

## 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.**

Stroke is a leading cause of death and disability worldwide. As such, treatment of patients with acute ischaemic stroke (AIS) occurs in a variety of hospital environments, from rural to urban, large stroke centres to smaller hospitals, and across different economic settings, cultures and countries. Whatever the environment, timeliness of treatment remains key. Therefore, it is important to assess and improve the stroke care pathway in all settings, to facilitate the rapid delivery of intravenous (IV) recombinant tissue plasminogen activator (rtPA) and other treatments.

In this issue of the Actilyse® Publication Alert Newsletter, we report on a meta-analysis that reinforces the time-related benefits of IV rtPA treatment, in this case in patients with stroke due to large vessel occlusion (LVO). We then highlight strategies to improve various stages of the stroke care pathway, in a range of healthcare settings around the world.

### RAPID IV rtPA IMPROVES OUTCOMES IN PATIENTS WITH STROKE DUE TO LARGE VESSEL OCCLUSION

A meta-analysis of the control arms of seven randomized clinical trials (RCTs) of endovascular thrombectomy (EVT) in patients with stroke due to LVO found that faster initiation of IV rtPA was associated with better outcomes and improved recovery.<sup>1</sup>

When given as a single treatment, IV rtPA has shown benefit in patients with LVO stroke. However, there is a lack of understanding of the time dependence of this benefit because RCTs comparing IV rtPA with control did not require pre-treatment imaging. By pooling data from EVT clinical trials that use acute intracranial vessel imaging and IV rtPA alone as the control arm, the HERMES (Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials) collaboration investigated the impact of the timeliness of IV rtPA on functional outcomes in LVO stroke.

Slower initiation of IV rtPA was associated with worse outcomes over the entire disability range and lower rates of excellent recovery and functional independence at 90 days. There was no evidence that more rapid treatment led to increased risk of symptomatic intracranial haemorrhage (SICH) or mortality.

The authors conclude that faster initiation of IV rtPA treatment is strongly associated with better outcomes in patients with LVO stroke. They also highlight the consistency of these findings with those from other studies demonstrating the benefit of IV rtPA in a broad range of patients with AIS.

#### Study details

- Meta-analysis of the control arms (patients with LVO treated with IV rtPA alone at an endovascular centre, n=601) from seven RCTs of EVT
  - Primary outcome – degree of disability at 90 days (modified Rankin Scale [mRS] score)
  - Secondary outcomes – excellent recovery (mRS score 0–1) and independent recovery (mRS score 0–2)
- Median (range) onset-to-treatment time (OTT) = 165 min (130–203)
  - 82% of patients were treated within 3 h of onset; 17% of patients were treated within 3–4.5 h
- Median (interquartile range, IQR) door-to-needle time (DNT) = 38 min (26–55)
- The odds of better disability outcomes at 90 days declined with longer OTT and DNT (adjusted analyses; see table)
  - Each 60-min increase in OTT and DNT was associated with a greater degree of disability and reduced chance of excellent recovery. Increases in DNT were also associated with reduced chance of functional independence
  - Faster OTT and DNT were not associated with increased risk of SICH or death
- Every 15-min delay in OTT was associated with 8 fewer patients (among 1000 patients) achieving an excellent recovery
- Every 15-min delay in DNT was associated with 20 fewer patients (among 1000 patients) achieving an excellent recovery

Outcome at 90 days	With each 60-min increase in OTT	With each 60-min increase in DNT
	Odds ratio (95% CI)	Odds ratio (95% CI)
mRS score (ordinal)	0.80 (0.68–0.95)	0.55 (0.37–0.81)
mRS score 0–2 (functional independence)	0.82 (0.66–1.03)	0.47 (0.28–0.80)
mRS score 0–1 (excellent recovery)	0.76 (0.58–0.99)	0.51 (0.29–0.92)
Death	0.99 (0.79–1.23)	1.07 (0.59–1.93)
SICH	0.74 (0.43–1.28)	0.44 (0.12–1.66)

## BEST PRACTICE STRATEGIES REDUCE DNT TO <30 MINUTES AT A COMPREHENSIVE STROKE CENTRE IN THE USA

Using gap analysis to identify areas for process improvement and then implementing best practice strategies has been shown to reduce DNT at a large, urban, academic, comprehensive stroke centre (CSC) in the USA.<sup>2</sup>

A multidisciplinary team identified factors that were contributing to delays in DNT. Based on this analysis, five of the Target Stroke: Best Practice Strategies were implemented: emergency medical services (EMS) prenotification; direct transfer from ambulance to CT scanner; storing and administering IV rtPA in the CT scanner; team-based approach; prompt data feedback.

After implementation, median DNT at the hospital was significantly decreased from 59 minutes to 29 minutes, with no change in thrombolysis-related complications. Half of patients achieved a DNT of <30 minutes and over three-quarters achieved a DNT of <45 minutes.

The authors conclude that implementation of targeted process improvement interventions requires real-time, coordinated team effort and leads to dramatic and sustained reductions in time to thrombolysis treatment.

### Study details

- Team members from the departments of neurology, emergency medicine, pharmacy and radiology at Jackson Memorial Hospital, Florida, USA, identified factors contributing to delays in DNT
- Five ‘Target Stroke: Best Practice Strategies’ were implemented based on the identified delays:
  - EMS prenotification activating the stroke team and support staff with a single call; direct transfer from ambulance to CT scanner; storing and administration of IV rtPA in the CT scanner; team-based approach; prompt data feedback to all parties involved (each case was reviewed by a multidisciplinary team on a daily basis, DNT delays were investigated, and recommendations for future cases were communicated within the next day)
- Data were analysed from patients with AIS arriving at the hospital emergency department (ED) who were treated with IV rtPA
  - 148 patients in the pre-implementation phase (1 Jan 2013–21 Mar 2015; data reviewed retrospectively)
  - 126 patients in the post-implementation phase (22 Mar 2015–30 Apr 2015, data collected prospectively)
- DNT, door-to-CT time, CT-to-IV rtPA time were all significantly decreased in the post-implementation group vs pre-implementation group (see table)
- There was no significant difference between pre-implementation vs post-implementation groups in symptomatic systemic bleeding (1% vs 3%, respectively;  $p=0.31$ ), SICH (3% vs 3%;  $p=0.82$ ), and treatment of stroke mimics (9% vs 12%;  $p=0.31$ )

Time metric	Pre-implementation (n=148)	Post-implementation (n=126)	p value
DNT, mins; median (IQR)	59 (52–80)	29 (20–41)	<0.001
Door-to-CT, mins; median (IQR)	17 (14–21)	16 (12–19)	0.016
CT to IV rtPA, mins; median (IQR)	43 (31–59)	13 (6–23)	<0.001
DNT, % of patients			
<30 minutes	2	52	<0.01
<45 minutes	15	77	<0.01

**“Individualized hospital gap analysis identifies targeted interventions that lead to rapid and sustained improvement in treatment times”<sup>2</sup>**

## IDENTIFYING REASONS FOR DELAY IN THROMBOLYSIS AT A CENTRE IN EGYPT

Bahnasy and colleagues investigated the reasons for delay in thrombolysis at their university hospital in Egypt.<sup>3</sup>

Firstly, they compared patients with AIS eligible for IV rtPA according to their onset-to-arrival time (<3.5 hours vs >3.5 hours). The main causes for delay in patients arriving >3.5 hours after onset were: stroke unawareness; long travel time; incorrect beliefs (e.g. nothing can be done, symptoms will improve); neurologists unavailable; and onset during sleep.

Patients who arrived within 3.5 hours of onset were then further divided into those who received IV rtPA and those who did not. The main reasons for non-administration of IV rtPA were: DNT >60 minutes; financial restraints; patients had minor/non-motor strokes; unavailability of stroke-ready beds; and fear of complications.

The authors make several recommendations for increasing IV rtPA use, including increasing social awareness of stroke symptoms and the value of early treatment, repeated training of EMS personnel, certifying hospitals as acute primary stroke-ready hospitals, increased governmental financial support, and ensuring that all necessary facilities are in the same building.

## USE OF A PRE-HOSPITAL STROKE CODE REDUCES DELAYS IN A UNIVERSITY HOSPITAL IN PARAGUAY

Pre-hospital stroke code activation has been shown to have a positive impact on in-hospital acute stroke management at a stroke unit in Paraguay.<sup>4</sup>

Flores and colleagues conducted a pilot observational study at a single centre from April 2015 to July 2018, during which time pre-hospital stroke code activation was implemented in November 2016. They found that pre-hospital stroke code patients had a lower mean door-to-CT time (24 vs 33 minutes,  $p=0.021$ ) and lower DNT (35.3 vs 76.3 minutes,  $p<0.001$ ) vs in-hospital stroke code patients. Among patients who received IV rtPA, pre-hospital stroke code activation was associated with more patients achieving DNT  $\leq 60$  minutes (95.1% vs 46.8%,  $p=0.001$ ) and DNT  $\leq 45$  minutes (76.4% vs 15.6%,  $p<0.001$ ) vs patients who did not have pre-hospital stroke code activation.

The authors suggest that pre-hospital stroke code activation is feasible and should be implemented nationwide.

## IMPROVING DNT ACROSS AN ENTIRE CANADIAN PROVINCE IN BOTH RURAL AND URBAN AREAS

The Quality Improvement and Clinical Research (QuICR) Alberta Stroke Programme aims to reduce median DNT across the province, in both rural and urban areas, to 30 minutes. This collaborative improvement process also aims to increase the percentage of patients treated within 60 minutes to 90%.<sup>5</sup>

Once these goals for the programme were established, a faculty was recruited who helped to decide on the measurement strategy and develop a change package. This package was then rolled out to participating sites via a face-to-face learning session, at which their interdisciplinary team could hear background and evidence, develop action plans, and be supported in developing maps of their thrombolysis processes. Subsequent learning sessions focused on hearing the results to date, discussing progress, and sharing successes and challenges. Sites were also supported via site visits, webinars and data feedback on DNT.

The change package included suggestions such as:

- EMS – place IV lines en route
- Prenotification – notify stroke team; create a code stroke protocol; look up patient history prior to arrival if possible
- ED arrival – register patient as ‘unknown’ to reduce time to enter patient information
- CT – go straight to the scanner on arrival; create a standard stroke imaging protocol
- rtPA – have it ready in the ED or CT room and mix immediately after deciding to treat; treat in the CT scanner
- Feedback – share DNT with staff and stress the importance of fast initiation of treatment

The authors feel that the methodology they describe for improving DNT across an entire population could be adapted for other health systems.

## MEDIAN DNT REDUCED TO 30 MINUTES AT A CANADIAN COMMUNITY HOSPITAL

Kamal and colleagues report that implementing a revised stroke treatment algorithm as part of the QuICR initiative noted above was successful in reducing DNT to 30 minutes at a community hospital in Alberta.<sup>6</sup>

The revised algorithm integrated several of the recommendations from the QuICR initiative and the changes were undertaken by a multidisciplinary team. After implementing the new process, median DNT was reduced from 77 minutes to 30 minutes. Furthermore, these results were sustainable, with improvements maintained after the initiative ended.

The authors conclude that community hospitals staffed with community neurologists can achieve a median DNT of  $\leq 30$  minutes.

### Study details

- Analysis of patients with AIS treated with IV rtPA at Red Deer Regional Hospital Centre, Alberta, a community hospital and primary stroke centre
- As part of the QuICR initiative, three key changes were made to hospital processes for dealing with patients with AIS:
  - Take the patient to the CT scanner on the EMS stretcher
  - Administer IV rtPA in the CT scanner or imaging area
  - Single-call activation of the stroke team for an incoming (when arriving by ambulance) or in-hospital stroke patient
- 165 patients received treatment before these changes (Jul 2007 to Jun 2015), 104 patients received treatment after (Jan 2016 to Dec 2017), and 20 patients were treated whilst the QuICR initiative was being implemented (Jul 2015 to Dec 2015)
- Median DNT (IQR) reduced from 77 min (60–103 min) in the pre-implementation period to 30 min (22–42 min) after implementation of the revised protocol ( $p<0.001$ )

## STROKE CERTIFIED REGISTERED NURSES DELIVER TIMELY CARE FOR HYPERACUTE STROKE IN THE USA

Stroke Certified Registered Nurses (SCRNs) are more knowledgeable, confident and timely in activating and implementing hyperacute stroke protocols than non-SCRNs.<sup>7</sup>

In a retrospective study at a small, rural hospital in the Southwestern region of the USA, Fant & Lakomy assessed whether there was a difference in achieving treatment time targets by SCRNs compared with non-SCRNs in the care of patients with hyperacute stroke who received IV rtPA. It was found that SCRNs delivered faster care vs non-SCRNs in terms of the proportions of patients who met target times for total care time, door-to-stroke team activation, door-to-CT scan, door-to-teleneurology initiation and DNT.

SCRNs met the targets for all stroke activation process times, whereas non-SCRNs were outside the target times for door-to-teleneurology initiation and DNT.

The authors conclude that, as experts, SCRNs consistently recognize stroke symptoms, activate the stroke process, follow protocols and deliver quality care to stroke patients.

## ED STAFF IDENTIFY MULTIPLE OPPORTUNITIES TO ENHANCE THE TRANSFER OF PATIENTS WITH AIS

The interdepartmental transfer of patients with AIS, viewed by ED staff as a complex process that can be delayed at numerous points, can be improved by enhancing communication and processes at transferring facilities.<sup>8</sup>

Hayes and colleagues conducted semi-structured interviews of staff at three EDs in Nashville, Tennessee, USA, to identify barriers to timely and quality care for patients with AIS who require transfer. From the interviews, four themes were identified: processes (for diagnosis, treatment and transfer of patients with AIS), historical experience (both positive and negative), communication (the need for direct, quality communication with specialists and post-transfer communication) and resources (human and physical).

Six opportunities to enhance the transfer of patients with AIS were identified:

- Collaborative protocol development – use an iterative process to develop a protocol that is robust to process breakdown
- Simple processes – reduce the number of steps involved in transfer
- Leadership engagement – leaders with authority should be involved in protocol review and provide feedback
- Feedback mechanism – communicate both positive and negative feedback
- Measure and report – quantify operational performance and clinical outcomes
- Education – identify opportunities for staff and provider education, especially regarding infrequently used processes

## AMBULANCE USE PROMOTES TIMELY THROMBOLYSIS OF AIS IN HONG KONG

A Hong Kong-based team has assessed the time delays experienced by patients with AIS arriving at an ED and compared those who arrived by ambulance with those who did not.<sup>9</sup>

Lau and colleagues found that significantly more ambulance users arrived within the IV rtPA treatment window than non-ambulance users. Time intervals between stroke onset and calling for help, between calling for help and arriving at the ED, and between arriving at the ED and receiving medical assessment were all significantly shorter for ambulance users.

The authors propose a variety of reasons for these differences, but central to them is that many patients are unaware of the symptoms of stroke and the urgency of getting to hospital (rather than a primary care physician) as soon as possible. The public should be educated on the signs and symptoms of acute stroke, emphasising the need to contact EMS after the onset of stroke.

### Study details

- Prospective cohort study of stroke patients (n=102) admitted to the acute stroke unit via the ED of Princess Margaret Hospital, Hong Kong (1 Jan 2017 to 30 Jun 2017)
- Patients were divided into those brought to the hospital by ambulance and those who attended by other means of transportation
- Time intervals in three phases were compared between these two groups
  - Phase I – time between stroke onset and calling for help
  - Phase II – time between calling for help and arriving at the ED
  - Phase III – time between arriving at the ED and receiving medical treatment
- The percentage of patients arriving within the IV rtPA therapeutic window (<3.5 h after stroke onset) was significantly higher in ambulance users vs non-ambulance users (64.6% vs 29.6%, respectively;  $p < 0.001$ )

### Study details (continued)

- Time intervals for all phases were significantly shorter for ambulance users than non-ambulance users (see table)

Time interval	Ambulance users (n=48)	Non-ambulance users (n=54)	p value
Phase, median (IQR), minutes			
I – onset to calling for help	77.5 (21.25–278.75)	720 (108.75–3023)	<0.001
II – calling for help to arrival at ED	32 (29–41.5)	44.5 (23.25–66.25)	<0.001
III – arrival at ED to receiving treatment	8 (2.25–12.5)	15 (8.75–27.75)	<0.001
I + II + III	120 (72.25–304.5)	1182 (180.75–3224.5)	<0.001

**“Transport of patients to the emergency department by ambulance is important for timely and effective stroke treatment”<sup>9</sup>**

### IMPROVING EMERGENCY DISPATCHER IDENTIFICATION OF ACUTE STROKE IN FINLAND

An analysis of patients with acute stroke/transient ischaemic attack at a stroke centre in Helsinki investigated factors associated with an incorrect dispatch code being assigned by emergency services dispatchers.<sup>10</sup>

Predictors of a dispatcher not identifying acute stroke included: having a bystander make the call; patient confusion; fall at onset; and older patient age. Recordings of calls that were assigned an incorrect dispatch code and a low-priority dispatch suggested that 72% could be improved, as there had either been a failure to recognize a FAST-symptom (most of these patients had speech disturbance) and/or a failure to thoroughly evaluate the patient’s symptoms.

The authors conclude that this inconsistent screening for FAST-symptoms, failure to identify speech disturbances and failure to evaluate symptoms all indicate room for improvement and areas of further training for dispatchers.

### SOCIOECONOMIC REASONS FOR DELAYED HOSPITAL ARRIVAL FOR PATIENTS WITH AIS IN SOUTHERN PORTUGAL

Analysis of the socioeconomic and clinical factors leading to delayed thrombolysis in patients with AIS in southern Portugal highlighted that poverty, lack of stroke awareness and difficulties in requesting help were primary factors.<sup>11</sup>

Sobral and colleagues performed a case-control study of patients with AIS who arrived at hospital within 4.5 hours of stroke onset, with the controls being patients who did not arrive within the time frame for thrombolysis.

Being a beneficiary of social insertion income, not having any telephone contact, having exclusive landline telephone and having posterior circulation stroke all decreased the chance of arriving within the treatment window for rtPA. The odds of arriving at the ED within 4.5 hours of stroke onset were increased when ambulance services were used.

The authors conclude that thrombolysis rates can be improved by stroke awareness campaigns and promoting the importance of calling the EMS.

**“Timely arrival is the biggest hurdle for rtPA provision for AIS”<sup>11</sup>**

### A ‘DIRECT-TO-CT’ POLICY DID NOT IMPROVE DNT IN AN OBSERVATIONAL US STUDY

A recent US study found that taking patients with suspected stroke straight to the CT scanner, and then to an ED bed for evaluation, reduced door-to-CT ordered time but did not affect DNT.<sup>12</sup>

Cone and colleagues conducted an observational, multicentre study that measured timeliness of stroke care before and after the implementation of a ‘direct-to-CT’ policy for patients with suspected stroke who arrive via the EMS.

Analysis of 975 patients from seven hospitals found that median door-to-CT ordered time reduced from 7 minutes to 4 minutes after the policy was introduced ( $p<0.0001$ ). However, there was no significant change in median DNT (44 minutes before vs 42 minutes after) or in mean DNT (48 minutes both before and after).

The authors suggest the reason for the lack of difference in DNT may be due to other rate-limiting steps, such as laboratory processes, and/or that six of the hospitals were accredited stroke centres, meaning that response processes were already optimized.

## SHORTER DNT IS ASSOCIATED WITH QUICKER DELIVERY OF ENDOVASCULAR THERAPY

Menon and colleagues describe the time intervals, from patient arrival at the ED to treatment initiation, in patients receiving EVT within Get With The Guidelines-Stroke hospitals.<sup>13</sup>

Data was collected for 2929 patients from 195 CSCs (October 2014 to September 2016). The results indicate that EVT treatment times are similar for hospitals participating in a large registry compared with those achieved in recent clinical trials.

- Median (IQR) door-to-first pass time (time of first deployment of a mechanical reperfusion device, of IV rtPA, or initiation of mechanical thrombectomy) was 140 (101–170) minutes
- There was a significant decrease in door-to-first pass time over the study period, from a median 134.5 minutes in Q4 of 2014 to 128 minutes in Q3 2016 ( $p=0.002$ )
- Only 3.2% of patients achieved a door-to-first pass time of  $\leq 60$  minutes; 17.1% of patients had a door-to-first pass time of  $\leq 90$  minutes
- In multivariate analysis, older age, arrival during non-regular hours and a history of diabetes were associated with longer door-to-first pass times. Patients who received IV rtPA had shorter door-to-first pass times
- Hospitals that achieved shorter DNT were more likely to achieve faster door-to-first pass times; a 10-minute increase in hospital DNT was associated with an 8% longer door-to-first pass time
- Among hospitals with  $\leq 40$  EVT cases per year, every 5 additional cases per year was associated with a 3% reduction in door-to-first pass time

The authors believe that CSCs that deliver EVT should focus on improving workflow during non-regular hours, implement parallel workflow processes and improve IV rtPA administration, and increase their experience in terms of annual case volume (up to 40 cases per year).

**“Efforts on streamlining workflow and saving time need to continue so that the true potential of EVT is realized”<sup>13</sup>**

AIS, acute ischaemic stroke; CI, confidence interval; CSC, comprehensive stroke centre; CT, computed tomography; DNT, door-to-needle time; ED, emergency department; EVT, endovascular thrombectomy; EMS, emergency medical services; IQR, interquartile range; IV, intravenous; LVO, large vessel occlusion; mRS, modified Rankin Scale; ; OTT, onset-to-treatment time; RCT, randomized controlled trial; rtPA, recombinant tissue plasminogen activator; SCRNC, Stroke Certified Registered Nurse; SICH, symptomatic intracranial haemorrhage; QuICR, Quality Improvement and Clinical Research

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