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Cerebrovascular Disease and Stroke (S Silverman, Section Editor)

Endovascular Treatment of Acute Ischemic Stroke

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Abstract

Purpose of review Endovascular thrombectomy (ET), the standard of treatment for emergent large vessel occlusion (ELVO) strokes, has been subject to rigorous efforts to further improve its usage and delivery for optimised patient outcomes. This review aims to provide an outline and discussion about the recently established and emerging recommendations regarding endovascular treatment of stroke.

Recent findings The indications for ET have expanded continually, with perfusion imaging now enabling selection of patients presenting 6–24 h after last-known-well, and improved device and operator proficiency allowing treatment of M2-MCA occlusions and tandem occlusions. Further inclusion of paediatric patients and patients with larger infarct core or milder stroke symptoms for ET has been proposed; however, this remains unproven. This growing applicability is supported by more efficient systems of care, employing modern techniques such as telemedicine, mobile stroke units and helicopter medical services. Ongoing debate exists regarding thrombolytic agent, thrombectomy technique, anaesthesia method and the role of advanced neuroimaging, with upcoming RCTs expected to provide clarification.

Summary The journey to further improving the efficacy of ET has advanced and diversified rapidly over recent years, involving improved patient selection, increased utility of advanced neuroimaging and ongoing device redevelopment, within the setting of more efficient, streamlined systems of care. This dynamic and ongoing influx of evidence-based refinements is key to further optimising outcomes for ELVO patients.

Introduction

Acute ischaemic stroke (AIS) is the second leading cause of death worldwide and leads to significant morbidity in survivors [1]. AIS due to emergent large vessel occlusion (ELVO) is an important subset of stroke associated with worse functional outcomes, increased hospital costs and considerably increased mortality [2]. The Society of Neurointerventional Surgery defines ELVO as occlusion of a vessel producing a significant clinical deficit and accessible to treatment by endovascular thrombectomy (ET) [3].

Rapid recanalisation of the occluded vessel results in brain tissue reperfusion and potential salvage of at-risk tissue ('penumbra') surrounding the already infarcted 'core'. As such, treatment of AIS due to ELVO is time-critical. ET is the standard of care treatment for LVO in eligible patients, with multiple randomized controlled trials demonstrating improved clinical outcomes at 90 days [4–10].

With further technical advances and increasing individual patient level data available for meta-analysis, the definition of ELVO may expand to potentially include additional distal occlusions [11].

The long and winding road

Intravenous thrombolysis (IVT) was approved by the Food and Drug Administration (FDA) in 1996 based on a randomized controlled trial (RCT) demonstrating improved 3-month clinical outcomes when administered within 3 h since last known well (LKW) [12]. Thereafter, several further positive trials resulted in IVT becoming the standard of care in AIS. Further studies expanded the time window for IVT to 4.5 h and more recently to 9 h from LKW [13, 14]. However, several studies noted poor efficacy amongst LVO, reporting recanalization rates of < 50% with no significant clinical improvements and number needed to treat (NNT) of 19 for patients 3–4.5 h since LKW (NNT = 10 for 0–3 h) [15–17]. Additionally, IVT is contraindicated in patients with elevated bleeding risk (for example; previous intracranial haemorrhage [ICH], recent intracranial/spinal surgery, recent AIS, thrombocytopenia < 100,000/mm^3) as IVT is independently associated with increased risk of symptomatic ICH and 7-day mortality in these cohorts [9••, 18].

In 2004, the MERCI Retriever[1] was introduced, followed by the Penumbra Aspiration Device.[2] Whilst both first-generation devices achieved better recanalisation than intra-arterial thrombolytics and anti-fibrinolytics, this was not associated with improved functional outcome [19–21]. Thus, the introduction of second-generation devices ('stent retrievers' [SRs]) in 2012 was

[1] Stryker, Kalamazoo, MI, USA
[2] Penumbra Inc., Alameda, CA, USA

pivotal to the adoption of ET, facilitating improved reperfusion in eligible patients *and* superior clinical outcomes. When compared to MERCI in RCTs, the two main SRs, Solitaire[3] and Trevo,[4] demonstrated superior recanalization (89 vs 67%, $p < 0.0001$ and 86 vs 60%, $p < 0.0001$ respectively), improved functional independence (58 vs 33%, $p = 0.0001$ and 40 vs 22%, $p = 0.01$ respectively) and better safety [22, 23].

Subsequently, three negative RCTs published in the *New England Journal of Medicine* (NEJM) in 2013 reported no clinical benefit in ET over IVT [24–26]. Nonetheless, these trials were weakened by the predominant usage of older-generation devices [27]. Additionally, IVT implementation may have been suboptimal: the IMS-III trial used a reduced dose in the IVT/ET arm (0.6 vs 0.9 mg/kg), and the SYNTHESIS trial performed ET without IVT [24, 26]. Notably, MR-RESCUE enrolled patients at a mean of 5.5 h, and SYNTHESIS randomising a large proportion of patients to ET without CTA-confirmed ELVO [24, 25, 27].

In 2015, five RCTs compared IVT (0.9 mg/kg alteplase) alone to IVT plus ET (IVT/ET) with newer-generation devices for advanced imaging-confirmed LVO [4–8]. These trials demonstrated a statistically significant benefit of IVT/ET over IVT alone. The pooled analysis with 1287 patients (634 ET, 653 control) from the 2016 HERMES meta-analysis demonstrated that SR-ET improves functional outcomes (adjusted cOR = 2.49, 95%CI = 1.76–3.53), without heterogeneity amongst subgroups of age, stroke severity, location and ethnicity [28••]. Treatment benefit was seen across multiple patient subgroups including patients older than 80 years, those not receiving IVT, tandem occlusions and low NIHSS strokes. The rate of major complications (90-day mortality, parenchymal haematoma, sICH) was similar between treatment groups and the NNT to reduce mRS by ≥ 1 was 2.6 [28••].

Thus, ET became the standard of care for ELVO in eligible patients, providing improved functional outcomes, along with increased quality and expectancy of life, and reduced length-of-stay and hospital costs [29, 30].

The renaissance

Continued expansionism

Late presenters

Recent RCTs have demonstrated efficacy of ET in 'late presenters' (> 6 h of LKW). The DAWN trial compared IVT/ET to IVT alone in 206 patients 6–24 h after LKW with infarct core < 51 ml and clinical imaging mismatch (see Table 1). There was a statistically significant improvement in 90-day clinical outcomes, with similar rates of mortality and sICH [31••]. These findings were subsequently reinforced when the DEFUSE 3 RCT enrolled 182 patients 6–16 h after LKW, with infarct core < 70 ml and target mismatch profile (see Table 1). This also demonstrated superiority of IVT/ET [32••]. These data were included in a recent meta-analysis of late presenters ($n = 518$, 4 RCTs), which observed significantly greater 90-day functional independence (OR = 3.33, 95%CI = 1.81–6.12, $p < 0.001$) and recanalization (OR = 13.17, 95%CI = 4.17–41.60, $p < 0.001$) with IVT/ET compared to IVT [36]. As such, the current American Heart Association and American Stroke Association (AHA/ASA) guidelines now

[3] Medtronic Neurovascular, MN, USA
[4] Stryker

Table 1. Imaging inclusion criteria amongst major RCTs

RCT	Occluded artery (CTA or MRA)	Baseline NCCT	Perfusion criteria (CTP, MRP or MR-DWI)	Collateral criteria
DAWN [31••]	ICA, M1-MCA	Hypodensity < 1/3 MCA territory	Clinical imaging mismatch: a. 0 to < 21 cc core infarct and NIHSS ≥ 10 (and ≥ 80 years old) b. 0 to < 31 cc core infarct and NIHSS ≥ 10 (and < 80 years old) c. 31 cc to < 51 cc core infarct and NIHSS ≥ 20 (and < 80 years old)	Not used
DEFUSE-3 [32••]	ICA, M1-MCA	Not used	Target mismatch profile: Ischemic core volume is < 70 ml Mismatch ratio > 1.8 Mismatch volume > 15 ml	Not used
PISTE (2017) [33]	ICA, M1-MCA, M2-MCA	Not used	Not used	Not used
THRACE (2016) [34]	ICA, M1-MCA, upper 1/3 of BAO	Not used	Not used	Not used
THERAPY (2016) [35]	ICA, M1-MCA, M2-MCA	Hypodensity < 1/3 of MCA territory Clot > 8 mm	Not used	Not used
SWIFT PRIME (2015) [7]	ICA, M1-MCA	ASPECTS > 6	Used for some patients. Core volume < 50 ml Total infarct > 100 ml Penumbra volume > 15 ml Mismatch ratio ≥ 1.8	Not used
EXTEND-IA (2015) [8]	ICA, M1-MCA, M2-MCA	Hypodensity > 1/3 of MCA territory	Mismatch ratio > 1.2 Absolute mismatch volume > 10 Core volume < 50 ml	Not used
ESCAPE (2015) [5]	ICA, M1-MCA or equivalent (≥2 M2-MCA occlusions)	ASPECTS > 5	CBV ASPECT score used with different cutoff depending on coverage	Multiphase CTA—collaterals seen in ≥ 50% of MCA region
MR CLEAN (2015) [4]	ICA, M1-MCA, M2-MCA, A1, A2	Not used	Not used	Not used
REVASCAT (2015) [6]	ICA or M1-MCA	ASPECT > 6 for patients > 80 years old ASPECT > 9 for patients aged 81–85	CBV ASPECT used in patients treated > 4.5 h from LKW	Not used

strongly recommend ET in late presenters satisfying the DAWN or DEFUSE selection criteria as standard of care [9••, 10].

Larger infarct core

Whilst patients with large infarct cores are thought to be unfavourable candidates for ET, this presumption is being increasingly challenged. As the first RCT

to include patients with larger infarct cores (ASPECTS: 0–4 [$n = 28$], 5–7 [$n = 92$], 8–10 [$n = 376$]) for SR-ET, MR CLEAN demonstrated overall efficacy of SR-ET over IVT for improving 90-day mRS (adjusted common OR = 1.67, 95%CI = 1.21–2.30) [4]. Post hoc analysis found that this treatment effect was not associated ($p > 0.80$) with CTP-derived parameters (ischemic-core volume, penumbral volume, percentage ischemic core), despite ischemic-core volume and percentage ischemic core being independently associated with poorer outcomes ($p < 0.001$, $p = 0.002$) [37].

Currently, at least three prospective RCTs are underway to investigate ET in patients with large infarct cores; TENSION [NCT03094715], which is still recruiting, and IN EXTREMIS LASTE [NCT03811769] and TELSA [NCT03805308], which are yet to recruit [38–41]. Proven benefit in this cohort of patients represents the potential for a large expansion in candidacy for therapy.

Milder stroke symptoms

Current AHA/ASA guidelines recommend ET for patients presenting with moderate to severe symptoms (NIHSS ≥ 6) [9••]. This recommendation is based on criteria from the positive 2015 NEJM trials [6, 22, 25, 32••].

However, patients with milder symptoms can reflect a subset of patients with ELVO with well-established pial collaterals and therefore better penumbral support, but who carry the risk of late clinical deterioration leading to poor outcomes.

This has prompted consideration of a lower severity threshold for ET [3]. This was investigated in a recent cohort study of 170 patients with NIHSS < 8, in which there was excellent outcome (mRS 0–1 at 3 months) in 64.5% of patients, however no clinical benefit of IVT/ET over IVT [42]. Further guidance on this topic will be obtained from IN EXTREMIS MOSTE, an upcoming multicentre RCT of ET in ELVO with NIHSS ≤ 5 and from the planned ENDOLOW trial [43].

Testing the limits

Distal occlusions

ELVO constitutes 7–13% of all AIS, leaving a large population potentially ineligible for ET, including patients with distal occlusions (occlusion in ACA, PCA or MCA distal to M2) [44–46]. ET for distal occlusions is contentious, as it is associated with inconsistent symptomatology, milder symptoms, delayed diagnosis and higher procedural risk including vessel perforation, vessel dissection, sICH and death [47, 48].

Pooled data from the HERMES meta-analysis provided initial suggestion that ET could be efficacious in distal (M2) occlusions, although the treatment effect in terms of 90-day mRS was non-significant ($n = 94$, adjusted cOR = 1.28 [95%CI = 0.51–3.21]) [28••]. Subsequently, in a 5-year database in which 69 patients with distal occlusion AIS were treated with ET (mostly SR), reperfusion was achieved in 83% whilst 30% achieved 90-day functional independence and 4% experienced parenchymal haematoma, implying the efficacy and safety of ET for distal occlusions [46]. Furthermore, this was consolidated by a 2019

meta-analysis of 1105 patients with isolated M2 occlusions who underwent ET. This study reported high reperfusion rates (75.4%, 95%CI = 67.7–84.1), high functional independence rates (58.3%, 95%CI = 51.7–63.8) and good safety profile (5.1% sICH, 12.2% 3-month mortality) [49].

As for technique choice in M2 occlusions, both CA and SR have demonstrated high recanalization (86.8 vs 80.5%, $p = 0.168$) and 90-day functional independence rates (74.5 vs 59.9%, $p = 0.120$) in a 2018 meta-analysis ($n = 835$, 12 studies), with similar complication rates [50]. However, this review is confounded by significantly faster onset-to-needle times in CA compared to SR cases (156.2 vs 259.9 min, $p = 0.02$), potentially explaining the higher rate of excellent mRS 0–1 in CA (65.6 vs 39.9%, $p = 0.003$). As such prospective, multicentre RCTs are needed to reliably assess technique choice, as well as delineate the role of novel small-diameter SRs, such as Trevo XP 3 x 20 mm and Catch Mini 3 x 20 mm, which have proven feasible for treating distal occlusions [51, 52].

Basilar artery occlusions

Basilar artery occlusions (BAOs) are associated with significant morbidity and mortality due to brainstem and thalamic infarction. Recanalisation is critical to improving prognosis even in delayed presentations; however, due to low disease incidence, there are no RCTs available to advise the best treatment modality [53]. The Basilar Artery International Cooperation Study (BASICS), a prospective international registry of 619 BAO patients, found no statistically significant superiority of any treatment strategy; antithrombotic only ($n = 183$), IVT ($n = 121$) and ET ($n = 288$) [54]. Nevertheless, these results are limited by being observational and non-randomised, warranting the subsequent BASICS phase III RCT [NCT01717755], which has recruited 282 patients for best medical care with or without ET [55]. Whilst awaiting these results, the AHA/ASA and European Stroke Organisation guidelines recommend consideration of ET for BAOs within 6 h of LKW; however, this is expert opinion based on limited data [9••, 10].

Tandem occlusions

Tandem occlusions (TOs) of the extracranial ICA with a proximal ipsilateral anterior circulation occlusion occur in 10–20% of LVO strokes [56, 57•]. As TOs independently predict poor outcomes post-IVT and ET, some earlier trials of ET excluded patients with TOs [7, 29, 58]. Subgroup analysis of the HERMES collaboration however demonstrated benefit of IVT/ET over IVT alone in patients with TO [28].

A further 2018 meta-analysis of 33 retrospective studies, comprising outcome data available in 509 patients treated with stent and 76 treated with angioplasty alone, demonstrated that SR is safe and efficacious in TOs (15% mortality, 8% sICH, 47% 90-day functional independence) [59]. Recent large-scale retrospective studies have further suggested efficacy of ET in TOs and consistently demonstrated that the addition of ICA reperfusion improves functional outcomes [57•, 60, 61].

Thus, the 2018 AHA/ASA guidelines now recommend ET for TOs (level IIb evidence), but technical strategy still varies between angioplasty and stenting or

both [9]. Furthermore, whether to treat the intracranial or extracranial lesion first remains unclear, with studies suggesting equanimity [59]. Amongst the various treatment combinations for TOs (antithrombotics, angioplasty, stenting, SR-ET), the TITAN registry (2012–2016) found that carotid stenting and antiplatelet therapy resulted in the greatest improvement in reperfusion compared to SR-ET only (83.1 vs 60.2%, OR = 2.66, 95%CI = 1.38–5.10, p = 0.003) [57•]. Additionally, TITAN dispelled concerns about periprocedural antithrombotics required for ICA reperfusion, showing systemic heparinisation did not affect efficacy or safety.

Paediatric patients

Paediatric AIS is rare and can be associated with significant morbidity and reported mortality up to 14% [62]. With only 68 published cases of ET for paediatric AIS between 1994 and 2017, no clinical trial data exist and 2019 AHA/ASA guidelines recommend supportive management as the mainstay of treatment, with IVT and ET to be considered on a patient- and clinician-dependent basis [63]. In the most recent case series of 19 paediatric AIS patients treated with SR-ET, rates of revascularization and functional independence were 89.5%, with safety outcomes comparable to ET in adults [64]. Larger studies are needed to explore this potential but are challenged by the rarity and often delayed detection of paediatric LVO.

Ongoing refinements

Imaging-time vs tissue

In the 6–24 h time window, current guidelines necessitate advanced neuroimaging with CT or MR perfusion in order to strictly select patients according to either the DAWN or DEFUSE-3 penumbral mismatch eligibility criteria (see Table 1) [9••, 10].

In patients presenting 0–6 h since LKW, non-contrast CT and CT angiography alone can be radiologically sufficient to inform management, as stated by the 2018 AHA/ASA guidelines [9••]. Supporting this, only three of the early-window RCTs (SWIFT PRIME, EXTEND-IA, ESCAPE) mandated advanced neuroimaging (see Table 1), and HERMES found that collateral grade did not influence treatment effect (p = 0.30) [5, 7, 28••, 29]. Additionally, the 'time is brain' mantra and expansion of ET to underdeveloped areas also favours minimalization of advanced neuroimaging.

Nonetheless, strong evidence has emerged that infarct and penumbral volumes are valuable prognosticators, prompting reconsideration of advanced neuroimaging selection of early presenters [65, 66]. For example, a 2019 meta-analysis showed that the three aforementioned RCTs with advanced imaging criteria, compared to other large-scale RCTs, achieved significantly greater functional independence (OR = 2.84 vs 1.75, p = 0.02) [10]. Another meta-analysis (n = 2813, 13 studies) found that perfusion imaging, which often ruled-in otherwise ineligible patients, improved 3-month functional independence (OR 1.89, 95%CI 1.43–2.51, $p < 0.01$) [67]. Likewise, in another recent meta-analysis (n = 2227, 10 RCTs), advanced neuroimaging greatly improved 3-month functional independence (OR 3.79 vs 1.89, $p < 0.001$), without differences in imaging-to-treatment time, sICH or mortality [68]. These benefits

may be explained by inter-individual variation in penumbral development, which implies that advanced radiographic evaluation is helpful to predict therapeutic effect, even in the early window [69]. Importantly, this must be weighed against the risk of advanced neuroimaging being too restrictive and excluding potentially suitable patients [10]. The use of advanced imaging may play a role in selecting patients with pre-treatment large core infarcts; further study is warranted.

Thrombectomy technique—stent retrieval vs contact aspiration

SR remains the recommended first-line thrombectomy approach, as SRs were the predominant device used in major RCTs [9••, 10, 36]. As a plethora of ET strategies have evolved, contact aspiration (CA) has emerged as an alternative to SRs. Whilst there are no trials comparing CA to SR *alone*, the two techniques have been compared as first-line options with the alternative technique offered second-line for rescue therapy.

For instance, the ASTER study, a multicentre RCT ($n = 381$), compared first-line SR to CA (mostly ACE64 or 5MAX aspiration catheters[5]) [70]. Notably, SR less often required rescue therapy compared to CA (23.8 vs 32.8%, $p = 0.05$, OR = 1.57 [95%CI = 0.99–2.47]); however, CA was non-inferior to SR in major outcomes, achieving similar revascularisation (85.4 vs 83.1%, $p = 0.53$, OR = 1.20 [95%CI = 0.68–2.10]) and 90-day functional independence (45.3 vs 50.0%, $p = 0.38$).

A similarly designed RCT, COMPASS ($n = 270$), also found CA non-inferior to SR first line [71]. Endpoints included 90-day functional independence (52 vs 49%, $p = 0.001$), time-to-recanalisation (22 vs 22 min, $p = 0.019$) and complications (mortality, sICH, any ICH) for which there were no significant differences. Additionally, cost savings were realised with the aspiration cohort.

These two RCTs, alongside a meta-analysis (6 RCTs, $n = 871$) demonstrating that Solitaire and CA devices have equal safety, provide sufficient evidence to recommend CA as a reasonable first-line approach [9••, 72]. Further data is needed [10, 73•].

Stentriever device development

Current thrombectomy technology includes stentrievers (devices that engage the clot) and aspirations systems (devices that suction clot out of cerebral vessels). The stent retriever has remained the most commonly used device in clinical practice since the 2015 NEJM trials. Several novel devices are currently being developed, aimed at overcoming mechanical challenges that can contribute to recanalisation failure rates up to 20% and subsequent high risk of functional dependency (see Table 2) [78].

In one prospectively collected ET database ($n = 1126$), platinum-rich devices—Solitaire Platinum and Trevo Provue—independently predicted first-pass reperfusion (OR = 2.1, 95%CI = 1.2–3.4), suggesting benefit in improved visibility with SR deployment, particularly during difficult cases performed under conscious sedation [51]. Moreover, longer SRs were independently associated with first-pass reperfusion (OR = 2.2, 95%CI = 1.3–3.6), suggesting that larger stent contact area allows for better clot integration.

[5] Both Penumbra, Alameda, California

Table 2. Examples of novel stent retrievers

Device	Company	Target issue	Design strategy
Solitaire Platinum [51]	Medtronic, Irvine, CA, USA	Poor visibility	Platinum markers along the device (3–4 distal, 3 body, 1 proximal) for increased visibility
Trevo Provue [51]	Stryker, Kalamazoo, MI, USA	Poor visibility	Entirely platinum-incorporated device with 4 mm distal tip marker and proximal marker for full visibility.
pREset [74]	Phenox	Vessel tortuosity	Closed cell wall pattern with slit spiralling down the wall of the body to allow expansion and contraction depending on vessel diameter
Embotrap [75]	Cerenovus, Galway, Ireland	Vessel tortuosity	Inner stent for immediate flow restoration and outer stent with segmented design for capturing thrombi
Versi [75]	NeuroVasc Technologies, Laguna Hills, CA, USA	Vessel tortuosity	2–4 articulating segments that are alternately located in the stent, enabling expansion when traction is applied
Geometric Clot Extractor (GCE) [76]	Neuravi, Galway, Ireland	Fibrin-rich clots	Tubular body in curved spiral configuration to improve clot engagement without exerting excessive radial force
Embolus Retriever with Interlinked Cages (ERIC) [77]	MicroVention, Tustin, CA	Clot fragmentation and distal emboli	3–5 spherical nitinol wire cages linked in line to increase contact area and thus increase cohesion and eliminate clot integration time

Tortuosity of vessels is a substantial barrier to ET, especially conventional SRs that collapse when stretched, leading to reduced recanalization and functional outcomes [75]. The dynamic pREset device with a closed cell wall pattern allows for better stent expansion and contraction demonstrating good efficacy and safety in one case series [74]. Additionally, segmented SRs, Embotrap and Versi, have been designed to better manoeuvre through tortuous vessels, with Versi achieving significantly better revascularisation rates than Solitaire ($p < 0.01$) and Trevo ($p < 0.05$) in severely tortuous in vitro models [75].

Moreover, the Geometric Clot Extractor has satisfactorily been trialled in vitro against tough fibrin-rich clots, whilst Embolus Retriever with Interlinked Cages, targeting clot fragmentation, has shown improved recanalization when used first-line over conventional SRs (82 vs 57%, $p < 0.001$) [76, 77]. These upcoming devices present promise for ongoing improvement within the realm of ET.

Recombinant tissue plasminogen activator—alteplase vs tenecteplase

Compared to alteplase, the cornerstone of IVT, tenecteplase has superior fibrin specificity and longer half-life, allowing it to be delivered at a lower dose over a shorter duration (bolus vs 1-h infusion) [79]. Thus, it has been postulated that

tenecteplase may offer greater thrombolytic activity leading to increased reperfusion rates [80•]. Furthermore, the ability to administer tenecteplase as a bolus dose has the added benefit of facilitating a 'drip-and-ship' model of care without time delays to endovascular therapy.

Tenecteplase is supported as superior by two phase II RCTs. The first, published in 2012, compared tenecteplase (0.1 mg/kg or 0.25 mg/kg) to alteplase within 6-h of LKW ($n = 75$) [81]. Despite similar 90-day outcomes, tenecteplase was significantly superior in 24-h reperfusion and clinical outcomes. These findings are however limited by small sample size and inapplicability to current practice, in which IVT is advocated within 4.5 h and 0.25 mg/kg is the recommended tenecteplase dose [9••, 10, 82]. In contrast, EXTEND-IA TNK compared tenecteplase (0.25 mg/kg) to alteplase in 202 patients within 4.5 h of LKW prior to ET [80•]. Tenecteplase was superior in penumbral reperfusion (22 vs 10%, $p = 0.03$) and 90-day functional ability (median mRS 2 vs 3, OR = 1.6, $p = 0.04$), with similar safety. However, other RCTs (2 phase III, 1 phase II) have only demonstrated non-inferiority but not superiority of tenecteplase, prohibiting the formation of clear guidelines about its usage [9••, 10, 83–85]. This equivocality was summarised in a recent meta-analysis ($n = 1585$, 5 RCTs), which found no differences in clinical, technical or safety outcomes, concluding 'tenecteplase is at least as effective and safe as alteplase' [86].

The several RCTs currently in progress, including EXTEND-IA TNK Part 2 [NCT03340493], should clarify the status of tenecteplase, whilst providing relevant technical and economic data [79, 87].

Anaesthetic—conscious sedations vs general anaesthesia

Anaesthetic choice for ET is currently an individualised or system level choice taking into account patient, interventionalist and institution-dependent factors [9••]. Theoretically, general anaesthesia (GA) offers lower risk of pain, agitation, aspiration, emergent intubation and movement-related vessel perforation and dissection [88]. Conversely, the perceived benefits of conscious sedation (CS) are faster reperfusion, intraprocedural neurological monitoring and better preservation of haemodynamic stability leading to sustained perfusion of pial collaterals within the effected ischaemic territory [89, 90].

Amongst RCTs in HERMES, three trials (REVASCAT, ESCAPE, SWIFT PRIME) promoted choice of CS, whilst anaesthetic choice was otherwise discretional, such that overall, 70% of ET-treated patients received CS [28••]. Evaluating CS versus GA in this population, CS enabled better 3-month functional outcomes (OR = 1.53, 95%CI = 1.14–2.04) and functional independence (OR = 1.65, 95%CI = 1.14–2.38) [91]. Nonetheless, as patients were not randomised, the data is likely confounded by medical comorbidities, operator preference and significant selection bias.

In subsequent RCTs of GA vs CS (SIESTA, AnSTROKE, GOLIATH), each found no difference in clinical outcomes [92–94]. A pooled analysis of these studies ($n = 368$ total), however, demonstrated that CS led to significantly lower odds of functional independence (OR = 0.55, 95%CI = 0.34–0.89, $p = 0.01$) [10]. Despite being prospective RCTs, these trials are suboptimal in quality due to their small sample sizes and results with wide confidence intervals.

Furthermore, the results indicate that use of GA should be protocolised, with particular attention to periprocedural blood pressure [10].

Systems of care implications

ELVO and the need for ET is resource-intensive, representing a significant challenge to healthcare systems; a time-critical emergency in which multi-organizational collaboration, expert skills and advanced resources can prevent long-lasting morbidity and mortality. This has major implications on the overarching system of care and how best to deliver reperfusion therapy.

Prehospital stroke scales

Emergency medical services (EMS) are key to promptly identifying ELVO and triggering mobilization of care, with prehospital notification leading to significant reductions in time to reperfusion [11]. As such, the National Institute of Health Stroke Scale (NIHSS), the gold standard for in-hospital assessment of stroke severity, has been criticised for being too technical and time-consuming for EMS [95]. Recognising this, prehospital stroke scales (PSSs) have been proposed to simplistically and effectively aid early stroke recognition, several of which have been validated in prehospital cohort studies [96–99]. Nonetheless, no clear consensus about PSSs has been reached since there are no RCTs to confirm improved outcomes using PSSs and systematic reviews have generally been inconclusive in identifying a superior PSS [100–102]. A recent Cochrane systematic review was the first to recommend PSSs, stating that the 'Cincinnati Prehospital Stroke Scale' and 'Recognition Of Stroke In the Emergency Room' scale have the highest sensitivities in the prehospital and emergency department (ED) settings respectively for detecting stroke or transient ischemic attack [103]. This review is however weakened by major heterogeneity between studies and few studies of each test.

Furthermore, PSSs may still be too complex for EMS. For example, FAST-ED assesses for inattention, whilst RACE requires subjective inclusion of aphasia and agnosia [97, 99]. This is relevant as paramedics have demonstrated sub-optimal stroke recognition, attributed to insufficient AIS teaching [104]. Thus, a simplified PSS was formulated via a recent group lasso analysis (7 PSS, 1316 patients) that identified the most predictive NIHSS-items [105]. The result was a decision-making tree with dichotomized items, GACE (Gaze, facial Asymmetry, level of Consciousness, Extinction/inattention), which uses only two steps to exclude patients (61% of study population) from transfer to a comprehensive stroke centre (CSC) [105]. Theoretically, GACE or similar efforts may reduce delays to ET; however, validation in prospective RCTs is necessary.

Telemedicine

Telemedicine has revolutionised the emergent outreach care of AIS ('telestroke'), by connecting imaging interpretation-limited centres with a telestroke team (neurologist, radiologist, interventional neuroradiologist). Telestroke expedites diagnosis and IVT-related decisions, reducing costs associated with inappropriate transfers [106, 107]. This enables safe and efficacious delivery of IVT comparable to in-hospital evaluation (Kepplinger, 2016). As for

ET, telestroke has been shown to reduce door-to-groin puncture time ($p = 0.04$) and improve functional independence ($p = 0.04$) in one retrospective study, but stronger evidence is required [108].

Levels of care

There is level IA evidence that the use of multidisciplinary specialised stroke care delivered by stroke units leads to improved clinical outcomes. Stroke centres are the hospitals that provide this full pathway of care, and in the widely adopted 'hub-and-spoke' model, can be stratified into primary or comprehensive stroke centres (PSCs or CSCs). From the periphery of each patient catchment, care is centralized from PSCs, which offer stabilisation, initial evaluation and IVT, to CSCs, which offer the full spectrum of neuroendovascular therapy, in addition to advanced neuroimaging, neurosurgical services, neuroanaesthesia and intensive care units [109].

Wide distribution of primary stroke centres (PSCs) and comprehensive stroke centres (CSCs), such as in European countries, allows increased accessibility and shorter, homogenous transport times, whilst increased centralization to CSCs, such as in the USA, may improve standardization, quality and cost-effectiveness of care [110]. Governing bodies must therefore evaluate the local balance between time metrics and centralization, in order to determine the optimally accessible, efficacious and viable distribution of stroke centres.

Organizational models of care

Several organizational models exist for coordinating care between EMS, PSCs and CSCs. Two main models are direct-to-mothership (MS) and drip-and-ship (DS) (see Fig. 1). Major RCTs support MS over DS, as a subgroup analysis of

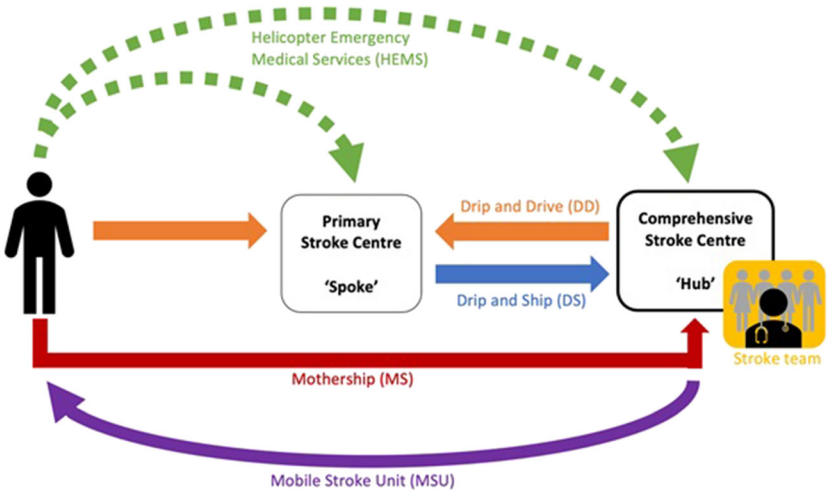

Fig. 1. Diagrammatic representation of 'hub-and-spoke' system of care depicting various organizational models. PSC: stroke centre equipped with EMS, ED, stroke unit, neuroimaging with angiography, anaesthesiology, pathology, IVT capabilities. CSC: stroke centre that in addition to PSC facilities, offers a full array of neuroendovascular therapy, neuro-ICU and open neurosurgical services. MS: direct transfer to CSC. DS: initial transfer to PSC for initiation of IVT prior to transfer to CSC. DD: neurointerventionalist meets the patient at the PSC to perform ET. MSU: transportation of the stroke team, EMS equipment, CT-scanner and point-of-care laboratory to the patient for decision-making and possibly IVT prior to hospital transfer. Stroke team: multidisciplinary teams dedicated to managing stroke, including a leading stroke physician (vascular neurologist or neurointerventionalist), emergency physician, radiologist, anaesthesiologist, radiographer, stroke-trained nurses and allied health.

HERMES demonstrated that MS achieved significantly faster onset-to-reperfusion time (median 251 vs 345 min, $p < 0.001$), which was associated with greater functional independence [111].

Subsequent prospective trials have reinforced these findings, with a recent meta-analysis (8 studies, $n = 2068$) reporting that MS significantly improves functional independence compared to DS, with similar sICH and mortality [112]. Whilst DS potentially improves onset-to-needle times, futile reperfusion for ELVO suggests that improving onset-to-reperfusion times with ET in a MS model is preferred [111, 112]. Thus, there is overwhelming evidence to advocate for MS over DS, which current guidelines may be updated to reflect [9••, 10].

A novel model drip-and-drive (DD) aims to maximally hasten ET. In small retrospective studies, DD appears feasible and much faster than DS in achieving reperfusion but is of limited applicability in many large metropolitan centres [113–115].

Another outreach-focussed model is the institution of mobile stroke units (MSU), which has been feasible across several stroke networks worldwide [116]. The strongest evidence for MSU is from PHANTOM-S, a Berlin-based RCT involving 6182 suspected AIS patients within 16-min travel to one of 28 hospitals [117]. In MSU patients, mean alarm-to-treatment time (51.8 min) was 25 min shorter than standard care (95%CI 20–29, $p < 0.001$). Correspondingly, IVT rates were higher in MSU versus standard care (33 vs 21%, $p < 0.001$), with more IVT occurring within 90-min (58 vs 37%, $p < 0.001$) [117]. Wider implementation of MSU would require larger studies demonstrating clinical efficacy and cost-effectiveness.

Transportation methods

Transport delays lead to worsening prognosis and potential treatment ineligibility [118]. As such, helicopter emergency medical services (HEMS) have gained uptake for time-critical conditions [119].

In an observational study of 25,332 suspected AIS patients transported to PSCs via HEMS in the USA, 59.2% arrived within 1 h from request, and 96.4% within 2 h, despite most patients originating from rural locations [120].

Transport times did not significantly differ across different times of day nor geographical location, thus suggesting HEMS can enable timely, wide-accessibly treatment.

When compared to ground transport, the benefit of HEMS appears location- and protocol-dependent. For example, in a prospective single-centre Danish study ($n = 330$), ground transport was faster than HEMS (median 55 vs 68 min) regardless of travel distance [121]. Conversely, in one retrospective French study ($n = 239$), HEMS reduced out-of-hospital time for distances over 35 km [122]. The difference in results between studies may be explained by the considerably greater travel distance of HEMS over ground transport in the French study (median 62.1 vs 27.6 km) compared to the Danish study (median 83 vs 67 km). Additionally, the Danish study was conducted in a relatively small city with good road accessibility, favouring ground transport.

Therefore, HEMS implementation requires analysis of region-specific traffic and cost factors, which will be facilitated by upcoming computational models that can accurately predict transfer delay [123].

Conclusion

Since ET became the standard of treatment for ELVO in 2015, a multitude of strategies have been proposed to continually improve access and outcome of ET. Perfusion imaging has enabled selection of late presenters for ET, whilst improved versatility and technical proficiency means tandem occlusions and proximal M2-MCA occlusions are now often included for ET. Geographically, the outreach of ET has expanded due to telemedicine, MSU and HEMS. Future expansion of ET to paediatric populations, milder stroke symptoms and larger infarct core has been suggested in the literature but remains unproven. Likewise, refinements about choice of IVT, thrombectomy technique, anaesthesia, organizational models and systems of care are expected to be clarified with upcoming RCTs. Beyond expansion of indications, it is the improved delivery of this treatment which represents the essential next step in achieving the highest rates of improved functional outcome for stroke patients.

Compliance with Ethical Standards

Conflict of Interest

Julian Maingard declares that he has no conflict of interest. Michelle Foo declares that she has no conflict of interest. Ronil V Chandra declares that he has no conflict of interest. Thabele M Leslie-Mazwi declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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