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.

Advancing the care of patients with acute ischaemic stroke (AIS) can take many forms. In particular, we should never underestimate the potential for established treatment options such as intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (rt-PA) to be used in new ways, for example in new patient groups, or in combination with novel interventional techniques such as endovascular thrombectomy (EVT).

In this issue of the rt-PA Publication Alert Newsletter, we report on the publication of data that reinforces the benefit seen from IVT with rt-PA in patients aged >80 years.[1] Published online by *Stroke* in July 2020, the pooled analyses of patient data from 7 randomized controlled trials (RCTs) and the SITS-UTMOST registry confirm that age alone should not be a barrier to rt-PA for AIS. Elsewhere in the newsletter, we consider recent papers on the relative roles of IVT and EVT, including a trial demonstrating the benefit and feasibility of adding EVT to IVT in a low-to-middle income country (Brazil); the potential utility of an extended therapeutic window for rt-PA in carefully selected patients with AIS due to large vessel occlusion (LVO); and the role that mobile stroke units (MSUs) can play in managing patients with AIS.

POOLED ANALYSES OF INDIVIDUAL PATIENT DATA CONFIRM POSITIVE BENEFIT–RISK PROFILE OF rt-PA FOR AIS IN PATIENTS AGED >80 YEARS WHEN ADMINISTERED ACCORDING TO OTHER EUROPEAN REGULATORY CRITERIA

Expert management guidelines issued by the European Stroke Organisation and American Stroke Association/American Heart Association no longer specify an upper age limit for treatment with rt-PA. However, until recently, use of rt-PA in Europe was restricted to patients aged 18–80 years. Given that approximately one-third of cases of AIS occur in people aged ≥80 years, there is an obvious need for effective, evidence-based treatment options in this group.

These pooled analyses clearly demonstrate the benefit that rt-PA offers to patients aged >80 years.[1] Analyses of individual patient data from RCTs showed a positive benefit–risk profile of rt-PA for AIS among patients aged >80 years, when administered according to other European regulatory criteria. More patients treated with rt-PA compared with placebo achieved a good stroke outcome in both ≤80 years and >80 years age subgroups. 90-day mortality was similar between treatment groups in both age subgroups, despite small but significant increases in symptomatic intracranial haemorrhage (sICH).

An additional analysis of data from the SITS-UTMOST registry provided reassurance that outcomes among patients aged >80 years who received rt-PA for AIS in routine clinical practice correspond well with those in RCTs.

A combined body of evidence, including these pooled analyses, led to agreement by the European regulatory authorities in 2018 to rescind the upper age restriction on use of alteplase for AIS.

This article was selected for an accompanying editorial from Janne Mortensen and Grethe Andersen, who emphasized that "the upper age limit for treatment is no longer justified" and that an upper age limit may also be unnecessary in future RCTs in AIS. Furthermore, Mortensen and Andersen highlight the importance of increasing societal awareness of stroke symptoms, particularly among elderly high-risk patients living alone, to ensure rapid hospital admission and treatment in this age group.[2]

Study details

- Pooled analysis of individual patient data from 7 RCTs of rt-PA vs placebo or open control for AIS; separate analyses were performed on data from patients treated with rt-PA in the SITS-UTMOST registry.
- In both the pooled RCT analysis and the registry analysis, two subgroups who received treatment in line with European regulatory criteria (excluding upper age restriction) were specified based on patient age (≤80 or >80 years).
- Key trial outcomes were compared in the age-defined subgroups.

Pooled analysis of patient data from RCTs

- The full RCT population comprised 6035 patients, of whom 3026 received rt-PA and 3009 received placebo or open control.
  - In total, 1699 patients (more than one quarter of the RCT study population) were aged >80 years.
- In the full RCT population, rt-PA administration within 4.5 h after symptom onset had a beneficial effect on good stroke outcome (time to treatment P=0.0203 for interaction). The estimated effect of rt-PA vs placebo on the odds of good stroke

outcome by patient age had a P value of 0.7383 for interaction (Figure); this clearly shows that the efficacy of rt-PA/lysis in AIS is independent of age.

- Patients aged >80 years, and who otherwise met existing European regulatory criteria, had more severe strokes (mean [SD] baseline National Institute of Health Stroke Scale [NIHSS] scores 12.9 [6.3] vs 11.0 [6.1], respectively) and higher rates of comorbidities compared with younger patients.
- Among patients aged >80 years who otherwise met European regulatory criteria, rt-PA was associated with a higher proportion of good stroke outcomes, higher rates of sICH and similar 90-day mortality compared with placebo or open control (Table).

Figure: Estimated effect of rt-PA vs placebo on the odds of good stroke outcome by patient age.
Solid line, estimated odds ratio; dashed lines, 95% CIs.

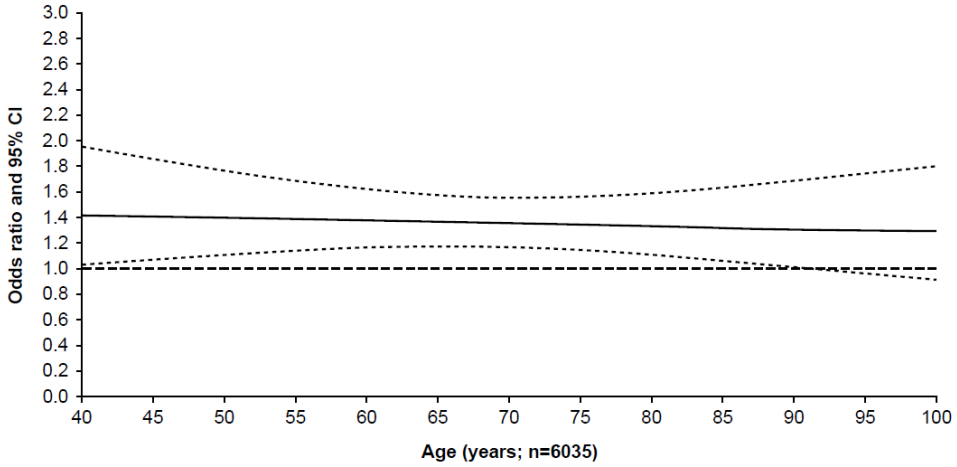

Table: Key clinical trial endpoints for patients who received rt-PA or placebo for AIS in age-defined subgroups who otherwise met European regulatory criteria (pooled analysis of individual patient data from 7 RCTs)

	≤80 years		>80 years	
	rt-PA (n=1182)	Placebo (n=1223)	rt-PA (n=518)	Placebo (n=510)
Good stroke outcome, n (%)	529 (44.8)	439 (35.9)	99 (19.1)	67 (13.1)
Difference, %	8.9 (p<0.0001)		6.0 (p=0.0109)	
Death within 7 days, n (%)	61 (5.2)	50 (4.1)	55 (10.6)	40 (7.8)
Difference, %	1.1 (p=0.2434)		2.8 (p=0.1325)	
Death within 90 days, n (%)	116 (9.8)	130 (10.6)	153 (29.5)	154 (30.2)
Difference, %	−0.8 (p=0.5448)		−0.7 (p=0.8382)	
sICH, n (%)	31 (2.6)	6 (0.5)	19 (3.7)	2 (0.4)
Difference, %	2.1 (p<0.0001)		3.3 (p=0.0002)	

Analyses of SITS-UTMOST registry data

- 11 911 patients met European regulatory criteria (except upper age limit) and were included in the analyses; 9491 aged ≤80 years and 2420 aged >80 years.
- Registry data echoed the functional outcomes achieved with rt-PA for AIS in RCTs; 26.6% of patients aged >80 years achieved a good stroke outcome.
- The incidence of sICH (1.4% vs 3.7%) and overall mortality (29.0% vs 29.5%) following thrombolysis of patients aged >80 years who otherwise met European regulatory criteria was not increased in routine practice vs clinical trials.

"Thrombolysis treatment for patients presenting with AIS should be evaluated on an individual benefit–risk basis. Importantly, age alone is no longer a barrier to alteplase treatment for AIS."[1]

"The lesson learned is that exclusion criteria should be individualized and based on comorbidity, premorbid function, and frailty."[2]

THE DIRECT-MT TRIAL INTENDED TO SHOW NON-INFERIORITY OF EVT ALONE VS A COMBINED TREATMENT WITH IV rt-PA AND EVT, WITHIN A 20% MARGIN. STUDY CONCLUSIONS ARE LIMITED AND CHALLENGED BY EDITORIAL

Combining IV rt-PA with EVT should achieve earlier and more complete recanalization of the occluded vessel, particularly if EVT is delayed, or the thrombus is challenging to reach. Other possible benefits of IV rt-PA include dissolution of fragments of thrombi that are dislodged during EVT, and recanalization before initiation of EVT. However, administering IV rt-PA could delay initiation of EVT, and increase the risk of bleeding and the cost.[3]

Recently, the DIRECT-MT study was conducted in China to compare EVT alone with combined treatment with EVT and IV rt-PA in patients with AIS with LVO. The study reported that EVT alone was non-inferior to combined IV rt-PA and EVT in terms of the modified Rankin scale (mRS) score at 90 days; however, EVT alone was associated with lower percentages of patients with successful reperfusion before thrombectomy and overall successful reperfusion. Mortality at 90 days was similar in both study arms.[4]

The study has a number of limitations, as highlighted by the study authors[4] and in an accompanying editorial by Greg Albers.[3]

- The short time allowed for IV rt-PA to act before EVT was initiated (infusion was completed before groin puncture in only 23 out of 319 patients) means that the results should be interpreted with caution.[4]
  - In the study, IV rt-PA was administered at tertiary care centres;[4] as highlighted in the editorial, in clinical practice in most countries IV rt-PA is frequently administered at primary stroke centres, often 2 or more hours before EVT is performed at a comprehensive stroke centre.[3]
  - The short interval in the study may not have allowed adequate time for IV rt-PA to show its effect.[3]
- The prehospital triage system in China, and need for informed consent before IV rt-PA can be administered, meant that the median time from symptom onset to initial treatment was relatively long (almost 3 hours in both study arms).[4]
- Although non-inferiority was established, the margin used was generous, and the confidence intervals did not exclude a benefit of approximately 20% in the combination therapy group.[4]

Study details

- Multicentre, prospective, randomized, open-label trial conducted at 41 academic tertiary care centres in China.
  - Eligible patients were adults aged ≥18 years with occlusion of the intracranial segment of the internal carotid artery, or of the first or proximal second segment of the middle cerebral artery, or both, that could be treated with IV rt-PA within 4.5 h of symptom onset, and with a neurological deficit.
  - Patients were randomized 1:1 to receive EVT alone (n=327), or IV rt-PA (0.9 mg/kg) before EVT (n=329).
- Demographics and baseline characteristics were similar between the two study arms. Median age was 69 y and 56.4% of patients were men. Overall, 27% of patients in the EVT arm and 24% in the combined treatment arm had an mRS score of 1 or 2 before stroke onset.
- Median time from stroke onset to randomization, and from randomization to groin puncture, was 167 min and 31 min, respectively, for EVT alone, and 177 min and 36 min, respectively, for combination treatment.
- EVT alone was non-inferior to combination treatment with IV rt-PA and EVT for all outcomes except successful reperfusion before EVT, which favoured the combination treatment group (Table).

Outcome	EVT (n=327)	IV rt-PA and EVT (n=329)	Odds ratio (OR) (95% confidence interval [CI])
Primary outcome			
mRS score at 90 days, median (interquartile range [IQR])	3 (2–5)	3 (2–5)	1.07 (0.81–1.40)
Selected secondary outcomes			
mRS score 0–1 at 90 days, n (%)	80 (24.5)	74 (22.5)	1.09 (0.74–1.59)
mRS score 0–2 at 90 days, n (%)	119 (36.4)	121 (36.8)	0.97 (0.68–1.37)
Successful reperfusion before EVT on initial digital subtraction angiography (DSA), n (%)	8 (2.4)	23 (7.0)	0.33 (0.14–0.74)
Extended thrombolysis in cerebral infarction (eTICI) score of 2b, 2c or 3 on final angiogram, n/N (%)	243/306 (79.4)	267/316 (84.5)	0.70 (0.42–1.06)
Safety outcomes			

Death, n (%)	58 (17.7)	62 (18.8)	0.94* (0.68–1.30)
Asymptomatic intracranial haemorrhage (ICH), n (%)	109 (33.3)	119 (36.2)	0.92* (0.75–1.14)
Symptomatic ICH, n (%)	14 (4.3)	20 (6.1)	0.70* (0.36–1.37)
Infarction in new territory at 5–7 days, n (%)	11 (3.4)	9 (2.7)	1.23* (0.52–2.93)

*Risk ratio

The authors concluded "Our trial showed that among patients with AIS with LVO in the anterior circulation who were eligible for treatment with both IV alteplase and EVT, EVT alone was noninferior to EVT preceded by alteplase […]
Larger trials in other populations are needed to compare alteplase plus EVT with EVT alone."[4]

The editorial commented "Until more data are available, it is appropriate to follow current guidelines that recommend that all eligible patients receive alteplase before thrombectomy."[3]

EVT IN COMBINATION WITH IVT IS A VIABLE AND BENEFICIAL TREATMENT STRATEGY FOR PATIENTS IN LOW- AND MIDDLE-INCOME COUNTRIES THAT MAY HAVE LIMITED HEALTHCARE RESOURCES (THE RESILIENT TRIAL)

Multiple RCTs have shown the benefit of mechanical thrombectomy in patients with AIS due to LVO, but these trials were conducted in high-resource countries with healthcare environments that have the ability to widely apply technological advances. Given the high cost of thrombectomy, the Brazilian government was reluctant to fund it without evidence of its efficacy and cost-effectiveness in a healthcare system with more limited resources.

A recent, government-funded study sought to address this evidence gap.[5] RESILIENT, a robust RCT conducted in 300 patients across 12 study sites in Brazil, compared disability at 90 days in patients treated with intra-arterial thrombectomy and guideline-based care vs guideline-based care alone, including IV rt-PA for eligible patients within 4.5 hours after the onset of symptoms.

The authors concluded that endovascular treatment within 8 hours after the onset of stroke symptoms in conjunction with standard care resulted in better functional outcomes at 90 days than standard care alone.

Study details

- Multicentre, prospective, randomised, open-label controlled trial conducted in 12 certified stroke centres within the Brazil Universal Public Health Care System.
- Eligible patients were aged ≥18 years; had an occlusion involving the intracranial internal carotid artery, the first segment of the middle cerebral artery (M1), or both that could be treated within 8 h after symptom onset; had a prestroke mRS score of 0 or 1; and had an NIHSS score ≥8 at presentation.
- Overall, 300 patients were included in the study. Of these, 79 had thrombectomy during a study roll-in phase (to ensure sufficient thrombectomy experience at participating centres – these patients were not included in the outcomes analyses).
  - Only one of the centres had previous experience with endovascular stroke treatment, but all operators were fellowship-trained neurointerventionalists who had previously performed at least five thrombectomies.
- The remaining 221 patients were randomized 1:1 to receive intraarterial thrombectomy and guideline-based care (thrombectomy group) or guideline-based care alone (control group), including IV rt-PA for eligible patients within 4.5 h after the onset of symptoms.
- Baseline characteristics were generally similar in the two groups. The percentages of patients with hypertension, diabetes mellitus, or current or past tobacco use were numerically higher in the control group; the percentage of patients with a baseline mRS score >0 was numerically higher in the thrombectomy group.
- IV rt-PA was received by 68.5% and 71.8% of patients in the thrombectomy and control groups, respectively.
- Adding thrombectomy to guideline-based care improved outcomes including mRS score at 90 days, mRS score 0–2 at 90 days, and vessel recanalization at 24 h (Table).
- Incidence of sICH was 4.5% in both study arms. Asymptomatic ICH was more common in the thrombectomy group (51.4%) than in the control group (24.5%; OR 3.24, 95% CI 1.77–6.01).
- 90-day mortality: 24.3% in the thrombectomy group vs 30.0% in the control group (hazard ratio 0.73, 95% CI 0.45–1.19).

Outcome	Thrombectomy (n=111)	Control (n=110)	OR (95% CI)
Primary outcome			
mRS score at 90 days	Not applicable (NA)	NA	2.28 (1.41–3.69)
Secondary outcomes			
mRS score 0–2 at 90 days, n (%)	39 (35.1)	22 (20.0)	2.55 (1.34–4.88)
Change in Alberta Stroke Program Early Computed Tomography Score (ASPECTS) from baseline to 24 h, median (IQR)	−2 (−4 to −1)	−3 (−6 to −1)	NA
Dramatic neurological improvement at 24 h, n/N (%)	33/105 (31.4)	26/108 (24.1)	1.45 (0.79–2.67)
EuroQoL Group 5-Dimension (EQ-5D) score at 90 days, median (IQR)	0.458 (0–0.737)	0.235 (0–0.522)	NA
Vessel recanalization at 24 h, n/N (%)	65/81 (80.2)	38/82 (46.3)	5.23 (2.53–10.82)
Successful recanalization immediately after thrombectomy, n (%)	91 (82.0)	NA	NA

"The trial showed that among patients in the public health care system of Brazil who were treated within 8 hours after a stroke due to a proximal occlusion in the anterior circulation, 90-day functional outcomes were better with thrombectomy plus standard care than with standard care alone."[5]

IN PATIENTS CAREFULLY SELECTED USING ADVANCED IMAGING TECHNIQUES, IVT IN A THERAPEUTIC WINDOW >4.5 H COULD INCREASE THE LIKELIHOOD OF COMPLETE RECANALIZATION

IV rt-PA in AIS is approved for use within 4.5 h of symptom onset, and guidelines recommend against IVT with rt-PA in patients with unclear or unwitnessed symptom onset time or in patients with an onset time exceeding the 4.5-hour time window.

It has been proposed that advanced neuroimaging could be used to carefully select patients with AIS who may benefit from IVT regardless of the time from symptom onset. A recent systematic review and meta-analysis determined the effects of IVT outside the 4.5-hour therapeutic window in patients with AIS and evidence of substantial viable hypoperfused tissue as shown by advanced baseline neuroimaging.[6] The studies included used computed tomography or magnetic resonance imaging to identify candidates with substantial ischaemic core–ischaemic penumbra mismatch, or fluid-attenuated inversion recovery (FLAIR)–diffusion-weighted imaging (DWI) mismatch, who could benefit from treatment with IVT.

Across four RCTs enrolling 859 patients in total, the median time from last seen well to symptom recognition was 5.1–7.7 hours, and from last seen well to rt-PA bolus was 7.2–10.3 hours. In analyses adjusted for age and baseline stroke severity, IVT was associated with a higher probability of 3-month favourable functional outcome (OR 1.62, 95% CI 1.20–2.20), 3-month functional improvement (OR 1.42, 95% CI 1.11–1.81), and sICH (OR 6.22, 95% CI 1.37–28.26). There was no association of IVT with 3-month functional independence (OR 1.61, 95% CI 0.94–2.75) or all-cause mortality (OR 1.75, 95% CI 0.93–3.29).

The authors conclude that eligible patients presenting with unknown symptom onset time and FLAIR–DWI mismatch, or patients with symptom onset outside the conventional time window of 4.5 hours and evidence of viable tissue on penumbral imaging, could benefit from prompt IVT administration, and suggest that this should be investigated further in future trials.

"IVT in patients with AIS with unknown symptom onset time or elapsed time from symptom onset >4.5 hours selected with advanced neuroimaging results in a higher likelihood of CR [complete recanalization] and functional improvement at 3 months despite the increased risk of sICH."[6]

MOBILE STROKE UNITS CAN REDUCE THE TIME FROM SYMPTOM ONSET TO TREATMENT AND MAY IMPROVE CLINICAL OUTCOMES

Time to reperfusion is one of the most important factors in determining the clinical outcome after stroke. MSUs, which are fully equipped with imaging and laboratory testing equipment and dedicated specialist staff, have been introduced to allow early identification and management of patients with AIS.

A recent systematic review and meta-analysis evaluated the clinical effectiveness of MSUs compared with conventional care for patients with AIS.[7] Overall, 21 297 patients from 11 studies (7 RCTs and 4 non-RCTs) were included in the analysis; 15 232 patients were treated in conventional settings (the control group) and 6065 patients were initially treated in MSUs. Mean time from symptom onset to therapy decision was significantly shorter for patients treated in MSUs (59.3 vs 75 minutes, *p*=0.03).

In the pooled analysis of clinical outcome at day 7, patients treated in MSUs had 1.46-fold higher likelihood of better clinical outcome (mRS 0–2) than those treated in the emergency department (OR 1.46, 95% CI 1.306–2.03, *p*=0.02). There was no significant difference in mortality (OR 0.98, 95% CI 0.81–1.18, *p*=0.80) or in stroke-related or neurological death (OR 1.37, 95% CI 0.81–2.32, *p*=0.24) between patients treated in MSUs or conventional settings. There was also no significant difference in other adverse events between the two groups (OR 0.69, 95% CI 0.39–1.20, *p*=0.19). The authors highlight that further prospective studies are needed that compare short- and long-term outcomes between conventional treatment and treatment in MSUs.

"Our study suggests that reducing the treatment time by starting thrombolytics in the MSU in patients with AIS improves the functional outcome without an increase in the mortality or adverse event rate."[7]

AIS, acute ischaemic stroke; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; CI, confidence interval; DSA, digital subtraction angiography; EQ-5D, EuroQoL Group 5-Dimension; eTICI, extended thrombolysis in infarction; EVT, endovascular thrombectomy; FLAIR–DWI, fluid-attenuated inversion recovery–diffusion-weighted imaging; ICH, intracranial haemorrhage; IQR, interquartile range; IV, intravenous; IVT, intravenous thrombolysis; LVO, large vessel occlusion; mRS, modified Rankin Scale; MSU, mobile stroke unit; NA, not applicable; NIHSS, National Institute of Health Stroke Scale; OR, odds ratio; RCT, randomized controlled trial; rt-PA, recombinant tissue plasminogen activator; SD, standard deviation; sICH, symptomatic intracranial haemorrhage.

References

1. Bluhmki E, Danays T, Biegert G *et al*. Alteplase for acute ischemic stroke in patients aged >80 years: pooled analysis of individual patient data. *Stroke* 2020: doi:10.1161/STROKEAHA.119.028396.
2. Mortensen JK, Andersen G. Closing the age gap in acute ischemic stroke treatment. *Stroke* 2020: doi:10.1161/STROKEAHA.120.030169.
3. Albers GW. Thrombolysis before thrombectomy – to be or DIRECT-MT? *N Engl J Med* 2020;382:2045–6.
4. Yang P, Zhang Y, Zhang L *et al*. Endovascular thrombectomy with or without intravenous alteplase in acute stroke. *N Engl J Med* 2020;382:1981–93.
5. Martins SO, Mont'Alverne F, Rebello LC *et al*. Thrombectomy for stroke in the public health care system of Brazil. *N Engl J Med* 2020;382:2316–26.
6. Tsivgoulis G, Katsanos AH, Malhotra K *et al*. Thrombolysis for acute ischemic stroke in the unwitnessed or extended therapeutic time window. *Neurology* 2020;94:e1241–8.
7. Fatima N, Saqqur M, Hussain MS *et al*. Mobile stroke unit versus standard medical care in the management of patients with acute stroke: a systematic review and meta-analysis. *Int J Stroke* 2020: doi:10.1177/1747493020929964.

ACTILYSE® PRESCRIBING INFORMATION