 min (p<0.0001)
 - Much of the delay occurred after the CT scan was completed, suggesting it was driven by evaluating physicians
 - This association was independent of potentially confounding factors (age, sex, race, and stroke severity)

Study details (continued)



Relationship between LKW-to-code time and code-to-rtPA time, divided by LKW-to-code time (n=122)
 Mean code-to-rtPA times: 80 min (0–59-min group); 67 min (60–119-min group); 52 min (≥120-min group)
 Analysis of variance: $p < 0.0001$

“Rather than simply giving tPA to all of the right patients, we must remain mindful that our goal is to give tPA as soon as safely possible to the right patients.”³

ASSESSING BARRIERS TO TIMELY TREATMENT CAN LEAD TO IMPROVEMENTS IN STROKE CARE

Several factors potentially contribute to delays in rtPA administration to eligible patients. By identifying barriers and rate-limiting steps in the stroke care pathway, areas of improvement can be addressed and timeliness of therapy improved.

A retrospective review of data from 130 patients with AIS treated with rtPA at a Primary Stroke Centre (Feb 2011–Nov 2013) found that 43% had a DNT ≤60 minutes.⁴ This identified five key steps that influenced the timeliness of thrombolysis: times to ED physician consultation, neurologist arrival, blood sample acquisition, CT scan, and laboratory results (table).

Except for time to laboratory results, most patients who received rtPA and had a DNT of ≤60 minutes were also on target for other outcomes. This suggests that rapid thrombolysis can be achieved in clinical practice when goals are achieved for individual steps within the acute stroke care chain.

The authors conclude that prompt physician evaluation, direct transfer to the CT scanner, and quick turnaround on laboratory values are all important in ensuring rapid delivery of rtPA.

OUTCOME	DNT ≤60 min (n=56)	DNT >60 min (n=74)	p VALUE
DNT, median (IQR) min	52 (8)	87.5 (37)	<0.001
Arrival to ED physician consultation, median (IQR) min	1.5 (8.5)	10 (21)	<0.001
N (%) within 10 min	43 (76.8)	36 (48.6)	0.001
Arrival to neurology consultation, median (IQR) min	6.5 (14.0)	21 (29)	<0.001
N (%) within 15 min	34 (60.7)	18 (24.3)	<0.001
Arrival to blood sample acquisition, median (IQR) min	13 (10)	24 (20.25)	<0.001
Arrival to CT scan, median (IQR) min	6 (6.25)	19 (17)	<0.001
N (%) within 25 min	51 (91.1)	47 (63.5)	<0.001
Arrival to laboratory results, median (IQR) min	48 (16.75)	56 (25.75)	0.004
N (%) within 45 min	21 (37.5)	21 (28.4)	0.271

“The development of protocols to ensure the rapid receipt of tPA therapy should focus on limiting any potential delay these steps may cause.”⁴

A MULTIDISCIPLINARY STROKE CARE PROTOCOL CAN REDUCE IN-HOSPITAL DELAYS AND IMPROVE THROMBOLYSIS TREATMENT RATES

Developing a protocol to target multiple steps within the stroke care chain can reduce in-hospital treatment delays so that it is possible for most patients with AIS to receive rtPA within 30 minutes of hospital arrival.

Implementation of a multidisciplinary stroke protocol at a single university hospital more than halved DNT without compromising safety; almost two-thirds of patients had a DNT ≤ 30 minutes and more than half had favourable functional outcomes at discharge.⁵

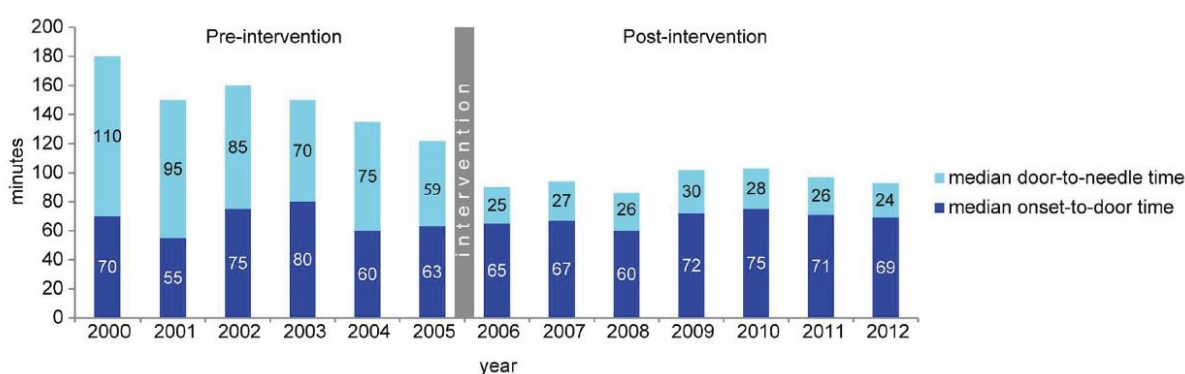
The authors believe that the simple strategies included in the protocol can be adopted easily into everyday clinical practice, to reduce in-hospital logistical and patient-related treatment delays in stroke care.

Study details

- Analysis of data from consecutive patients with AIS treated with rtPA at Academic Medical Center, Amsterdam, to evaluate the effect on DNT of the 'ABC' multidisciplinary stroke protocol that combines multiple strategies with 24/7 stroke coverage

Acute Brain Care protocol: strategies to reduce DNT	
Pre-hospital phase Education of EMS staff to recognize and prioritize acute stroke Hospital pre-notification by EMS in case of suspicion of acute stroke Collective pager warning of stroke team prior to patient's arrival Pre-registration of patient in hospital information system and pre-order of laboratory tests Direct availability of a CT room in ED History, medication use, and point-of-care glucose measurement during ambulance transport	In-hospital phase Direct transfer onto CT table upon hospital arrival Simultaneous EMS briefing, neurological evaluation, and blood withdrawal on CT-table Treatment decision before laboratory results are available Point-of-care INR if needed Dedicated Acute Brain Care room adjacent to CT room at the ED Use of bed with built-in scales for exact weight determination Predefined tables with weight-adjusted rtPA dosage

- In-hospital treatment delays were significantly reduced in the post-intervention period (Jul 2006–Dec 2012) compared with the pre-intervention period (Jan 2000–Dec 2005) (see figure and table)
 - Pre-intervention: No patients had a DNT ≤ 30 min
 - Post-intervention: 63% of patients had a DNT ≤ 30 min
- Proportion of patients with a favourable outcome increased post-intervention (52%) vs pre-intervention (39%)
- SICH rate remained stable (3.0% pre-intervention vs 4.4%)



TIME INTERVALS, median (IQR) min	PRE-INTERVENTION (n=100)	POST-INTERVENTION (n=373)	p VALUE
Onset-to-door	65 (50–90)	71 (48–120)	0.156
Door-to-CT	35 (27–47)	6 (4–10)	<0.001
CT-to-needle	40 (31–55)	20 (15–28)	<0.001
DNT	75 (60–105)	28 (20–37)	<0.001
OTT	158 (135–177)	105 (75–160)	<0.001

“...important and sustained reduction of DNT to less than 30 minutes can be safely achieved by optimizing in-hospital stroke work flow and treatment”⁵

PATIENT-RELATED FACTORS CAN BE TARGETED TO IMPROVE THROMBOLYSIS TREATMENT RATES

Thrombolysis treatment rates can be improved by targeting modifiable patient- and hospital-related reasons for lack of treatment.

Of 61 698 eligible patients with AIS admitted to Get With The Guidelines-Stroke hospitals within 2 hours of stroke onset (Apr 2003–Dec 2011), 75% received rtPA within 3 hours on onset.⁶ Failure to treat the remaining 25% of potentially eligible patients in this time frame was associated with many different factors, some of which may be modifiable:

- Patient-related: characteristics (older age, female, non-white race); medical history (diabetes mellitus, prior stroke)
- System-related: pre-hospital delays (arrival not via EMS; longer onset-to-arrival time), in-hospital delays (out-of-hours arrival; longer door-to-CT time); admission to a rural hospital or non-stroke centre

The authors conclude that, to improve thrombolysis treatment rates and timeliness:

- Patients with stroke risk factors and their families should be educated about potential stroke systems and encouraged to call EMS if stroke is suspected
- Standardized protocols for stroke recognition by EMS dispatchers and providers should be implemented
- ED triage should be accelerated for AIS patients, with an emphasis on rapid brain imaging
- Efforts to develop stroke systems of care and establish stroke centres should be continued

“...to improve thrombolysis rates, continued development of systems of care for stroke should remain a high priority.”⁶

EMS TRAINING HELPS TO REDUCE PRE-HOSPITAL DELAYS FOR POTENTIAL THROMBOLYSIS CANDIDATES

An on-scene time (OST) of ≤15 minutes is recommended by the ASA for EMS responders to patients with suspected AIS. While the OST is a modifiable part of the stroke care chain with time-saving potential, it has received little attention until now.

In a novel study at a Helsinki comprehensive stroke care centre, the median OST of potential thrombolysis candidates was significantly decreased by 10% (from 25 to 22.5 min) after implementing a low-cost EMS training programme.⁷

The programme aimed to increase awareness of time spent on-scene and to encourage a ‘load and go’ approach where possible. Ambulance crew who received the training package, and those who had advanced life support training, were more likely to have shorter OST.

The authors conclude that a focused training programme targeting how to operate on the scene of an acute stroke can save several minutes in the pre-hospital chain of care.

MANAGING THE NUMBER OF PATIENTS IN THE EMERGENCY ROOM CAN REDUCE TREATMENT DELAYS

The timely management of patients with AIS upon arrival in the ED is dependent on rapid triage and access to the CT scanner. Overcrowding of the ED (by patients in the waiting room, in treatment areas or occupying beds after admission) reduces the likelihood of meeting door-to-imaging goals for acute stroke.⁸

A retrospective analysis of 463 Code Stroke activations at a US regional stroke centre hospital showed that 61% of patients met the target door-to-imaging time of 25 minutes (median 21 min; range 4–221). The median ED occupancy rate (total number of patients in the ED divided by the number of licensed ED beds) when these patients were admitted was 122%. For each 10% increase in ED occupancy rate, the odds of a door-to-imaging time ≤25 minutes decreased by 17% (OR: 0.83; 95% CI: 0.75–0.91).

The article highlights that, although a low level of overcrowding may be accommodated, the ED becomes less able to support timely stroke care as it becomes more overcrowded. Reducing ED overcrowding using a variety of hospital-wide coordinated strategies may help to avoid in-hospital delays in acute stroke care.

“In addition to improving stroke-specific processes of care, efforts to reduce ED overcrowding should be considered central to optimizing the timeliness of acute stroke care”⁸

ADMISSION OF PATIENTS DIRECTLY TO A STROKE UNIT IS ASSOCIATED WITH HIGH THROMBOLYSIS RATES

Introduction of a new care pathway, in which patients with suspected AIS ‘under thrombolysis alert’ were admitted directly to the hospital stroke unit rather than to the ED, resulted in a large proportion of patients with AIS receiving rtPA.⁹

Of 81 patients admitted directly to the stroke unit of a university hospital in France, 57 (70%) had confirmed stroke (45 had cerebral infarcts) and 26 (58% of those with AIS) received IV rtPA. Median onset-to-door time in the rtPA-treated group was 90 minutes (IQR: 68–142), door-to-imaging time was 33 minutes (IQR: 23–38) and DNT was 63 minutes (IQR: 58–70).

The authors conclude that, despite a high proportion of stroke mimics, direct and fast admission of suspected stroke patients to a neurological stroke unit can facilitate timely thrombolysis treatment of patients with AIS.

PSC CERTIFICATION CAN LEAD TO RAPID IMPROVEMENTS IN THROMBOLYSIS RATES

Increases in rtPA use are possible when hospitals commit to providing high-quality stroke care, such as that offered by PSCs.

A retrospective analysis of 5277 cases of AIS treated at seven acute-care community hospitals in Texas identified large increases in thrombolysis use between January 2000 and June 2012.¹⁰ Two of the hospitals were certified as PSCs during this period and this probably contributed to the substantial increase in thrombolysis. However, thrombolysis rates were higher and increased more rapidly in patients with most-severe stroke than in those with least-severe stroke, and there were also differences in rtPA use between ethnic groups. This reinforces the need to examine patient subgroups for treatment differences that may be masked by overall stroke care improvements, so that any gaps in the level of care received can be identified and addressed.

THE QUALITY OF STROKE CARE PROVISION MAY VARY ACROSS DIFFERENT PSCs

There can be differences between the organizations that certify PSCs in terms of how stroke care standards are assessed. This may lead to variations in the quality of care provided by PSCs.

An analysis of 477 297 patients with AIS admitted to 977 certified PSCs participating in the US Get With The Guidelines-Stroke programme (Jan 2010–Dec 2012) found that all hospitals had high conformity with performance measures.¹¹ However, PSCs certified by state-based agencies performed significantly less well than PSCs certified by the Joint Commission in two key areas: rtPA use (7.1% vs 9.0%) and in-hospital mortality (5.6% vs 4.5%).

This information may be useful in improving standards of care as well as the ways in which those standards are assessed.

HIGH- AND MIDDLE-INCOME COUNTRIES DIFFER IN STROKE CARE ORGANIZATION AND TREATMENT

A survey completed in 2014–2016 by 94 hospitals from nine different countries revealed stroke care organization and delivery varied across the whole stroke care pathway according to the national level of income.¹²

All responding hospitals had an established stroke care programme and almost all offered thrombolysis, yet those situated in high income countries (HIC) were significantly more likely to administer rtPA than those in middle income countries (MIC) (10% vs 5% of patients with AIS; $p=0.002$). This may be because patients admitted to HIC hospitals had shorter pre-hospital delays (81% of patients arrived via EMS and 35% arrived within 4 h of stroke onset, compared with 21% and 10%, respectively, for MIC).

The article highlights that stroke care protocols and pathways need to be supported by appropriate healthcare resources and educational campaigns, to ensure they can translate into improvements in rtPA treatment rates and timeliness.

LOCALIZATION OF STROKE IN THE POSTERIOR CIRCULATION AFFECTS TIMELINESS OF TREATMENT

Analysis of data from 71 010 patients with AIS in Austria revealed that those with posterior circulation stroke (PCS) had significantly longer onset-to-door time (27 min longer) and DNT (13 min longer) than those with anterior circulation stroke (ACS).¹³ Fewer PCS patients than ACS patients arrived at hospital within 3 hours of stroke onset (54% vs 68%) and rtPA treatment rates were lower (8.6% vs 16.6%).

Understanding the causes of pre-hospital and in-hospital delays for patients with PCS is necessary, so that these can be addressed. Using diagnostic tools that include symptoms relating to the posterior circulation might facilitate earlier identification of PCS, enabling more-efficient triage and reducing pre-hospital and in-hospital delays in this patient group.

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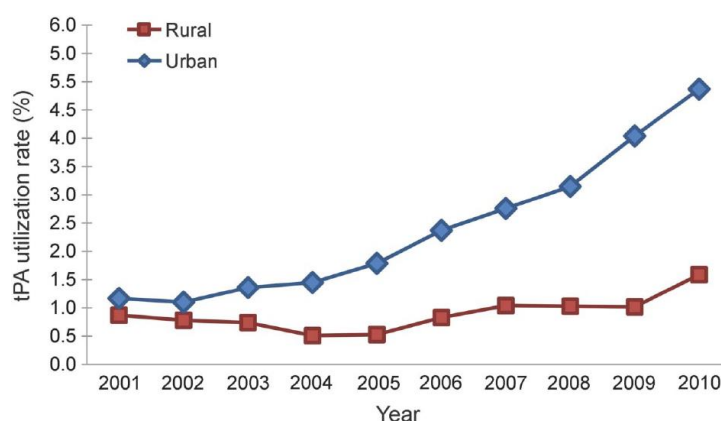
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rtPA USE IS INCREASING AT DIFFERENT RATES ACROSS URBAN AND RURAL SETTINGS

In addition to improving stroke care quality and outcomes, PSC certification is intended to reduce disparities in stroke care. However, in 2010 the proportion of US hospitals that were PSCs was higher in urban (18.7%) than in rural (2.4%) areas. A growing disparity between urban and rural stroke care has been observed, with patients with AIS admitted to urban hospitals being twice as likely to receive rtPA than those admitted to rural hospitals.¹⁴ Greater understanding of the factors affecting rtPA use is necessary to ensure that access to thrombolysis is equitable for all. Increasing the number of ‘stroke ready’ hospitals and PSCs, improving processes of care, and developing stroke networks would help to address disparities in stroke care.

Study details

- Analysis of data from 914 500 patients with AIS included in the US Nationwide Inpatient Sample, to explore temporal trends in rtPA use in urban and rural areas between 2000 and 2010
- Overall, 21 190 patients (2.3%) received rtPA, with an increase in treatment rates over time
- Treatment rates were higher and increased faster in urban hospitals than in rural hospitals (see figure)
 - In urban hospitals, rtPA use quadrupled between 2001 and 2010 (from 1.2% to 4.9%)
 - In rural hospitals, rtPA use less than doubled between 2001 and 2010 (from 0.9% to 1.6%)
 - rtPA thrombolysis for AIS was twice as likely to occur in an urban hospital (adjusted OR: 2.11; 95% CI: 1.97–2.27).



Trends in rtPA utilization rates by hospital location, Nationwide Inpatient Sample, 2001–2010

“...fewer patients with AIS receive rtPA at rural hospitals compared to urban hospitals and this disparity has increased”¹⁴

RURAL TELESTROKE NETWORKS CAN MATCH THROMBOLYSIS TREATMENT TIMES IN URBAN AREAS

Comparison of two different systems of stroke care has shown that a rural telestroke network can match an urban centralized hospital in terms of thrombolysis treatment rates and timeliness of therapy.¹⁵

Within the TEMPiS telestroke network in rural Germany, a thrombolysis rate of 13% was achieved from January 2011 to December 2013 that matched that achieved by the urban Helsinki University Central Hospital over the same period. Onset-to-treatment times in the two systems were also similar, with significantly shorter onset-to-door times offsetting longer DNT in the telestroke network compared with the central hospital (see table).

Opportunities may exist to improve in-hospital delays within telestroke networks and reduce treatment times further.

TREATMENT TIME, median (IQR) min	HELSINKI URBAN HOSPITAL (n=826)	TEMPI S TELESTROKE NETWORK (n=1600)	p VALUE
Onset-to-door time	88 (60–135)	65 (48–101)	<0.001
DNT	18 (13–30)	39 (26–56)	<0.001
OTT	117 (81–168)	115 (87–155)	0.452

Abbreviations: ACS, anterior circulation stroke; AIS, acute ischaemic stroke; ASA, American Stroke Association; CI, confidence interval; CT, computed tomography; DALY, disability-adjusted life years; DNT, door-to-needle time; ED, emergency department; EMS, emergency medical services; HIC, high-income country; INR, international normalised ratio; IV, intravenous; LKW, last known well; MIC, medium income country; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; OST, on-scene time; OTT, onset-to-treatment time; PCS, posterior circulation stroke; PSC, Primary Stroke Centre; rtPA (tPA), recombinant tissue plasminogen activator; SICH, symptomatic intracranial haemorrhage.

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The Angels initiative aims to increase the number of patients treated in stroke-ready hospitals and to optimize the quality of treatment in all existing stroke centres.

See more at:

<https://angels-initiative.com/>

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