

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.

Optimizing treatment strategies for the benefit of patients is a key goal of evidence-based medicine. By testing new approaches and questioning current assumptions we strive for better outcomes. This desire to improve is of course prevalent across all of medicine but, given that the consequences of stroke can be so devastating, we perhaps feel this desire more acutely than most.

In recent years, in addition to intravenous (IV) recombinant tissue plasminogen activator (rt-PA), endovascular treatment (EVT) in the form of mechanical thrombectomy (MT) has become established in the treatment of acute ischaemic stroke (AIS) due to large vessel occlusion (LVO). Its availability has naturally led to a desire to refine and optimize treatment strategies in this setting. As noted in the November newsletter, some groups have looked at the potential of removing the lytic from their reperfusion strategies and opting only for MT. However, it is important to acknowledge the recommendations within stroke management guidelines. Recently, the American Heart Association (AHA)/American Stroke Association (ASA) and the Australian Clinical Guidelines for Stroke Management have renewed their recommendations on the benefits of combination therapy compared with EVT alone.^{1,2}

In this issue of the Actilyse® Publication Alert Newsletter we look at four publications that give insights on this topic and provide evidence that a combined approach of IV thrombolysis (IVT) plus EVT may indeed yield better outcomes for patients with AIS due to LVO.

META-ANALYSIS SHOWS THAT ADMINISTERING IV THROMBOLYSIS PRIOR TO MECHANICAL THROMBECTOMY IMPROVES FUNCTIONAL INDEPENDENCE IN PATIENTS WITH LARGE VESSEL OCCLUSION STROKE

No randomized controlled trial (RCT) reported to date has prospectively compared IVT plus MT versus MT alone in patients with LVO stroke. Therefore, the authors of a recent meta-analysis aimed to investigate the comparative safety and efficacy of the two approaches, based on data from observational studies and *post hoc* analyses of RCTs.³

A systematic review identified 8 prospective cohort observational studies, 26 retrospective observational studies, and 4 *post hoc* RCT analyses that were eligible for inclusion, providing data on 11,798 patients.

Based on unadjusted analyses, patients receiving IVT plus MT (which the authors term ‘bridging therapy’ [BT]) had a higher likelihood of functional independence at discharge or at 3 months compared with patients receiving MT alone (which the authors term ‘direct MT’).

Patients receiving IVT plus MT also had: a higher likelihood of functional improvement at discharge or 3 months; a higher likelihood of successful recanalization; a higher likelihood of successful recanalization with less than two device passes; lower odds of mortality at discharge or 3 months. The odds of symptomatic ICH (sICH) were similar between groups.

After adjustment, IVT + MT was associated with a higher likelihood of functional independence, and lower odds of mortality, at discharge or 3 months.

There was no documented increase in the risk of post-MT complications (any ICH, groin haematoma, distal embolization, infarct in new vessel territory) for IVT + MT compared with direct MT. In addition, bridging therapy was not related to delays in groin puncture-to-reperfusion time or onset-to-groin puncture times.

The authors conclude that the meta-analysis provides reassurance to clinicians that pre-treatment with IVT does not increase complications, nor result in measurably delayed reperfusion, in patients with LVO stroke treated with MT. The findings also indicate a potential beneficial effect on functional outcome and mortality in patients who received IVT + MT compared with direct MT alone.

The authors note that the ongoing SWIFT DIRECT (NCT03192332), DIRECT-MT (NCT 03469206), MR CLEAN-NO IV (ISRCTN80619088) and DIRECT-SAFE (NCT 03494920) trials will provide definitive answers on the potential clinical benefit of IVT pre-treatment. Until then, all rt-PA-eligible patients with LVO stroke should swiftly receive both IVT and MT.

“The present meta-analysis shows that bridging therapy [IVT + MT] is associated with a higher likelihood of functional independence, lower odds of mortality, and no increase in the risk of sICH compared to direct MT”³

IN ROUTINE CLINICAL PRACTICE, PATIENTS TREATED WITH IV THROMBOLYSIS PLUS ENDOVASCULAR TREATMENT HAD BETTER CLINICAL OUTCOMES THAN PATIENTS WHO RECEIVED ENDOVASCULAR TREATMENT ALONE

The question of whether IVT should still be administered before EVT has been investigated in a large, nationwide registry of patients who underwent EVT, reflecting daily clinical practice in the Netherlands.⁴

Analysis of data from the MR CLEAN registry has shown that, in addition to having better outcomes, patients treated with IVT + EVT more often had reperfusion of the occluded vessel before EVT than patients treated with EVT alone. Successful reperfusion, first-pass effect, and sICH did not differ between groups. In terms of workflow, procedure time was shorter in the combination group, though IVT + EVT patients who were not transferred from a primary stroke centre had longer door-to-groin puncture times than EVT alone patients.

The authors note that these findings may demonstrate a true benefit of IVT before EVT, but RCTs are needed. As with the authors of the meta-analysis summarized previously, the authors of this study highlight that four such trials are ongoing. However, in the meantime, they also state that IVT should not be withheld in patients outside these trials who are eligible for both IVT and EVT, and current guidelines should remain unchanged.

Study details

- Analysis of data from the MR CLEAN registry – an ongoing, nationwide, multicentre, prospective, observational, Phase IV study for centres that provide EVT in the Netherlands
- This study included adult patients treated in a MR CLEAN trial centre between March 2014 and June 2016, with an LVO of the anterior circulation and who underwent groin puncture within 6.5 h of symptom onset
 - Patients for whom it was unknown whether they received IVT were excluded
- 1485 patients were included; 1161 received IVT + EVT and 324 received EVT alone
 - The most common reason for withholding IVT was coagulation abnormalities and/or antithrombotic treatment
- Patients in the IVT + EVT group were younger (median age 70 vs 72 years; $p=0.03$), had less severe deficits (median National Institutes of Health Stroke Scale [NIHSS] score 16 vs 17; $p<0.01$), less often had atrial fibrillation (16% vs 44%; $p<0.01$) and previous ischaemic stroke (14% vs 26%; $p<0.01$), and more often had a pre-stroke modified Rankin Scale (mRS) score of 0 (73% vs 52%; $p<0.01$) than patients treated with EVT alone
- Onset-to-computed tomography (CT) time (median 67 vs 83 min; $p<0.01$) and onset-to-groin puncture time (median 206 vs 215 min; $p=0.04$) were shorter in the IVT + EVT group
- mRS scores at 90 days were more favourable in the IVT + EVT group compared with the EVT alone group, even after adjustment for potential confounders (see Table)
 - A greater proportion of the IVT + EVT group had functional independence at 90 days
 - Change in NIHSS score was larger and mortality was lower in the combination group
 - The risk of severe extracranial haemorrhage and sICH did not differ between groups

Outcome	IVT + EVT (n=1161)	EVT (n=324)	p value	OR (95%CI)	Adjusted OR (95%CI)
mRS score at 90 days, median (IQR)	3 (2–6)	4 (2–6)	<0.01	1.80 (1.43–2.26)	1.47 (1.10–1.96)
mRS score 0–2 at 90 days, n/N (%)	431/1061 (41)	86/299 (29)	<0.01	1.65 (1.25–2.17)	1.32 (0.85–1.87)
Change in NIHSS score, median (IQR)	-4 (-9 to 0)	-3 (-8 to 1)	0.02	-0.9 (-1.9 to 0.2)	-1.5 (-2.6 to -0.3)
Procedure time, median (IQR), min	62 (39–87)	68 (45–95)	<0.01	-5.6 (-9.9 to -1.3)	-6.2 (-11.0 to -1.3)
Safety outcomes					
Mortality at 90 days, n (%)	275 (24)	122 (38)	<0.01	0.51 (0.40–0.67)	0.58 (0.40–0.82)
Severe extracranial haemorrhage, n (%)	28 (2.4)	5 (1.5)	0.35	1.58 (0.60–4.12)	1.96 (0.66–5.81)
sICH, n (%)	69 (5.9)	17 (5.3)	0.64	1.14 (0.66–1.97)	1.20 (0.64–2.25)

“Patients treated with both IVT and EVT had a better functional outcome and lower mortality at 90 days than those with contraindications for IVT who were treated with EVT alone”⁴

REGISTRY DATA SUPPORT THE COMBINATION OF IV THROMBOLYSIS AND MECHANICAL THROMBECTOMY IN PATIENTS WITH LARGE VESSEL OCCLUSION STROKE

An analysis of data from a multicentre, prospective, observational registry in Italy suggests that IVT treatment before MT can lead to a better outcome, without affecting safety, in patients with anterior circulation stroke due to LVO (and eligible for IVT).⁵

Data from 1148 patients treated between 2011 and 2015 show that there was a significant shift in distribution of mRS scale scores in favour of the combined intervention. In addition, patients treated with combined therapy had significantly lower rates of death/severe disability compared with patients undergoing MT alone. There were no differences observed between groups in terms of haemorrhagic transformation or procedure complications.

The authors suggest that the current practice of administering IV thrombolysis in eligible patients, followed by MT, remains the standard approach in this patient population. They note that definitive evidence needs to come from an RCT.

Study details

- Analysis of data from the multicentre, prospective, observational, Italian Registry of Endovascular Stroke Treatment
- Analysis included patients treated at 13 centres between 2011 and 2015, either with IVT followed by MT (combined group; n=635) or with MT alone (MT group; n=513), for anterior circulation stroke due to proximal vessel occlusion
 - The analysis was restricted to those patients eligible for IVT according to 2015 Italian guidelines
- Patient demographics, disease characteristics and risk factor distribution were similar between the two groups
 - The most common reason for not giving IVT were exclusion criteria that were recommended in previous guidelines (and in the Actilyse[®] SPC) but which are no longer reported in current guidelines
- The median time from onset to groin puncture was significantly longer in the combined group versus the MT group, whereas the median time from groin puncture to recanalization was significantly shorter in the combined group. The median time from onset to end of procedure was similar between groups
- A shift in 90-day mRS score distribution towards a better outcome was found in favour of combined treatment (see Table)
- Multivariate analysis showed that the proportion of patients with 90-day mRS score 0–3 was significantly higher in the combined group, while the risk of death or very unfavourable outcome (mRS score 5–6) was significantly lower in this group. The 90-day case fatality rate was also significantly lower in the combined group
- No differences between groups were found for haemorrhagic transformation or procedure complications

Outcome	Adjusted OR (95% CI)* Combined group (IVT + MT) vs MT group
Primary outcome, common OR for a shift towards better outcomes	1.3 (1.04–1.66)
mRS score	
0–1	1.16 (0.7–1.65)
0–2	1.23 (0.9–1.7)
0–3	1.42 (1.04–1.95)
5–6	0.62 (0.45–0.84)
Death	0.6 (0.44–0.9)
TICI 2b–3	1.22 (0.9–1.66)
TICI 3	1.29 (0.97–1.7)
sICH	1.9 (0.78–5.0)
Any haemorrhagic transformation	1.2 (0.9–1.6)

*Adjusted for age, sex, history of diabetes, atrial fibrillation, hypertension, previous stroke or transient ischaemic attack in previous 3 months, presence of carotid stenosis >70%, baseline NIHSS score, baseline ASPECTS score, onset-to-endovascular-capable centre arrival time, onset-to-groin puncture time, site of occlusion

“These data seem to indicate that combined IV thrombolysis and MT could be associated with lower probability of death or severe dependency after 3 months from stroke due to LVO, supporting the current guidelines of treating eligible patents with IV thrombolysis before MT”⁵

rt-PA MAY IMPROVE OUTCOMES OF PATIENTS WITH LARGE VESSEL OCCLUSION STROKE UNDERGOING ENDOVASCULAR THROMBECTOMY

Data from a single-centre, retrospective study from Italy support the use of IVT followed by ET (combined therapy) vs direct ET only for anterior circulation AIS with LVO.⁶

Patients with anterior circulation AIS due to LVO who fulfilled AHA/ASA 2018² criteria for ET were identified; outcomes were evaluated among patients fulfilling criteria for IVT and ET vs those with IVT exclusion criteria. Significantly better rates of good recanalization and first-pass success, and smaller cerebral infarct volume (CIV) were reported with combined therapy vs ET only. Functional outcomes at 90 days (mRS score 0–1: and mRS score 0–2) were also significantly better with combined therapy vs ET only. Key safety outcomes were similar in both groups.

The authors acknowledge limitations of this study, including the study design, small sample size and potential risk of confounding due to treatment allocation bias (most patients in the ET group had contraindications to IVT and thus potentially a worse prognosis). However, they do conclude that the study confirms the safety and beneficial effect of combined therapy for anterior circulation AIS with LVO compared with direct ET. As with the authors of the other papers summarized in this newsletter, they note that the four ongoing, prospective RCTs will better clarify this issue.

Study details

- Single-centre, retrospective, observational cohort study involving patients referred to a Stroke Unit in Brescia, Italy, between January 2014 and January 2017
- Patients with anterior circulation AIS due to LVO who fulfilled AHA/ASA 2018 criteria for ET were included in the analysis
 - Patients fulfilling criteria for IVT and ET were considered the combined therapy group (IV rt-PA then ET; n=70)
 - Those with IVT exclusion criteria were considered the ET group (n=75)
- Baseline demographic and disease characteristics, including baseline NIHSS score, were similar between the two groups
 - The most common reason for exclusion of IVT was current anticoagulant therapy (28.6%)
- Better radiological and functional outcomes were achieved with combined therapy vs ET only (see Table)
 - Higher recanalization and first-pass success rates were observed in the combined therapy vs ET group
 - Moreover, smaller CIV was reported in the combined therapy vs ET group on early follow-up CT scan (at 2–4 days; among patients with good recanalization)
 - Functional independence at 90 days was significantly better among patients in the combined therapy group
- Rates of mortality and sICH were similar in both groups
- Multivariable regression analysis showed low baseline NIHSS score (OR, 0.73; 95% CI: 0.62–0.86; $p<0.05$), vessel recanalization (OR, 7.30; 95% CI: 0.60–88.62; $p=0.05$) and combined therapy (OR, 3.75; 95% CI: 1.09–12.85; $p=0.03$) to be independent predictors of a favourable outcome

Outcome	Combined therapy (n=70)	ET (n=75)	p value
Time from symptom onset to groin puncture, mean (SD), min	194.1 (59.9)	204.8 (60.4)	0.32
Time from symptom onset to recanalization, mean (SD), min	245.9 (75.8)	245.1 (58.6)	0.95
Good recanalization (TICI 2b or 3), n (%)	59 (84.3)	49 (65.3)	0.009
First-pass success rate, %	62.7	38.6	<0.05
CIV*, mean (SD), ml	16.4 (25.3)	62.3 (81.7)	0.003
sICH, n (%)	7 (10.0)	8 (10.6)	0.87
90-day outcomes			
mRS score 0–1, %	48.5	18.6	<0.001
mRS score 0–2, %	67.1	37.3	<0.001
Mortality, n (%)	5 (7.1)	11 (14.6)	0.15

*Among patients with good recanalization; measured manually by one experienced neurologist on CT brain scan 2–4 days after stroke onset

“Our data seems to confirm a favorable role of rt-PA in improving clinical and neuroradiological outcome of patients treated by endovascular mechanical thrombectomy for a large vessel occlusion stroke.”⁶

AIS, acute ischaemic stroke; AHA, American Heart Association; ASA, American Stroke Association; BT, bridging therapy; CI, confidence interval; CIV, cerebral infarct volume; CT, computed tomography; ET, endovascular therapy; EVT, endovascular treatment; IQR, interquartile range; IV, intravenous; IVT, intravenous thrombolysis; LVO, large vessel occlusion; mRS, modified Rankin Scale; MT, mechanical thrombectomy 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; TICI, thrombolysis in cerebral infarction

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