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.

Efforts by hospitals to improve thrombolysis rates and times are limited to patients with AIS* who are eligible for rtPA on arrival. However, for many patients, delays in presenting to hospital mean they arrive outside of the treatment window for rtPA.

In this issue of the Actilyse® Publication Alert Newsletter, we report on efforts to bridge the gap between patients who are potentially eligible for rtPA and those who actually receive it. We discuss the importance of team communication, parallel workflow, and the need to treat all stroke patients in a timely manner regardless of their care pathway. Additionally, the impact of administering IV thrombolysis to AIS patients with LVO is explored.

*Abbreviations are defined at the end of the newsletter.

THE NUMBER OF POTENTIAL CANDIDATES RECEIVING THROMBOLYSIS COULD BE INCREASED

Various factors, including stroke onset >4.5 hours, exclude patients from receiving IV rtPA. In 2015, in an effort to increase rtPA treatment rates, Italian Stroke Organisation guidelines were revised to distinguish 'relative' exclusion criteria from 'absolute' exclusion criteria. The guidelines suggest that patients without 'absolute' exclusion criteria should be considered 'potentially eligible' for rtPA. A recent study by Forlivesi and colleagues assessed what proportion of patients with AIS are 'potentially eligible' for rtPA, the proportion that are treated, and the reasons for not administering thrombolysis.

Regional data from Italy suggest that 59% of patients with AIS arrive within 4.5 hours of stroke onset, have no other 'absolute' exclusion criteria, and are thus 'potentially eligible' for thrombolysis. However, only 27% of patients with AIS (46% of those 'potentially eligible') received rtPA.[1]

The authors suggest that the number of patients presenting within 4.5 hours of AIS onset could be increased by improving pre-hospital organization, raising public awareness of stroke, and providing continuous education to healthcare professionals. Furthermore, the authors suggest that administering rtPA to patients without 'absolute' exclusion criteria, such as patients with mild deficits or uncertain stroke onset time, would close the gap between treatment eligibility and delivery.

Study details

- Analysis of 1184 consecutive patients with AIS admitted to 22 stroke units in the Veneto region of Italy (Sep–Dec 2017), to assess the proportion of 'potentially eligible' patients treated with rtPA and to explore reasons for deciding not to treat
  - 16 stroke units were Level 1 (rtPA-enabled) and 6 were Level 2 (able to administer rtPA and endovascular therapy)
  - 'Absolute' exclusion criteria were defined as: stroke onset >4.5 h; use of VKA with INR >1.7; use of DOAC with therapeutic effect; clinical suspicion of ICH despite normal CT; administration of IV heparin in the previous 48 h and aPTT above laboratory normal upper limit; platelet count <100 000/mm^3; known haemorrhagic diathesis; current or recent severe bleeding; bacterial endocarditis or pericarditis; acute pancreatitis; neoplasm with increased haemorrhagic risk; severe liver disease; haemorrhagic retinopathy; increased haemorrhagic risk due to comorbidity; recent (<10 days) traumatic external heart massage, childbirth, or puncture of non-compressible blood vessel; ulcer of the gastrointestinal tract <3 months
  - 'Relative' exclusion criteria were defined as: mild deficit or rapidly improving symptoms; unknown time of onset or stroke on awakening; seizure at stroke onset; use of VKA and INR ≤1.7; use of DOAC with subtherapeutic effect; history of stroke and concomitant diabetes; blood glucose <50 or >400 mg/dl; history of stroke in the last 3 months; uncontrolled severe arterial hypertension; clinically severe stroke (e.g. NIHSS >25); administration of LMWH in the last 24 h; history of CNS disease; history of ICH; pregnancy; major surgery or severe trauma in the last 3 months
    (Please note: this classification was based on based on local clinical guidelines, not on local alteplase labelling)
- 480 patients (41%) were ineligible for rtPA due to ≥1 'absolute' exclusion criterion, including:
  - 343 (29%) with symptom onset >4.5h before admission (primarily due to pre-hospital delays)
- 704 patients (59%) were 'potentially eligible' for rtPA (onset within 4.5 h and no other 'absolute' exclusion criteria)
- 323 patients (27%; 46% of those 'potentially eligible') received rtPA (see table)
  - Level 2 stroke units administered rtPA to more patients than Level 1 stroke units

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Study details (continued)

- 381 patients (32% of those admitted; 54% of those 'potentially eligible') were **not** treated with rtPA, despite an absence of 'absolute' exclusion criteria:
  - 283 (24%) had ≥1 'relative' exclusion criterion and no 'other reason' for not treating
  - 56 (5%) had no 'relative' exclusion criteria and ≥1 'other reason' for not treating
  - 42 (4%) had a combination of 'relative exclusion' criteria and 'other reasons' for not treating
  - 'Other reasons' for exclusion from treatment included: hypodensity on brain CT; old age; cognitive impairment; pre-stroke mRS score >2; posterior circulation stroke with NIHSS score 0; severe leukoaraiosis on brain CT; absence of informed consent; night or weekend/holiday admission; suspicion of amyloid angiopathy; large vessel occlusion; suspicion of stroke mimic; double antiplatelet therapy; absence of a stroke specialist

PATIENT OUTCOME, n (%)	LEVEL 1 STROKE UNIT (n=752)	LEVEL 2 STROKE UNIT (n=432)	ALL (n=1184)
Not eligible for rtPA	334 (44)	146 (34)	480 (41)
Stroke onset >4.5 h without other 'absolute' exclusion criteria	257 (34)	86 (20)	343 (29)
Potentially eligible for rtPA	418 (56)	286 (66)	704 (59)
Treated with rtPA	153 (20)	170 (39)	323 (27)
Not treated with rtPA	265 (35)	116 (27)	381 (32)

"All healthcare professionals involved in the acute stroke pathway should make an effort to bridge the gap between eligibility and reality."[1]

rtPA TREATMENT RATES OF OVER 80% CAN BE ACHIEVED IN ELIGIBLE PATIENTS WITH AIS

For more than two decades, IV rtPA has been at the forefront of treatment of AIS. In recent years, endovascular therapy (ET) has begun to be used in certain patients. Feda and colleagues decided to assess IV rtPA use during this 'new era of stroke management'.[2]

During 2014, a stroke centre in Germany was able to achieve a thrombolysis rate of 82% among potential candidates for rtPA. Approximately one-quarter of these patients also received ET after rtPA. A small group of potentially eligible patients did not receive rtPA due to relative contraindications (mild symptoms) and had longer imaging delays than rtPA-treated patients.

High thrombolysis rates were achieved among potentially eligible patients, but overall this represented a minority (34%) of all patients admitted with a confirmed diagnosis of AIS. Many patients were ineligible for rtPA due to arrival >4.5 hours after symptom onset. Efforts to reduce pre-hospital delays would therefore increase the number of patients potentially eligible for rtPA.

The authors conclude that rtPA remains the most frequently applied reperfusion therapy in AIS patients presenting within 4.5 hours of onset in a tertiary stroke centre, and more than 80% of eligible patients can receive rtPA without increased risk of SICH.

Study details

- Retrospective analysis of data from 1034 patients presenting with suspected AIS at the ED of a university hospital in Germany (Jan–Dec 2014), to explore rtPA treatment rates as a proportion of all AIS patients and of rtPA-eligible patients
  - Stroke management was streamlined by establishing a multidisciplinary stroke rescue chain with documented processes and periodic feedback
- 718 patients had a confirmed diagnosis of AIS; 419 of these patients arrived within 4.5 h of symptom onset
- 123/419 patients had absolute contraindications to rtPA other than time of onset. Therefore, 296 patients were potentially eligible for rtPA
- **243/296 (82%) potentially eligible patients received rtPA alone or in combination with ET** (median DNT 30 min)
  - 183/296 patients (62%) received rtPA alone
  - 63/296 patients (21%) received ET, either alone (n=3) or after rtPA (n=60)
  - 50/296 patients (17%) did not receive rtPA due to relative contraindications, primarily mild or improving symptoms (other reasons for not receiving rtPA included patient refusal, recent surgery, cardiopulmonary instability, active neoplastic disease, and hypertensive crisis)
- Patients who received rtPA had favourable clinical outcomes (49% with 90-day mRS 0–2; 1.1% with SICH)

"This study showed that IV rtPA treatment remains an essential cornerstone in times of modern acute stroke therapy and that an effective thrombolysis rate [in eligible patients] of over 80% can be achieved."[2]

REDUCING PRE-HOSPITAL DELAYS MAY IMPROVE IN-HOSPITAL CARE IN DEVELOPING COUNTRIES

Most strokes happen in middle-income or developing countries, where the time taken to arrive at hospital varies greatly and few patients have access to advanced care. When ED resources are limited, patients with AIS who arrive at hospital quickly – and are eligible for rtPA – may be prioritized.

A study in Iran revealed that 72% of AIS patients arrived at hospital more than 4.5 hours after symptom onset.[3] Only 20% of patients were deemed potentially eligible for rtPA on initial assessment: this group had substantially shorter in-hospital delays than other patients. The authors observe that all patients with AIS should receive rapid and comprehensive care, regardless of rtPA eligibility, and make several recommendations to overcome identified barriers.

The authors conclude that clinical care was poor for patients who were not candidates for rtPA. As the most common reason for rtPA ineligibility was arrival more than 4.5 hours after symptom onset, they believe increasing public awareness of stroke urgency represents the largest opportunity to improve stroke care in Iran and countries with similar stroke care systems.

Study details

- Retrospective chart review of 394 patients with AIS/TIA admitted to the ED of a university hospital in Iran (Mar–Jun 2017) to evaluate treatment delays and describe barriers to care
  - Stroke code was activated in the ED after diagnosis, if the patient was deemed eligible for rtPA
- Only 66 patients (16.8%) arrived via EMS; most patients (n=209; 53.1%) were walk-ins
- Most patients (n=316; 80.2%) did **not** receive stroke code activation; they were deemed ineligible for rtPA on initial assessment for one or more reasons:
  - **283 (71.8%) arrived >4.5 h after symptom onset**
  - 80 (20.3%) were aged >80 years
  - 58 (14.7%) had wake-up stroke or unclear onset time
  - 55 (14.0%) had minor symptoms
  - 26 (6.6%) had rapidly improving symptoms
  - 18 (4.6%) had major symptoms and unstable medical condition
- Stroke code was activated for 78 patients (19.8%)
  - 21 patients (5.3% of those admitted; 26.9% of those eligible) received rtPA, with a median DNT of 69 (IQR 46–91) min
- Patients with stroke code activation had shorter in-hospital delays than patients without stroke code activation (see table)
- Barriers to care included: ED overcrowding; prolonged boarding time; evaluation on 'first come, first served' basis; delays in stroke team notification; delays in CT scans; delays in neurology consultations
- Author recommendations to overcome specific barriers and improve stroke care quality include:
  - EMS prenotification; direct-to-CT admission; rtPA administration in the ED or CT suite; multidisciplinary collaboration; establishment of MT services; implementation of performance goals; continuous evaluation and quality improvement; 24/7 neurology resident support; appointment of a nursing stroke co-ordinator

IN-HOSPITAL METRIC, MEDIAN (IQR) MIN	INELIGIBLE FOR rtPA (n=316)	ELIGIBLE FOR rtPA (STROKE CODE ACTIVATED) (n=78)
Door-to-physician time	20 (10–30)	9 (0–19)
Door-to-stroke team notification time	67.5 (22–141.5)	10 (0–19.5)
Door-to-CT time	75 (59–96.5)	33.5 (17–61)

"A patient's eligibility for intravenous rtPA should not dictate whether he or she receives rapid and complete assessment and documentation for stroke."[3]

SIMULATION-BASED STROKE TRAINING IMPROVES DNT BY ALMOST 10 MINUTES

Increasing physician confidence and familiarity with stroke care protocols can improve the quality of care delivery.

A US hospital implemented acute stroke care training that used a live actor to portray the symptoms of AIS.[4] This simulation-based training, implemented without additional resources or costs, increased the confidence of first-year neurology residents to deliver critical stroke care. Door-to-CT time was reduced and mean DNT decreased by 9.6 minutes.

Ongoing simulation-based training of neurology residents and neurology nursing staff is therefore feasible and can result in improvements in stroke care delivery.

Study details

- Retrospective analysis of all patients with AIS who received rtPA at a US hospital (Oct 2008–Sep 2014), to evaluate the impact on DNT of implementing (in July 2011) stroke simulation-based training
  - No changes were made to stroke triage processes during the study period
- Simulation-based training for first-year neurology residents was introduced to enhance co-operation between nurses and neurology residents and to streamline acute stroke care management
  - A trained live actor simulated stroke symptoms in the presence of a board-certified vascular neurologist
  - Trainee performance was assessed against a critical action checklist (e.g. timely arrival, initial assessment, medical history, vital signs, laboratory tests, CT scan, rtPA eligibility, endovascular intervention candidacy, action plan)
  - Feedback was provided immediately, with areas for improvement identified
  - The simulation was repeated until the trainee was able to deliver stroke care without missing any critical actions
- During the simulations, all participants arrived on location within 5 min of stroke code activation and completed NIHSS evaluation within 5 min of arrival; average time to rtPA decision was 10.2 min
- Most trainees reported that simulation training increased their comfort in managing AIS patients
- Treatment delays were reduced after implementation of simulation-based training (see table)
- Simulation-based training was independently associated with a reduction in mean DNT of 9.6 min (95% CI –15.3 to –4.0; *p*=0.001) on multivariate regression analysis

METRIC IN rtPA-TREATED PATIENTS	PRE-INTERVENTION (n=172)	POST-INTERVENTION (n=276)	*p* VALUE*
Door-to-CT time, mean (SD) min	26.0 (5.0)	21.6 (2.2)	0.0001
DNT, mean (SD) min	68.0 (25.1)	58.3 (25.9)	0.0001

*Univariate analyses

BEDSIDE PREPARATION OF rtPA IMPROVES TIMELY THROMBOLYSIS

Streamlining in-hospital processes can significantly reduce in-hospital delays. For example, by preparing rtPA at bedside in the ED rather than ordering it from the central pharmacy, an academic hospital was able to significantly reduce DNT and increase the proportion of patients treated within 60 minutes of arrival without adversely affecting safety.[5]

METRIC AND OUTCOME	PRE-INTERVENTION (n=16)	POST-INTERVENTION (n=15)	*p* VALUE
DNT, mean (SD) min	96 (45)	67 (22)	0.024
Imaging-to-needle time, mean (SD) min	92 (43)	54 (26)	0.003
DNT ≤60 min, %	19	53	0.044
ICH, %	13	0	0.488

A MULTITIERED STROKE NOTIFICATION SYSTEM IMPROVES DOOR-TO-REPERFUSION TIMES

Effective communication within multidisciplinary stroke teams is key to the efficient care of patients. Many assessments and preparations can be carried out in parallel to minimize in-hospital delays, but this requires co-ordination of team members.

A Florida clinic performed process mapping to identify inefficiencies in their stroke care pathway and found that communication, particularly with the neurointerventional team, could be improved.[6] They devised a tiered activation system that escalated as the probability of requiring neurointerventional services increased, so that key team members could be alerted at appropriate times, and necessary assessments and preparations could be carried out in parallel.

The tiered activation system successfully reduced door-to-reperfusion time for patients with AIS requiring MT, and was also associated with shorter length of stay in neurocritical care and cost savings for the hospital.

Study details

- Prospective study of 62 patients with AIS and LVO treated with MT at the Mayo Clinic (Apr 2015–May 2017), to assess the impact on time to reperfusion of a three-tiered notification system implemented in April 2016
  - Current state process mapping identified inefficiencies in patient triage and interdisciplinary communication, which were then targeted using a three-tiered paging platform

Study details (continued)

- The tiered paging system was designed to streamline patient care and reduce in-hospital delays by improving interdepartmental communication and enabling parallel patient assessment and preparation for endovascular procedure
  - Tier 1: activated by EMS for patients presenting with suspected AIS
  - Tier 2: activated by neurology residents for patients with suspected LVO and probably requiring MT
  - Tier 3: activated by neurology residents for patients proceeding with MT
- Door-to-reperfusion time was significantly reduced after implementation of the tiered paging system (see table)
- Implementation of the tiered paging system reduced neurocritical care length of stay and medical costs (see table)
- 5 patients (19%) in the post-intervention group had a 90-day mRS score of 0; other functional and safety outcomes were similar in both groups

METRIC AND OUTCOME	PRE-INTERVENTION (n=34)	POST-INTERVENTION (n=28)	*p* VALUE
rtPA, n (%)	20 (59)	13 (46)	0.38
Door-to-reperfusion time, median (range) min	129 (71–434)	114.5 (64–364)	0.02
Onset-to-reperfusion time, median (range) min	399 (151–868)	328 (148–1150)	0.22
Neurocritical care length of stay, median (range) days	4 (2–21)	3 (1–9)	0.006
Hospital costs, median (range) USD	117 217 (67 350–474 053)	86 964 (48 457–193 789)	<0.001

rtPA ADMINISTRATION DOES NOT DELAY ENDOVASCULAR THERAPY IN PATIENTS WITH AIS AND LVO

Stroke units often have well-established processes to streamline patient care and minimize delays in rtPA administration, and patients who are candidates for ET may benefit from being managed along these existing stroke care pathways.

At a stroke centre in Germany, more than 60% of patients who underwent ET received rtPA beforehand.[7] Receiving rtPA prior to ET did not delay revascularization and had no adverse impact on clinical outcomes, including SICH. In fact, patients who received rtPA were treated slightly quicker, possibly because their care was more streamlined.

The authors observe that therapeutic decisions may be less complicated for patients receiving rtPA, resulting in faster in-hospital procedural times without increased adverse effects. It is possible that patients with AIS and LVO may benefit from receiving rtPA therapy prior to endovascular intervention.

Study details

- Analysis of 188 patients with AIS who received rtPA and/or ET at a tertiary stroke centre in Germany (Jan 2015–Mar 2016), to assess the impact of prior rtPA administration on treatment times and outcomes in patients undergoing ET for LVO
  - 118/188 (63%) of patients received standard rtPA prior to ET
  - Patients were treated using simultaneous procedures and parallel workflow where possible: rtPA was administered in the CT suite, and candidates for ET were transferred immediately after CT to the neurointerventional suite
- Patients in the rtPA + ET group had similar or better in-hospital treatment times than the ET-only group (see table)
  - Door-to-imaging time was significantly shorter in the rtPA + ET group
  - Overall median intervention time was 78 min in the ET-only group and 90 min in the rtPA + ET group
- Prior rtPA treatment did not adversely affect clinical outcomes (see table)

METRIC AND OUTCOME	ET ONLY (n=70)	rtPA + ET (n=118)	*p* VALUE
Time intervals, median (range) min			
Onset-to-door	113 (29–575)	77 (2–820)	0.22
Onset-to-puncture	203 (20–955)	153.5 (53–883)	0.16
Door-to-imaging	22 (1–287)	19 (6–289)	**<0.001**
Imaging-to-puncture	44.5 (4–427)	42 (10–188)	0.53
Door-to-puncture	65.5 (17–447)	62.5 (16–346)	0.16
Puncture-to-revascularization	36 (9–264)	40 (5–157)	0.99
Door-to-revascularization	115 (44–529)	107.5 (51–399)	0.29
Clinical outcomes, %			
Successful revascularization (TICI ≥2b)	81.4	80.5	0.68
Good functional outcome (mRS 0–2 at 90 days)	11.8	24.5	0.06
SICH	4.3	6.8	0.48

TELESTROKE NETWORKS DELIVER rtPA EFFECTIVELY AND SAFELY

Telestroke networks can increase patient access to expert care and enable more patients to receive thrombolytic treatment. Patients who require additional care (such as neurointerventional services) can then be transferred to specialist centres.

Between March 2013 and December 2015, 951 patients with AIS were evaluated via telestroke within a 12-hospital network in Catalonia, Spain.[8] After telestroke consultation, 322 patients (34%) received rtPA and 237 (25%) were considered candidates for ET and subsequently transferred to the nearest CSC for further care.

Overall, treatment times and clinical outcomes were comparable between telestroke centres and patients treated at PSCs/CSCs elsewhere in the region (see table). DNT was longer for telestroke patients vs PSC/CSC patients, but did decrease over the study period for all patients (as did the rate of rtPA treatment).

The authors conclude that telestroke favours safe and effective thrombolysis, helps to increase the population rate of IV thrombolysis, and avoids unnecessary hospital transfers.

METRIC AND OUTCOME	PSC or CSC (n=2897)	TELESTROKE (n=322)	*p* VALUE
Onset-to-door time, median (IQR) min	71 (45–121)	65 (38–114)	0.09
Door-to-imaging time, median (IQR) min	22 (15–31)	23 (14–31)	0.78
DNT, median (IQR) min	44 (32–59)	55 (45–70)	**<0.01**
OTT, median (IQR) min	120 (80–175)	120 (87–180)	0.34
Thrombectomy after rtPA, %	13.9	11.1	0.17
SICH, %	4.2	6.1	0.15
Good functional outcome (mRS 0–2 at 90 days), %	57.5	53.7	0.23

TELESTROKE SPOKE HOSPITALS DELIVER THE SAME CARE QUALITY AS HUB HOSPITALS

Patients who receive rtPA at telestroke spoke hospitals may be transferred subsequently to the hub hospital for further care ('drip-and-ship') or remain at the spoke hospital ('drip-and-stay'). For the 'drip-and-stay' model to be acceptable, patient care needs to be of similar quality to that provided by the hub hospital.

In a 26-hospital telestroke network in South Carolina, patients treated at spoke hospitals using 'drip-and-stay' (n=366) showed similar outcomes to patients treated at the hub hospital (n=60) across three assessed measures:[9]

- **DNT**: mean 61.3 minutes for the drip-and-stay group vs 68.3 minutes for the hub group (p=0.165)
- **SICH**: 1.7% in the drip-and-stay group vs 1.1% in the hub group (p=0.534)
- **Good functional outcome** (mRS 0–2 at 90 days): 69.7% in the drip-and-stay group vs 61.7% in the hub group (p=0.216)

The authors conclude that their study shows no difference in the long-term functional outcome for patients who received rtPA and subsequent care at spoke hospitals, compared with patients who received rtPA at the hub hospital. Following rtPA administration via telestroke, spoke hospitals are capable of delivering high-quality patient care and rehabilitation.

TELESTROKE NETWORKS ARE A COST-EFFECTIVE APPROACH TO CARING FOR RURAL PATIENTS

Telestroke networks enable patients in rural areas to access stroke care expertise quickly, increasing their chances of early diagnosis and timely rtPA treatment. These treatment metrics should translate into improved clinical outcomes, long-term quality-of-life benefits, and overall payer savings.

Using data from the ACCESS telestroke program in New Mexico, Whetten et al developed a 90-day cost-effectiveness model.[10] Use of ACCESS reduced patient transfers to urban hospitals and improved functional outcomes compared with routine care. This reduction in unnecessary transportation in combination with better health outcomes resulted in a potential saving of 4241 USD and a gain of 0.20 QALYs per patient (ICER –21 205 USD).

The authors conclude that "in addition to providing financial benefits, a teleneurology program produces better patient outcomes, and offers societal benefits through reduction of stroke-related disability and increased convenience to patient's families."

AIS, acute ischaemic stroke; aPTT, activated partial thromboplastin time; CI, confidence interval; CNS, central nervous system; CSC, comprehensive stroke centre; CT, computed tomography; DNT, door-to-needle time; DOAC, direct oral anticoagulants; ED, emergency department; EMS, emergency medical services; ET, endovascular therapy; ICER, incremental cost-effectiveness ratio; ICH, intracranial haemorrhage; INR, international normalised ratio; IQR, interquartile range; IV, intravenous; LMWH, low molecular weight heparin; LVO, large vessel occlusion; mRS, modified Rankin Scale; MT, mechanical thrombectomy; NIHSS, National Institutes of Health Stroke Scale; OTT, onset-to-treatment time; PSC, primary stroke centre; QALY, quality-adjusted life-year; rtPA, recombinant tissue plasminogen activator; SD, standard deviation; SICH, symptomatic intracranial haemorrhage; SPC, summary of product characteristics; TIA, transient ischaemic attack; TICI, thrombolysis in cerebral infarction scale; USD, United States dollars; VKA, vitamin K antagonist.

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