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Review

Mechanical thrombectomy and the future of acute stroke treatment

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A R T I C L E I N F O

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A B S T R A C T

After being staggered by numerous negative trials in 2013, the interventional stroke community saw four years of vindication for mechanical thrombectomy showing efficacy and safety, even beyond a hopeful 6–8 hour window out to 24 h. A landmark set of five trials in 2015 provided a foundation upon which years of incremental follow-ups, meta-analyses and new breakthroughs would be built. With optimized devices for thrombectomy and image analysis, the neurointerventional community has turned to workflow and systemization in this new era of acute ischemic stroke treatment. The aim of this review is to chronicle the evidence in the epoch of positive trials, synthesize ancillary studies to these, and discuss the imminent challenges that remain.

1. Introduction

The treatment of acute ischemic stroke has advanced considerably since the early advent of mechanical thrombectomy (MT). Over the past two years, overwhelming evidence for MT for large vessel occlusion in the anterior circulation arose from five randomized control trials (RCTs): MR CLEAN, ESCAPE, EXTEND IA, SWIFT PRIME and REVASCAT [1–5]. These learned from the lessons of earlier negative trials, included the next-generation stent retrievers, utilized baseline imaging as an inclusion criteria. and aimed for a faster stroke onset to procedure/puncture time. All of these trials yielded decisively positive results that favoured MT over IV t-PA alone. In 2016, the state of MT continued to advance. Results from two additional trials, THERAPY and THRACE (albeit the latter was underpowered at the time of its termination) became available. Following the publication of the RCT results, several systematic reviews and meta-analyses pooled data from these RCTs to provide more robust evidence. Currently, research in the MT field involves investigations aiming to optimize aspects of the procedure. For instance, the mode of anesthesia was investigated in meta-analyses and subsequently a recently RCT. Moreover, potential balance between the benefits and risks of IV t-PA prior to MT is another question of ongoing investigation in recent non-randomized studies. Lastly, a new technique named direct aspiration first pass technique (ADAPT) is gaining attention, and its efficacy is being compared to standard stent-retriever technique in recent analyses. The purpose of this review is to chronicle the evidence in the epoch of positive trials including meta-analysis and follow-up studies, synthesize ancillary studies to these such as evolving workflow, catheter and anesthetic techniques, and discuss the challenges that remain in the immediate future for thrombectomy such as imaging and patient selection.

2. 2016 trials

While MR CLEAN, ESCAPE, SWIFTPRIME, EXTEND IA and REVASCAT were published in 2015, the results of THRACE and THERAPY became available only a year later. Similar to MR CLEAN and ESCAPE, THRACE studies compared IV t-PA alone to IV t-PA with mechanical thrombectomy. The MT procedures employed primarily stent retrievers, as well as occasionally aspiration devices. Patients were enrolled based on a confirmed occlusion in a large vessel of the anterior circulation or superior basilar artery as evident on CTA or MRA. Unfortunately only two patients were enrolled with occlusions of the superior basilar artery in each arm (i.e. 4 total), thus the results of the trial only meaningfully reflect strokes in the anterior circulation. The trial was stopped early after an unplanned interim analysis showed superiority of the MT group. At its termination, 208 patients were randomized to receive t-PA alone and 204 patients were to receive t-PA with MT. The primary endpoint of functional independence (mRS $\leq$ 2) at 90 days favoured the intervention group (53%) over the control (42%) (OR = 1.55, 95% CI 1.05–2.30). There were no differences in mortality or symptomatic intracranial haemorrhage (sICH) rates. While the THRACE trial affirmed the results of the trials published in 2015, there were some differences in its methodology. One major difference is that patient selection was not based on the size of the ischemic core. In THRACE, 30% of patients who scored 0–4 on the Alberta Stroke Program Early CT Score (ASPECTS) achieved functional independence at 90 days. Thus, the potential benefit of treatment in this group of patients should not be discounted. Another important difference was the short delay from IV t-

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PA to randomization compared to other studies. As a result of this, patients were not excluded based upon their response to IV t-PA. However, this did result in a large proportion (30%) of crossover from the MT group to the control group, as many patients did not receive MT. The time from randomization to groin puncture was longer than the other comparable studies. All of these factors contributed to the decreased absolute difference in functional independence as compared with other trials. Nevertheless, THRACE demonstrated the efficacy of MT without exclusion of patients with large ischemic cores and an initial response to IV t-PA, offering potentially yet another paradigm shift for acute stroke [6].

Around the same time as THRACE, results from THERAPY were also published. Enrolment was stopped early at 108 enrolled patients after results from MR CLEAN were made available and it was subsequently considered unethical to treat patients with t-PA alone. The major difference between THERAPY and the other trials is that THERAPY only investigated the efficacy of the Penumbra Aspiration System (Penumbra Inc, Alameda, CA). The study compared treatment with IV t-PA with aspiration against IV t-PA alone. The primary efficacy endpoint of functional independence at 90 days failed to reach significance since THERAPY was underpowered at the time of termination. However, the data appeared to favour intervention over control (OR = 1.76, 95% CI 0.86–3.59). Moreover, per protocol analyses of primary and secondary endpoints consistently favoured the intervention, with some secondary endpoints reaching statistical significance. There were no differences in mortality or SICH rates detected. THERAPY was the first study to examine the effect of aspiration devices alone. While it was stopped prematurely and ultimately underpowered, the results suggested a potential benefit of aspiration devices over standard medical management. What must be noted is that the trial does not answer the question of whether aspiration or stent retrievers are more efficacious, and further RCTs comparing (and possibly combining) these two currently procedures is required to provide a definitive answer [7].

With the publication of MR CLEAN, ESCAPE, EXTEND IA, SWIFT PRIME, THRACE and THERAPY, the case for endovascular therapy became irrefutable. These trials learned from the earlier lessons of IMS III, SYNTHESIS and MR RESCUE. Using mainly stent retrievers such as the Solitaire device (Medtronic, Dublin, IE), stream-lining workflow to reduce door-to-treatment/puncture times, and employing innovative imaging techniques for optimal patient selection, these new trials discovered a significant benefit in the functional outcomes, neurological improvement, reperfusion rates and mortality [1–7]. Moreover, endovascular therapy has consistently been proven to be as safe as medical treatment. These results amount to a powerful case for endovascular therapy as standard care for acute ischemic stroke patients (Tables 1–4).

3. Systematic reviews and meta-analyses

After publication of the positive trials in 2015, many systematic reviews and meta-analyses sought to pool the data from these trials to form a more robust evidence regarding MT. Four meta-analyses were published in 2016 that used a variety of methods to pool together patient data and perform further analyses across the RCTs.

Badhiwala et al pooled data from 8 RCTs with published results at the time: IMS III, SYNTHESIS, MR RESCUE, MR CLEAN, ESCAPE, EXTEND-IA, SWIFT-PRIME, and REVASCAT. A total of 2423 patients were included, with 1313 who received endovascular therapy and 1110 who received standard medical treatment. The study concluded that MT was associated with an improvement in modified Rankin Score (mRS) (OR = 1.56, 95% CI 1.14–2.13), greater rate of achieving functional independence (mRS $\leq$ 2) at 90 days (OR = 1.71, 95% CI 1.18–2.49) and higher rate of revascularization (OR = 6.49, 95% CI 4.79–8.79). There were no differences in sICH or all-cause mortality at 90 days. However, the heterogeneity between the studies was high for mRS, and thus subgroup and sensitivity analyses were performed. In the subgroup analysis, functional outcomes were significantly better in patients with confirmed proximal artery occlusions on imaging, those who received a combination therapy of both endovascular and t-PA and those who were treated with stent retrievers. In addition, there was interaction between the study year and functional outcomes. Unsurprisingly, older trials revealed smaller effect sizes. This meta-analysis synthesized the results from multiple RCTs, and despite the presence of heterogeneity amongst the trials, endovascular therapy was still shown to result in better functional outcomes and better revascularization rates when compared with standard medical management [8].

Another meta-analysis was by Campbell et al included patient-level data from RCTs that primarily used the Solitaire device (ESCAPE, SWIFT PRIME, EXTEND-IA and REVASCAT). The primary analysis included 787 patients from all four trials, of which 401 were randomized to endovascular group and 386 to the standard medical therapy. In the primary analysis, the common odds ratio (cOR) for mRS improvement was 2.7 (95% CI 2.0–3.5). The number needed to treat (NNT) to reduce disability was found to be 2.5 and the NNT for a better independent functional outcome was 4.25. Mortality and SICH rates were not significantly different. The benefit of MT was consistently observed in all predefined subgroups, regardless of age, sex, NIHSS score, site of lesion, presence of tandem cervical carotid occlusions, ASPECTS and administration of IV-tPA. Furthermore, though elderly age has frequently been an exclusion criteria for MT, the results of this meta-analysis suggest that there is no evidence for reduced benefit in the elderly ($\geq$ 80 years of age). In fact, there was an observed clinically significant 20% absolute reduction in mortality rates. Moreover, in IMS III and MR CLEAN, NIH Stroke Score (NIHSS) was a selection criteria for patients. This meta-analysis found no significant difference in benefit for patients with NIHSS $\leq$ 15 in comparison to patients with NIHSS $>$ 20. Lastly, the pooled data affirmed that better functional outcome is achieved with decreased time from onset to intervention. The results from this meta-analysis suggest that the Solitaire device is safe and effective in treating large vessel occlusions, leading to improvement in functional outcome and reduced disability in all patient subgroups [9].

A subsequent systematic review conducted by Rodrigues et al included all the studies analyzed in Badhiwala et al with the addition of THERAPY and THRACE. Endovascular treatment was found to have a higher proportion of patients with good or excellent functional outcomes (mRS < = 2 or 1). The risk ratio of a good functional outcome was 1.37 (95% CI 1.14–1.64). Mortality and sICH rates were not significantly different. Similar to Badhiwala et al., heterogeneity of the studies was high. After excluding the 2013 trials, MR RESCUE, SYNTHESIS and IMS III, there was no longer felt to be heterogeneity among the trial results, and the risk ratio of a good functional increased to 1.56 (95% CI 1.38–1.75). Due to methodological issues with MR RESCUE, SYNTHESIS and IMS III, the OR of 1.56 was deemed to be a more accurate reflection of true effect of the current MT procedure [10].

Lastly, Goyal et al analyzed only data from the five RCTs published in 2015. This meta-analysis included 1287 patients with 634 randomized to endovascular thrombectomy and 653 to medical therapy. The pooled results indicate that endovascular treatment was associated with significant reduction of disability, as measured by mRS, at 90 days (adjusted common OR = 2.49, 95% CI 1.76–3.53). Moreover, the NNT to reduce at least one score of mRS was 2.6. Mortality and sICH rates did not differ between the intervention and control groups. There were many subgroups of clinical interest associated with a significant effect favouring endovascular thrombectomy. In particular, patients > 80 years of age achieved a cOR of 3.68 (95% CI 1.95–6.92) favouring the intervention. Patients who were randomized 300 min after onset of symptoms achieved a cOR of 1.79 (95% CI 1.05–2.97). Patients who were not eligible for IV t-PA had cOR of 2.43 (95% CI 1.30–4.55). Contrary to certain prior beliefs, this meta-analysis discovered benefit of MT for patients who were older, randomization late and contraindicated to IV t-PA [11].

With these systematic reviews and meta-analyses, it has become

Table 1
Essential Trial Composition.

	Arms	Size	Era	Centres	Age Range	Clinical Criteria	Vessel occlusion	Time Window (onset to groin puncture)	CT Criteria	Advanced Imaging Criteria
MR RESCUE	Rescue EVT v standard	118	2004 - 2011	North America – 22 sites	18- 85 yr	NIHSS 6- 29	CTA/MRA showing persistent occlusion post IVT – ICA, M1 or M2	< 8 hr	None	Penumbra assessment with multimodal CT or MRI for stratification but not for trial eligibility
IMS III	Bridging v IVT	656	Aug 2006 – Apr 2012	58 Centres (US, Canada, Australia, Europe)	18- 82 yr	NIHSS ≥10 Or NIHSS 8-9 with proven vessel occlusion (ICA, M1, BA)	Not required at randomization	< 5 hr	None	None
SYNTHESIS	EVT v IVT	362 (181 v 181)	Feb 2008 – Apr 2012	Italy – 24 centres	18- 80 yr	NIHSS > 25 excluded	Not required at randomization	< 4.5 hr	None	None
PISTE	Bridging v IVT	65 (33 v 32)	Apr 2013- Apr 2015	10 Centres (UK)	≥18 yr	NIHSS ≥6	I-ICA, M1, M2 *Extra-cranial-ICA excluded*	< 5.5 hr	Evidence of extensive established infarction excluded	None
THERAPY	Bridging v IVT	108 (55 v 53)	Mar 2012 - Oct 2014	36 Centres (US and Germany)	18-85 yr	NIHSS ≥8	I-ICA, M1	eligible for tPA (< 4.5 hr)	Any acute ischemic changes > 1/3 MCA excluded	clot length ≥8 mm
MR CLEAN	EVT v standard	500 (233 v 267)	Dec 2010- Mar 2014	Netherlands - 16 centres	≥18 yr	NIHSS ≥2	I-ICA,M1,M2,A1,A2 *Additional extra-cranial ICA or dissection at discretion of treating physician*	< 6 hr	None	None
ESCAPE	EVT v standard	315 (165 v 150)	Feb 2013- Oct 2014	22 Centres (Canada, US, Ireland, South Korea, Uk)	≥18 yr	NIHSS > 5	I-ICA,M1, 2-M2s, A1 *Additional extracranial ICA or dissection at discretion of treating physician*	< 12 hr	ASPECTS > 5	CTA filling > 50% of MCA pial collaterals, CTP = vlCBF/CBV ASPECTS > 5
EXTEND_IA	Bridging v IVT (Solitaire only)	75 (35 v 35)	Aug 2012- Oct 2014	10 centres (9 Aus, 1 NZ)	≥18 yr	No NIHSS cut-off	ICA, M1 or M2 *dissection excluded*	< 6 hr	None	Target mismatch: mismatch > 1.2, rCBF core < 70 ml, 6 sec Tmax penumbra > 10 ml
SWIFT PRIME	Bridging v IVT (Solitaire only)	196 (98 v 98)	Dec 2012- Nov 2014	39 centres (US and Europe)	18-80	NIHSS 8-29	I-ICA, M1 Extra-cranial-ICA excluded (including dissection)	< 6 hr	Revised small core (ASPECTS > 5)	Initially target mismatch (core < 50 ml, 10 sec Tmax lesion < 100 ml, penumbra > 15 ml and mismatch ≥1.8)
REVASCAT	EVT v standard (Solitaire only)	206 (103 v 103)	Nov 2012- Dec 2014	4 centres Spain (Catalonia)	18-80	NIHSS > 5	I-ICA,M1,	< 8 hr	ASPECTS > 6 (> 5 on DWI)	No recanalization on CTA/MRA after ≥30 min from start of tPA infusion If CTA/MRA performed > 4.5 hr from onset then CBV ASPECTS, CTA-SI ASPECTS or DWI-MR ASPECTS must be performed
THRACE	Bridging v IVT		June 2010- Feb 2015		18-80	NIHSS 10-25 I	I-ICA, M1, upper 1/3 basilar artery,	< 5 hr	None	None

(*continued on next page*)

Table 1 (*continued*)

Arms	Size	Era	Centres	Age Range	Clinical Criteria	Vessel occlusion	Time Window (onset to groin puncture)	CT Criteria	Advanced Imaging Criteria
	412 (208 v 204)		26 centres France (Mothership only model)			*Ipsilateral E-ICA, stenosis/occlusion excluded*			

more evident than ever that mechanical thrombectomy is more effective than t-PA alone in treating patients with acute ischemic strokes. The functional outcome was consistently better with MT even with patient data included from the negative 2013 trials. When results from only the newer trials were analyzed, the effect size was considerably larger. There was also new evidence that the intervention is effective regardless of patient age, NIHSS score, ASPECTS score, site of lesion, presence of tandem cervical carotid occlusions, whether concomitant t-PA was administered and whether randomization was delayed [8,9,11]. Essentially, endovascular therapy is safe and effective in almost all patient groups.

4. Mode of anesthesia during mechanical thrombectomy

After establishing evidence for the efficacy of MT, a number of questions remain regarding the endovascular procedure. One of these is the choice between general anesthesia with intubation and conscious sedation with local anesthesia. Both of these techniques are commonly used, with purported advantages supporting each one. The advantages of general anesthesia had been cited as involving less pain, anxiety, patient movement and aspiration risk, and thus is generally considered a more safe and efficacious choice [12,13]. Conscious sedation, on the other hand, consumes less time, potentially provides more hemodynamic stability, avoids risks of intubation and allows the monitoring of neurological status [12,13]. Thus, numerous studies have attempted to elucidate the balance of risks and benefits between these anesthesia choices. Theoretically, it has also been suggested that the transient hypotension that follows induction might exacerbate the ischemic milieu.

Prior to the RCT in this domain, meta-analyses and *post-hoc* studies suggested the potential superiority of conscious sedation over general anesthesia. A *post-hoc* analysis of MR CLEAN found the loss of statistical significance in functional outcome between MT and medical management for patients who underwent general anesthesia [14]. Murad et al conducted a meta-analysis on studies reporting mode of anesthesia during endovascular treatment of acute ischemic stroke. The results showed that patients undergoing general anesthesia had higher mortality (OR = 2.59; 95% CI, 1.87–3.58), higher respiratory complications (OR = 2.09; 95% CI, 1.36–3.23), lower good functional outcomes (OR = 0.43; 95% CI, 0.35– 0.53) and lower successful angiographic outcome (OR = 0.54; 95% CI, 0.37– 0.80) [12]. Another meta-analysis focusing on data from the five 2015 RCTs suggested that functional outcomes was better with conscious sedation (OR, 2.08; 95% CI, 1.47–2.96), but there were no differences in short term mortality [13]. However, both of these studies recognized that patients indicated for general anesthesia commonly had more severe strokes with higher NIHSS scores. Thus, an RCT was warranted to maintain prognostic balance.

SIESTA was a single-centre RCT conducted in 2016 to compare conscious sedation against general anesthesia. Of the 150 patients included in the study, 73 were randomized to the general anesthesia group and 77 to conscious sedation. The primary outcome of neurological improvement after 24 h (based on NIHSS) was not significantly different between the groups. General anesthesia was associated with better functional outcome (37.0% vs 18.2% P = .01), and decreased patient movement. However, it was also associated with intubation-related complications such as hypothermia, delayed extubation and pneumonia. No difference in mortality was noted. The other 41 secondary outcomes related to peri-procedural management also did not reach significance. The findings of this RCT were in direct contrast to earlier studies and meta-analyses suggesting worse outcomes with general anesthesia. Conscious sedation did not appear to be superior to general anesthesia in short-term neurological outcome, peri-interventional management and mortality. Though the secondary outcome of functional independence favoured general anesthesia, it must be interpreted with caution, since this study was not adequately powered to

Table 2
Enrollee Characteristics.

	Age (median)	Male (%)	NIHSS (median)	Vessel occlusion	Tandem lesion (extrancranial ICA occlusion)	ASPECTS (median)	IVT (%)	Retrievable stent (%)
MR RESCUE	66	50	16	71% ICA or M1*	nr	predicted core 36 ml*	47*	0
IMS III	69	50	17	18% of EVT group had no occlusion	nr	nr	100	4
SYNTHESIS	66	59	13	2% no occlusion	nr	nr	0	41
PISTE	67	39	18	90% carotid T/L or M1	3%	9	100	68
THERAPY	67	62	17	89% I-ICA or M1	excluded	7.5	100	13% (majority used aspiration thrombectomy)
MR CLEAN	66	58	17	92% I-ICA, carotid T or M1	32%	9	87 (44% drip & ship)	82
ESCAPE	71	48 (87% white)	16	96% carotid T/L or M1	13%	9	73	73
EXTEND_IA	69	49	17	88% I-ICA or M1	n/r	n/r (median core 12 ml)	100	100
SWIFT PRIME	65	55 (89% white)	17	86% carotid T/L or M1	excluded	9	100 (44% drip & ship)	100
REVASCAT	65	55	17	90% carotid T/L or M1		7	70	70
THRACE	66	57	18	98% ICA or M1	excldued	nr	100 (100% mothership)	77

[a] MR RESCUE values reported for penumbral group receiving embolectomy.

detect a difference in functional outcomes [14].

Anesthesia type during endovascular treatment of acute ischemic stroke remains an area of ongoing debate. Though earlier *post-hoc* analyses and meta-analyses suggested worse outcomes for patients with general anesthesia, a recent RCT has tentatively refuted that claim. The results of the RCT even potentially favour general anesthesia in long-term functional outcomes. Subsequent to this, the Anesthesia During Stroke (AnStroke) trial randomized 90 patients between the two modalities at a single centre in 2017, finding no difference in neurological outcome after 3 months [15]. Finally, the General or Local Anesthesia in Intra Arterial Therapy (GOLIATH) trial randomized 128 patients at a single centre and general anesthesia was found to be non-inferior [16].

5. IV t-PA prior to mechanical thrombectomy

Another area of active research surrounds the risks and benefits of IV t-PA prior to MT. The potential benefits include possible early recanalization, increase in the likelihood of successful recanalization (putatively though clot softening) and benefits in case of MT failure. However, in the 2015 trials, early response to IV t-PA was rare. The use of IV t-PA is not without risks, including a potential increase in sICH rates, fragmentation of the thrombus, and delay in MT [17]. Though no randomized controlled trials has yet been conducted, a number of studies examine the topic retrospectively.

Leker et al compared the use of IV t-PA in 24 patients who received IV t-PA prior to MT and 33 patients who received only MT. Mortality and favourable outcome rates were similar between the two groups. However, there was a significantly decreased number of passes required with IV t-PA prior to MT [18].

In a retrospective matched-pair analysis conducted by *Broeg-Morvay* et al, 40 patients who received only MT but who would have qualified for IV t-PA was matched with 40 controls who received both IV t-PA and MT. The groups had similar baseline clinical and radiologic characteristics, but the MT-only group had shorter symptom onset to intervention times (P = 0.01). They did not observe any significance in functional independence, mortality or sICH rates. Further multivariate analysis did reveal lower rates of asymptomatic haemorrhage and mortality favouring the MT group. Though the study matched patients between the two groups, the sample size was relatively small [19].

Weber et al performed a retrospective analysis on 283 consecutive patients who either received or did not receive IV t-PA prior to MT. No differences were found in the recanalization rates, complications, and

Table 3
Reported Workflows.

	Onset to IVT (median., min)	Onset to randomisation (median., min)	Onset to groin puncture (median., min)	Onset to first reperfusion (median., min)	Groin puncture to reperfusion (median., min)	IVT to groin puncture (median., min)	CT to groin puncture (median., min)	CT to reperfusion (median., min)
MR RESCUE	nr	nr	381	nr	nr	nr	124	nr
IMS III	122	nr	208	nr	nr	nr	nr	nr
SYNTHESIS	165	148	225	nr	nr	nr	nr	nr
PISTE	120	150	209	259	49*	82	58#	nr
THERAPY	108	181	227	nr	nr	nr	123	nr
MR CLEAN	85	204	260	332	nr	nr	nr	nr
ESCAPE	110	169	208	241	30	51	51	84
EXTEND_IA	127	256	210	248	43	74	93	nr
SWIFT PRIME	111	191	244	252	nr	nr	58	87
REVASCAT	118	223	269	355	59	nr	67	nr
THRACE	150	168	250	nr	nr	nr	nr	nr

[a] Groin puncture to device removal.
[b] Randomisation to groin puncture.

Table 4
Essential Trial Outcomes.

	Recanalization (%, EVT v control)	Reperfusion (mTICI 2b/3, %)	Primary outcome	mRS at day 90	mRS 0-2 at day 90	Final infarct volume (mL)	sICH (PH-2, %)	Death at day 90 (%)	New AIS in a different territory (%)	SAE (%)
MR RESCUE	69	27	mRS 3.8 v 3.4	3.8 v 3.4	21 v 26	32 v 32	9 v 6	18 v 21	1.4	62
IMS III	81 ICA; 86 M1; 88 M2	38 ICA; 44 M1; 44 M2	mRS 0-2 41 v 39%	nr	41 v 39	nr	6 v 6	19 v 21	nr	nr
SYNTHESIS	nr	nr	mRS 0-1 30 v 35%	nr	42 v 46	nr	6 v 6	8 v 6	nr	nr
PISTE	69	87	OR 2.12 mRS 0-2 p = 0.2	nr	51 ϖ 40 νσ NNT = 9	nr	0 v 0	7 v 4	nr	45 v 34
THERAPY	nr	70	mRS 0-2 38 v 30% p = 0.44	nr	38 v 30 ns	nr	9.3 v 9.7	12 v 24	nr	42 v 48
MR CLEAN	75 v 33	59	mRS 3v4 day 90	3 v 4	33 v 19 NNT = 7	49 v 79	6 v 5	21 v 22	5.6	47 v 42
ESCAPE	nr v 31 (mAOL 2-3)	72	cOR 2.6	2 v 4	53 v 29 NNT = 4	nr	4 v 3	10 v 19 (significant)	nr	21 v 18
EXTEND_IA	94 v 43 (TIMI 2-3)	86	24 hr reperfusion 100 v 37% Early neurological recovery 82 v 37%	1 v 3	71 v 40 NNT = 3	23 v 53	0 v 6	9 v 20 (p = 0.18)	5.7	nr
SWIFT PRIME	nr	88	Shift analysis p = 0.0002	2 v 3	60 v 36 NNT = 4	nr	1v 3	9 v 12 (p = 0.5)	nr	36 v 31
REVASCAT	nr	66	cOR 1.7	nr	44 v 28 NNT = 6	16 v 39	5 v 2	18 v 16	5	30 v 25
THRACE	78	69	mRS 0-2 at day 90 53v42%	nr	53 v 42 NNT = 9	nr	2 v 2	12 v 13	6	8 v 7

EVT endovascular thrombectomy, tPA tissue plasminogen activator, Bridging IV tPA + thrombectomy, NIHSS National Institutes of Health Stroke Scale, I-ICA intracranial internal carotid artery, MCA middle cerebral artery, M1 first portion of the middle cerebral artery, from the origin to the bifurcation/trifurcation, M2 s portion of the middle cerebral artery, CTA Computer Tomography Angiography, CTP Computed Tomography Perfusion, vlCBV very low cerebral blood volume, ASPECTS Alberta Stroke Program Early CT Score, nr not recorded, mAOL modified arterial occlusion lesion score, TIMI thrombolysis in myocardial infarction score, mTICI modified thrombolysis in cerebral infarction score, mRS modified Ranking Scale, sICH symptomatic intracranial haemorrhage, PH-2 parenchymal hematoma 2, ie. > 30% of the infarcted area with significant space-occupying effect, or clot remote from infarcted area, AIS acute ischemic stroke, SAE serious adverse events.

rates of achieving functional independence. Out of those who only received MT, patients who could have received IV t-PA had better rates of functional independence than patients who were contraindicated in the first place. Moreover, MT alone group had shorter workflow times [20].

Most recently, in a post-hoc analysis of data from the STAR and SWIFT trials, MT with IV-tPA was compared with MT alone. Out of 291 patients available for analysis, 131 received only MT and 160 received both IV t-PA and MT. After performing multivariate analysis to adjust for confounders, there were no statistically significant differences found in any outcome, including time from symptom onset to groin puncture, number of passes required, rate of successful reperfusion, functional independence (mRS ≤ 2) at 90 days, mortality at 90 days, risk of emboli to new territory, SICH rates, and vasospasm. Though no statistical significance was reached, there was an absolute lower risk of SICH and greater rate of functional independence in the group that received IV t-PA prior to MT [17].

The question of whether to administer IV t-PA prior to MT remains inconclusive. Most studies did not find a difference whether or not IV t-PA was administered. However, studies in this subject have mostly been retrospective analyses of small sample size, and not randomized to eliminate confounding. Thus, further comparative and RCTs in on this subject are warranted.

6. Combined thombectomy techniques

One of the most contemporary advances in mechanical thrombectomy is A Direct Aspiration First Pass Technique (ADAPT). This technique combines a large-bore catheter with a stent retriever, where the large-bore catheter is first passed to remove the clot via aspiration. If this fails, a stent retriever can be inserted afterwards for a second attempt. This technique has the advantage of being fast without being costly, and has become increasingly popular [21,22]. To date, no randomized trial and only a limited number of comparative studies had examined the efficacy and safety of ADAPT versus other MT techniques [21]. A recent systematic review pooled the results from 17 studies on the ADAPT technique and six RCTs on stent retrievers (IMS III, ESCAPE, EXTEND, MR CLEAN, REVASCAT, and SWIFT PRIME). The pooled results indicate that recanalization rate was higher for the ADAPT technique than stent retrievers (89.6% vs 67.2%, $p < 0.001$). However, the functional outcome of 90 day mRS ≤ 2 was not statistically different between the two groups. The secondary outcome of excellent functional outcome (mRS ≤ 1) at 90 days favoured the ADAPT group but failed to reach statistical significance. SICH and mortality rates were also not significant. Lastly, time from symptom onset to groin puncture was lower in the ADAPT group but this also failed to reach significance. Though higher recanalization rates were observed in this pooled analysis of multiple studies, there were no differences detected in the functional outcomes [21]. Two bailout combined techniques are the aspiration-retriever technique for stroke (ARTS) and the stent retriever assisted vacuum-locked extraction (SAVE) methods which have now been suggested as possible primary methods which involve comparatively distal stent retriever placement and proximal aspiration.

By contrast, a switching technique can be used rather than a simultaneous approach as seen in Solumbra and forced arterial suction thrombectomy (FAST). Solumbra is a combined technique, the conception for which is apparent from its very portmanteau as a use of Solitaire followed by aspiration with large-bore Penumbra. The logic behind this method is that initial aspiration may promote easier clot entrapment within the stent construct by some preliminary liberation from the vessel wall and decrease the likelihood of fragmentation as well. Solumbra also touts improved rates of recanalization against MT alone, however direct comparisons are lacking. FAST is a switching technique which has recently been disregarded a precursor to ADAPT which involved smaller-bore catheters such as 032 and 041 Penumbra models but was otherwise kin to it albeit with 5MAX-era models. FAST demonstrated in a 22 patient series, an 85% rate of recanalization

(45.5% TICI 2b and 36.4% TICI 3) [22].

However, despite the fact that FAST was supplanted by ADAPT and a slightly higher rate on recanalization, it may be that a marriage of the two will ultimately represent a new standard. This is due to the underlooked FAST parameter of a balloon guide catheter (BGC), with a recent meta analysis showing that its use in any MT technique was associated with better clinical and angiographic outcomes [23]. Among the benefits of BGC in the meta-analysis were higher odds of first pass recanalization, shorter mean procedure time, and lower odds of mortality. As a further potential evolution of adjunctive BGC use and of Solumbra, the Proximal balloon Occlusion TogEther with direct Thrombus aspiration (PROTECT) technique has been proposed. The important innovation with PROTECT is the insertion of a large bore aspiration catheter into the BGC, affording flow reversal and distal aspiration during stent retrieval. Thought the initial study is small, this technique yielded yet shorter procedure times and higher rates of recanalization/reperfusion.

7. Redefining the tissue clock

The remarkable progress of endovascular therapy continued rapidly in the heels of HERMES in 2018 with the publication of the DAWN trial. With this Trevo-exclusive study, our understanding of candidacy changed as ictus 6–24 hours earlier in patients who also had a mismatch between clinical deficit and infarct volume, outcomes for disability at 90 days favoured thrombectomy with an adjusted difference of 2.0 points (95% CI, 1.1–3.0; posterior probability of superiority, > 0.999). Importantly, the coprimary end point of the rate of functional independence at 90 days was 49% in the thrombectomy group and 13% in the control. These patients did not experience a significant different in symptomatic ICH.

Shortly thereafter, DEFUSE-3 was terminated on equipoise grounds, showing that MT for ELVO in patients last seen week 6–16 hours earlier, resulted in improved outcomes as along as the at-risk region had not already infarcted. Important difference were that eligible constituted initial infarct volume measured less than 70 ml on RAPID CTP. The OR was 2.77 (95% confidence interval [CI], 1.63–4.70; P < 0.001) for disability scores as determined by mRS at 90 days and the risk ratio was 2.67 (95% CI, 1.60–4.48; P < 0.001) for functional independence. The uniform use of RAPID software was a defining characteristic, as DAWN utilized DWI or CTA/CTP of any kind. Debate is ongoing regarding the utility of MRI for selection, for while is sensitive, the DWI-ASPECTS and DWI-FLAIR studies to-date have shown suboptimal inter-rater agreement and perhaps do not predict disability as well as clinical scores do.

8. Conclusions

In 2018, the effectiveness and comparable safety of mechanical thrombectomy versus medical therapy are now well established. Not only did results from the 2015 trials provide a solid base of evidence, the 2016 trials and subsequent meta-analyses on these further consolidated this evidence. In an era where the superiority of MT is no longer the question, the focus of research has shifted to optimizing the endovascular procedure and improving the thrombectomy technique. In particular, general anesthesia versus conscious sedation remains an ongoing debate. A recently-conducted RCT suggests that neurological status at 24 h is similar, and is inconclusive regarding long-term functional outcome. Another area of debate is regarding the benefits and risks of IV t-PA prior to MT. Recent analyses were unable to discover a definite difference in outcomes. Lastly, the newly popular ADAPT technique provides a promising new method that is potentially more efficacious and less costly than traditional aspiration and stent retrievers.

Conflict of interest

None.

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