

# 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.**

‘Time is brain’ is true for all stroke patients. Efforts to streamline and improve the AIS\* care pathway must therefore aim to reduce treatment delays and achieve optimal patient outcomes for all, regardless of race/ethnicity, sex, geographical region or other factors.

In this issue of the Actilyse® Publication Alert Newsletter, we highlight the importance of achieving equality of stroke care for all patients, particularly those with in-hospital stroke. We also look at how educational initiatives in combination with protocols can help to overcome treatment gaps and reduce treatment delays in different settings.

\*Abbreviations are defined at the end of the newsletter.

## DISPARITIES IN STROKE CARE CAN BE IDENTIFIED AND TARGETED

Initiatives to improve thrombolysis treatment should ideally improve outcomes for all patients, regardless of race/ethnicity, sex, geographical region or other factors. Failure to do so can lead to treatment gaps, which need to be identified and addressed.

The Florida-Puerto Rico Collaboration to Reduce Stroke Disparities (FL-PR CRESD) study is specifically designed to address disparities in stroke care.<sup>1</sup> Recent analysis of more than 6000 patients included in the registry revealed prominent disparities in rtPA treatment according to sex, race/ethnicity, and geographical region:

- Women less likely than men to have DNT ≤60 minutes or ≤45 minutes (regardless of admission time)
- Blacks less likely than whites to have DNT ≤45 minutes (when admitted during non-office hours). Florida Hispanics had the lowest median DNT, followed by Puerto Rico Hispanics, whites and Blacks
- Achievement of target DNT highest in South Florida and lowest in West Central Florida

Substantial improvements were made between 2010 and 2015 in the proportions of patients with DNT ≤60 minutes or ≤45 minutes, although achievement of these targets is still low. The degree of improvement varied by sex, race/ethnicity, and region; in some cases existing treatment gaps have widened, whereas in other cases gaps have been reduced.

The authors conclude that further research is needed to identify reasons for delayed treatment in some groups as well as factors contributing to regional disparities in DNT.

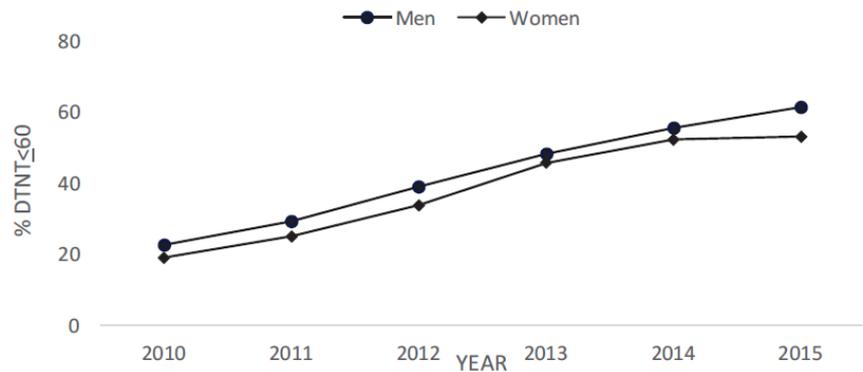
### Study details

- Analysis of data from 6181 patients with AIS who received rtPA at 84 Get With The Guidelines-Stroke hospitals (Jan 2010–Jun 2015), to assess disparities in achievement of, and temporal changes in, DNT ≤60 min and ≤45 min
- Sex, race/ethnicity and regional disparities were observed in DNT (see table)
- Women were less likely than men to have DNT ≤60 min (OR: 0.81; 95% CI: 0.72–0.92) or DNT ≤45 min (OR: 0.73; 95% CI: 0.57–0.93)
  - This result was similar between working hour and non-office hour admissions
- Blacks were less likely than whites to have DNT ≤45 min during non-office hour admissions (OR: 0.68; 95% CI: 0.47–0.98)
- ‘Arrival by EMS’ and ‘treatment in larger hospitals/CSCs’ were independent predictors of DNT ≤60 and ≤45 min

OUTCOME	DNT ≤45 min, %	DNT ≤60 min, %	MEDIAN DNT (IQR), min
Overall	18 (1117/6181)	42 (2605/6181)	67 (51–91)
Sex			
Women	16	40	68 (52–93)
Men	20	44	65 (49–88)
Race/ethnicity			
Hispanic (Florida)	28	56	58 (43–79)
Hispanic (Puerto Rico)	14	44	67 (52–88)
White	17	40	68 (52–91)
Black	14	39	71 (53–95)
Region			
South Florida	23	50	
West Central Florida	11	28	

**Study details (continued)**

- Proportions of patients with DNT ≤60 min improved over time, from 21% in 2010 to 57% in 2015 (+36%) overall
  - Improvements were lower for women than men, leading to a widening treatment gap (see figure)
  - Improvements differed by region: largest in South Florida (+46%) and smallest in Puerto Rico (+15%)
  - Improvements differed by race: largest among blacks (+41%) and smallest among Puerto Rico Hispanics (+15%)
  - Similar trends and patterns were seen for DNT ≤45 min, which increased from 6% in 2010 to 28% in 2015 (+22%) overall



**“The FL-PR Stroke Registry...supports the study of delivery of evidence-based best practices, identification of disparities, and development of future interventions to reduce disparities in acute stroke care.”<sup>1</sup>**

**DNT VARIES ACCORDING TO THE ROUTE OF HOSPITAL ADMISSION**

Ideally, initiatives to improve in-hospital treatment times should be effective for all AIS patients, regardless of the route of hospital admission. Routing *all* patients with suspected stroke directly to the specialist stroke team may be the most effective way to achieve efficient in-hospital management of AIS, as the stroke team has the necessary expertise and experience to provide timely assessment and treatment.

Multiple strategies were introduced in a Tokyo hospital with the aim of reducing in-hospital delays for patients with stroke.<sup>2</sup> Mean DNT was significantly reduced from 87 minutes to ~67 minutes overall, but this improvement was inconsistent, with considerable differences between the routes of admission. Patients deemed to have less-serious symptoms were routed via the ER, and saw an *increase* in DNT during the post-intervention period. Even when patients were treated with greater urgency, by the Emergency Medical Centre (EMC) or by the stroke team, disparities in DNT were apparent. Reassuringly, the stroke team achieved the shortest DNT, with a mean of under 60 minutes.

**Study details**

- Analysis of data from 96 consecutive patients who received rtPA at a hospital in Tokyo, Japan (Jul 2012–Jun 2015), to examine the impact of multiple initiatives (implemented from July 2014) on DNT according to admission route:
  - ER (admits patients with mild to severe conditions); EMC (receives patients with life-threatening or serious conditions); stroke team (receives patients with suspected stroke, directly or via the EMC)
- Multidisciplinary initiatives included pre-notification of ER and imaging staff; priority access to imaging facilities for stroke patients; written protocols; monthly training seminars
- Post-intervention DNTs were reduced by ~20 min overall (see table)
  - Improvements seen for patients admitted via the EMC or stroke team, but not for those admitted by the ER
  - Patients admitted via the stroke team had the shortest DNT; patients admitted via the ER had the longest DNT
- An additional analysis of data from 52 patients who underwent endovascular recanalization found that treatment times, including DNT and onset-to-recanalization time, were shorter after adoption of stent retrievers

OUTCOME	ER ROUTE (n=17)	EMC ROUTE (n=20)	STROKE TEAM ROUTE (n=59)	ALL PATIENTS (n=96)
Pre-intervention mean DNT, min				
2012	51	103	82	87
2013	82	102	88	87
Post-intervention mean DNT, min				
2014	80	74	59	67
2015	119	79	53	68

## TREATMENT OF IN-HOSPITAL STROKE PRESENTS UNIQUE CHALLENGES

Identifying and treating patients who experience AIS while already in hospital presents unique challenges: stroke symptoms may be under-recognized in this group; hospitalized patients are likely to be sicker than community-based patients (with more comorbidities and contraindications); and it may be difficult to access to the stroke unit quickly from other departments.

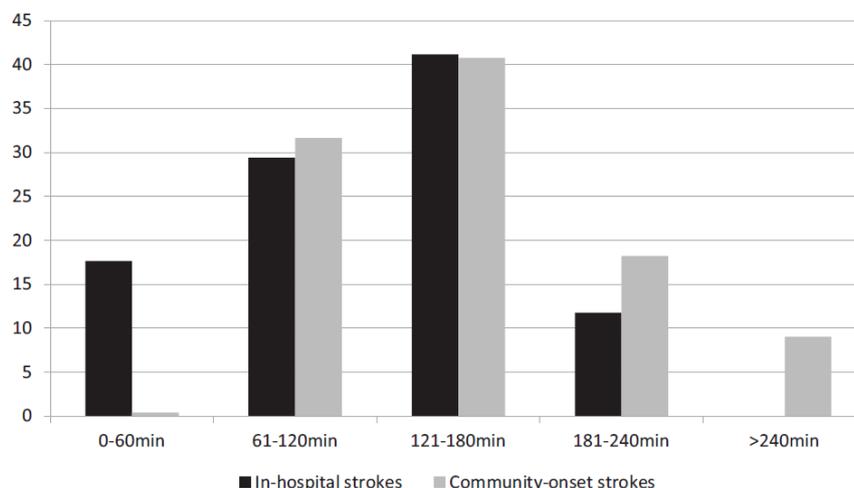
Caparros *et al.* report that patients with in-hospital stroke (IHS) have significantly shorter ONT than patients with community-onset stroke (COS), but the 17-minute difference is small given the patients are already at the hospital and could be improved further.<sup>3</sup>

The authors conclude that pre-specified care pathways should be put in place for IHS. Treatment delays should be targeted in this group of AIS patients, who may be especially vulnerable to poor outcomes.

### Study details

- Analysis of registry data from 1209 consecutive AIS patients treated with rtPA, thrombectomy, or both at a large university hospital in Lille, France (Sept 2003–Sept 2016), to evaluate characteristics and outcomes in patients with IHS and COS
  - 64/1209 cases (5.3%) were IHS (three of these occurred in hospital staff/visitors rather than in hospitalized patients)
  - Proportion of IHS cases increased over time, reaching just over 10% in 2016
- IHS patients typically had a worse pre-existing medical status than COS patients
  - TIA in past 7 days and anticoagulant treatment before hospitalization were more common among IHS patients
  - More than a third of IHS patients were already admitted to the stroke unit for recent cerebral ischaemia
- Many IHS patients had contraindications to rtPA, and almost half required treatment for a LVO (see table)
  - 67.2% received rtPA treatment
  - 45.3% received mechanical thrombectomy
- ONT was 17 minutes shorter among IHS than COS patients (see figure and table)
  - Median ONT varied according to the hospital site of IHS onset ( $p < 0.001$ ): shortest for onset in the stroke unit (64 min) and longer for onset in the ED (111 min) and other departments (138 min)
  - Median ONT among IHS patients who received only rtPA was 130 min (IQR: 78–145)
- IHS patients had worse functional outcomes than COS patients at 3 months; these differences disappeared after adjustment for the presence of pre-existing medical conditions

OUTCOME	COMMUNITY-ONSET STROKE (n=1145)	IN-HOSPITAL STROKE (n=64)	p VALUE
Treatment with IV thrombolysis, n (%)	1144 (99.9)	43 (67.2)	<0.001
ONT, median (IQR)	145 (115–186)	128 (68.75–145)	<0.001
Treatment with mechanical thrombectomy, n (%)	119 (10.4)	29 (45.3)	<0.001



Proportions of patients with HIS and COS treated in <60, 61–120, 121–180, 181–240, and >240 min after stroke onset

**“...patients with IHS are treated 17 min earlier than patients with COS, but, taking into account that they were already in the hospital, delays are still too long.”<sup>3</sup>**

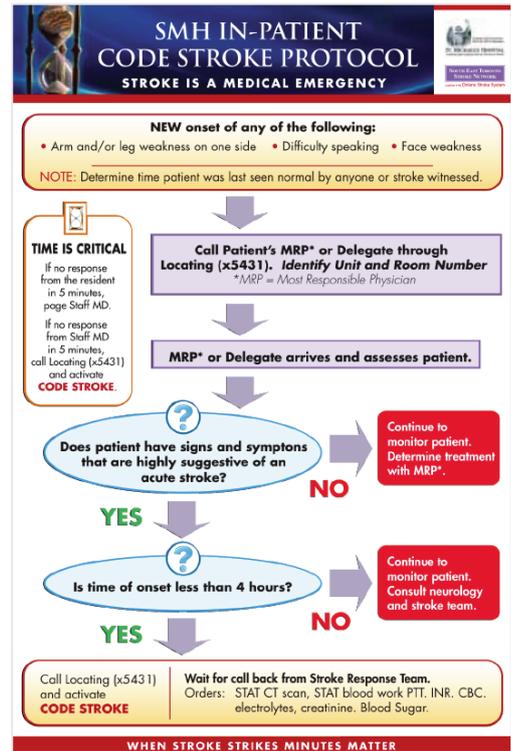
## CODE STROKE PROTOCOL AND EDUCATIONAL INTERVENTION IMPROVE TREATMENT OF IN-HOSPITAL STROKE

To ensure that IHS patients have, “the same opportunity to receive assessment, diagnosis, and treatment as quickly as those who come through the emergency department”, Kassardjian *et al.* developed an in-patient code stroke algorithm for use at their centre in Florida, USA, and delivered an education programme to nurses and other HCPs.<sup>4</sup> Following implementation of these interventions, the time taken from symptom onset to initial assessment and CT scan in IHS patients fell dramatically.

The authors of the study conclude that the prompt management of IHS was optimized by the code stroke algorithm and educational intervention. Quicker assessment should result in faster treatment and better outcomes for patients with IHS.

### Study details

- Analysis of data from 218 patients with IHS at an academic and teaching hospital in Toronto, Canada (Apr 2006–Feb 2011), before and after implementation (May–Oct 2009) of an in-patient code stroke algorithm combined with stroke education targeted at nursing staff and allied HCPs, to assess the impact on IHS management delays
  - An algorithm for identification and management of IHS was developed with key stakeholders (see figure)
  - 60-min education sessions were delivered to personnel from cardiovascular surgery, cardiovascular intensive care, cardiology, general internal medicine, neurosurgery, and other wards; information included stroke signs and symptoms, the importance of prompt treatment, and the process of activating a code stroke
- Almost half of IHS cases (45%) occurred on cardiovascular wards; 60% of cases occurred during the perioperative period
  - IHS response times fell significantly during the post-implementation period (see Table)
  - The post-implementation group contained a large proportion of mild strokes, suggesting recognition of stroke symptoms had improved as a result of the education intervention



- In-patient code stroke was activated 35 times in the post-implementation period
  - Code stroke patients had a median onset-to-assessment time of 75 min and a median onset-to-imaging time of 125 min
  - The most common reason for not activating code stroke was ‘time from symptom onset unknown or >4 hours’
  - Only a few IHS patients received rtPA, which was attributed to the presence of contraindications (e.g. recent surgery) and comorbidities in many patients

OUTCOME	PRE-IMPLEMENTATION (n=131) (APR 2006–APR 2009)	POST-IMPLEMENTATION (n=87) (NOV 2009–FEB 2011)	p VALUE
Onset*-to-assessment time, median (IQR), min	600 (109–1460)	160 (35–630)	0.0065
Onset*-to-imaging time, median (IQR), min	925 (213–1965)	348.5 (128–1587)	0.023
Assessment-to-imaging time, median (IQR), min	135 (43–480)	110 (51–331)	0.509
IV thrombolysis, n (%)	9 (6.9)	3 (3.5)	0.370
Discharge destination, n (%)			0.681
Rehabilitation	66 (50.4)	42 (48.8)	
Home	33 (25.2)	22 (25.6)	
Death	19 (14.5)	16 (18.6)	
Long-term care	6 (4.6)	1 (1.2)	
Other acute care hospital	7 (5.3)	5 (5.8)	

\*last seen normal; data reported as in the publication

**“In-patient strokes are medical emergencies and should be afforded the same high-quality care as strokes that occur out of hospital.”<sup>4</sup>**

## INCLUDING A PHARMACIST ON THE STROKE RESPONSE TEAM REDUCES DNT

The inclusion of a pharmacist in the stroke response team can reduce in-hospital delays, particularly imaging-to-needle time, among patients with IHS or COS.<sup>5</sup>

The effect on DNT of having pharmacist bedside cover was examined at a PSC in Illinois, USA. Stroke-competent pharmacists were responsible for tasks relating to rtPA preparation and administration. The presence of a pharmacist at bedside reduced DNT by 25 minutes and increased the proportion of patients with DNT ≤60 minutes to 71%. This benefit was retained after adjustment for out-of-hours differences in stroke service availability.

### Study details

- Analysis of data from 125 patients who received rtPA within 4.5 h of AIS onset at an academic US PSC (Jan 2012–Dec 2015), to examine whether the presence of a pharmacist at bedside during AIS care reduced DNT
  - Patients were either admitted via the ED or experienced IHS
  - Pharmacist bedside cover was available 07:00–21:30 on weekdays and 06:30–21:00 at weekends and holidays
- Stroke-competent pharmacists received annual training to:
  - Review medical history and medications; evaluate rtPA contraindications; manage blood pressure; provide thrombolysis risk counselling; calculate rtPA dose; administer rtPA; monitor patient after rtPA administration
- Median DNT was significantly shorter in the presence of a bedside pharmacist (see table)
  - Improvement was driven by a reduction in imaging-to-needle time; door-to-imaging time was unaffected
- 98% of patients with bedside pharmacist cover, vs 61% of those without, presented during daytime hours
  - Positive effect of pharmacist cover was retained when patients presenting out-of-hours were excluded from analysis
- Pharmacist at bedside was the only factor independently associated with DNT reduction in multivariate analysis
- The presence of bedside pharmacist cover did not affect ICH or mortality, or functional outcomes

OUTCOME	NO BEDSIDE PHARMACIST (n=80)	BEDSIDE PHARMACIST (n=45)	p VALUE
DNT, median (IQR), min	73 (58–97.5)	48 (36–65)	<0.01
Door-to-imaging time, median (IQR), min	16 (8–25)	16 (10–21)	0.85
Imaging-to-needle time, median (IQR), min	55.5 (42–70.5)	28.5 (22–42.5)	<0.01
DNT goal met, n (%)			
≤60 min	23 (28.8)	32 (71.1)	<0.01
≤45 min	7 (8.8)	20 (44.4)	<0.01
DNT by subgroup, median (IQR), min			
Dayshift admission only (n=79)	67 (56.5–89)	47 (36–57)	<0.01
Weekday dayshift admission only (n=63)	65 (56–91)	47.5 (36–61)	<0.01

**“These findings support the inclusion of a stroke-competent pharmacist in the bedside response team for acute ischemic stroke patients.”<sup>5</sup>**

## 24/7 NEUROLOGIST AVAILABILITY IMPROVES THROMBOLYSIS RATES

Introduction of 24/7 neurology shifts in the ED of a public hospital in Chile had a positive effect on thrombolysis treatment, as data from 106 consecutive patients treated with rtPA between May 2012 and April 2016 show:<sup>6</sup>

- Thrombolysis rate increased year-on-year, from 0.7% in 2012 to 6% in 2016
- Overall, median (IQR) DNT was 80 (57–113) minutes; 28% of patients had a DNT <60 min
- 27% of patients had a favourable outcome (mRS score 0–1) at discharge

## SHORTER PRE-HOSPITAL DELAYS ARE ASSOCIATED WITH BETTER FUNCTIONAL OUTCOMES

Reducing EMS transport time is beneficial for all patients with AIS, not just for those who go on to receive rtPA.<sup>7</sup>

A retrospective regression analysis of data from 122 patients with cerebral infarction who were transported to a hospital in Tokyo (Jan 2012–Aug 2015) demonstrated that shorter EMS-to-door times were associated with better functional outcome. The same effect was seen among the subgroup of patients who received rtPA (n=52; 43%): functional outcomes were best when EMS-to-door time was short. The authors conclude that attempts must be made to reduce the time delay between EMS contact and treatment to ensure better outcomes for patients.

**“SAVE A MINUTE, SAVE A WEEK”: SMALL REDUCTIONS IN TREATMENT DELAYS RESULT IN MARKED BENEFITS**

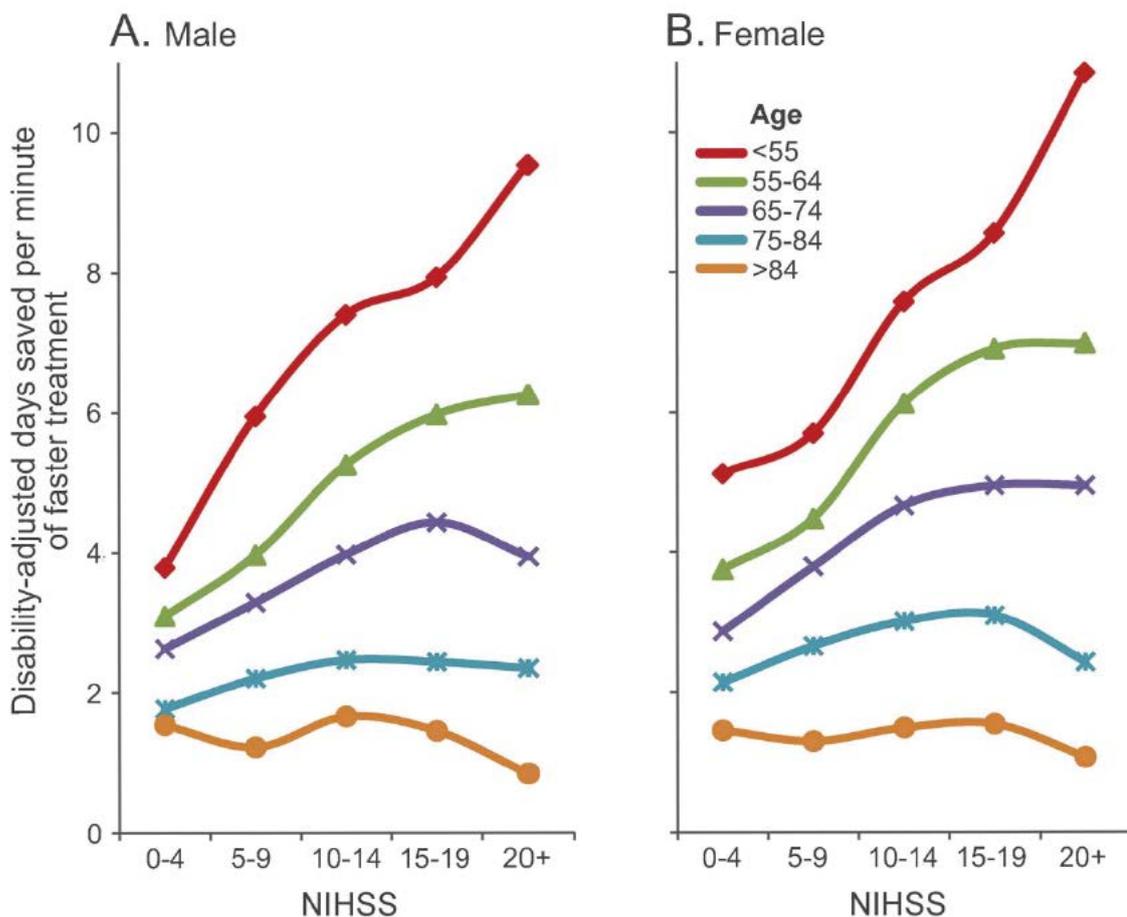
Timely recanalization can improve functional outcomes in patients with LVO who may require treatment with EVT, alone or in combination with rtPA.

As seen with rtPA treatment alone, small reductions in EVT delays lead to marked health benefits over stroke patients’ lifetimes. According to modelled data, every 20-minute decrease in treatment delay leads to a gain of 3 months of disability-free life.<sup>8</sup>

The authors conclude that services need to be optimized to reduce delays to EVT and they also observe that, importantly, **“...all patients gain from faster treatment.”**

**Study details**

- Analysis of data from 2474 consecutive stroke patients who received rtPA in Helsinki, Finland (1998–2014), to model the shift in functional outcomes associated with reducing treatment delays
  - 1745 patients received rtPA only; 729 patients were suitable for EVT
  - For this model, all patients were assumed to receive rtPA followed by EVT 90 min later
  - rtPA OTT was varied to model the impact on mRS score 0–1 (favourable outcome) and mRS score 6 (death)
- Each minute saved in OTT grants an average of 4.2 days of extra healthy life in patients suitable for EVT (see figure)
  - Those with longer overall life expectancies (younger patients and women) gain more over their lifetime
  - Young patients (age <55 years) with severe strokes (NIHSS score >10) gain more than a week for every minute saved



Healthy days gained per minute of faster treatment, by stroke severity (NIHSS) and age

**“...every minute counts when one intervenes with endovascular therapy, even more so than for tPA alone.”<sup>8</sup>**

## DIRECT PATIENT TRANSPORT TO A HOSPITAL WITH ADDITIONAL STROKE CARE CAPABILITIES MAY BE BENEFICIAL

As with any case of AIS, direct transfer to a hospital that offers the required level of stroke care, bypassing nearer hospitals if necessary, may be beneficial for the patient. For patients with LVO, early triage to a hospital with EVT capability is critical, but not all stroke hospitals are equipped to deliver EVT.

By adopting a simple 4-question EMS survey to identify patients with LVO, and then preferentially transporting these patients directly to a CSC with EVT capability, Mohamad *et al.* were able to reduce treatment delays and enable more patients to achieve functional independence.<sup>9</sup>

The authors conclude that a triage system designed to identify patients with LVO can shorten delays for EVT patients, particularly in-hospital delay, resulting in a better outcome.

### Study details

- Analysis of registry and EMS data from 476 AIS patients who received revascularization therapy (rtPA and/or EVT) at a CSC in Denmark (Jun 2011–Sept 2013), to examine the impact on treatment delays and outcomes of preferential transport
  - EMS personnel were taught how to use a stroke triage questionnaire to identify LVO
  - Patients with suspected LVO were given priority transport direct to the CSC (which has both rtPA and EVT capabilities), bypassing the nearer PSC (which has only rtPA capability) if necessary
  - Previously, LVO patients arriving at the PSC would have been given rtPA before being transferred to the CSC for EVT
- Among patients who received rtPA only, who could have been treated at the nearer PSC, treatment delays (see table) and functional outcomes were unaffected post-intervention
  - Bypassing the PSC in favour of the CSC did not appear to have any adverse effect on this group of patients
  - Proportion of patients with 90-day mRS scores of 0–2 was 75% in each period
- For patients receiving EVT (alone or in combination with rtPA), treatment delays decreased post-intervention (see table) and significantly more patients achieved functional independence
  - Reduction in overall treatment time was driven largely by a decrease in in-hospital delay (door-to-groin puncture time)
  - Proportion of patients with 90-day mRS scores of 0–2 increased from 43% to 62% (adjusted OR 3.08; 95% CI: 1.08–8.78)

OUTCOME MEDIAN (IQR) MIN	rtPA only		EVT ± rtPA	
	PRE-INTERVENTION (n=118)	POST-INTERVENTION (n=258)	PRE-INTERVENTION (n=35)	POST-INTERVENTION (n=65)
EMS-to-door time	53 (38–68)	56 (43–69)	64 (45–76)	58 (43–74)
Door-to-treatment time (DNT/door-to-groin puncture)	59 (50–73)	51 (42–71)	173 (119–227)	115 (90–156)
EMS-to-treatment time	119 (96–143)	112 (92–140)	234 (184–282)	185 (141–226)

**“Direct transfer of patients with suspected large-vessel occlusion to a comprehensive stroke centre leads to shorter treatment times for endovascular therapy patients and is, in turn, associated with an increase in functional independence.”<sup>9</sup>**

## TRANSPORT VIA MEDICAL HELICOPTER CAN BE USEFUL FOR ACUTE STROKE PATIENTS

Air transport of patients with AIS directly to a specialist stroke hospital may facilitate timely administration of thrombolysis, particularly in regions that lack a telestroke network.

Over a 5-year period (2011–2015), at the request of EMS in Ohio, USA, 136 adult patients with suspected AIS were transported by helicopter directly to a CSC.<sup>10</sup> Among these patients, 91 (67%) had a discharge diagnosis of AIS or TIA, and 28 (21%) received rtPA. The number of patients transported by helicopter decreased after the introduction of a telestroke network.

The authors observe that telestroke networks enable patients to be transported locally to a hospital offering specialist neurologist care; in the absence of this option, direct helicopter transfer to a CSC offers potential benefits to patients.

**“Helicopter scene response and transport to a comprehensive stroke center can provide substantial benefits for prospective stroke patients.”<sup>10</sup>**

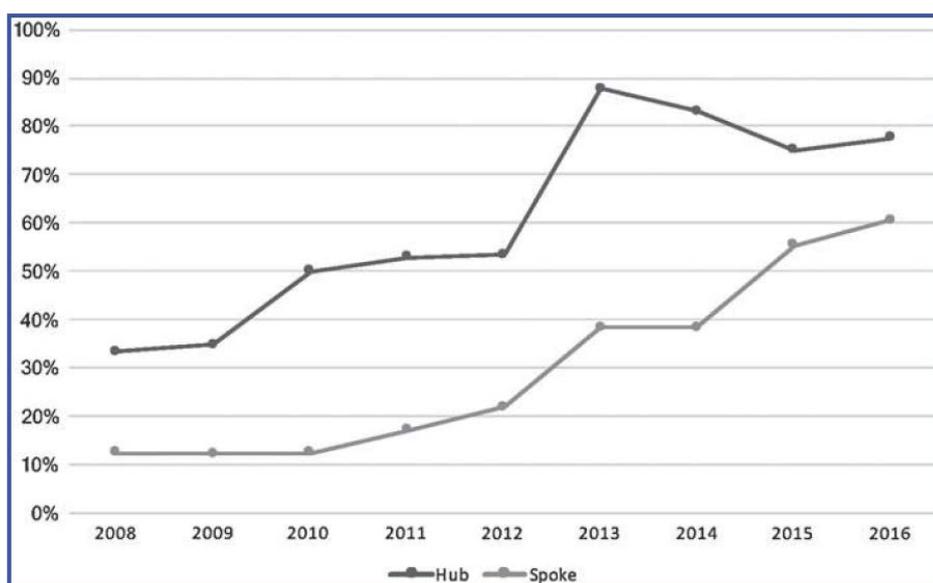
## DNT AT SPOKE HOSPITALS CAN BE IMPROVED BY MULTIDISCIPLINARY INTERVENTIONS

Telestroke networks provide patients with local access to specialist stroke care. However, treatment times at regional spoke hospitals can be longer than at hub hospitals. Multiple interventions, including education and training initiatives, can be implemented to narrow this gap.<sup>11</sup>

To implement stroke education programmes and improve stroke care at regional spoke hospitals, a telestroke network in South Carolina, USA, employed two telestroke coordinators in 2014. Between 2008 and 2016, improvements in stroke care were seen at hub and spoke hospitals: rtPA use and proportions of patients with DNT <60 minutes or <45 minutes all increased over time. During the post-intervention period (from 2014), treatment gaps between hub and spoke hospitals lessened significantly (see table and figure).

The authors observe that it is possible to improve DNT in spoke hospitals using interventions that target training, education, and improving the comfort level of staff when treating acute stroke patients. Reducing treatment gaps between hub and spoke hospitals is important to ensure patients treated via telestroke have access to the same quality of stroke care.

OUTCOME	PRE-INTERVENTION (n=695)		POST-INTERVENTION (n=970)	
	HUB (n=167)	SPOKE (n=528)	HUB (n=175)	SPOKE (n=795)
Mean DNT, min	62.3	90.1	46.1	64.6



Percentage of patients with DNT <60 min at hub and spoke hospitals

**“While the percentage of patients in the spoke sites meeting 60- or 45-min guidelines is lower compared to hub DTN times, the gap between the two locations is narrowing.”<sup>11</sup>**

AIS, acute ischaemic stroke; CSC, comprehensive stroke centre; CI, confidence interval; CT, computed tomography; COS, community-onset stroke; DNT, door-to-needle time; ED, emergency department; EMC, emergency medical centre; EMS, emergency medical services; ER, emergency room; EVT, endovascular therapy; HCP, healthcare practitioner; ICH, intracranial haemorrhage; IHS, in-hospital stroke; IQR, interquartile range; IV, intravenous; LVO, large vessel occlusion; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; ONT, onset-to-needle time; OR, odds ratio; OTT, onset-to-treatment time; PSC, primary stroke centre; rtPA, recombinant tissue plasminogen activator; TIA, transient ischaemic attack.

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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