

ACUTE ISCHAEMIC STROKE PUBLICATION ALERT NEWSLETTER

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Clinicians are constantly striving to identify the widest possible range of patients with acute ischaemic stroke (AIS) who may benefit from life-saving reperfusion therapies. The benefits of intravenous (IV) recombinant tissue plasminogen activator (rt-PA) have been established for many years but its use is restricted to patients with known symptom onset within a 4.5-hour time window. An important target of current research is to investigate treatment options for patients whose stroke occurs outside this time window, which should help refine protocols to ensure patients have the greatest chance of obtaining the best possible outcome.

In this issue of the Acute Ischaemic Stroke Publication Alert Newsletter, two recent meta-analyses are featured, which focus on alteplase treatment selection in patients who would be ineligible for treatment according to the current label. One analysed randomized controlled trial (RCT) data from patients with unknown time of symptom onset while the other analysed RCT data from patients either 4.5–9-hours post-stroke onset or with wake-up stroke.

In addition, many patients with AIS present with minor neurological deficits. Clinical teams need to differentiate between patients whose symptoms may deteriorate and thus may benefit from reperfusion strategies vs those whose symptoms may improve without the need to attempt revascularization. Herein, papers that explore the benefits and risks of revascularization strategies in patients presenting with mild strokes are highlighted. The final article considers the merits and limitations of the DIRECT-MT and SKIP trials, both recently presented Direct Thrombectomy trials.

The list of presented publications is as follows:

1. [Thomalla G *et al.* Intravenous alteplase for stroke with unknown time of onset guided by advanced imaging: systematic review and meta-analysis of individual patient data. *Lancet* 2020.](#)
2. [Campbell B *et al.* Association of reperfusion after thrombolysis with clinical outcome across the 4.5- to 9-hours and wake-up stroke time window: a meta-analysis of the EXTEND and EPITHET randomized clinical trials. *JAMA Neurol* 2020](#)
3. [Volny O, Hill M *et al.* Thrombectomy vs medical management in low NIHSS acute anterior circulation stroke. *Neurology* 2020](#)
4. [Campbell B. Challenges of mild stroke. *Stroke* 2020](#)
5. [Nogueira R, Tsivgoulis G. Large vessel occlusion strokes after the DIRECT-MT and SKIP trials: is the alteplase syringe half empty or half full? *Stroke* 2020](#)

1 – SYSTEMATIC REVIEW AND META-ANALYSIS ASSESSED WHETHER ALTEPLASE IMPROVES FUNCTIONAL OUTCOMES VS CONTROL IN PATIENTS WITH AIS WITH AN UNKNOWN TIME OF ONSET GUIDED BY ADVANCED IMAGING

Patients with unknown time of symptom onset (up to 25% of patients with stroke) were excluded from RCTs of intravenous thrombolysis (IVT) for stroke and thrombolytic treatment in clinical practice.¹ Treatment with IVT has been tested with use of imaging biomarkers to select patients with unknown time of stroke onset for treatment in the WAKE-UP trial, which provided evidence of benefit of alteplase if the treatment decision was based on diffusion weighted imaging-fluid attenuated inversion recovery (DWI-FLAIR) mismatch. Current US and European guidelines recommend IVT with alteplase in patients with unknown time of symptom onset if patients meet the WAKE-UP criteria. To establish whether IV alteplase is safe and effective in this population when salvageable tissue is identified with imaging biomarkers, the authors of this study completed a systematic review and meta-analysis of individual patient data.¹

Study details

- Individual patient data for trials published before 21 September 2020 were included
- Eligible RCTs examined IV alteplase versus standard of care or placebo in adults with stroke with unknown time of onset with perfusion-diffusion magnetic resonance imaging (MRI), perfusion computed tomography (CT), or MRI with DWI-FLAIR mismatch
- Four studies met the criteria: WAKE-UP, EXTEND, THAWS and ECASS-4
- The prespecified primary outcome was a favourable outcome defined by a score of 0–1 on the modified Rankin Scale (mRS) at 90 days after stroke
- Secondary outcomes were functional improvement across the entire mRS (mRS shift analysis) at 90 days and independent outcome defined by a score of 0–2 on the mRS at 90 days; safety outcomes were death, severe disability or death (mRS score 4–6) and symptomatic intracranial haemorrhage (sICH) according to the Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS–MOST) criteria
- Data were obtained from 843 patients; 429 (51%) were assigned to receive alteplase and 414 (49%) to receive placebo or standard of care (control group)
- Baseline characteristics (see Table) were balanced between the two groups
- Prespecified subgroup analyses were also completed, including dose of alteplase (0.9 vs 0.6 mg/kg), age (≤ 60 years vs >60 years), sex, baseline stroke severity (National Institutes of Health Stroke Scale [NIHSS] ≤ 10 vs >10), any vessel occlusion, large vessel occlusion (LVO), imaging modality (CT vs MRI), history of atrial fibrillation, previous antiplatelet use, delay from symptom recognition to treatment (≤ 3 h vs >3 h), penumbral or DWI-FLAIR mismatch present, and history of transient ischaemic attack (TIA) or stroke

Table. Baseline characteristics

| | Alteplase group (n=429) | Control group (n=414) |
|---|-------------------------|-----------------------|
| Mean age, yrs (SD) | 68.5 (12.2) | 68.5 (12.7) |
| Reason for unknown time of symptom onset, n (%) | | |
| Overnight sleep | 385 (90) | 366 (88) |
| Other | 44 (10) | 48 (12) |
| Median time between last seen well and symptom recognition, h (IQR) | 7.0 (4.7–9.0) | 7.0 (5.0–9.0) |
| Median NIHSS score (IQR) | 7 (4–12) | 7 (4–12) |
| Imaging modality, n (%) | | |
| CT | 65 (15) | 64 (15) |
| MRI | 364 (85) | 350 (85) |
| Mismatch present, n/N (%) | | |
| Penumbral | 114/214 (53) | 109/199 (55) |
| DWI-FLAIR | 335/353 (95) | 320/339 (94) |

IQR, interquartile range

Study results

- A favourable outcome (mRS score 0–1) at 90 days was observed in 199/420 (47%) patients in the alteplase group and 160/409 (39%) patients in the control group (adjusted odds ratio [OR]: 1.49 [95% CI: 1.10–2.03]; $p=0.011$)
 - The increase in functional outcome with alteplase represents an absolute increase of 8% of patients with favourable outcome corresponding to a number needed to treat of 12
 - This is similar to the treatment effect obtained with IV alteplase within 4.5 hours of known stroke onset, both within 3 hours (adjusted OR: 1.75 [95% CI: 1.35–2.27]) and after 3.0–4.5 hours (1.26 [95% CI 1.05–1.51])
- Alteplase treatment was associated with a significant shift towards better functional outcome and an increase in the proportion of patients who reached functional independence vs the control group (lower scores on the mRS at 90 days: adjusted common OR: 1.38 [95% CI: 1.05–1.80], $p=0.019$; mRS score 0–2 at 90 days: adjusted OR: 1.50 [95% CI 1.06–2.12], $p=0.022$)
- Death at 90 days was reported in 27 (6%) patients in the alteplase group vs 14 patients (3%) in the control group (adjusted OR: 2.06 [95% CI: 1.03–4.09], $p=0.040$); most deaths were considered unrelated and of non-neurological cause
- In the alteplase group, 90 (21%) patients were severely disabled or had died (mRS score 4–6) vs 102 (25%) in the control group (adjusted OR: 0.76 [95% CI 0.52–1.11], $p=0.15$)

- The number of patients with sICH was higher in the alteplase vs the control group (11 [3%] vs two [<1%], adjusted OR: 5.58 [95% CI 1.22–25.50], $p=0.024$)
- Significant treatment benefits were observed in the subgroup of patients with an LVO (adjusted OR: 2.35 [95% CI 1.04–5.32])
- No evidence of significant heterogeneity for the primary outcome was observed across the prespecified subgroup analyses with the exception of a history of TIA, with patients with a prior stroke or TIA experiencing a larger benefit (p interaction=0.015)
- No evidence of heterogeneity of treatment effect was observed across any of the subgroups for mortality

Study conclusions

- IV alteplase is beneficial in patients with stroke with unknown time of onset selected by imaging biomarkers using MRI or CT perfusion
- Any of the mismatch concepts are effective and can be recommended for guiding IVT with alteplase in stroke with unknown time of onset for clinical practice
- No excess of ICH was observed in unknown onset strokes compared with those with known onset
- The increase in mortality did not negate the net benefit of IV alteplase, as the analysis of functional outcome across the entire range of the mRS, including death, showed a significant benefit
- The results of the pooled analysis support treatment with alteplase in patients with LVO and stroke with an unknown time of onset, especially if patients present to centres in which thrombectomy is not immediately available

Study limitations

- No inference on possible effects of the different dose of alteplase can be drawn (THAWS was the only trial that used the lower 0.6 mg/kg dose); thus, a possible interaction of treatment effect with alteplase dose cannot be separated from the overall trial effects
- All four RCTs were terminated early due to external reasons, resulting in an overall smaller number of patients for the meta-analysis and limited statistical power to provide adjusted treatment-effect estimates for smaller subgroups
- As most patients had mild-to-moderate strokes, results might not be generalizable to those with severe stroke and large core
- Although there was no heterogeneity of treatment effect between the trials, the results are to some extent driven by the WAKE-UP trial, representing almost 60% of the patients included in the analysis

The authors concluded that the requirement for advanced imaging beyond non-contrast CT and vessel imaging—i.e. either perfusion CT or MRI, might still represent a potential limitation for implementation of the studied treatment approach in some regions or hospitals. The results of this meta-analysis should further support efforts to make these necessary imaging techniques more widely available, so that access to this effective treatment is available to as many patients with stroke as possible.

“This individual patient data meta-analysis extends the evidence from individual trials and supports the use of imaging biomarkers to guide treatment with intravenous alteplase in patients with stroke with an unknown time of onset.”¹

2 – META-ANALYSIS ASSESSED WHETHER ALTEPLASE TREATMENT IN THE EXTEND AND EPITHET RCTS WAS ASSOCIATED WITH IMPROVED FUNCTIONAL OUTCOMES WHEN STROKE ONSET IS >4.5 HOURS

IVT improves functional outcome in patients with favourable perfusion imaging 4.5–9 hours after last known well and within 9 hours of the midpoint of sleep for those with wake-up stroke. The EXTEND, ECASS4-EXTEND and EPITHET trials demonstrated overall benefit of IV alteplase, with no statistical heterogeneity between the 4.5–6 hours, 6–9-hours, and wake-up stroke strata. Because the number of patients treated at 4.5–6 hours and 6–9 hours was relatively small, the authors performed a meta-analysis of functional outcomes by reperfusion status to further explore the benefits of treatment >4.5 hours after stroke onset.²

Study details

- EXTEND was an RCT of alteplase vs placebo in 225 patients with CT perfusion-or MR perfusion-diffusion mismatch
- EPITHET was an RCT of alteplase vs placebo in 100 patients who were treated 3–6 h after stroke onset; only patients treated 4.5–6 h after onset and with known reperfusion status were included in this meta-analysis

- Data were collected between August 2001 and June 2018
- Functional outcome at 90 days after stroke was assessed using the mRS by clinicians blinded to treatment allocation
- Early neurological improvement was defined as a reduction of ≥ 8 points on the NIHSS between baseline and 3 days or reaching 0 to 1; symptomatic haemorrhage was defined as parenchymal haematoma type 2 associated with an NIHSS increase of ≥ 4 points within 36 h of treatment
- Reperfusion was assessable in 270/295 patients (92%); median (IQR) age was 75 (65–81) years; 149 (55%) patients were male
- Alteplase was associated with significantly increased reperfusion vs placebo (alteplase: 68/133 [51%] vs placebo: 38/137 [28%]; risk ratio, 1.84; 95% CI: 1.34–2.53; $p < 0.001$)
- In ordinal logistic regression analysis, reperfusion was associated with a common OR of 7.7 (95% CI: 4.6–12.8; $p < 0.001$) for improvement by at least 1 mRS category
- In each time strata (4.5–6 h, 6–9 h, and wake-up), reperfusion was associated with significant improvements in ordinal analysis of mRS score, mRS score 0–2, and early neurological improvement, but the 95% CI crossed unity for mRS score 0–1 in the 6–9-h group
- No evidence of association between time to randomization and beneficial effect of reperfusion was found ($p = 0.63$)
- Symptomatic haemorrhage, assessed in all 295 patients, occurred in 3/51 (5.9%) in the 4.5–6-h group, 2/28 (7.1%) in the 6–9-h group, and 4/73 (5.5%) in the wake-up stroke group in the alteplase-treated patients

Limitations of the meta-analysis included that the true onset time was often unknown and may have been within 4.5 hours in some patients (however, all of these patients were ineligible for thrombolysis using the standard criterion of < 4.5 hours since last known well), and patients excluded because of lack of reperfusion data may have been more severely affected.

The authors concluded that reperfusion was associated with improved functional outcome and stable sICH within the 4.5–6-hours, 6–9-hours, and wake-up stroke epochs, with no evidence of an interaction by the time since last known well to treatment. Further trials will test whether IVT can benefit patients with perfusion mismatch up to 24 hours after the time they were last known to be well.

“These data provide support for implementation of IV thrombolysis in patients who fall within the full time window up to 9 hours since last known well or midpoint of sleep and who were eligible for the EXTEND trial.”²

3 – OBSERVATIONAL MULTICENTRE STUDY ASSESSED THE EFFECTIVENESS AND SAFETY OF EVT VS MEDICAL MANAGEMENT IN PATIENTS WITH LVO AND NIHSS ≤ 6

Although AIS with NIHSS ≤ 6 is routinely considered to be ‘mild’ and ‘non-disabling’, one in four LVO patients with low baseline NIHSS suffer early neurological deterioration, resulting in a poorer outcome. Milder deficits can restrict patients’ daily activities and seriously reduce their quality of life. Because few patients with low baseline NIHSS scores were enrolled in the RCTs comparing endovascular thrombectomy (EVT) with medical care, Level 1A guideline recommendations for EVT are currently restricted to LVO patients with NIHSS score ≥ 6 . The aim of this observational multicentre study was to assess the effectiveness and safety of EVT versus medical management in patients with LVO and NIHSS ≤ 6 using propensity-score matched data from comprehensive datasets.³

Study details

- Patients with anterior circulation occlusion demonstrated by CT angiography and admission NIHSS score ≤ 6 were retrospectively identified
- EVT data were retrieved from the Safe Implementation of Treatments in Stroke –Thrombectomy (SITS-TBY) registry and compared with medical management data derived from the INTERSeCT and PROVE-IT studies
- The primary outcome was mRS score 0–1 at 90 days; secondary outcomes were the neurological deterioration at 24 h (defined as increase of NIHSS score by ≥ 2 points), mRS 0–2 at 90 days, and all-cause mortality at 90 days
- There were 236 patients included in the analysis; 139 received EVT and 97 medical management
- The EVT group was younger (65 vs 72 years), with more proximal occlusions and less concurrent IV alteplase treatment compared with the medical management group
- Overall, 62.7% ($n = 148$) of patients achieved an mRS score of 0–1 at 90 days

- In the unadjusted analysis, there was no difference between the EVT and medical management groups (61.9% vs 63.9%, $p=0.785$)
- After propensity-score matching, patients in the EVT group had an 8.6% (95% CI: -8.8–26.1) higher chance of excellent outcome at 90 days compared with the medical management group
- Patients in the EVT group had a 22.3% (95% CI: 3.0–41.6) higher risk of neurological deterioration at 24 h compared with patients in the medical management group
- Patients in the EVT group had a 2.2% (95% CI: -3.6–7.9) higher risk of death from any cause within the first 90 days after the index event compared with the medical management group

Study limitations

- The study is retrospective and there is a risk of residual confounding due to unmeasured variables
- Data on intracranial haemorrhage (ICH), anaesthesia or sedation during EVT, and race and ethnicity were missing
- Because the mRS lacks sensitivity at the minor disability end of the scale, a significant difference in the primary outcome might not have been detected
- The sample size of the matched analysis, while larger than the sample size of prior studies, might have affected the statistical power

Conclusion

- This multicenter observational post-hoc study showed that EVT for LVO in patients with low NIHSS resulted in similar 90-day outcomes compared with best medical management despite an increased risk of neurological deterioration at 24 hours

“A well-designed randomized controlled trial would be able to finally answer the question about the risk-benefit-ratio of EVT for low NIHSS strokes.”³

4 – CLINICAL TRIALS INVOLVING PATIENTS WITH MILD STROKE AND ADVANCED IMAGING ARE NEEDED TO ASSIST IDENTIFICATION OF PATIENTS WHO ARE MORE LIKELY TO BENEFIT FROM THROMBOLYSIS

In patients with mild stroke, whether or not to attempt revascularization is a challenging dilemma. Although reperfusion therapies carry a risk of sICH and death, this has to be balanced by the possibility of patients subsequently deteriorating and becoming disabled once the time window for reperfusion treatments has passed. This recent *Stroke Editorial* outlines the data currently available for this common clinical scenario and suggests potential approaches to enhance risk-versus-benefit decisions in mild stroke.⁴

Data on EVT in mildly affected patients are sparse, with only 14 patients with NIHSS score 0–5 enrolled in the pivotal trials. A pooled analysis of alteplase RCT data showed an increase in excellent functional outcome with alteplase from 59% to 69% of patients with baseline NIHSS score 0–4. However, no benefit was detected in the PRISMS trial that enrolled patients with non-disabling symptoms at baseline.

In a recent retrospective analysis of administrative data from the USA, patients with mild stroke (NIHSS score 0–5) comprised 58% of total AIS admissions over a 15-month period; of these, 10% received alteplase. Alteplase was associated with an increased likelihood of discharge home without assistance and a reduction in poor functional outcome at discharge. Although adverse outcomes and in-hospital mortality were more frequent in those aged >80 years, the observed benefits were not offset.

In the *Editorial*, Prof. Campbell highlights that efforts are ongoing to improve identification of patients with mild stroke who would benefit from reperfusion therapies. The ongoing TEMPO-2 RCT builds on non-randomized data that indicated improved outcomes in patients with mild stroke or TIA who had vessel occlusion if they underwent reperfusion, in this case with IV tenecteplase. ENDO-LOW and MOSTE studies are investigating EVT in mildly affected patients. Two potential approaches to enhancing risk-versus-benefit decisions in mild stroke using imaging are also discussed: one approach is to identify markers of haemorrhage risk. The second approach involves identification of reperfusion benefit markers on imaging.

“Randomized trials, including the use of more advanced imaging, may help differentiate patients at risk of deterioration and disability from those with a benign natural history for whom revascularization poses an unnecessary risk.”⁴

5 – THE DIRECT-MT AND SKIP TRIALS HIGHLIGHT THAT MANY FACTORS SHOULD BE CONSIDERED WHEN CHOOSING PRIMARY EVT VS rt-PA BRIDGING AND EMPHASIZE THE IMPORTANCE OF INDIVIDUALIZING PATIENT CARE

Two recent RCTs, DIRECT-MT and SKIP, assessed whether primary EVT was noninferior to bridging with IVT immediately prior to EVT in patients with LVO initially presenting to thrombectomy capable centres (TCCs). The authors of a recent *Stroke Emerging Therapy Critique* discuss the main limitations of both trials and emphasize their merits, which includes the opportunity for greater individualization of care.⁵

Trial limitations

Both trials used overly generous non-inferiority margins and included only Asian patients. SKIP was noticeably underpowered and used a 0.6 mg/kg alteplase dose. In DIRECT-MT, 9.4% and 5.2% of patients in the bridging and primary EVT groups, respectively, did not undergo EVT. This difference may have influenced the outcomes in favour of primary EVT. The median door-to-needle time in the bridging group was 59 minutes, a substantial delay compared with that reported in the HERMES meta-analysis (40 minutes). The delay may be partly attributed to existing financial barriers in China, where enrolled patients or their families have to pay in advance to have access to rt-PA treatment (and this may also have introduced a substantial income-based selection bias). rt-PA infusion was completed before EVT initiation in only 7% of bridging patients, thereby disproportionately favouring the EVT workflow in the presence of suboptimal IVT treatment times.

Trial merits

Despite their deficiencies, the DIRECT-MT and SKIP trials have clearly demonstrated that IVT before EVT in patients primarily presenting to a TCC is not a panacea. However, it is crucial to continue to recognize the potential advantages of the mothership bridging strategy, including the fact that rt-PA can be started much earlier and may not only lead to faster reperfusion, but also circumvent the need for EVT, therefore avoiding added cost and potential risks. Even when IVT fails, it may optimize EVT by facilitating proximal recanalization. Conversely, there are known disadvantages to IVT, including poor recanalization rates in the presence of LVO with large clot burden or tandem occlusions, a higher risk of haemorrhagic (and more rarely allergic) complications, the potential to produce thrombus migration and distal fragmentation with worsened perfusion, and the possibility of causing delays to EVT initiation.

Future pooled analysis of these trials may shed further light on the bridging conundrum at mothership centres. In the meantime, the authors state that it is reasonable for clinicians to customize their decisions based on the individual characteristics of the patients, while also considering the local realities of treating centres. These factors may impact on the efficacy, safety and cost-effectiveness of any given choice.

“While we keenly wait for the results of the additional ongoing trials, it is possible that they are already conceptually outdated given the growing evidence to support the advantages of bridging with tenecteplase versus alteplase”⁵

AIS, acute ischaemic stroke; CI, confidence interval; CT, computed tomography; DWI-FLAIR, diffusion weighted imaging-fluid attenuated inversion recovery; EVT, endovascular thrombectomy; HERMES, Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials; ICH, intracranial haemorrhage; INTERRSeCT, Identifying New Approaches to Optimize Thrombus Characterization for Predicting Early Recanalization and Reperfusion With IV Alteplase and Other Treatments Using Serial CT Angiography; IQR, interquartile range; IV, intravenous; IVT, intravenous thrombolysis; LVO, large vessel occlusion; mRS, modified Rankin Scale; MR, magnetic resonance; MT, medical treatment; NIHSS, National Institute of Health Stroke Scale; OR, odds ratio; PRISMS, Potential of rtPA for Ischemic Strokes With Mild Symptoms; PROVE-IT, Precise and Rapid Assessment of Collaterals Using Multi-Phase CTA in the Triage of Patients With Acute Ischemic Stroke for IA Therapy; RCT, randomized controlled trial; rt-PA, recombinant tissue plasminogen activator; SD, standard deviation; sICH, symptomatic intracranial haemorrhage; SITS-MOST, Safe Implementation of Thrombolysis in Stroke Monitoring Study; SITS-TBY, Safe Implementation of Treatments in Stroke –Thrombectomy; TCC, thrombectomy capable centre; TIA, transient ischaemic attack.

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- 2 [Campbell BCV, Ma H, Parsons MW *et al*. Association of reperfusion after thrombolysis with clinical outcome across the 4.5- to 9-hours and wake-up stroke time window: a meta-analysis of the EXTEND and EPITHET randomized clinical trials. *JAMA Neurol* 2020; doi: 10.1001/jamaneurol.2020.4123. Epub ahead of print.](#)
- 3 [Volny O, Demchuk AM, Menon BK, Mikulik R, Hill MD *et al*. Thrombectomy vs medical management in low NIHSS acute anterior circulation stroke. *Neurology* 2020; doi: 10.1212/WNL.0000000000010955. Epub ahead of print.](#)
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