

ACUTE ISCHAEMIC STROKE PUBLICATION ALERT NEWSLETTER (11/2021)

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.

Rapid treatment is the foundation on which standard of care in acute ischaemic stroke (AIS) is based. Current guidelines recommend that all eligible patients should receive intravenous thrombolysis (IVT) as soon as possible after onset of AIS, followed by mechanical thrombectomy (MT) in patients with large vessel occlusion (LVO). Mobile stroke units (MSUs) have been developed as a strategy to accelerate the delivery of recombinant tissue plasminogen activator (rt-PA) following an AIS. This issue of the Acute Ischaemic Stroke Publication Alert Newsletter outlines the results of the BEST-MSU trial, which was designed to evaluate clinical outcomes in patients treated by MSUs, as compared with standard management. This is followed by discussion of a comparative clot composition analysis from patients who had undergone bridging therapy versus MT alone.

The COVID-19 pandemic is a global health crisis that has had a substantial impact on the admission, treatment, and clinical outcomes of patients with AIS. The issue concludes with a summary of results from a multicentre cohort study demonstrating that rt-PA should be the standard of care for patients with AIS and COVID-19.

The list of presented publications is as follows:

1. [Grotta JC *et al.* Prospective, multicenter, controlled trial of mobile stroke units. *N Engl J Med* 2021.](#)
2. [Rossi R *et al.* Does prior administration of rtPA influence acute ischemic stroke clot composition? Findings from the analysis of clots retrieved with mechanical thrombectomy from the RESTORE registry. *J Neurol* 2021.](#)
3. [Sasanejad P *et al.* Safety and outcomes of intravenous thrombolytic therapy in ischemic stroke patients with COVID-19: CASCADE initiative. *J Stroke Cerebrovasc Dis* 2021.](#)

1. DO PATIENTS WITH AIS WHO ARE ELIGIBLE FOR RT-PA HAVE BETTER CLINICAL OUTCOMES WHEN TREATED BY MOBILE STROKE UNITS COMPARED WITH STANDARD MANAGEMENT BY EMERGENCY MEDICAL SERVICES?¹

SUMMARY

- The BEST-MSU trial compared utility-weighted disability outcomes at 90 days in patients who received care by an MSU versus standard management by emergency medical services (EMS)
- Patients who were treated through an MSU were more likely to be given rt-PA and, on average, had rt-PA more rapidly than patients who received standard care by EMS
- Utility-weighted disability outcomes were better in patients treated by MSUs compared with standard management by EMS, with favourable safety and secondary clinical outcomes

Following an AIS, it is standard care for patients to receive primary on-scene treatment by EMS, before being transported to an emergency department for supplementary care. Guidelines recommend the organization of stroke systems to accelerate the delivery of thrombolytic and thrombectomy treatment. MSUs consist of an ambulance equipped with computed tomography (CT) scanners, point-of-care laboratory testing, and personnel trained to administer rt-PA to eligible patients. Whether, and by how much, MSUs alter patient outcomes has not been extensively studied.

The BEST-MSU trial was a prospective, multicentre, cluster-controlled trial designed to compare clinical outcomes in patients with AIS eligible for rt-PA, who received care from an MSU versus standard care by EMS.¹

Study details

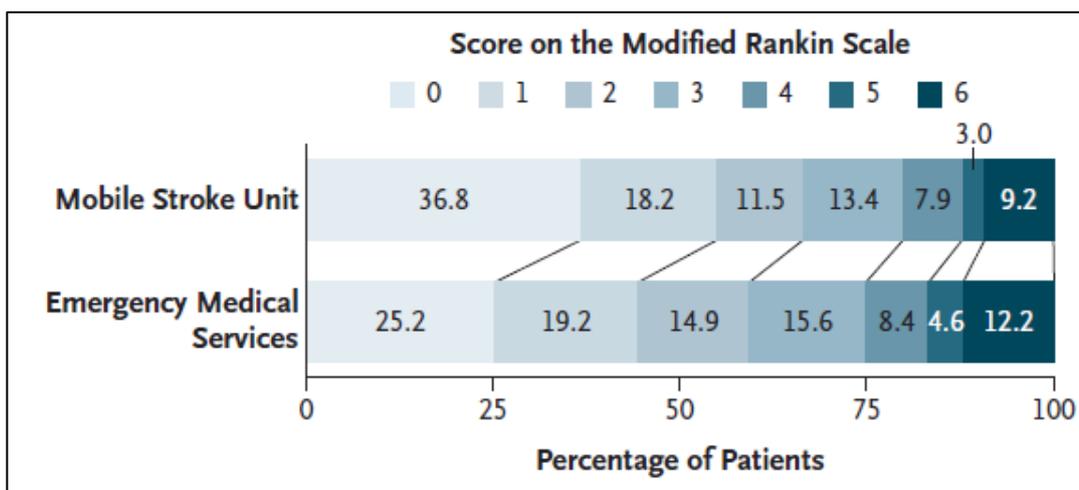
- 10 443 stroke alerts were screened across seven urban centres in the USA, resulting in 1047 patients (617 MSU and 430 EMS) eligible for rt-PA who were included in the primary analysis
- Enrolment criteria were identical in MSU and EMS groups and included:
 - Examination features consistent with AIS that produced any degree of disability
 - Stroke onset within the previous 4.5 h
 - No obvious contraindications to the use of rt-PA

- The primary outcome was disability at 90 days, as measured by the utility-weighted modified Rankin Scale (UW-mRS), which ranges from 0 (death) to 1 (no disability)
 - UW-mRS scores were derived by weighting each level on the mRS by the patients' value of that level of function
 - A binary logistic regression for dichotomized scores was used on the UW-mRS of ≥ 0.91 or < 0.91 , which is approximately equivalent to an mRS score of ≤ 1 or > 1 , respectively
- Secondary outcomes included:
 - The change in mRS scores for patients eligible for rt-PA and patients who received rt-PA
 - The percentage of patients with a 30% reduction in the National Institutes of Health Stroke Scale (NIHSS) score from baseline to 24 h
 - The percentage of eligible patients treated with rt-PA and endovascular thrombectomy (EVT)
 - Treatment time from stroke onset
- Safety outcomes included symptomatic intracerebral haemorrhage (ICH) and death
- At baseline, the median NIHSS score was the same for patients treated by an MSU and by EMS (9) but patients in the EMS group were more likely to have a prestroke mRS score of 0 (corresponding to no disability) compared with patients in the MSU group (67.0% vs 61.4%)

Study results

- Compared with patients in the EMS group, patients treated by an MSU were more likely to receive rt-PA (97.1% vs 79.5%) and less likely to receive EVT (23.7% vs 27.0%)
- A 30% reduction in NIHSS score from baseline to 24 h was observed in 75.0% of patients treated by an MSU, compared with 67.8% of patients treated by EMS (odds ratio [OR]: 1.45; 95% confidence interval [CI]: 1.09–1.91)
- Patients in the MSU group received rt-PA more rapidly after a stroke than patients in the EMS group
 - Median time to rt-PA treatment from when the patient was last known to be well: 72 vs 108 min
 - Percentage of patients in each group treated within 60 min of stroke onset: 32.9% vs 2.6%
- Disability outcomes were significantly better in patients who received care from an MSU than in patients receiving standard care (**Figure 1**)
 - Patients in the MSU group had a mean (standard deviation [SD]) UW-mRS score of 0.72 (0.35), compared with 0.66 (0.36) in the EMS group (pooled difference: 0.07; 95% CI: 0.03–0.11)
 - Patients in the MSU group were significantly more likely to have no or low disability at 90 days (UW-mRS ≥ 0.91) compared with patients in the EMS group (OR: 2.43; 95% CI: 1.75–3.36, $p < 0.001$)
- Patients in the MSU group had a similar incidence of symptomatic ICH (~2%) but lower mortality at 90 days (8.9% vs 11.9%) compared with patients receiving standard care by EMS

Figure 1. mRS score distribution by treatment group



Study limitations

- Non-randomized design: patients were adjudicated for rt-PA eligibility after trial-group assignments, introducing the possibility of bias

- Screening and enrolment were conducted by a physician, nurse, and medic in the MSU group, compared with an MSU nurse in the EMS group
- Baseline NIHSS scores were not fully assessed in the EMS group but were extrapolated and amended from scores reported by the MSU nurse
- Study generalizability was limited, with 77.6% of trial participants recruited from a single site (Houston)
- Trial sites were primarily urban and results may not be reflective of rural settings

Study conclusions

- Utility-weighted disability outcomes at 90 days were more favourable for patients with AIS who received care from MSUs than for patients who received standard care with EMS
- Patients given care through an MSU were more likely to receive rt-PA and, on average, received rt-PA more rapidly than patients who were given standard care by EMS

“There were 10 448 possible stroke alerts resulting in 1047 patients eligible for t-PA in the trial, findings that suggest an opportunity to improve the efficiency of MSU and EMS dispatch”¹

2. DOES THE PRIOR ADMINISTRATION OF RT-PA AS BRIDGING THERAPY INFLUENCE THE COMPOSITION OF CLOTS EXTRACTED FROM PATIENTS WITH AIS?²

SUMMARY

- Analysis of the composition of clots extracted from MT from the RESTORE registry to assess the effect of IVT bridging therapy versus MT alone
- Compared with clots extracted from patients treated with MT alone, clots from patients treated with bridging therapy were significantly smaller but had a similar composition of main components
- Administering IVT prior to MT significantly reduces thrombus size by releasing the main histological components proportionally

Current guidelines on treating AIS in LVO recommend the use of both IVT and MT as soon as possible after stroke onset. However, questions remain as to whether pre-treatment with IVT significantly affects MT success and patient outcomes. This study sought to determine the effect of previous IVT administration on the size and histological composition of clots extracted by MT.

Clots were collected from 1000 patients who were included in the RESTORE registry, which contains thrombotic material extracted via MT from patients with AIS who presented at one of four stroke centres in Europe between February 2018 and December 2019.² Clots recorded in the RESTORE registry were classified according to whether or not the patient received IVT prior to MT, and gross photos of each clot were taken and used to estimate the extracted clot area (ECA). The main histological clot components (red blood cells [RBC], fibrin, and platelets) were characterized using Martius Scarlett Blue staining and quantified using Orbit Image Analysis. The area occupied by each main component was calculated by multiplying the component percent by the ECA.

Of the 1000 patients included in the analysis, 451 (45%) were treated with bridging therapy, and 549 (55%) were treated with MT alone. There was no significant difference between patients receiving bridging therapy versus MT alone in terms of suspected aetiology, first-line approach used, or revascularization outcome.

No significant difference in occlusion type was observed between patients who received bridging therapy and those who received MT alone (anterior/posterior occlusion: chi-squared test [χ^2]=4.575, $p=0.102$; singular/multiple occlusion: $\chi^2=0.061$, $p=0.804$). Clots from patients undergoing bridging therapy were significantly smaller than those extracted from patients treated with MT alone (median ECA [range]: 32.7 [14.8–64.9] vs 36.8 [20.1–79.8] mm², $p=0.006$) and were associated with a significantly lower number of fragments compared with MT alone (2 [1–4] vs 3 [2–5], $p=0.044$).

The authors reported no significant difference in the composition of main histological components between bridging therapy and MT-only clots. In analyses combining clot size and composition, clots from patients who received bridging therapy (vs MT only) had numerically fewer RBCs (median ECA x RBC: 13.25 vs 14.97 mm², $p=0.056$), and significantly less fibrin (median ECA x fibrin: 9.10 vs 10.54 mm², $p=0.005$) and platelets/other (median ECA x platelets: 5.04 vs 6.54 mm², $p=0.002$).

This study had a number of important limitations. Data were available only on patients from whom a clot could be extracted, and thus patients that recanalized after IVT alone or had unsuccessful thrombectomy were not captured. In addition, there was incomplete information on the eventual anticoagulation regimens for each patient, and the dosage and specific thrombolytic agents administered to bridging therapy patients. The two patient groups also differed in rt-PA eligibility; patients receiving MT only would have been ineligible for rt-PA treatment.

Conclusions

In patients with AIS, bridging therapy was associated with significantly smaller clots, which had a smaller area of fibrin and platelet/other but a similar composition of main components, compared with clots extracted from patients treated with MT alone.

“Patients receiving bridging therapy often have a shorter time window from symptoms onset to hospital admission. Further studies should address the effect of time frame on thrombus size.”²

SHOULD RT-PA TREATMENT REMAIN THE STANDARD OF CARE IN PATIENTS WITH AIS AND COVID-19?³

SUMMARY

- Observational, prospective, multicentre cohort study to assess safety outcomes of rt-PA treatment in patients with AIS and COVID-19
- Patients with COVID-19 presented with more severe strokes at admission
- The odds of disability, in-hospital mortality, and haemorrhagic transformation following treatment with rt-PA for an AIS were similar in patients with and without COVID-19
- rt-PA should continue to be the standard of care in patients with AIS and COVID-19

COVID-19 is associated with increased risk of AIS and the pandemic has had a global impact on the admission, treatment, and clinical outcomes of patients with AIS. Reperfusion therapies including rt-PA are recommended as the standard of care in patients following an AIS; however, the safety of rt-PA in patients with AIS and COVID-19 has not been assessed. This multicentre, observational, cohort study was designed as part of the CASCADE initiative to assess the safety of rt-PA in patients with AIS and COVID-19.³

Patients treated with rt-PA for AIS at nine stroke centres between 18 February 2019 and 31 December 2020 were eligible for inclusion, and were categorized into those with and without COVID-19. The primary study outcomes included disability at discharge (mRS score ≥ 2), haemorrhagic transformation, and in-hospital mortality rates. Secondary outcomes included stroke severity, door-to-needle time, and length of hospital stay.

A total of 542 patients were eligible for study inclusion, of which 101 (18.5%) had COVID-19. Patients with and without COVID-19 did not differ significantly by age, sex, or baseline vascular risk factors. Patients with COVID-19 had significantly higher levels of high-sensitivity C-reactive protein (HS-CRP) compared with patients without COVID-19. Large-artery atherosclerosis was the most common cause of stroke across all patients with AIS (31.5%) and the rate was higher in patients with COVID-19 (47.3%).

Patients with COVID-19 presented with more severe strokes (median NIHSS at admission [interquartile range, IQR]: 13 [9–19] vs 11 [7–17] in patients with and without COVID-19, respectively). The median door-to-needle time was similar in patients with and without COVID-19. Patients with COVID-19 experienced a significantly longer median hospital stay (IQR) vs patients without COVID-19: 8 (5–17) vs 7 (4–13) days, respectively; hazard ratio (HR): 1.78 (95% CI: 1.31–2.25). There were no significant differences between patients with and without COVID-19 in regard to disability at discharge (discharge mRS score ≥ 2 , adjusted OR: 0.50; 95% CI: 0.09–2.64), in-hospital mortality (adjusted OR: 3.60; 95% CI: 0.83–6.60), or haemorrhagic transformation (adjusted OR: 1.51; 95% CI: 0.66–3.30). HS-CRP level was found to be an accurate predictor of haemorrhagic transformation in all patients, including those with COVID-19.

This study had a number of limitations. Symptomatic vs asymptomatic haemorrhagic transformation could not be analysed, and subgroup analyses in thrombectomy cases could not be performed due to the low sample size. In some centres, follow-up data on NIHSS scores were unavailable, and mRS at discharge is not the usual time point for assessing functional outcome.

Conclusions

This study found that the risk of disability, mortality, and haemorrhagic transformation following rt-PA treatment for an AIS was similar in patients with and without COVID-19. Consistent with the standard of care for patients with AIS, patients with COVID-19 should be offered rt-PA following an AIS.

“Treatment with IV-tPA should not be delayed while the possibility of COVID-19 is ruled out.”³

AIS, acute ischaemic stroke; BEST-MSU, The Benefits of Stroke Treatment Delivered by a Mobile Stroke Unit Compared with Standard Management by Emergency Medical Services trial; CASCADE, call to action: SARS-CoV-2 and cerebrovascular disorders; CI, confidence interval; COVID-19, coronavirus disease 2019; CT, computed tomography; ECA; extracted clot area; EMS, emergency medical services; EVT, endovascular thrombectomy; h, hours; HR, hazard ratio; HRS-CRP, high-sensitivity C-reactive protein; ICH, intracerebral haemorrhage; IQR, interquartile range; IVT, intravenous thrombolysis; LVO, large vessel occlusion; MSU, mobile stroke unit; mRS, modified Rankin scale; MT, mechanical thrombectomy; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; RBC, red blood cells; rt-PA, recombinant tissue plasminogen activator; SD, standard deviation; UW-mRS, utility-weighted modified Rankin scale

References

1. [Grotta JC *et al.* Prospective, multicenter, controlled trial of mobile stroke units. *N Engl J Med* 2021;385:971–81.](#)
2. [Rossi R *et al.* Does prior administration of rtPA influence acute ischemic stroke clot composition? Findings from the analysis of clots retrieved with mechanical thrombectomy from the RESTORE registry. *J Neurol* 2021; doi:10.1007/s00415–021–10758–5.](#)
3. [Sasanejad P *et al.* Safety and outcomes of intravenous thrombolytic therapy in ischemic stroke patients with COVID-19: CASCADE initiative. *J Stroke Cerebrovasc Dis* 2021; doi:10.1016/j.jstrokecerebrovasdis.2021.106121.](#)