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When treating acute ischaemic stroke of LVO type, time window prevails over tissue window

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Time is brain. How fast an occluded cerebral artery can be reopened is directly related to how many brain cells can be saved. The identification of a tissue window as indicated by the presence of a penumbra on multimodality imaging study has opened the time window of treatment to 24 hours after the onset.[1] From 2019 to 2022, the issue of direct intra-arterial (IA) mechanical thrombectomy (MT) is non-inferior to bridging therapy or not has been settled.[2] Bridging therapy may have slight advantage in re-opening the occluded arteries than direct IA MT.[3] Recently published data on IA MT to treat acute ischaemic stroke (AIS) from a large vessel occlusion but with a low Alberta Stroke Programme Early CT (ASPECT) score indicated that in these patients, performing a multimodality imaging study may not be necessary. Multimodality imaging study including MRI of head, MRA of head and neck and magnetic resonance perfusion (MRP) of head or CT of head, CTA of head and neck and CT perfusion (CTP) of head are must-to-do tests when evaluating patients with AIS with an onset time between 6 and 24 hours in current clinical practice. This practice was based on the results of Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo (DAWN)[4] and Endovascular Therapy Following Imaging Evaluation for Ischaemic Stroke (DEFUSE 3)[5] trials, which were to look for opportunities to perform direct IA MT to remove the clot while minimising haemorrhagic risk since 2018. Later, such multimodality imaging studies are used to select patients with AIS with an onset between 4.5 and 9 hours for intravenous thrombolysis. One must admit, finding a penumbra (tissue window) with multimodality brain imaging has extended the treatment window to 24 hours in patients with AIS with an LVO. However, overrelying on it may have delayed the treatment time. Many interventionists in practice have asked for MRP or CTP to be repeated if a patient with AIS has a long transport timer. Some prefer to have an MRP or CTP even if the time of onset is within 6 hours.

Recent data from trial of Endovascular Therapy for Acute Ischaemic Stroke with Large Infarct (ANGEL-ASPECT),[6] Endovascular Therapy for Acute Stroke with a Large Ischaemic Region (RESCUE-Japan LIMIT),[7] Trial of Endovascular Thrombectomy for Large Ischaemic Strokes (SELECT-2),[8] Thrombectomy for Emergent Salvage of Large Anterior Circulation Ischaemic Stroke (TESLA),[9] Endovascular Thrombectomy for Acute Ischaemic Stroke with Established Large Infarct (TENSION)[10] and LArge Stroke Therapy Evaluation[11] have showed that if a patient with an AIS from a LVO with an ASPECT score of 0–5 on either a non-contrast CT or MRI-defusion-weighted imaging (DWI) of brain, IA MT may be beneficial. In these patients with either no penumbra or a large core infarction, IA MT may help up to 47% of patients reach a modified Rankin Scale (mRS) score of 0–3 at 90 days. The moratlity rate was similar comparing to those not treated. The rate of symptomatic intracranial haemorrhage (sICH) was between 0.6% to 6.1%, a very acceptable range (table 1). If one believes in these results, brain perfusion scans (MRP or CTP) are not needed if a patient with an AIS presents to the emergency room (ER) beyond 10 hours of onset. Only a CT or MRI of brain and either a CTA or MRA should be done to look for an LVO. Brain perfusion scans are needed in those with an onset between 4.5 and 10 hours of onset and without an LVO. This is to look for a patient with AIS who has no LVO but may still qualify for intravenous thrombolysis (see proposed algorithm in figure 1). Furthermore, the other positive trial result that has hardly been implemented clinically is from the Effect of Intra-arterial Alteplase vs Placebo Following Successful Thrombectomy on Functional

Table 1 Characteristics and outcome comparison of six trials treating patients with AIS with low ASPECT from an LVO

Trial	TENSION	RESCUE-Japan LIMIT	LASTE	TESLA	SELECT-2	ANGEL-ASPECT
Year started	July 2018	November 2018	April 2019	July 2019	October 2019	September 2020
Country	European eight countries and Canada	Japan	USA-Europe	USA	USA, Canada, Europe, Australia and New Zealand	China
Age (years)	>18	>18	≥18	18–85	18–85	18–80
National Institute of Health Stroke Scale (NIHSS)	<26	≥6	>5	>6	≥6	6–30
Imaging criteria	NCCT or DWI ASPECT 3–5	CT or DWI ASPECT 3–5	NCCT or DWI ASPECT 0–5	NCCT ASPECT 2–5	1. ASPECT >6 and core ≥50 cc 2. ASPECT 3–5 and core ≥50 cc 3. ASPECT 3–5 and core <50 cc	1. ASPECT 3–5 2. ASPECT 0–2: 70–100 cc
Imaging characteristic	NCCT ASPECT 82%	DWI-ASPECT >90%	ASPECT 0–2 56%	Only NCCT ASPECT 2–5	ASPECT+Core	ASPECT+Core 24 hours, all had NCCT
Time window	<12 hours LKW	<6 hours LKW, 6–24 hours FLAIR (-)	<6.5 hours LKW	<24 hours	<24 hours (0–12 vs 6–24)	<24 hours
No. of patients enrolled (ITT)	253 (125 vs 128) of 665 planned	202 (100 vs 102), 200 planned	324 (165 vs 159) of 450 planned	300 planned	352 (178 vs 174) of 560 planned	455 (230 vs 225) of 502 planned
90-day mRS 0–2	17% vs 2% 7.16 (95% CI 2.12 to 24.21) P=0.0016	14.0% vs 7.8%	13.2% vs 4.8%	14.6% vs 8.9%	20.3% vs 7.0% 2.97 (95% CI 1.60 to 5.51) P<0.0001	30.0% vs 11.6% 2.62 (95% CI 1.69 to 4.06) P<0.0001
90-day mRS 0–3	31% vs 13% 2.84 (95% CI 1.48 to 5.47) P=0.0018	31% vs 12.7%	46% vs 12.7%	30% vs 20%	37.9% vs 18.7% 2.06 (95% CI 1.43 to 2.96) P<0.0001	47.0% vs 33.3% 1.50 (95% CI 1.17 to 1.91) P<0.0001
sICH	5% vs 5%	9.0% vs 4.9%	9.6% vs 5.7%	3.97% vs 1.34%	0.6% vs 1.1%	6.1% vs 2.7%
Death	40% vs 51% HR 0.67 (95% CI 0.46 to 0.98) P=0.038	18.0% vs 23.5%	55.5% vs 36.1%	35.3% vs 33.3%	38.4% vs 41.5% Relative Risk (0.91 (95% CI 0.71 to 1.18)	21.7% vs 20.0% HR 1.00 (95% CI 0.65 to 1.54) P=0.99
NNT for functional independence at 90 days (mRS of 0–2)	7	16	12	18	8	5
NNT for independent ambulation at 90 days (mRS of 0–3)	5	5	3	10	5	7
NNH for symptomatic intracranial haemorrhage	143	24	26	38	–200 Negative NNH favours intervention	29

ANGEL-ASPECT, Endovascular Therapy for Acute Ischaemic Stroke with Large Infarct; ASPECT, Alberta Stroke Programme Early CT Score; ITT, intention to treat; LASTE, LArge Stroke Therapy Evaluation; LKW, last known well; mRS, modified Rankin Scale; NCCT, non-contrast CT; NNH, number needed to harm; NNT, number needed to treat; RESCUE-Japan LIMIT, Endovascular Therapy for Acute Stroke with a Large Ischaemic Region; SELECT-2, Trial of Endovascular Thrombectomy for Large Ischaemic Strokes; sICH, symptomatic intracranial haemorrhage; TENSION, Endovascular Thrombectomy for Acute Ischaemic Stroke with Established Large Infarct; TESLA, Thrombectomy for Emergent Salvage of Large Anterior Circulation Ischaemic Stroke.

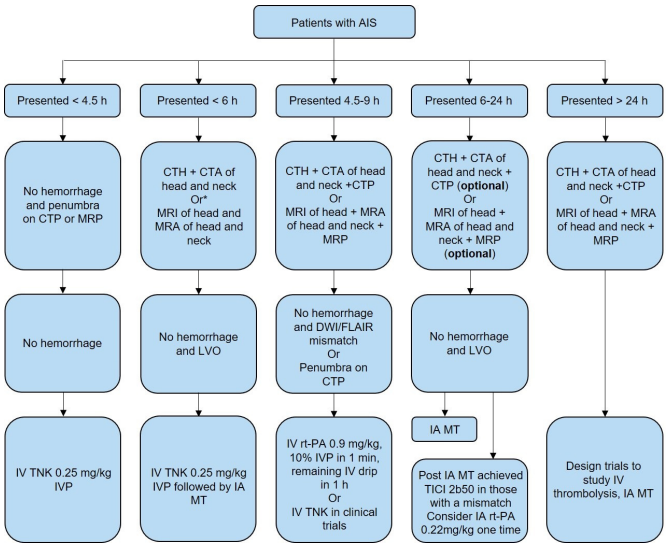

Figure 1 New proposed algorithm in AIS workup and treatment. *When IV contrast cannot be used. AIS, acute ischaemic stroke; CTA, CT angiogram; CTH, CT of head; CTP, CT perfusion; IA, intra-arterial; IV, intravenous; IVP, intravenous push; MRA, magnetic resonance angiogram; MRP, magnetic resonance perfusion; MT, mechanical thrombectomy; rt-PA, recombinant tissue plasminogen activator; TICI, thrombolysis in cerebral infarction; TNK, tenecteplase.

Outcomes in Patients With Large Vessel Occlusion Acute Ischaemic Stroke (CHOICE) trial, which showed that if a thrombolysis in cerebral infarction (TICI) grade 2b50 has been achieved post-IA MT for an LVO, additional recombinant tissue plasminogen activator (rt-PA) (0.225 mg/kg) given IA may be beneficial.[12] Compared with the non-treatment group, additional IA rt-PA achieved an mRS score of 0 or 1 at 90 days was 59.0% vs 40.4% (95% CI 0.3% to 36.4%; p=0.047). sICH within 24 hours in the treated group was 0% vs 3.8% in the placebo group, and the treated group had a 90-day mortality 8% vs 15% in the placebo group.

The new data on treating patients with AIS from an LVO with low ASPECT scores have provided enough evidence to change our daily clinical practice. These data are as meaningful as those that proved bridging therapy within 6 hours of onset and direct thrombectomy between 6 and 24 hours of onset of an LVO-related stroke can save brain and lives. When comparing the number needed to treat to reach an mRS of 0–2 or 0–3 with number needed to harm to cause an sICH in each of these six trials, the benefit remains substantial.

Therefore, it is about time to rewrite the AIS guidelines and revise the care plans in the ER (figure 1). When would a perfusion scan be helpful? Perhaps perfusion scan to look for a mismatched penumbra should be used in patients with AIS presented beyond 24 hours. In these patients, if a penumbra is present, MT can be attempted if there is an LVO. Intravenous thrombolysis can be considered if there is no LVO.

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