Therapeutics

In acute ischemic stroke, early intraarterial treatment plus usual care improved functional independence

Clinical impact ratings: **EM** ★★★★★☆ **HO** ★★★★★☆ **N** ★★★★★★★

Question

In patients with acute ischemic stroke caused by proximal intracranial occlusion, what are the efficacy and safety of early intraarterial treatment (IAT)?

Methods

Design: Randomized controlled trial (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands [MR CLEAN]). Netherlands Trial Registry NTR1804; Current Controlled Trials ISRCTN10888758.

Allocation: Concealed.*

Blinding: Blinded* (data collectors and outcome assessors).

Follow-up period: 90 days.

Setting: 16 medical centers in the Netherlands.

Patients: 502 patients ≥ 18 years of age (mean age 65 y, 58% men, median National Institutes of Health Stroke Scale [NIHSS] score 18) who had acute ischemic stroke caused by proximal arterial occlusion in the anterior circulation artery confirmed with imaging, an NIHSS score ≥ 2, and possibility of initiation of IAT within 6 hours of stroke onset.

Intervention: IAT comprised arterial catheterization with a microcatheter to the level of occlusion and delivery of a thrombolytic agent, mechanical thrombectomy, or both, at the discretion of the local interventionist, plus usual care (*n* = 233) or usual care alone (*n* = 269).

Outcomes: Primary outcome was the modified Rankin scale score (score range 0 [no symptoms] to 6 [death]). Secondary outcomes included serious adverse events and mortality.

Patient follow-up: 99.6% (intention-to-treat analysis).

Main results

196 of 233 patients (84%) in the IAT group received IAT; 190 of 233 (82%) procedures used retrievable stents. Main results are in the Table. Mortality did not differ between groups.

Conclusion

In patients with acute ischemic stroke caused by proximal intracranial arterial occlusion of the anterior circulation, early intraarterial treatment plus usual care improved functional independence compared with usual care alone.

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*See Glossary.

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Intraarterial treatment (IAT) plus usual care (UC) vs UC alone for acute ischemic stroke†

Outcomes	Median (IQR)		At 90 d
	IAT + UC	UC	Adjusted common odds ratio (95% CI)‡
Modified Rankin score§	3 (2 to 5)	4 (3 to 5)	1.67 (1.21 to 2.30)
	Event rates		RBI (CI)	NNT (CI)
Modified Rankin score 0 to 2§	33%	19%	77% (29 to 132)	7 (4 to 18)
			RRI (CI)	NNH (CI)
Any serious adverse event	47%	42%	12% (−8 to 36)	NS
New ischemic stroke‖	5.6%	0.4%	1390% (153 to 8762)	20 (12 to 39)
Symptomatic intracerebral hemorrhage	7.7%	6.4%	21% (−35 to 128)	NS

†IQR = interquartile range; NS = not significant; other abbreviations defined in Glossary. RBI, RRI, NNT, NNH, and CI calculated from control event rates and adjusted odds ratio or group event rates in article.

‡Adjusted for age; baseline National Institutes of Health Stroke Scale score; time from stroke onset to randomization; previous stroke, atrial fibrillation, or diabetes mellitus; and occlusion of the internal carotid artery terminus.

§Score range 0 (no symptoms) to 6 (death); score ≤ 2 = functional independence.

‖In a different vascular territory.

Commentary

For 20 years, IV t-PA has remained the mainstay of treatment for acute ischemic stroke, with best results when therapy starts early after symptom onset (1). The MR CLEAN, ESCAPE, and EXTEND-IA trials show that functional outcomes can be further improved in patients with stroke due to proximal intracranial vessel occlusion by adding IAT with retrievable stents to perform clot removal. This is a major advance in the treatment of acute ischemic stroke.

A previous major trial did not show endovascular therapy to be better than best medical treatment, including IV t-PA (2). This trial had low enrolment rates and included patients without major arterial occlusion, whereas MR CLEAN, ESCAPE, and EXTEND-IA only included patients with proximal arterial occlusions (i.e., carotid artery, middle cerebral artery, anterior cerebral artery). Also, in contrast to previous trials, these trials almost exclusively used newer endovascular devices (retrievable stents), which have been shown to improve efficacy by leading to faster and higher rates of vessel recanalization (3, 4).

In EXTEND-IA, all patients met the eligibility criteria for t-PA and received IV thrombolysis. In MR CLEAN and ESCAPE, most patients were eligible and treated with IV t-PA before IAT, but patients who were ineligible for IV t-PA could also be enrolled. MR CLEAN and

EXTEND-IA enrolled patients who could start clot retrieval within 6 hours of symptom onset. ESCAPE included patients up to 12 hours after symptom onset, although most were treated within the 6-hour window. Benefits of IAT within 6 hours from symptom onset are clear, but fewer conclusions can be drawn from patients treated between 6 and 12 hours due to low numbers (*n* = 49) in this subgroup. Patients presenting late after onset will probably require more careful evaluation than patients presenting early.

Dynamic CT angiography and perfusion CT were included in the ESCAPE and EXTEND-IA trials, respectively, to help identify patients with a favorable ischemic penumbra (potentially salvageable vs irreversibly infarcted brain tissue). The relative benefit of IAT in ESCAPE and EXTEND-IA, where imaging-based inclusion criteria were stricter, seems to be slightly greater. Between-study comparisons are inappropriate, and the benefit gained by stricter inclusion criteria based on ischemic penumbra and collateral blood flow is therefore unclear. We see from the results of MR CLEAN that even without imaging-based patient selection, clot retrieval was effective. Whether advanced imaging should be done to select patients and if so what kind will be key questions in implementation of IAT in clinical practice.

Therapeutics

In acute ischemic stroke, rapid intraarterial treatment plus usual care improved functional independence

Clinical impact ratings: Ⓔ ★★★★★★☆ Ⓝ ★★★★★★★

Question

In patients with acute ischemic stroke caused by proximal vessel occlusion; a small infarction core; and moderate-to-good collateral circulation on imaging, what is the effect of rapid intraarterial treatment (IAT) added to usual care?

Methods

Design: Randomized controlled trial (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times [ESCAPE] trial). ClinicalTrials.gov NCT01778335. The trial was stopped early for benefit after unplanned interim analysis.

Allocation: Concealed.*

Blinding: Blinded* (outcome assessors).

Follow-up period: 90 days.

Setting: 22 centers in Canada, the USA, South Korea, Ireland, and the UK.

Patients: 316 adults (median age 71 y, 52% women, median National Institutes of Health Stroke Scale [NIHSS] score 16) who had acute ischemic stroke caused by proximal arterial occlusion in the anterior circulation artery, a small infarction core (ASPECTS 6 to 10), and moderate-to-good collateral circulation confirmed on imaging, and were enrolled within 12 hours of symptom onset.

Intervention: Rapid IAT, comprising a cerebral angiogram procedure started within 60 minutes of computed tomography (CT) and thrombectomy to achieve reperfusion (retrievable stents recommended) plus usual care (*n* = 165), or usual care alone (*n* = 150). All patients meeting local guideline criteria were treated with IV alteplase within 4.5 hours of symptom onset.

Outcomes: Primary outcome was the modified Rankin scale score (score range 0 [no symptoms] to 6 [death]). Secondary outcomes included intracerebral hemorrhage and mortality.

Patient follow-up: 98% (intention-to-treat analysis).

Main results

In the IAT group, 151 of 165 patients (92%) received rapid IAT, 130 (79%) received retrievable stents, and 120 (72%) received IV tissue plasminogen activator (t-PA) before IAT. The main results are in the Table.

Conclusion

In patients with acute ischemic stroke caused by proximal vessel occlusion, with a small infarction core and moderate-to-good collateral circulation, rapid intraarterial treatment plus usual care improved functional outcome compared with usual care alone.

Rapid intraarterial treatment (IAT) plus usual care (UC) vs UC alone for acute ischemic stroke†

Outcomes	Median		At 90 d	
	IAT + UC	**UC**	**Common odds ratio (95% CI)**	
Modified Rankin score‡	2	4	2.6 (1.7 to 3.8)	
	Event rates		**RBI (CI)**	**NNT (CI)**
Modified Rankin score 0 to 2‡	53%	29%	80% (40 to 140)	5 (3 to 9)
			RRI (CI)	**NNH (CI)**
Symptomatic intracerebral hemorrhage	3.6%	2.7%	40% (−60 to 370)	Not significant
			RRR (CI)	**NNT (CI)**
Mortality	10%	19%	50% (0 to 70)	11 (8 to ∞)

†Abbreviations defined in Glossary. RBI, RRI, RRR, NNT, and CI calculated from control event rates and unadjusted rate ratios in article.

‡Score range 0 (no symptoms) to 6 (death); score ≤ 2 = functional independence.

*See Glossary.

Commentary (continued from page JC2)

Although patients in these trials could be enrolled with mild stroke severity (NIHSS scores as low as 2), the median NIHSS scores in the trials were much higher (range 13 to 18). Most patients with proximal arterial occlusion will have large areas of ischemia and an NIHSS score ≥ 8. CT angiography in all patients, including those with minor symptoms and low NIHSS scores, may identify a few more patients for clot retrieval but increases exposure to radiation and contrast dye.

The results of the trials allow us to treat patients with contraindications to IV t-PA, such as those in the postoperative period or receiving anticoagulation therapy. Importantly, none of the trials showed an increased risk for major complications from the endovascular procedures, including intracerebral hemorrhage. Rather, in ESCAPE, the IAT group had reduced mortality.

IAT is generally available only in specialized stroke centers and may be inaccessible in many areas. Compared with IV t-PA, where noncontrast CT head scans and stroke-trained physicians are needed, endovascular therapy requires specialized teams and advanced neuroimaging, all at a relative high cost. Providing IAT will require restructuring of stroke systems of care. For now, patients eligible for IV t-PA should start treatment and not wait for IAT, as t-PA remains the standard of care. Patients identified as candidates for clot retrieval at non-IAT sites will need to start IV t-PA and be transported to an interventional site in a "drip-and-ship" model of care.

The proportion of patients with acute ischemic stroke who are eligible for IAT is unclear. In highly trained and efficient stroke centers, 15% to 20% of patients admitted with ischemic stroke are treated with IV t-PA. An estimated one third of these patients will have proximal clots and be eligible for IAT (5). This may be an underestimate and, based on the ESCAPE trial, a group of patients not eligible for IV t-PA will now be eligible for IAT. Sites offering IAT will encounter sizeable numbers of eligible patients.

The endovascular approach for acute ischemic stroke treatment is a "game changer" in stroke therapeutics and will become a new standard of care based on these recent positive trials. IAT is an effective adjunct to IV t-PA and an alternative when IV t-PA is contraindicated. The challenge will be to find ways to implement IAT in clinical practice.

Therapeutics

In ischemic stroke, early intraarterial treatment plus alteplase improved reperfusion and functional outcome

Clinical impact ratings: 🔵GM ★★★★★☆ 🔵EM ★★★★★☆ 🔵HO ★★★★★☆ 🔵N ★★★★★★

Question

In patients with anterior circulation ischemic stroke caused by proximal vessel occlusion and favorable computed tomography (CT) perfusion imaging, what is the effect of early intraarterial treatment with a stent retriever added to alteplase treatment?

Methods

Design: Randomized controlled trial (Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-Arterial [EXTEND-IA] trial). The trial was stopped early for efficacy.

Allocation: Concealed.*

Blinding: Blinded* (outcome assessors, {data collectors, data analysts, and safety committee}†).

Follow-up period: 90 days.

Setting: 10 centers in Australia and New Zealand.

Patients: 70 patients (mean age 69 y, 51% women, median National Institutes of Health Stroke Scale [NIHSS] score 13 to 17)

who had ischemic stroke and occlusion of the internal carotid artery or of the first or second segment of the middle cerebral artery confirmed by imaging, evidence of salvageable tissue on CT perfusion imaging using RAPID automated software, and could receive IV alteplase within 4.5 hours of symptom onset.

Intervention: Intraarterial treatment using the Solitaire FR retrievable stent, started within 6 hours and completed within 8 hours of symptom onset, plus IV alteplase, 0.9 mg/kg (n = 35), or IV alteplase alone (n = 35).

Outcomes: Primary outcomes were reperfusion and early neurologic improvement (NIHSS reduced by ≥ 8 points or NIHSS of 0 to 1 at 3 d; score range 0 [no symptoms] to 42 [death]). Secondary outcomes included the modified Rankin scale (score range 0 [no symptoms] to 6 [death]), symptomatic intracerebral hemorrhage, and mortality.

Patient follow-up: 100% (intention-to-treat analysis).

Main results

The main results are in the Table.

Conclusion

In patients with anterior circulation ischemic stroke caused by proximal vessel occlusion and favorable computed tomography perfusion imaging, early intraarterial treatment with a stent retriever added to alteplase improved reperfusion, neurologic status, and functional independence compared with alteplase alone.

Intraarterial treatment (IAT) plus alteplase vs alteplase alone for ischemic stroke‡

Outcomes	Median (IQR)		Generalized odds ratio (95% CI)	
	IAT + alteplase	**Alteplase alone**		
Reperfusion at 24 h§	100% (100 to 100)	37% (−0.5 to 96)	4.7 (2.5 to 9.0)	
Modified Rankin score at 90 d‖	1 (0 to 3)	3 (1 to 5)	2.1 (1.2 to 3.8)	
	Event rates		**RBI (CI)**	**NNT (CI)**
Neurologic improvement at 3 d¶	80%	37%	110% (46 to 1461)	3 (2 to 6)
Modified Rankin score 0 to 2 at 90 d‖	71%	40%	84% (21 to 122)	3 (3 to 13)
			RRR (CI)	
Symptomatic intracerebral hemorrhage	0%	6%	100% (−85 to 100)	Not significant
Mortality	9%	20%	49% (−72 to 88)	Not significant

‡IQR = interquartile range; other abbreviations defined in Glossary. RBI, RRR, NNT, and CI calculated from control event rates and odds ratios or group event rates in article.

§Percentage of reduction in perfusion-lesion volume between initial and 24-h imaging; adjusted for site of vessel occlusion at baseline.

‖Score range 0 (no symptoms) to 6 (death); score ≤ 2 = functional independence; scores 0 to 2 at 90 d adjusted for baseline National Institutes of Health Stroke Scale (NIHSS) score and age.

¶NIHSS reduced by ≥ 8 points or NIHSS of 0 to 1 at 3 d; score range 0 (no symptoms) to 42 (death); adjusted for NIHSS score and age.

*See Glossary.

†Information provided by author.

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Commentary *(continued from page JC3)*

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References

1. **Emberson J, Lees KR, Lyden P, et al; Stroke Thrombolysis Trialists' Collaborative Group.** Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. Lancet. 2014;384:1929-35.

2. **Broderick JP, Palesch YY, Demchuk AM, et al; Interventional Management of Stroke (IMS) III Investigators.** Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. N Engl J Med. 2013;368:893-903.

3. **Nogueira RG, Lutsep HL, Gupta R, et al; TREVO 2 Trialists.** Trevo versus Merci retrievers for thrombectomy revascularisation of large vessel occlusions in acute ischaemic stroke (TREVO 2): a randomised trial. Lancet. 2012;380:1231-40.

4. **Saver JL, Jahan R, Levy EI, et al; SWIFT Trialists.** Solitaire flow restoration device versus the Merci Retriever in patients with acute ischaemic stroke (SWIFT): a randomised, parallel-group, non-inferiority trial. Lancet. 2012;380:1241-9.

5. **Hansen CK, Christensen A, Ovesen C, Havsteen I, Christensen H.** Stroke severity and incidence of acute large vessel occlusions in patients with hyperacute cerebral ischemia: results from a prospective cohort study based on CT-angiography (CTA). Int J Stroke. 2015;10:336-42.