Neurology® Clinical Practice

Review

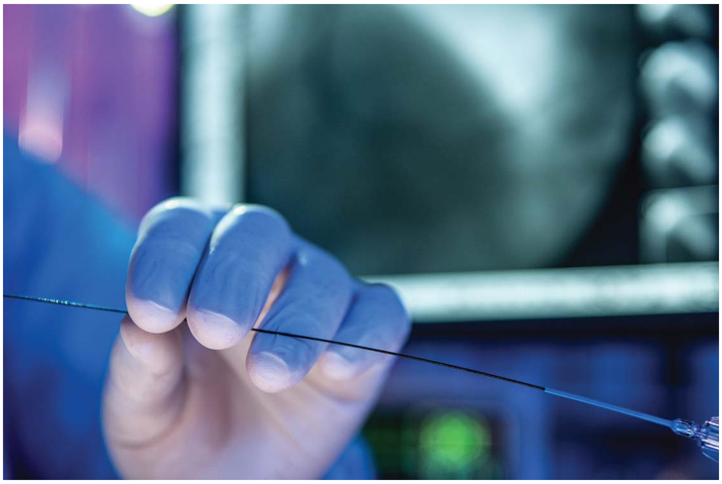
Advances in endovascular therapy for ischemic stroke

A whole new ball game

Lai Yin Law, MBBS; Bruce C.V. Campbell, PhD, FRACP; Tissa Wijeratne, MD, FRACP

Abstract

Purpose of review: The burden of disability from ischemic stroke continues to intensify. Any acute therapeutic option that reduces disability after ischemic stroke should be encouraged and further studied. In particular, the need for an effective treatment in patients with large vessel occlusion has been long overdue. **Recent findings:** Consistent trial evidence has answered this need in an emphatic fashion, demonstrating improved functional outcomes with endovascular therapy following better patient selection, new device technology, and reduced treatment times. The article discusses the current evidence and guidelines and highlights the inherent complexities of a specialized intervention whose demand will grow exponentially. The scope for future investigation especially using advanced imaging to expand patient selection will be considered. **Summary:** Endovascular thrombectomy is an established and highly efficacious acute treatment for ischemic stroke that we need to apply and implement to maximize benefit to the population. ***Neurol Clin Pract* 2016;6:49–54**



Until recently, evidence-based therapy for acute ischemic stroke was limited to IV recombinant tissue plasminogen activator (IV-rtPA) within 4.5 hours of symptom onset. Uptake of IV-rtPA has risen gradually since the first landmark publication establishing its efficacy.[1] Meta-analysis confirmed better functional outcomes with shorter onset-to-needle times regardless of age or stroke severity, prompting local and national initiatives that successfully promoted models of care focusing on efficiency and improved workflow.[2,3] Patients with severe strokes due to proximal large vessel occlusion remained a challenge as the probability of recanalization with IV-rtPA alone remained modest.[4] To facilitate timely reperfusion, endovascular thrombectomy was studied, as intra-arterial thrombolysis alone had not been shown to be more effective than IV-rtPA.[5] Neutral endovascular trials published in 2013 were limited by long treatment delays, low recanalization rates with early generation device technology, and heterogeneous patient characteristics, often without requiring proven vessel occlusion.

Western Health (LYL, TW), St. Albans; and Royal Melbourne Hospital (BCVC), Parkville, Australia.
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Correspondence to: twijeratne@gmail.com

> *The concept of waiting to assess failure of IV-rtPA is strongly discouraged.*

Now, 5 published randomized controlled trials have established the efficacy of endovascular thrombectomy,[6–10] with 2 further trials yet to be published[11,12] (table 1). Improved reperfusion and functional outcomes were observed without increased adverse effects, including symptomatic intracranial hemorrhage. These trials combined more effective stent retriever devices with faster workflow to reduce treatment delays and imaging to prove large vessel occlusion and, in several cases, exclude patients with large areas of irreversibly injured brain using perfusion or collateral imaging. The majority had intracranial internal carotid artery and proximal middle cerebral artery occlusion and achieved arterial puncture within 6 hours. Most trials included a proportion of patients who required transfer from a peripheral hospital (primary stroke center) to the endovascular-equipped comprehensive stroke center. Trial selection criteria varied but the largest and most inclusive trial (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands [MR CLEAN]) was robustly positive, indicating the broad generalizability of this treatment. There were relatively few patients treated beyond 6 hours after onset, with mild neurologic deficit (e.g., NIH Stroke Scale sore <6), or with distal (M2) occlusion. Subsequent meta-analysis may clarify effects in these subgroups. Patients with posterior circulation occlusion were also not included in these trials. However, further trials are ongoing to definitively assess effectiveness in the extended time window (Perfusion Imaging Selection of Ischemic Stroke Patients for Endovascular Therapy [POSITIVE] [NCT01852201] 6–12 hours and DWI/PWI and CTP Assessment in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention [DAWN] [NCT02142283] 6–24 hours) and in basilar artery occlusion (Basilar Artery International Cooperation Study [BASICS] NCT01717755).

These definitive trials have led to updated US, Canadian, and European guidelines.[13–15] However, they also generate further important questions. Systems of care for patient triage and interhospital transfer networks require development. Demand for trained neurointerventionalists will substantially increase and training of the entire stroke team (from ambulance paramedics to endovascular suite staff) to achieve efficient and safe workflow is crucial. Whether it is more efficient to transport a patient to a primary stroke center for initial imaging and IV-rtPA before selected transfer of patients with large vessel occlusion or instead transport direct (bypassing the primary center) to a comprehensive stroke center for patients meeting simple clinical severity criteria[16] remains uncertain and will likely vary according to local geographical considerations. The optimal approach to making IV-rtPA and endovascular treatment decisions in parallel during the imaging process in order for one treatment not to delay the other is also a critical area for development. The concept of waiting to assess failure of IV-rtPA is strongly discouraged.

The package of IV-rtPA for all eligible patients combined with immediate endovascular thrombectomy is recommended in the American Heart Association guideline update.[13] This also ensures patients who are not eligible for endovascular thrombectomy (e.g., inappropriate vascular anatomy) still benefit from timely systemic thrombolysis. However, analogous to management of ST-elevation myocardial infarction, further trials may examine whether a direct to endovascular approach could be appropriate when it is immediately available. There may be further advances in thrombolytic efficacy, for example using tenecteplase or a combination of rtPA with argatroban or eptifibitide.[17,18] The potential to slow progression of the ischemic cascade using cytoprotective strategies that have previously failed may now be revisited in the era of highly effective reperfusion.[19]

Implementation of acute stroke therapies including thrombectomy at the population level is being explored. This includes promoting community awareness of acute stroke symptoms and

Table 1 Recent randomized controlled trials of endovascular thrombectomy

Patient and study characteristics	MR CLEAN[6]	ESCAPE[7]	EXTEND-IA[8]	SWIFT-PRIME[9]	REVASCAT[10]	THRACE[11]	THERAPY[12]
No. patients	500 total; 233 EVT; 267 control	315 total; 165 EVT; 150 control	70 total; 35 EVT; 35 control	196 total; 98 EVT; 98 control	206 total; 103 EVT; 103 control	385 total; 190 EVT; 195 control	108 total; 54 EVT; 54 control
Inclusion criteria; time from onset to arterial access	Age ≥18 y; NIHSS ≥2, <6 h	Age ≥18 y; NIHSS ≥6, <12 h (84% within 6 h)	Age ≥18 y; any NIHSS, <6 h, had received, IV-rtPA	Age 18–85 y; NIHSS 8–29, <6 h, had received, IV-rtPA	Age 18–80y[a]; NIHSS ≥6, <8 h, failed/ ineligible for IV-rtPA	Age 18–80 y; NIHSS 10–25, <5 h	Age 18–85 y; NIHSS ≥8, <5 h
Baseline, NIHSS	17 EVT; 18 control	16 EVT; 17 control	17 EVT; 13 control	17 both	17 both	Median 18	Median 17.5
Baseline imaging assessment (in addition to CTA)	Aspects (not used for exclusion)	Aspects 6–10 multiphase CTA: moderate to good collaterals	CT perfusion: mismatch ratio >1.2, mismatch volume >10 mL, ischemic core <70 mL	Aspects 6–10, CT/MR perfusion[b]: mismatch ratio >1.8, mismatch volume >15 mL, ischemic core <50 mL	CT aspects 7–10	MRA used in some	CT for clot length ≥8 mm
Median aspects	9 both	9 both	9 both	9 both	7 EVT; 8 control	N/A	N/A
EVT: MCA-M1 or ICA occlusion, %	92	96 (including if all M2 segments involved)	83	93	90	N/A	N/A
EVT: IV-rtPA used, %	87	73	100	100	68	100	100
Stent retrievers, %	82	86	100	100	100	N/A (any approved)	0 (Penumbra aspiration device)
Workflow: time from stroke onset, min							
IV-rtPA	85 EVT; 87 control	110 EVT; 125 control	127 EVT; 145 control	111 EVT; 117 control	118 EVT; 105 control	N/A	N/A
Arterial access	260	N/A	210	224	269	N/A	N/A
Reperfusion	N/A	241	248	252 (stent deployed)	355	N/A	N/A
Outcomes							
EVT: mTICI 2b or 3 reperfusion, %	59	72	86	88	66	N/A	N/A
Death at 90 d, %	21 EVT; 22 control	10 EVT; 19 control	9 EVT; 20 control	9 EVT; 12 control	18 EVT; 16 control	N/A	N/A
mRS ≤2 at 90 d, %	33 EVT; 19 control	53 EVT; 29 control	71 EVT; 40 control	60 EVT; 35 control	44 EVT; 28 control	N/A	N/A
Symptomatic ICH, %	8 EVT; 6 control	4 EVT; 3 control	0 EVT, 6 control	0 EVT; 3 control	2 EVT; 2 control	N/A	N/A

Abbreviations: ASPECTS = Alberta Stroke Program Early CT score; CTA = CT angiography; ESCAPE = Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times; EVT = endovascular thrombectomy; EXTEND-IA = Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial; ICA = internal carotid artery; ICH = intracranial hemorrhage; IV-rtPA = IV recombinant tissue plasminogen activator; M2 = second segment of middle cerebral artery; MCA-M1 = first segment of middle cerebral artery; MR = magnetic resonance; MR CLEAN = Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; MRA = magnetic resonance angiography; mRS = modified Rankin Scale (0 = no symptoms; 1 = symptoms but no disability; 2 = slight disability but able look after own affairs without assistance); mTICI = modified Treatment in Cerebral Ischemia grading of angiographic reperfusion (2b = >50% reperfusion of affected territory; 3 = complete restoration of flow to the affected territory); NA = not available; NIHSS = NIH Stroke Scale; REVASCAT = Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours; SWIFT-PRIME = Solitaire™ with the Intention for Thrombectomy as Primary Endovascular Treatment; THRACE = Trial and Cost Effectiveness Evaluation of Intra-arterial Thrombectomy in Acute Ischemic Stroke; THERAPY = Assess the Penumbra System in the Treatment of Acute Stroke.

[a] Later changed to include patients aged 80–85 if ASPECTS >8.

[b] Inclusion criteria for first 71 patients, suggested if available thereafter.

implications and optimizing emergency triage protocols to assist its timely recognition.[3,20] Adopting established models of care has been shown[21] but finite resources and personnel will likely limit applicability to all settings. A culture that encourages data collection for consecutive patients will identify delays in current protocols to improve performance measures.[3,22]

Minimizing time from onset to reperfusion is essential to maximize the population benefit, with shorter onset-to-needle and onset-to-reperfusion times clearly associated with better outcomes.[2,23] However, at an individual level, there are patients with salvageable brain tissue well beyond 6 hours after stroke onset, and recent studies have indicated the feasibility of identifying these individuals using brain imaging.[7,24] Noncontrast CT provides some information on the extent of irreversible injury (e.g., Alberta Stroke Program Early CT Score [ASPECTS] > 6). Specificity is high but sensitivity is modest, particularly in the first 1–2 hours after stroke onset,

Table 2 Summary of American Heart Association/American Stroke Association guidelines for endovascular therapy in acute ischemic stroke[14]

Noncontrast CT for all suspected ischemic strokes, noninvasive vascular imaging (e.g., CTA) if endovascular therapy considered
Advanced penumbral imaging[a,b] may improve selection but requires further study in randomized controlled trials
IV-rtPA should be given as soon as possible when eligible and both IV-rtPA and endovascular therapy should proceed in parallel[c]
Criteria[d]
Age ≥18 years (no upper limit but consider premorbid function)
Functionally disabling stroke (NIHSS ≥6)
No evidence of large ischemic core on CT brain (ASPECTS ≥6)
Functional independence (mRS 0–1)
IV-rtPA received within 4.5 hours of onset if eligible
Proven occlusion of ICA or MCA-M1
Arterial puncture within 6 hours of onset
Aim to maximize reperfusion (at least mTICI 2b/3) using thrombectomy[e] as soon as possible
Systems of care[b]
Efficient regional hub and spoke program
Rapid transport to endovascular equipped comprehensive stroke center if appropriate[f]
Trained credentialed neurointerventionalist

Abbreviations: ASPECTS = Alberta Stroke Program Early CT score; CTA = CT angiography; ICA = internal carotid artery; IV-rtPA = IV recombinant tissue plasminogen activator; M2 = second segment of middle cerebral artery; MCA-M1 = first segment of middle cerebral artery; mRS = modified Rankin Scale (0 = no symptoms; 1 = symptoms but no disability; 2 = slight disability but able look after own affairs without assistance); mTICI = modified Treatment in Cerebral Ischemia grading of angiographic reperfusion (2b = >50% reperfusion of affected territory; 3 = complete restoration of flow to the affected territory); NIHSS = NIH Stroke Scale.

[a] Measures of infarct core, penumbra, and collateral flow status (e.g., CT perfusion and multiphase CT angiography).

[b] Will depend on local expertise and geographical considerations.

[c] Waiting for IV-rtPA response is strongly discouraged.

[d] There is limited evidence outside of these criteria but benefit may be seen in selected patients (e.g., IV-rtPA ineligible, mild stroke [NIHSS <6] or distal (M2) occlusion, ASPECTS <6, arterial puncture >6 hours); penumbral imaging may be useful.

[e] Stent retriever preferred.

[f] Potential for selection for endovascular thrombectomy based on noninvasive imaging at the primary stroke center.

A culture that encourages data collection for consecutive patients will identify delays in current protocols to improve performance measures.

and interrater agreement is also imperfect. Thresholded cerebral blood flow or cerebral blood volume using perfusion imaging (as used in Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial [EXTEND-IA] and most Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment [SWIFT PRIME] patients) has greater sensitivity for large ischemic core and can be standardized using automated software.[8,9] Collateral scoring of CT angiography (CTA) as performed in the Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE) trial can similarly identify patients likely to have a large area of irreversible injury but should be assessed using a multiphase acquisition (as used in most ESCAPE trial patients) as standard static CTA tends to underestimate collateral flow, which, by its nature, is delayed, leading to unwarranted exclusion of patients who may benefit from thrombectomy.[7,25] Imaging-based selection may lead to effective treatment in an extended time window to include late presenting and wake-up stroke patients. However, improved functional outcomes will need to be demonstrated in randomized trials before this approach is widely accepted. A summary of current guidelines is presented in table 2.

Endovascular thrombectomy is transforming outcomes for those who have the most devastating of ischemic strokes. However, there is still much work to be done and medical champions must demonstrate leadership to implement the new evidence and guidelines. Further work to better understand treatment effect in subgroups underrepresented in the trials, streamline treatment delivery, and expand access to geographically disadvantaged areas is required to maximize the effect of this new era in stroke reperfusion therapy.

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