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.

Reducing pre-hospital delays remains a primary goal of stroke care, to ensure as many patients with AIS* as possible reach hospital in time to receive rtPA treatment. As the number of AIS patients presenting to hospital increases, stroke care pathways need to adapt to maintain or improve access to stroke expertise and appropriate treatment despite limited healthcare resources.

In this issue of the Actilyse® Publication Alert Newsletter, we look at various barriers to timely stroke treatment and how these may be overcome. We also highlight initiatives that can be adopted to meet the growing demands for expert stroke care, such as nurse-led protocols and integrated hospital networks.

*Abbreviations are defined at the end of the newsletter.

SITS-EAST ANALYSIS DEMONSTRATES SAFETY AND EFFECTIVENESS OF rtPA FOR IN-HOSPITAL STROKE

Patients who experience AIS while in hospital may be particularly vulnerable to poor outcomes. Firstly, they are likely to be sicker than community-based patients, with more comorbidities. Secondly, access to rtPA treatment may be delayed by under-recognition of symptoms and a lack of pre-specified in-hospital care pathways.

Observational data from the international SITS-EAST registry confirm that patients with in-hospital stroke (IHS) have substantially longer door-to-imaging time and DNT than do patients with out-of-hospital stroke (OHS).[1] However, after adjusting for differences in baseline characteristics (including higher prevalence of cardiovascular disease in IHS patients), rtPA treatment in IHS patients shows similar safety and efficacy outcomes to that in OHS patients.

The authors conclude that rtPA treatment is both safe and effective in eligible patients with IHS. Delivery of rtPA to this patient group could be improved by raising awareness of IHS among hospital staff and by establishing IHS care protocols.

Study details

- Analysis of data from 196 patients with IHS (stroke onset during hospitalization for any reason) and 5124 matched patients with OHS (patients who were not hospitalized at stroke onset), all of whom received IV thrombolysis treatment for AIS during a 12-year period (Oct 2003–Dec 2015), to compare treatment outcomes
  - Data were collected prospectively for the observational SITS-EAST registry, which includes 12 countries (Bulgaria, Croatia, Czech Republic, Estonia, Greece, Hungary, Lithuania, Poland, Russia, Slovakia, Slovenia and Turkey)
  - The comparator OHS group was propensity-score matched to the IHS group using all baseline characteristics, to balance factors – other than stroke onset location – that might influence treatment outcome
- 2% of AIS patients treated with rtPA in the SITS-EAST registry had IHS
  - Before propensity-score matching, patients with IHS were more likely than OHS patients to have congestive heart failure, and to be treated with antiplatelets, antihypertensives or statins
- After matching, patients with IHS had longer treatment delays than did patients with OHS (see table)
  - Median DNT among patients with IHS was 90 min, 25 min longer than in patients with OHS (p<0.001)
- Despite longer delays, patients with IHS had similar treatment outcomes to patients with OHS (see table)
  - <2% of all patients experienced SICH; 60% achieved functional independence at 3 months

OUTCOME	IHS (n=196)	OHS (n=5124)	*p* VALUE
Onset-to-door, median (IQR) min		76 (55–111)	
DNT, median (IQR) min	90 (60–140)	65 (47–95)	<0.001
Door-to-imaging, median (IQR) min	40 (20–90)	24 (15–35)	<0.001
SICH, %	1.6	1.9	0.756
3-month mRS score, median (IQR)	2 (0–4)	2 (1–4)	0.273
Favourable functional outcome (mRS score 0–1) at 3 months, %	46.4	42.3	0.257
Functional independence (mRS score 0–2) at 3 months, %	60.7	60.0	0.447
3-month mortality, %	14.3	15.1	0.764

"Our findings underline the safety and efficacy of intravenous thrombolysis treatment for in-hospital stroke."[1]

rtPA TREATMENT RATES HAVE BEEN INCREASING IN POLAND

Timely access to rtPA treatment depends on many factors, which may be patient-related, hospital-related or system-related.

In Poland, rtPA treatment became fully reimbursed by the National Health Fund in 2009. A recent analysis found that rtPA use has increased continuously since 2009. However, thrombolysis rates remain suboptimal, and women are less likely than men to receive rtPA.[2]

The authors conclude that the thrombolysis rate in Poland "is still relatively low despite the continuous increase" and that further actions, such as public health education initiatives, are required to improve the timely detection and treatment of AIS.

Study details

- Analysis of data from 69 403 patients hospitalized with AIS in the Silesian Province of Poland (2009–2015), to assess the treatment of AIS since rtPA became fully reimbursed by the National Health Fund in 2009
- 3282 patients (4.7% of AIS cases) received rtPA between 2009 and 2015
  - A significantly lower proportion of women (4.5%) than men (5.1%) received rtPA (p<0.001)
- The rate of rtPA administration has increased gradually over time, from 1.2% to 9.3% (see table)
  - Thrombolysis rates increased over time for both men and women, but in each year women were less likely to receive rtPA

YEAR	2009	2010	2011	2012	2013	2014	2015
Number (%) of patients with AIS treated with rtPA	107 (1.2%)	196 (2.0%)	296 (2.9%)	453 (4.4%)	537 (5.2%)	806 (8.2%)	**887 (9.3%)**

RECOGNIZING STROKE AS AN EMERGENCY IS AN ESSENTIAL STEP IN THE AIS CARE PATHWAY

The first step in the AIS care pathway is crucial. Unless stroke symptoms are recognized promptly and dealt with as a medical emergency, patients cannot reach hospital in time to receive rtPA.

A study of 223 AIS patients admitted to a tertiary care centre in Warangal, India, over a 6-month period (Oct 2016–Mar 2017) demonstrated that pre-hospital delays result in low thrombolysis rates:[3]

- On average, AIS patients waited 4.4 h after symptom onset before contacting a medical professional
  - In 183 cases (82%), the first point of contact was a rural doctor
  - Only 18 cases (8%), presented directly to an rtPA-enabled hospital
- 210 patients (94%) arrived at hospital more than 4.5 h after symptom onset
  - 122 (58%) recognized their symptoms promptly, but only 24 (11%) were rushed for emergency care
- 13 patients (6%) arrived at hospital within 4.5 h of symptom onset, and 9 (4%) received rtPA
  - 12 (5%) of these patients were advised by their doctor to go to hospital quickly to receive thrombolysis
  - 2 (1%) patients did not receive rtPA due to in-hospital delays, and 2 (1%) patients elected not to receive treatment

The greatest barriers to early hospital presentation in this study were lack of awareness of stroke as an emergency and lack of awareness among HCPs of thrombolysis as a treatment option.

- None of the 210 late-arriving patients or their relatives were aware of rtPA treatment
- 186 (89%) did not consider stroke to be an emergency
- 139 (66%) were not told about rtPA treatment by their attending HCP(s)
- 130 (62%) were referred by their first attending HCP to a medical centre not offering rtPA
- 101 (48%) experienced transport delays

These results highlight the importance of increasing public recognition of stroke as an emergency, as well as promoting awareness among the public and HCPs of rtPA as a treatment option.

"It is crucial for the rural doctors to understand that stroke patients must be immediately sent to a hospital offering stroke thrombolysis."[3]

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HEALTHCARE SYSTEM FACTORS CAN BE TARGETED TO IMPROVE EARLY STROKE CARE

When developing stroke care protocols, it is useful to understand the factors that inhibit (barriers) or support (enablers) the delivery of care. Once these have been identified, targeted improvements may be achieved with specific behaviour-change or organizational interventions.

Craig *et al.* set out to identify and classify barriers and enablers to evidence-based stroke care using a theoretical domains framework.[4] They found that most barriers fell into the domains of 'environmental context and resources' and 'knowledge', whereas most enablers were in the domains of 'knowledge' and 'skills'.

Barriers to rapid triage and thrombolysis included lack of recognition of stroke as a priority, lack of stroke care protocols and pathways, uncertainty around rtPA administration, and limited resources. By contrast, enablers of rapid triage and thrombolysis included education, availability of policies/protocols, personal experience of rtPA use, and access to experienced colleagues. Between-hospital collaboration and ongoing quality assessment were also found to support the delivery of better stroke care.

Due to the importance of environmental context and resources in stroke care delivery, the authors observe that to improve rtPA treatment rates, specific health system factors need to be targeted.

Review details

- Systematic review of data from nine published studies (2004–2015) to identify and classify barriers and enablers to clinical behaviours in acute stroke care. Among the outcomes assessed were factors affecting triage behaviour and thrombolysis behaviour. Identified barriers and enablers were classified according to a theoretical domain framework
- Lack of knowledge – of stroke symptoms, urgency, guidelines or rtPA use – were significant barriers (see table)
  - Lack of practice, skills or training were important barriers in the 'knowledge' domain
  - Competing demands for limited time and facilities were additional environmental barriers
- Availability of checklists, policies and protocols to guide stroke care were important enablers (see table)
  - Education, experience, access to expertise, and regular feedback all helped to deliver high-quality AIS care
- Involving trained stroke nurses expands the skills of the stroke care team, and hospital networks support the sharing of expertise and experience

CLINICAL BEHAVIOUR	KEY BARRIERS	KEY ENABLERS
Triage (all patients with suspected AIS to be seen within 10 min of arrival)	Lack of stroke awareness among public/GPs Lack of awareness of stroke as a priority Limited resources (staff and facilities) Competing demands in the ED Lack of staff coordination Lack of training	 Availability of a stroke care protocol Triage checklist/decision aid
Thrombolysis (all AIS patients to be assessed for rtPA eligibility; all eligible patients to receive rtPA)	Pre-hospital delays Arrival outside treatment window Delayed GP referral ED delays/lack of urgency in ED ED-neurology communication delays Lack of guideline awareness/familiarity Lack of skills or experience (imaging interpretation; patient eligibility) Lack of thrombolysis knowledge/experience Reluctance to administer rtPA (risk/benefit uncertainty) Limited resources (time, human, financial)	 Availability of hospital stroke care policies (e.g. rapid referral from ED to stroke specialists) Continuing professional education Access to advice from senior colleagues rtPA eligibility checklist/decision aid Exposure to, and experience of, thrombolysis (via mentoring, protocols, telemedicine) Education on rtPA use and SICH risk Short intra-hospital distances Availability of trained stroke nurses Collaboration with staff outside the stroke unit Between-hospital benchmarking and sharing of experiences Quality assurance/continuous feedback Participation in quality improvement and research programmes

NURSE-DRIVEN STROKE PROTOCOLS CAN REDUCE IN-HOSPITAL TREATMENT DELAYS

Training ED nurses to run stroke codes may speed up triage and reduce treatment delays, particularly in hospitals that lack stroke neurologists. A single spoke hospital in Texas, USA, adopted a parallel workflow protocol that included empowering nurses to lead the stroke code alert and initiate telestroke consultations.[5] Following implementation, three-quarters of stroke codes and telestroke encounters were driven by nurses and nurse-led treatment times were significantly shorter: mean door-to-CT time was <25 minutes, and mean door-to-rtPA decision time was <45 minutes.

The authors conclude that the use of a nurse-driven protocol is feasible and effective, and when used in conjunction with a telestroke specialist, may improve patient outcomes by decreasing door-to-decision time.

Study details

- Prospective study of a quality-improvement initiative at a single medical centre in Texas (implemented May 2014–Oct 2014), to assess whether a nurse-driven acute stroke protocol is feasible and reduces in-hospital delays
  - ED nurses had defined roles, such as getting the CT scan and initiating telestroke, while other stroke team members worked in parallel to assess and prepare the patient
  - At the end of each stroke code, nurses self-evaluated the level of their involvement as the code driver
  - 153 stroke codes were analysed, 57 of which had symptom onset within 4.5 h ('level 1')
- 78% of level 1 strokes were primarily nurse-driven; 75% (34 of 45) telestroke consultations were primarily nurse-driven
- Nurse-driven stroke alerts had shorter delays to physician evaluation, CT scan, and rtPA treatment decision (see table)
- Only three patients received rtPA; each of these patients had a nurse-driven stroke code

PERFORMANCE INDICATOR	NON-NURSE-DRIVEN	NURSE-DRIVEN	*p* VALUE
All stroke codes (onset-to-arrival <72 h)	N=96	N=57	
Door-to-physician evaluation, mean (SD) min	35.6 (63.7)	16.1 (26.6)	0.03
Door-to-CT, mean (SD) min	38.9 (47.0)	24.4 (29.9)	0.04
Level 1 stroke code (onset-to-arrival <4.5 h)	N=32	N=25	
Door-to-physician evaluation, mean (SD) min	14.4 (17.2)	9.8 (19.1)	0.36
Door-to-decision, mean (SD) min	149.6 (234)	43.5 (18.1)	0.04

"Our study shows that effective teamwork using a parallel processing model can increase efficiency in the management of acute stroke patients and demonstrates the feasibility of a nurse-driven protocol."[5]

OPTIMAL ORGANIZATION AT ALL LEVELS IS KEY TO MAXIMIZING ACCESS TO EXPERT AIS CARE

Well-organized pre-hospital and in-hospital phases of AIS care are necessary to achieve timely rtPA treatment. However, as it is not possible to equip all hospitals with the staff and facilities needed to provide specialist care, stroke care organization must also extend beyond individual hospitals. Integrated networks of hospitals providing different levels of stroke unit care are now recommended to maintain access for all patients.[6]

Based on the healthcare system in Italy, key recommendations for optimal organization of the stroke care pathway include:

- EMS transportation for all stroke patients; use of 'stroke code' pre-notification by EMS
- Use of shared protocols between EMS and hospitals to reduce avoidable delays
- Two levels of stroke centre (PSCs, offering thrombolysis, and CSCs, offering endovascular treatment)
- Adoption of 'hub and spoke' networks for acute stroke management; patients may be transferred initially to a spoke PSC then on to the CSC ('drip and ship' model) or directly to the hub CSC ('mothership' model)
- Strategic location of CSCs to optimize access for as many stroke patients as possible

Continual training is needed for everyone involved in the acute stroke management pathway. The quality of care delivered by individual centres or by the entire network can be assessed regularly using metrics such as onset-to-door time, door-to-imaging time, DNT, in-hospital mortality, 90-day mRS scores, and rates of SICH and thrombolysis.

By working together using shared protocols, hospital networks can offer the appropriate level of care to the greatest number of patients. If expertise or resources are limited, telemedicine can be introduced to support remote or round-the-clock care.

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A STREAMLINED TELESTROKE PROTOCOL IMPROVES THROMBOLYSIS TREATMENT RATES AND TIMES

Streamlined stroke care protocols that improve rtPA treatment have been implemented successfully at individual centres. Nguyen-Huynh and colleagues combined the Helsinki stroke thrombolysis model with a centralized telestroke service across 21 community hospitals in California, USA.[7]

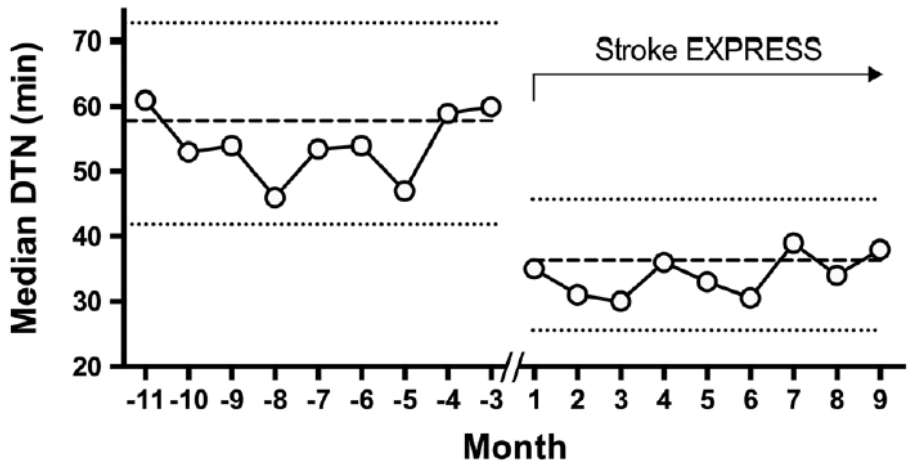
Implementation of the integrated stroke care delivery programme, called Stroke EXPRESS, led to increased rtPA use and improved DNT with no significant impact on patient safety.

The authors observe that a streamlined protocol developed for single centres can be scaled up to provide standardized, efficient care across a telestroke network. Telestroke may therefore be administered via an integrated system of stroke centres, as well as via the traditional hub-and-spoke model.

Study details

- Retrospective review of data from 867 AIS patients treated with rtPA, before and after implementation of a 21-hospital telestroke network with standardized stroke care workflow, to evaluate impact on DNT and SICH
- The Stroke EXPRESS programme was implemented between Sept 2015 and Jan 2016:
  - A streamlined workflow protocol was rolled out to 21 hospitals that connected to form a single telestroke network
  - There was no central hub hospital: all integrated hospitals were certified PSCs or CSCs
  - Key protocol elements were EMS pre-notification; stroke code activation; telestroke evaluation; rtPA pre-order by telestroke neurologist; direct transfer to CT room; parallel imaging evaluation by radiologist and telestroke neurologist
  - All acute stroke cases admitted between 7 am and midnight were managed by a single dedicated telestroke neurologist
- After implementation of Stroke EXPRESS, more AIS patients received rtPA and rtPA treatment rates increased
  - 310 AIS patients before (13.1% of 2375 stroke alerts) vs 557 AIS patients after (17.6% of 3168 stroke alerts) (p<0.001)
  - 34.4 rtPA administrations per month before vs 61.8 rtPA administrations per month after (p<0.001)
- All measures of DNT improved after implementation of Stroke EXPRESS (see table and figure)
  - Median DNT decreased by ~20 minutes and >40% of patients received rtPA within 30 min of arrival
  - Median DNT decreased across nearly all centres
- Rates of SICH were not significantly affected by Stroke EXPRESS (see Table)

PERFORMANCE INDICATOR	Pre-EXPRESS (n=310)	EXPRESS (n=557)	*p* VALUE
DNT, median (IQR) min	53.5 (42–73)	34 (26–45)	
Mean (SD) min	63.2 (31.2)	41.8 (30.6)	<0.001
<60 min, n (%)	189 (61.0)	485 (87.1)	<0.0001
<45 min, n (%)	95 (30.6)	407 (73.1)	<0.0001
<30 min, n (%)	13 (4.2)	227 (40.8)	<0.0001
SICH, n (%)	7 (2.2)	21 (3.8)	0.29



Impact of Stroke EXpediting the PRocess of Evaluating and Stopping Stroke (EXPRESS) programme on DNT

Median DNT (DTN) in min for each month across the two periods. The scale of the x axis is centred on 1 for the first month of the Stroke EXPRESS programme introduction at each centre, with a 3-month gap between the before period and the Stroke EXPRESS period (interrupted x axis line). Dashed horizontal lines correspond to the overall median DNT time for each period, flanked by horizontal dotted lines indicating the IQR.

"Introduction of a standardized modified Helsinki protocol across 21 hospitals using telestroke management was associated with increased alteplase [rtPA] administrations, significantly shorter door-to-needle times, and no increase in adverse outcomes."[7]

TELESTROKE NETWORKS CAN IMPROVE THROMBOLYSIS TREATMENT TIMES

Implementation of telestroke networks is known to improve rates of rtPA delivery at spoke hospitals. A recent study has expanded this finding to show that telestroke networks can also improve rtPA treatment times across all spoke hospitals.[8]

Quality control metrics were evaluated over a 3-year period at a telestroke network in Illinois, USA. During this time, the number of patients who received rtPA at spoke hospitals doubled (129 were treated in the first 2 years, whereas 130 were treated in the third year alone). Treatment delays were shortest in the third year, with each spoke hospital showing a reduction in time from telestroke consult to rtPA administration. The authors conclude that timely delivery of rtPA improved due to faster responses in both the hub site (rtPA was recommended sooner) and in each spoke site (rtPA was administered faster).

The telestroke network offers immediate access to specialist neurologist care plus an educational partnership with the hub hospital. These two-fold benefits are associated with ongoing clinical improvement, as assessed by multiple quality measures.

Study details

- Retrospective review of data from 259 consecutive AIS patients treated with rtPA within a US telestroke network (Jul 2011–Jul 2014), to evaluate changes in treatment delays over time
  - Data analysed for eight spoke community hospitals networked to one CSC hub
  - Telestroke programme began in March 2011; time periods analysed were Jul 2011–Jun 2013 and Jul 2013–Jul 2014
- Overall mean time from consult to rtPA administered was 42 min (range 30–55 min across spoke sites)
  - Mean time from telestroke consult to rtPA advised was 15 min (range 13–20 min across sites)
  - Mean time from rtPA advised to rtPA administered was 27 min (range 17–35 min across sites)
- Treatment delays improved significantly over time across all assessed measures (see table)
  - In the third year, rtPA treatment was recommended (by the hub site) 5 min sooner and was administered (by the spoke site) 10 min quicker, resulting in an overall 15-min reduction in mean consult-to-rtPA administration time
- All sites reduced time from consult to rtPA administration, with improvements ranging from 5 to 20 min

PERFORMANCE INDICATOR	2011–2013 (n=129)	2013–2014 (n=130)	*p* VALUE
Telestroke consult to rtPA advised, mean min	17.4	12.5	<0.0001
rtPA advised to rtPA administered, mean min	33.1	22.5	<0.0001
Telestroke consult to rtPA administered, mean min	49.9	35.0	<0.0001
'Last known well' to rtPA administered, mean min	160.9	148.6	0.045

"Participation in a telestroke program not only increases rate of IV tPA but is also associated with improvement in the timeliness of IV tPA delivery."[8]

TELESTROKE IMPROVES ACCESS TO STROKE CARE EXPERTISE AND TREATMENT

The demand for stroke care expertise is increasing, but current numbers of neurology trainees may not be sufficient to meet this need. As noted by Zerna *et al.* in a recent review, telestroke offers one solution to this challenge:[9]

"Telestroke networks enable stroke-specific procedures to be performed by less experienced physicians under the guidance of stroke neurology experts."

A single telestroke neurologist can offer guidance to multiple stroke teams, so that high-quality stroke care can be delivered to greater numbers of patients. Hub hospitals can also provide educational initiatives and quality management support to ensure remote spoke teams are able to deliver optimal care. Evidence from several studies in North America and Europe suggests that safety and effectiveness of rtPA in telestroke spoke hospitals is comparable to that achieved in dedicated stroke centres. Data also show that when telestroke networks are implemented, rtPA treatment rates increase, patient outcomes improve, and healthcare costs are reduced.

"Using telestroke, more AIS patients are treated with intravenous alteplase [rtPA] more quickly."

As additional benefits, the authors observe that telestroke networks may increase recruitment of a broad range of patients into emergency stroke trials, as well as serve as sources of standardized data for stroke care research and quality control.

AIS, acute ischaemic stroke; CSC, comprehensive stroke centre; CT, computed tomography; DNT, door-to-needle time; ED, emergency department; EMS, emergency medical services; GP, general practitioner; HCP, healthcare practitioner; IHS, in-hospital stroke; IQR, interquartile range; IV, intravenous; mRS, modified Rankin Scale; OHS, out-of-hospital stroke; PSC, primary stroke centre; (r)tPA, recombinant tissue plasminogen activator; SD, standard deviation; SICH, symptomatic intracranial haemorrhage; SITS-EAST, Safe Implementation of Treatments in Stroke: Eastern Europe

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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