

# PUBLICATION ALERT NEWSLETTER

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The benefits of intravenous (IV) recombinant tissue plasminogen activator (rtPA) for patients with acute ischaemic stroke (AIS) have been established for many years, as has the fact that time to treatment is critical, but knowledge does not always lead to action. How successful have we been in applying this knowledge and trying to improve the timeliness of treatment?

In this issue of the Actilyse® Publication Alert Newsletter, we report on an analysis of temporal changes in door-to-needle time (DNT) over the last decade at over 400 hospitals participating in a programme to improve stroke care. On a smaller scale, we also highlight a single centre’s experience in trying to improve DNT. In addition, we discuss a case report on pre-hospital thrombolysis and we continue to explore the treatment of AIS by telemedicine.

## A DECADE OF REDUCTION IN DOOR-TO-NEEDLE TIME, BUT STILL ROOM FOR IMPROVEMENT

An analysis of nearly 40 000 patients with AIS who received IV rtPA at 419 US hospitals over a 10-year period showed significant improvements in DNT.<sup>1</sup>

Between 2008 and 2017, there were significant increases in the proportions of patients with DNT ≤60 minutes and DNT ≤45 minutes among hospitals taking part in the Paul Coverdell National Acute Stroke Program, an acute stroke quality-of-care registry. Furthermore, DNT ≤60 minutes and DNT ≤45 minutes were both significantly associated with lower all-cause in-hospital mortality, lower symptomatic intracranial haemorrhage (SICH) within 36 hours, and higher odds of discharge home compared with longer DNT. This shows that the decrease in DNT has not come at the cost of worse clinical outcomes.

An analysis of the factors associated with achieving these DNT targets found that patients arriving by emergency medical services (EMS) and those with severe stroke were more likely to receive IV rtPA within 60 and 45 minutes of reaching hospital.

The authors cite the significant improvements in DNT as evidence of the success of quality improvement programmes for acute stroke. However, they also highlight that women and black patients (vs white) were less likely to achieve DNT ≤60 minutes and DNT ≤45 minutes. Therefore, opportunities remain to reduce disparities in treatment and further improve stroke care.

In an accompanying editorial, Xian and Fonarow note that, in addition to arrival by EMS, receiving care at high-volume academic centres, certified stroke centres or hospitals with a stroke unit were also associated with increased likelihood of achieving DNT ≤60 minutes and DNT ≤45 minutes.<sup>2</sup> They highlight the need to raise public awareness of stroke, promote EMS use and develop triage protocols to ensure suspected strokes are rapidly identified, assessed and transported to suitable hospitals that can administer IV rtPA in a timely fashion. Although they agree that there is still more to be done to further eliminate treatment delays, Xian and Fonarow call the observed improvements in stroke care ‘remarkable’ and conclude that:

**“These findings of this study lend further support about the favourable impact of applying performance improvement techniques of identifying best practices, clinical decision support, guideline-driven care improvement tools, educational efforts, collaborative support, and performance feedback.”<sup>2</sup>**

### Study details

- Analysis of data from 39 737 patients with AIS treated with IV rtPA within 4.5 hrs of the time last known to be well, between 2008 and 2017, at 419 hospitals participating in the Paul Coverdell National Acute Stroke Program
  - 47% of hospitals had a stroke unit, 52% were teaching hospitals, 59% were certified stroke centres
  - 50.3% of patients were men, 74.7% were white, 77% arrived by EMS, 17.6% had a prior stroke
  - Median (interquartile range [IQR]) age was 71 (59–82) yrs and National Institutes of Health Stroke Scale (NIHSS) score was 8 (5–15)
- Median DNT decreased significantly from 79 min in 2008 to 51 min in 2017 ( $p < 0.0001$ )
- From 2008 to 2017, there were significant increases in the proportions of patients with DNT ≤60 min (26.4% to 66.2%;  $p < 0.001$ ) and ≤45 min (10.7% to 40.5%;  $p < 0.001$ ; see table)

DNT	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
≤60 min, %	26.4	31.1	32.6	37.8	43.2	51.0	54.1	60.1	62.7	66.2
45 min, %	10.7	14.5	13.2	15.3	19.3	25.1	28.2	34.0	36.5	40.5

February 2019

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### Study details (continued)

- Generalized estimating equations adjusted analyses showed that:
  - Patients aged 55–84 yrs (vs aged 18–54 yrs), those arriving via EMS and those with NIHSS score of 5–20 (vs 0–4) were all more likely to have DNT ≤60 min than >60 min
  - Women and black patients (vs white) were less likely to be treated within 60 min
  - Hospitals with ≥200 beds (vs <200), those with ≥300 stroke admissions per year (vs <300) and those with a stroke unit were all associated with achieving DNT ≤60 min
  - Patients aged 55–74 yrs (vs aged 18–54 yrs), those arriving via EMS and those with NIHSS score of 5–20 (vs 0–4) were all more likely to have DNT ≤45 min than >45 min
  - Women and black patients (vs white) were less likely to be treated within 45 min
  - Hospitals with ≥400 beds (vs <400), those with ≥300 stroke admissions per year (vs <300) and those with a stroke unit were all associated with achieving DNT ≤45 min
- Both DNT ≤60 min and DNT ≤45 min were significantly associated with lower in-hospital all-cause mortality, SICH within 36 hrs, and higher odds of discharge to home compared with longer DNT (see table)

Outcome	DNT ≤60 min		DNT ≤45 min	
	Adjusted odds ratio (95% CI)	p value	Adjusted odds ratio (95% CI)	p value
Discharge to home	1.16 (1.10–1.22)	<0.001	1.15 (1.09–1.22)	<0.001
In-hospital death	0.88 (0.80–0.97)	0.01	0.87 (0.78–0.97)	0.01
SICH within 36 hrs	0.77 (0.68–0.87)	<0.001	0.69 (0.61–0.80)	<0.001

**“Focusing on shortening DNT times through dedicated quality improvement activities has been successful, and has not been associated with an increase in serious adverse events related to thrombolysis.”<sup>1</sup>**

### EDUCATIONAL EMERGENCY-ROOM MEETINGS CAN IMPROVE DOOR-TO-NEEDLE TIME

Efforts to improve stroke care don’t just have to be on the scale of nationwide programmes; individual institutions can take steps to improve DNT.

In January 2015, the stroke team at Sakarya University and Education Research Hospital in Turkey met to discuss AIS management, guideline recommendations and what could be done to improve DNT.<sup>3</sup> Further meetings were then held any time there was a ≥25% increase in DNT between consecutive patients with AIS treated with IV rtPA. These meetings covered similar topics to the inaugural meeting as well as a review of previous cases and DNT data.

Assessment of the data from 20 patients with AIS treated between January 2015 and August 2017 showed that six meetings were conducted and after each meeting there was a notable reduction in DNT for the following patient. Considering the intervals between meetings, there was a steady increase in the proportion of patients treated within 60 minutes of arrival.

Some of the measures taken after each review meeting were to establish specific protocols and guidelines, order sets, dosing charts, methods for stroke team activation (via smartphone app), record and prospectively analyse patient data on timeliness of therapy, and the inclusion of emergency room (ER) doctors and EMS staff in the review meetings.

**“Educational and motivational meetings held in the ER are beneficial in improving DNT when repeated within specific frameworks.”<sup>3</sup>**

### PRE-HOSPITAL THROMBOLYSIS DELIVERED BY A CRITICAL-CARE PHYSICIAN IN A MOBILE STROKE UNIT

When stroke occurs, diagnosis and appropriate treatment are required without delay. However, getting the patient to hospital takes time. An option increasingly being explored is pre-hospital intervention via a mobile stroke unit (MSU).

Larsen and colleagues give a case report from the Norwegian Treat-NASPP trial, in which thrombolysis for AIS was administered in an MSU by a critical care physician.<sup>4</sup> In addition to the physician, the MSU is staffed by a paramedic and a nurse paramedic, all additionally trained in specialized acute stroke evaluation and treatment. The MSU includes a point-of-care laboratory and a computed tomography (CT) scanner. CT images were transferred by teleradiology to hospital, allowing for review and consultation with a neurologist to confirm the preliminary diagnosis (cerebral ischaemia) and the absence of contraindications against thrombolysis. IV rtPA was administered in the MSU, just 17 minutes after the patient entered (DNT). The time from

entering the MSU to CT scan (door-to-CT) was only 3 minutes. Time from symptom onset to treatment was 56 minutes – within the ‘golden hour’.

The patient was transported to hospital and discharged home 7 days later.

By training the pre-hospital critical care physician to conduct the NIHSS, perform a CT scan and interpret the images, and initiate thrombolytic treatment when indicated, time from symptom onset to treatment was minimized as diagnosis-specific measures were all performed before the patient arrived at hospital. Having these stages performed by a team with expertise in critical care and the skills to treat acute medical and traumatic emergencies (not just stroke) helped ensure patient safety.

**“Early decision-making and early onset of treatment is mandatory to improve the prognosis and outcome for stroke patients, and accumulating evidence strongly suggests that the Norwegian MSU model contributes to this achievement.”<sup>4</sup>**

### A MULTIDISCIPLINARY APPROACH TO rtPA ADMINISTRATION MAY REDUCE COSTS AND DELAYS

Hospitals may struggle to implement process improvements if the changes are not cost-effective.

A US primary stroke centre (PSC) implemented a new multidisciplinary approach to AIS treatment that utilized bedside mixing of rtPA and salvaging waste in the main centralized pharmacy.<sup>5</sup> The goal was to utilise rtPA in a more cost-effective way that would not adversely affect DNT. In fact, the new process led to significant reductions in DNT and an estimated annual cost saving of more than US\$ 120 000.

The authors acknowledge that these data are preliminary and that this pilot study looked only at pharmacoeconomic impact in terms of rtPA costs. However, they believe that the utilization of bedside mixing with the ability to salvage rtPA could potentially lead to significant decreases in cost burden and DNT in stroke centres.

#### Study details

- Retrospective cohort study at a PSC emergency department (ED) between May 2017 and February 2018
- Old process for rtPA administration (n=25; May 2017 – September 2017):
  - Centralized pharmacy prepared entire rtPA dose using 100 mg vial and delivered to nursing staff for administration
- New multidisciplinary process for rtPA administration (n=25; October 2017 – February 2018):
  - First rtPA dose mixed and administered bedside by nursing staff using the entirety of a 50 mg vial (dose permitting) and included the initial bolus and the first portion of the infusion
  - Second rtPA dose prepared by centralized pharmacy from a second 50 mg vial and delivered to nursing staff for administration; any excess rtPA from this second vial was frozen in aliquots by the pharmacy
  - The majority of the salvaged rtPA was used for catheter clearance
- A total of 605 mg rtPA was salvaged using the new process, associated with US\$ 51 170.99 savings over the 5-month period (estimated over US\$ 120 000 annually)
- Patients in the new process group had faster mean DNT (52 min vs 60 min;  $p=0.01$ ) and median DNT (50 min vs 58 min;  $p=0.03$ ) compared with the old process group
- There was no significant difference between processes in door-to-CT or CT-to-rtPA order time, but median rtPA order-to-rtPA administration was significantly lower with the new process (12 min vs 22 min;  $p=0.04$ )

### DOOR-IN-DOOR-OUT TIME MAY PREDICT OUTCOME FOR PATIENTS WITH EMERGENT LARGE VESSEL OCCLUSION

Mechanical thrombectomy for patients with stroke with emergent large vessel occlusion (ELVO) in the anterior circulation often requires patient transfer between hospitals, as many are not equipped to perform the procedure (e.g. it often requires patient transfer from a PSC to a comprehensive stroke centre [CSC]). As earlier reperfusion is associated with improved outcomes, a US study has examined the association between the time it takes for a patient to enter and leave a PSC (en route to a CSC for mechanical thrombectomy for ELVO stroke) and outcomes.

An analysis of data from 130 patients found that prolonged time taken at the PSC (termed ‘door-in-door-out’ time) may have a deleterious association on outcomes.<sup>6</sup> This was particularly so for patients for whom complete reperfusion was not possible. Door-in-door-out time was not associated with stroke severity. Additionally, the time did not improve over the ~2-year period studied, despite education and feedback efforts, which suggests that there was no improvement as hospitals gained increasing experience with the transfer protocol.

The authors suggest using door-in-door-out time as a performance measure to track the transfer of patients with ELVO to thrombectomy-capable centres when they do not initially present to one. They regard this as important a metric as DNT is for IV rtPA and, as for DNT, process improvements should be employed to decrease door-in-door-out time.

## TELESTROKE PATIENTS WITH AIS HAVE SIMILAR OUTCOMES TO THOSE MANAGED WITH ON-SITE EXPERTISE

Telestroke can enable timely assessment, diagnosis and treatment of AIS in hospitals without on-site neurologist support. An assessment of patient data from Ontario, Canada, has found that patients receiving IV rtPA supported by telestroke had similar outcomes to those managed with on-site experience.<sup>7</sup>

Patients with AIS who received telestroke-assisted IV rtPA were not at greater risk of death within 7 or 90 days, nor at greater odds of experiencing SICH or poor functional ability at discharge, compared with non-telestroke patients. DNT was longer among telestroke patients, but door-to-CT time was shorter.

The authors conclude that the findings support the ongoing use of telestroke services for thrombolysis administration.

### Study details

- Analysis of data from two audits of the Ontario Stroke Registry (in 2010 and 2012), including 2099 patients with AIS treated with IV rtPA; 214 of these patients were treated at a hospital in the telestroke programme
- Patient characteristics were similar between groups, though telestroke patients were more likely to be from a rural location
- Patients treated by telestroke had a longer DNT but a shorter door-to-CT than those in the non-telestroke group
  - Median (IQR) for telestroke vs non-telestroke:
    - Symptom onset to ED arrival: 77 (48–111) min vs 73 (50–114) min ( $p=0.88$ )
    - Door-to-CT: 17 (6–27) min vs 20 (12–30) min ( $p=0.002$ )
    - DNT: 70 (54–92) min vs 65 (48–86) min ( $p=0.005$ )
    - Symptom onset to needle: 153 (120–195) min vs 148 (115–192) min ( $p=0.37$ )
- Administration of IV rtPA using telestroke was not associated with an increased risk of death within 7 days or 90 days of arrival at the ED. It was also not associated with an increased risk of SICH or poor functional outcome at hospital discharge (see table)

Outcome	Telestroke, % of patients	Non-telestroke, % of patients	Adjusted hazard ratio (95% CI)
7-day mortality	13.1	9.0	1.29 (0.68–2.44)
90-day mortality	22.0	21.7	1.01 (0.67–1.50)
			Adjusted odds ratio (95% CI)
SICH	5.1	6.9	0.71 (0.29–1.71)
modified Rankin Scale (mRS) score 3–5 at discharge	48.6	54.7	0.75 (0.46–1.23)

## TELESTROKE IS NOT INFLUENCED BY AN ADVERSE 'AFTER HOURS' EFFECT

The standard of stroke care may be influenced by the time and day of hospital presentation, with potentially worse outcomes if patients present overnight or at weekends. However, a recent analysis has shown that patients receiving rtPA after evaluation by telemedicine did not show any difference in treatment times or mortality between those treated 'after hours' versus 'on hours'.<sup>8</sup>

Analysis of patient data ( $n=424$ ) from a US telemedicine registry found no differences in relevant time metrics between patients receiving IV rtPA after hours (5pm to 7:59am on weekdays, or at weekends) compared with those managed during on-hours (weekdays 8am to 4:59pm). Median (IQR) DNT was 59 (47–80) minutes after-hours vs 61 (47–81) minutes on-hours ( $p=0.62$ ). Last-known well-to-needle time was 141.5 (102–193) minutes vs 150 (104–192) minutes ( $p=0.37$ ), respectively.

Rate of SICH, 90-day mortality and favourable outcome (mRS score 0–2 at 90 days) were also similar between the two groups.

The authors conclude that their study shows no evidence of a 'weekend effect' for patients with AIS treated with IV rtPA at hospitals equipped with telestroke services.

**“Hospitals that cannot provide around the clock in-hospital acute stroke expertise may consider implementing telemedicine on weekends and after-hours, as this may help to reduce mortality and potentially decrease long-term complications of stroke.”<sup>8</sup>**

February 2019

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AIS, acute ischaemic stroke; CI, confidence interval; CSC, comprehensive stroke centre; CT, computed tomography; DNT, door-to-needle time; ED, emergency department; ELVO, emergent large vessel occlusion; EMS, emergency medical services; ER, emergency room; IQR, interquartile range; IV, intravenous; mRS, modified Rankin Scale; MSU, mobile stroke unit; MT, mechanical thrombectomy; NIHSS, National Institutes of Health Stroke Scale; PSC, primary stroke centre; rtPA, recombinant tissue plasminogen activator; SICH, symptomatic intracranial haemorrhage

## References

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