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.

For patients with AIS,* the key to maximizing favourable treatment outcomes is to do as much as possible as soon as possible. Streamlined pre-hospital care that enables ultra-early, effective treatment is therefore a vital first step in the stroke pathway, but downstream in-hospital and post-hospital processes are also important. Evidence-based quality improvement efforts aimed at multiple individual components of stroke care may have a synergistic effect on health outcomes, as a recent editorial by Fassbender and Sheth notes,

> **"Considering the stroke chain of survival as a continuum beginning with symptom onset and ending with causal treatment, a synergistic combination of both pre- and in-hospital stroke management improvements… may be the key for fastest possible treatment times and best possible outcomes."[1]**

In this issue of the Actilyse® Publication Alert Newsletter, we report on the success of accelerated stroke management protocols and ways in which pre-hospital processes have evolved to expedite appropriate triage and treatment. We also discuss the importance of maintaining stroke care quality regardless of admission time, to optimize outcomes for all patients.

*Abbreviations are defined at the end of the newsletter.

ULTRA-EARLY THROMBOLYSIS CAN BE ACHIEVED SAFELY USING ULTRAFAST ADMISSION EVALUATION

Achieving a highly optimized DNT requires patients with suspected acute stroke to be evaluated as quickly as possible on hospital admission, leaving less time for diagnostic certainty. A stroke hospital that first achieved median DNT <20 min in 2011 has evaluated the impact of rapid admission evaluation on diagnostic accuracy, and the possible consequences of misdiagnosis.[2]

Over a 2.5-year period, rates of correct admission diagnosis at an experienced stroke department with optimized DNT were high, while rates of over- and under-treatment due to misdiagnosis were within normal ranges. A small proportion of patients (15%) were misdiagnosed at admission, but in many cases this did not affect subsequent medical management; no patient died because of misdiagnosis, and misdiagnosis was found to contribute to worse outcomes in <1% of patients overall.

The authors conclude that using ultrafast admission evaluation to gain shorter door-to-treatment times is sufficiently safe when performed in a centre with expertise and comprehensive training. These outcomes support the use of hyper-acute patient evaluation to optimize thrombolysis.

Study details

- Observational study of 1015 EMS-transported patients with suspected AIS evaluated and treated at an experienced neurological ED in Helsinki (May 2013–Nov 2015) to examine diagnostic accuracy and consequences of misdiagnosis
- To achieve optimal rtPA administration times, EMS–ED interactions and in-hospital protocols have been refined over 20 years
  - All patients with suspected AIS are deemed 'stroke-code' and transported as high priority with EMS pre-notification
  - Medical records are reviewed and blood samples are collected during the pre-hospital phase
  - On ED arrival, patients are transferred directly to the CT suite for clinical assessment and neuroimaging by an experienced stroke neurologist (minimum of 3 months training in stroke diagnosis and treatment)
  - Median DNT in 2016 was 19 minutes
- During the study period, 865/1015 patients (85%) were diagnosed correctly at admission
  - Diagnostic accuracy was highest for AIS/TIA (91%) and haemorrhagic stroke (99%), and lowest for stroke mimics (62%)
- Most of the 150 (15%) misdiagnosed patients had no acute findings on imaging and/or had mild impairment
- Misdiagnosis influenced medical management in 70 cases (6.9%), including:
  - 37 patients who received unnecessary treatments (including rtPA)
  - 5 patients who missed out on rtPA treatment
  - 27 patients who had delays to treatment (antiplatelet therapy or stroke mimic treatments)
- Misdiagnosis possibly or probably worsened outcomes in 8 cases (0.8%); in most cases, adverse consequences of misdiagnosis were prevented by mild symptoms or correction of diagnosis during further work-up

"These findings support the safety of gradually optimized DNTs in a high-volume neurologic ED, when sufficient physician training and support are in place."[2]

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SMALL IMPROVEMENTS IN STROKE CARE CAN LEAD TO LARGE IMPROVEMENTS IN PATIENT OUTCOMES

Quality improvement efforts that target several components along the stroke chain may result in greater-than-expected benefits. Additionally, although clinical trials are used primarily to provide evidence that an intervention is effective in improving outcomes, they may also embed practice change and provide the means to deliver long-term quality care.

The GOLDEN BRIDGE AIS trial in China randomized 40 secondary or tertiary public hospitals (25 of which had a stroke unit) to continue to deliver usual care or to receive a multifaceted quality improvement intervention.[3] Compared with control hospitals, intervention hospitals had greater adherence to evidence-based performance measures, and this was associated with significantly better short- and long-term patient outcomes. One year after admission, less than 10% of patients treated at intervention hospitals had experienced a new vascular event, and only 13% of survivors had stroke-related disability.

This trial demonstrates that effective stroke interventions can be implemented within a national network of hospitals. An editorial concerning the trial notes that although the reported improvement in meeting quality targets was small, the improvement in clinical outcomes was large, and reported performance measures are probable surrogate markers for, "good stroke unit care from initial patient evaluation to discharge".[4] In addition, as well as achieving good-quality stroke care, the intervention hospitals now have processes in place to sustain and improve stroke care delivery further.

Study details

- Open-label, cluster-randomized clinical trial enrolling 4800 consecutive patients with AIS who received rtPA at 40 stroke-ready hospitals in China (Aug 2014–Jun 2015), to evaluate the impact of a multifaceted quality improvement intervention on adherence to nine predefined evidence-based performance measures and on patient outcomes up to 12 months later
  - Intervention included use of an evidence-based clinical pathway (from admission to discharge), written protocols, staff training, appointment of a quality coordinator, and ongoing monitoring and feedback of performance
  - Performance measures included four in-hospital outcomes and five discharge outcomes (specific medication use)
  - Patient outcomes included incidence of new clinical vascular event (AIS, haemorrhagic stroke, myocardial infarction, or vascular death), disability (mRS score 3–5) and all-cause mortality
- **Adherence to performance measures was higher** in the intervention group than in the control group (see table 1)
  - Differences in the composite, but not the all-or-none measure, were statistically significant
  - Twice as many eligible patients received rtPA within 3 h of stroke onset in intervention hospitals
- **Patient outcomes were superior** in the intervention group than in the control group at each time point (see table 2)
  - At each time point, the risk of new clinical vascular events was reduced and fewer patients had stroke disability
  - HR for risk of new vascular events was 0.72 (95% CI: 0.60–0.87; $p<0.001$)
- Rates of SICH and 1-year all-cause mortality were similar in both groups

TABLE 1: ADHERENCE TO PERFORMANCE MEASURES

	CONTROL (USUAL CARE) (n=2400)	INTERVENTION (n=2400)	*p* VALUE†
'Composite', mean (SD) % of measures*	**84.8 (18.2)**	**88.2 (15.1)**	**0.003**
'All-or-none', % of patients*	47.8	53.8	0.31
Individual measures, n/N eligible (%)			
ONT ≤3 h	23/204 (11.3)	46/212 (21.7)	0.06
Antithrombotics within 48 h	2253/2330 (96.7)	2307/2353 (98.0)	0.07
Dysphagia screening	2040/2139 (95.4)	2255/2328 (96.9)	0.10
DVT prophylaxis by day 2	66/592 (11.1)	178/645 (27.6)	**0.04**
Antithrombotics at discharge	2141/2305 (92.9)	2272/2324 (97.8)	0.10
Anticoagulation at discharge	39/137 (28.5)	63/155 (40.6)	0.23
Lipid-lowering medication at discharge	1439/1547 (93.0)	1415/1481 (95.5)	0.40
Antihypertensive medication at discharge	1372/1771 (77.5)	1510/1838 (82.2)	0.07
Antidiabetic medication at discharge	557/663 (84.0)	653/728 (89.7)	**0.02**

*Composite = the proportion of measures performed; all-or-none = the proportion of patients for whom all measures were performed
†Based on the population average odds ratio between the two groups

Study details (continued)

TABLE 2: PATIENT OUTCOMES			
	CONTROL (ROUTINE CARE) (n=2400)	INTERVENTION (n=2400)	*p* VALUE
New vascular events, n (%)			
3 months	127 (5.3)	93 (3.9)	**0.007**
6 months	186 (7.8)	150 (6.3)	**0.02**
12 months	282 (11.8)	218 (9.1)	**0.005**
Disability (mRS 3–5), n/N (%)			
3 months	443/2105 (21.0)	418/2180 (19.2)	**0.01**
6 months	360/2009 (17.9)	326/2058 (15.8)	**0.006**
12 months	264/1798 (14.7)	236/1852 (12.7)	**0.02**
SICH among rtPA-treated patients, n/N (%)	2/23 (8.7)	1/46 (2.2)	0.26
In-hospital mortality, n (%)	23 (1.0)	11 (0.5)	**0.009**
12-month mortality, n (%)	160 (6.7)	139 (5.8)	0.05

"These [multifaceted] quality improvement interventions significantly improved short-term and long-term outcomes in reductions of new vascular events and reduced stroke disability."[3]

A MOBILE THROMBOLYSIS TEAM CAN OVERCOME OUT-OF-HOURS DELAYS IN rtPA TREATMENT

Patients with AIS admitted to hospital out of hours (overnight or at weekends) can experience greater in-hospital delays than do those admitted during daytime hours. Addressing this discrepancy would help to ensure all patients have equal access to care.

A university hospital evaluated the impact of stepwise introduction of a mobile thrombolysis team (MTT) on in-hours and out-of-hours care.[5] The MTT comprised a specialist stroke nurse and a vascular neurologist who were responsible for evaluating the patient and administering rtPA as soon as possible after imaging. Introduction of the MTT resulted in quicker administration of rtPA and an increase in the proportion of patients receiving rtPA within 60 minutes of arrival. Out-of-hours care improved with the availability of around-the-clock cover, so that treatment times matched those seen during in-hours care: at least half of all patients had DNT ≤60 minutes.

The authors suggest that implementation of an around-the-clock MTT shortens in-hospital delays and enables similar thrombolysis treatment metrics to be achieved regardless of patient admission time.

Study details

- Retrospective analysis of 504 patients with AIS who received rtPA within 4.5 h of symptom onset at a university hospital in France (Jan 2013–Dec 2017), to assess the impact on time to thrombolysis of an MTT (stroke nurse + vascular neurologist)
  - Outcomes were assessed for patients admitted in-hours and out-of-hours (6 PM to 8 AM and weekends)
  - MTT availability was phased in, starting with in-hours cover and then adding out-of-hours cover
- The MTT stroke nurse performed initial patient evaluation, set up intravenous access, and transported the patient to the radiology department; the MTT vascular neurologist administered rtPA immediately after brain imaging
- Discrepancies in care were apparent in the pre-intervention period, with significantly longer delays from imaging to rtPA administration and DNT in the out-of-hours group (see table)
- Staged implementation of the MTT, first in hours (2015) and then round the clock (2017) resulted in quicker administration of rtPA and an increase in the proportion of patients receiving rtPA within 60 min of arrival
  - Availability of an in-hours MTT substantially reduced delays to rtPA administration (>60% of patients had DNT ≤60 min but only during the hours when the MTT was available)
  - Round-the-clock cover enabled those arriving out of hours to receive the same level of care as those arriving in hours
  - Onset-to-door and door-to-imaging times remained similar for in-hours and out-of-hours care throughout the study period

Study details (continued)

PERIOD AND OUTCOME	IN HOURS	OUT OF HOURS	*p* VALUE
2013–2014 (usual care)	**N=69**	**N=64**	
Onset-to-door time, median (IQR) min	95 (71–123)	90 (71–113)	0.7
Door-to-imaging time, median (IQR) min	24 (15–32)	24 (13–35)	0.8
Imaging-to-needle time, median (IQR) min	52 (44–63)	57 (49–73)	**0.02**
DNT, median (IQR) min	75 (63–90)	85 (70–111)	**0.01**
DNT ≤60 min, n (%)	16 (23)	6 (9)	**0.04**
2015–2016 (MTT available in-hours)	**N=83**	**N=140**	
Onset-to-door time, median (IQR) min	94 (65–124)	85 (62–110)	0.3
Door-to-imaging time, median (IQR) min	28 (19–37)	31 (19–43)	0.3
Imaging-to-needle time, median (IQR) min	24 (18–37)	47 (31–63)	**<0.001**
DNT, median (IQR) min	54 (46–66)	78 (63–95)	**<0.001**
DNT ≤60 min, n (%)	53 (64)	30 (21)	**<0.001**
2017 (MTT available all hours)	**N=59**	**N=89**	
Onset-to-door time, median (IQR) min	86 (67–135)	95 (61–124)	0.6
Door-to-imaging time, median (IQR) min	34 (27–41)	28 (21–42)	0.1
Imaging-to-needle time, median (IQR) min	32 (24–42)	35 (28–47)	0.1
DNT, median (IQR) min	67 (56–83)	67 (55–84)	0.7
DNT ≤60 min, n (%)	32 (54)	45 (50)	0.7

OUT-OF-HOURS HOSPITAL CARE IS DELAYED IN PATIENTS WITH AIS AND LARGE-VESSEL OCCLUSION

It is important that all stroke patients have access to timely and appropriate treatment, at any time of day. For patients with AIS and large-vessel occlusion, this means receiving recanalization therapy at an endovascular-enabled hospital.

Löwhagen Hendén *et al.* analysed data from 198 patients with AIS who received endovascular therapy at a university hospital in Sweden over a 9-year period (2007–2016) and compared metrics and outcomes between those who received in-hours treatment (n=89) and those who were treated out of hours (weekdays between 4 PM and 8 AM and at weekends; n=109).[6] Although pre-hospital performance and rtPA treatment rates were similar in both groups, out-of-hours patients had significantly longer in-hospital delays (imaging-to-groin puncture and imaging-to-recanalization times). Imaging-to-recanalization delay was an independent predictor of poor neurological outcome.

The authors conclude that additional out-of-hours resources would probably help to deliver effective round-the-clock care.

STROKE CARE PARADIGMS CONTINUE TO EVOLVE TO REFLECT ADVANCES IN TREATMENT

To ensure patients can benefit as quickly as possible from new advances in stroke care, protocols and treatment paradigms must be continually adapted and incorporated into the stroke care pathway.

A review by Mendez *et al.* discusses how pre-hospital care, reperfusion therapy and post-reperfusion management have evolved in recent years, particularly in the treatment of AIS patients with large-vessel occlusion, and the increasing use of mobile stroke units (MSUs) and telestroke.[7]

The authors outline the latest pre-hospital stroke algorithm and different transport options available to EMS.

Although EMS aim to provide rapid evaluation, triage and transport of patients with AIS, it is also important that patients are transferred to hospitals with appropriate capabilities. For this reason, pre-hospital evaluation should extend beyond stroke *recognition* to include stroke *severity*.

The authors conclude that substantive advances have been made in the acute management of AIS, and further research is needed to continue to optimize existing strategies of pre-hospital and post-hospital care.

"Prompt assessment and adequate triaging of patients with acute ischemic stroke is crucial for timely delivery of reperfusion therapies and optimize[d] outcome[s]."[7]

MOBILE STROKE UNITS CAN FACILITATE HYPERACUTE STROKE CARE

A review by Bowry and Grotta states that adoption of MSUs into existing systems of care requires careful consideration of existing EMS systems and protocols, regional stroke hospital capabilities, geographical setting and population dynamics.[8] Accounting for these local factors, there are different ways in which MSU intervention can be applied. In addition to enabling early administration of rtPA to eligible patients, MSUs may improve the efficient identification and transport of patients with large-vessel occlusion to endovascular-capable hospitals. In rural settings, MSUs could travel to meet ambulances transporting AIS patients and so avoid the need for long-distance transfers to expert stroke centres before beginning treatment.

The authors observe that, "although reducing time to thrombolysis is a key goal of MSUs, the potential benefits of earlier assessment and MSU intervention are far more expansive."

OPTIMAL TRANSPORT STRATEGY FOR PATIENTS WITH AIS IS DETERMINED BY MULTIPLE FACTORS

When transporting patients with suspected AIS, EMS may bypass a nearby hospital in favour of a more distant stroke unit offering specialist services (such as endovascular therapy). To identify which pre-hospital transfer strategies work best in different scenarios, Holodinsky *et al.* created a theoretical model of stroke transport for patients with AIS and suspected large-vessel occlusion.[9] They found that the probability of a patient achieving an excellent functional outcome (after both rtPA and endovascular therapy) was affected by several factors and thus different circumstances favour different approaches:

- **Bypassing a nearby thrombolysis centre** was the superior strategy if the specialist endovascular centre was close by (≤60 min away), if DNT at the thrombolysis centre was typically ≥60 min, or if rtPA was contraindicated
- **'Drip and ship'** was the superior strategy if the thrombolysis centre was close by, the patient had to pass the thrombolysis centre en route to the endovascular centre, the endovascular centre was ≥2 hours away, or if travel delay to the specialist centre would make the patient ineligible for rtPA
- **Either strategy** was effective if the two centres were close together (≤60 min travel time apart) and in-hospital treatment times were optimal

The authors conclude that the decision whether to bypass a hospital or to use 'drip and ship' for patients with AIS and suspected large-vessel occlusion should be based on regional factors, including stroke centres' treatment metrics and locations.

"DRIVE THE DOCTOR" IS A FEASIBLE OPTION FOR REMOTE DELIVERY OF AFTER-HOURS ACUTE STROKE CARE

Remote hospitals may not have 24/7 availability of an on-site interventional neurologist, and instead adopt a 'drip and ship' approach where rtPA is administered and then the patient is transferred to a specialist stroke centre for further care. However, an alternative option for out-of-hours care may be to 'drive the doctor': the on-call neurologist travels by car to deliver interventional stroke care locally.[10]

Retrospective comparison of two models of after-hours care at a single tertiary hospital found that onset-to-imaging times, thrombolysis rates, and clinical outcomes were similar for 'drip and ship' and 'drive the doctor'. Notably, time to recanalization therapy was significantly shorter in the 'drive the doctor' group, suggesting that a neurologist can travel to the referring hospital faster than a patient can be transferred to the specialist stroke unit.

'Drive the doctor' appears to be a feasible alternative to 'drip and ship' for out-of-hours delivery of interventional stroke care.

Study details

- Retrospective analysis of data from 126 consecutive AIS patients with large-vessel occlusion admitted after hours to a remote tertiary hospital and then referred to a university hospital for mechanical thrombectomy (Feb 2012–Dec 2016), to compare outcomes between 'drip and ship' and 'drive the doctor' protocols
  - In all cases, CT angiography was performed at the remote hospital to confirm large-vessel occlusion
  - With 'drip and ship', the patient was then transferred to the university hospital for mechanical thrombectomy
  - With 'drive the doctor', an on-call neurointerventionalist was alerted and drove 100 km to deliver mechanical thrombectomy at the remote hospital
- rtPA treatment rates and clinical outcomes were similar in each group (see table)
- Onset-to-imaging times were similar, but door-to-groin puncture time was half as long in the 'drive the doctor' group

Study details (continued)

METRIC AND OUTCOME	'DRIVE THE DOCTOR' (n=60)	'DRIP AND SHIP' (n=66)	*p* VALUE
rtPA, n (%)	37 (62)	46 (70)	0.35
Onset-to-imaging time, median (IQR) min	70 (56–117)	77 (58–114)	0.68
Imaging-to-groin puncture time, median (IQR) min	112 (87–128)	232 (194–266)	**<0.0001**
Successful recanalization, n (%)	52 (87)	51 (77)	0.25
Good clinical outcome, n (%)	22 (37)	22 (33)	0.71

NURSE-LED STROKE RESPONDER TEAMS CAN IMPROVE STROKE CARE DELIVERY VIA TELEMEDICINE

Including specialist nurses on stroke teams may improve the efficiency and quality of care, as these nurses can respond to the stroke alert, perform initial evaluations, coordinate care delivery with other team members, and facilitate the delivery of rtPA.

The addition of a stroke responder nurse to the telemedicine team at a regional community hospital led to significant improvements in several treatment metrics between 2014 and 2016, including door-to-imaging time (decreased from 30 to 12 minutes) and DNT (decreased from 107 to 65 minutes).[11] All stroke responders underwent 8 hours of stroke-related education each year to maintain their competency.

The authors conclude that local, specially trained nursing staff can improve treatment metrics in an AIS telemedicine system.

SPOKE AND HUB HOSPITALS DELIVER SIMILARLY HIGH-QUALITY CARE RELATING TO rtPA ADMINISTRATION

For telestroke networks to be successful, spoke hospitals must deliver the same high quality of care as the central hub hospital.

Demaerschalk *et al.* analysed stroke care delivery, from initial alert to hospital discharge, over a 4-year period (2010–2014) within the Mayo Clinic Telestroke Program and found that "**evidence-based stroke thrombolysis decision making, thrombolysis administration, and thrombolysis emergency stroke metrics were uniformly excellent**" across hub and spoke hospitals.[12] However, post-thrombolysis hospitalization and discharge metrics were inferior within spoke hospitals (see table).

The authors emphasize the importance of maintaining stroke team presence throughout the stroke care pathway, and recommend an additional telestroke consultation before hospital discharge to ensure that quality of stroke care is maintained.

OUTCOME	SPOKE HOSPITALS (n=500)	HUB HOSPITAL (n=500)	*p* VALUE
rtPA eligibility correct decision making, n (%)	**478 (95.6)**	**484 (96.8)**	0.32
rtPA administered, n (%)	200 (40.1)	180 (36.0)	0.18
Post-thrombolysis SICH, n (%)	13 (6.5)	5 (2.8)	0.09
VTE prophylaxis, n (%)	215 (45.8)	312 (63.4)	**<0.001**
Antithrombotic therapy administered by day 2, n (%)	338 (84.5)	422 (89.6)	**0.02**
Length of hospital stay, median (IQR) days	4 (3–6)	3 (2–5)	**<0.001**
Favourable discharge outcome, n (%)	104 (20.8)	173 (34.6)	**<0.001**

AIS, acute ischaemic stroke; CI, confidence interval; CT, computed tomography; DNT, door-to-needle time; DVT, deep vein thrombosis; ED, emergency department; EMS, emergency medical services; HR, hazard ratio; IQR, interquartile range; mRS, modified Rankin Scale; MSU, mobile stroke unit; MTT, mobile thrombolysis team; ONT, onset-to-needle time; rtPA, recombinant tissue plasminogen activator; SD, standard deviation; SICH, symptomatic intracranial haemorrhage; TIA, transient ischaemic attack; VTE, venous thromboembolism.

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