Endovascular therapy for large vessel occlusion stroke: an update on the most recent clinical trials

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The advent of DAWN (DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo) and DEFUSE-3 (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke) has marked a pivotal landmark amongst the newer generation of randomized clinical trials of endovascular therapy (EVT).¹,² These two latest trials have demonstrated that EVT imparts significant benefit to patients with large vessel occlusion (LVO) of the anterior circulation and salvageable ischemic penumbra at 6 to 24 h after stroke onset, similarly to patients treated before 6 h. Here, we briefly review the cumulative evidence from newer generation EVT trials that has led to the current standard of care in stroke management and highlight future directions for continued improvement and more widespread applicability of endovascular thrombectomy.

The benefit of EVT for anterior circulation LVO strokes was first demonstrated in MR CLEAN, ESCAPE, EXTEND IA, SWIFT PRIME, REVASCAT and THRACE trials that were published between 2015 and 2016.³⁻⁸ These trials targeted early, substantial reperfusion of patients who had moderate to severe symptoms within 6 h of onset, occlusion of the intracranial internal carotid artery or proximal middle cerebral artery on CTA or MRA, and small to moderate infarct size on non-contrasted head CT (ASPECTS ≥ 6). Advanced perfusion imaging was required in EXTEND IA and encouraged in SWIFT PRIME but not formally used for patient selection in MR CLEAN, ESCAPE, REVASCAT or THRACE. In the HERMES meta-analyses of the five endovascular trials published in 2015, the median time of onset to reperfusion was 285 min and successful reperfusion defined as ≥ 50% of the downstream vessel territory (modified Thrombolysis in Cerebral Ischemia (mTICI) score 2b or 3) occurred in approximately 70% of all cases.⁹,¹⁰ EVT led to significantly higher rates of functional independence at 90 days relative to medical therapy (adjusted cOR: 2.71, 95% CI: 2.07–3.55) and the number needed to treat was 2.6 for any reduced functional disability.⁹ The main treatment effect of EVT was preserved across different sub-groups irrespective of age, sex, NIHSS severity, and pre-treatment with IV tPA. However, the probability of functional independence with EVT was significantly reduced with increasing time of onset to reperfusion (from 64.1% at 3 h to 46.1% at 8 h).¹⁰ This apparent time-dependency in the overall benefit from EVT was likely due in part to inclusion of patients who were fast progressors, experiencing rapid infarct growth leading to large infarct core volumes by the time of tissue reperfusion.¹¹,¹²

In comparison to the early time window EVT trials, DAWN and DEFUSE-3 targeted anterior circulation LVO patients who were slow progressors of infarct growth and had small ischemic cores with significant volumes of reversible ischemic tissue (penumbra) after 6 h of stroke onset.¹¹,¹² The DAWN trial¹ was designed to include patients with salvageable penumbra based on the degree of clinical core mismatch for up to 24 h after stroke onset. The clinical core mismatch is an estimate of salvageable penumbral volume based on the disproportionate severity of neurological symptoms relative to an established infarct volume (ischemic core) on CT perfusion or MRI. Patients met eligibility criteria if they had NIHSS ≥ 10 with ischemic core < 21 ml (age ≥ 80), NIHSS ≥ 10 with ischemic core < 31 ml (age < 80), or NIHSS ≥ 20 with ischemic core of 31 to < 51 ml (age < 80). Out of a total of 206 randomized patients, 49% of patients in the intervention group achieved functional independence at 90 days as compared to 13% of patients in the control group (absolute difference 36%, 95% CI: 21–44). The rate of mortality

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and severe disability was 25% versus 36% in the intervention versus control groups (absolute reduction 11%). This translated into a 73% relative risk reduction in functional dependency with EVT and a number needed to treat of 2 to achieve any lower disability. There was no significant heterogeneity of treatment effect in pre-specified sub-group analysis including age, symptom severity, artery occlusion site or stroke onset category such as wake-up, witnessed versus unwitnessed. The rate of symptomatic intracranial hemorrhage in the intervention group was 6%, which was not statistically different from that in the control group as in previous early time window EVT trials.9

In DEFUSE-3,2 the target LVO population was similar to DAWN except that patients were included if they had NIHSS ≥ 6, could receive EVT between 6 and 16 h from stroke onset, and met imaging-based mismatch criteria on CT or MR perfusion. Patients were included if they had ischemic core volume < 70 ml, estimated penumbra volume of ≥ 15 ml (tissue with perfusion delay > 6 s minus ischemic core volume), and a ratio of hypo-perfused tissue to ischemic core volume of ≥ 1.8. This trial enrolled a total 182 patients, of which 62% met DAWN eligibility criteria. The rate of functional independence at 90 days was 45% in the endovascular group versus 17% patients in the control group (risk ratio 2.67, 95% CI: 1.6–4.48). The rate of mortality and severe disability was 22% versus 42% in the intervention versus control groups (absolute reduction: 20%). The relative risk reduction of functional dependency with EVT was 62% and the number needed to treat to achieve any lower disability was 2, comparable to the earlier DAWN results. The rate of symptomatic intracranial hemorrhage in the intervention group was 7% and not statistically different from control. Similarly to DAWN and other EVT trials, DEFUSE-3 demonstrated no heterogeneity of EVT effect in pre-specified sub-group analysis. In particular, the treatment effect was maintained when patients were stratified per DAWN eligibility status.

Despite the fundamental progress in extending the therapeutic window of endovascular therapy achieved in DAWN and DEFUSE-3, there remains an important need to broaden EVT applicability to more stroke patients.13 It has been previously estimated that only 4% of all patients with acute ischemic stroke and 38% of patients with anterior circulation LVO presenting within 6 h of onset may be eligible for EVT using strict AHA level IA guideline criteria.14 In another single center analysis, approximately 1.7 to 2.7% of all ischemic strokes and 30% of LVO patients presenting beyond 6 h of onset were eligible for EVT when adhering to strict DAWN or DEFUSE-3 criteria (level IA/IIB evidence).15 Therefore, the majority of LVO patients presenting within 24 h of onset may remain excluded from endovascular therapy due to over-selective eligibility criteria. Another study demonstrated that the most common reasons for exclusion of patients from EVT per DAWN/DEFUSE-3 criteria included ischemic core > 70 ml, absence of target mismatch on presentation, poor functional baseline (MRS > 2), and distal occlusion (MCA-M2).16 However, delayed-presenting patients who were treated with EVT outside of trial criteria and had MCA-M2 branch occlusions, baseline MRS 0–2, ischemic core < 70 ml achieved functional independence in up to 38% of cases versus 12% in the untreated group, with a similar safety profile.16 Future prospective studies are warranted to test the benefit of EVT in similar patients who fall outside strict selection criteria but may still benefit from timely reperfusion, since the natural progression of untreated LVO is otherwise dismal.

There is also a need to maximize the benefits of EVT in LVO patients who meet well-established eligibility criteria within 24 h of presentation. In the HERMES, meta-analysis of the early time window EVT trials, 18.6 to 32.5% of patients who achieved successful reperfusion within 3 to 8 h after symptom onset still experienced functional dependency or death at 90 days.10 In the DAWN and DEFUSE-3 trials, less than 50% of EVT patients experienced long-term functional independence although substantial reperfusion was achieved in 70 to 80% of cases.1,2 Failure to achieve excellent clinical outcomes after adequate endovascular reperfusion is likely due to multiple factors. One potential reason is that complete reperfusion (mTICI 3) rather than ≥ 50% reperfusion (mTICI 2b) criteria may be required for maximal clinical efficacy.17,18 Another important factor may be that significant infarct growth occurs due to collaterals failing between the initial time of brain imaging and subsequent vessel recanalization. In addition, a significant minority of patients with hemorrhagic transformation will experience poor outcomes despite successful arterial recanalization. Other factors such as age, in-hospital complications, and rehabilitation quality may also influence the long-term efficacy of EVT.

In sum, the latest generation of EVT trials has led to a new therapeutic paradigm focused on stroke physiology-based patient selection beyond fixed time-based windows. Despite significant advances and broader selection beyond 6 h after onset, many patients with LVO stroke remain untreated or experience poor outcomes. Additional trials are needed to test the net benefit of EVT in patients with distal branch occlusions, milder initial symptoms, larger presenting infarcts or delayed presentation beyond 24 h.19 Future comprehensive strategies including improved systems of care, technological advances and neuroprotective therapies targeting faster, complete reperfusion with reduction
of hemorrhagic transformation and reperfusion injury will be poised to maximize the benefits of endovascular therapy to a larger number of stroke patients.

Funding
The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: MR is supported by University of Pittsburgh Physician Foundation Research grant, NIH/NINDS grant U10NS086489.

Declaration of conflicting interests
The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: TGJ: Consultant: Cerenovus (Steering Committee – modest), Stryker Neurovascular (PI DAWN – unpaid), Fundacio Ictus (PI REVASCAT/Steering committee RACECAT – unpaid). Stock: FreeOx Biotech, Anaconda, Silk Road, Blockade Medical (modest). RGN: Stryker-Neurovascular (Trevo-2 & DAWN Trial PI), Covidien (SWIFT & SWIFT PRIME/Steering Committee, STAR Trial/ Core Lab), Penumbra (3-D Separator Trial/Executive Committee).

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